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A Comparison of the Thulium Fiber Laser versus Holmium:YAG Laser Lithotripsy of Upper Urinary Tract Calculi: Preliminary Results of a Randomized Prospective Clinical Trial

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Abstract

The Holmium:yttrium-aluminium-garnet (Ho:YAG) laser has become an indispensable tool in Endourology since its introduction in 1995, due to its safe and efficient urinary stone fragmentation capabilities. The Thulium Fiber Laser (TFL), is the latest innovation with early clinical experience suggesting improvements over the Ho:YAG. This prospective, randomized controlled study aims to compare clinical outcomes of Ho:YAG versus TFL lithotripsy for upper urinary tract calculi. Patients undergoing ureteroscopy for renal stones (size 8-20mm, density >600 HU) from a single institution were prospectively recruited.

Thirty-eight patients have been recruited (Ho:YAG=20, TFL=18). The laser-on time (p=.330), total operative time (p=.849), total laser energy (p=.745), ablation speed (p=.745) and ablation efficiency (p=.745) were not statistically different between groups. Multiple trends in favor the TFL were documented, including shorter laser-on time and total operative time, improved ablation efficiency and ablation speed.

Preliminary results suggest similar outcomes for both technologies. Several parameters are trending in favor of the TFL being more efficient; however, recruitment fulfillment will be necessary to determine if there are significant differences.

Keywords

Lasers Lithotripsy, Holmium:YAG laser, Thulium Fiber Laser, Ureteroscopy, Urolithiasis, Randomized Controlled Trial

Summary for Lay Audience

Kidney stone disease is a common disease and has an estimated lifetime prevalence of 1-15%. Lithotripsy is a generic term used to describe procedures to destroy a stone inside the urinary tract, and can involve various technologies. Laser lithotripsy became the mainstay treatment since 1995, using the Holmium:yttrium-aluminium-garnet (Ho:YAG) wavelength. The laser delivers energy directly to the stone via an endoscope that allows direct vision and precise stone destruction. The Ho:YAG is widely used because of its safety and efficiency in destroying stones but has some inherent limitations. In 2005, a new laser technology was introduced, the Thulium Fiber Laser (TFL). The TFL has different physical properties, and laboratory and early clinical evidence demonstrated that it results in faster and more efficient laser destruction of urinary stones. The existing international literature is still scarce however, with few properly conducted high-quality clinical trials and controversy regarding the TFL's advantages exists.

The aim of this research was to compare the Ho:YAG and TFL laser technologies in a clinical setting. A prospective recruitment of patients was undertaken, and patients were randomly assigned to each technology. To compare the efficiency of the lasers, different parameters were analyzed including: lasering time, surgical time, energy needed to destroy a stone and the speed at which the stone was destroyed. The preliminary findings of the research documented no statistical difference, but multiple parameters favored the TFL, as being a faster and more efficient laser. Nevertheless, recruitment fulfillment is needed to confirm any clinical differences. The clinical relevance of a more efficient laser lithotripsy laser is the ability to manage more complex and larger stones via a minimally invasive surgical approach which would improve patient care.

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List of Abbreviations

NHANES	United States National Health and Nutrition Examination Survey
OHIP	Ontario Health Insurance Plan
CIHI	Canadian Institute for Health Information
RR	Relative Risk
CI	Confidence Intervals
OR	Odds Ratio
BMI	Body Mass Index
SWL	Shock Wave Lithotripsy
DHA	2,8-Dihydroxyadenine
NCCT	Non-Contrast Computed Tomography
NSAIDs	Non-steroidal anti-inflammatory drugs
URS	Ureteroscopy
PCNL	Percutaneous Nephrolithotomy
RIRS	Retrograde Intrarenal Surgery
EHL	Electrohydraulic Lithotripter
LASER	Light Amplification by Stimulated Emission of Radiation
Nd:YAG	Neodymium:YAG
Ho:YAG	Holmium:yttrium-aluminium-garnet or Holmium:YAG
TFL	Thulium Fiber Laser
µsec	microseconds
J	Joules
Hz	Hertz
KJ	kilojoules
W	Watt
IQR	Interquartile Range
RCT	Randomized Controlled Trial
SFR	Stone-free rate
FLEXOR	Flexible Ureteroscopy Outcomes Registry
PSM	Propensity Score-Matched
SD	Standard Deviation
SMD	Standardized Mean Difference

HU	Hounsfield Units
REDCap	Research Electronic Data Capture
UPJ	Uretero-pelvic junction
ASA	American Society of Anesthesiologists
TOT	Total Operative Time
CONSORT	Consolidated Standards of Reporting Trials
BMI	Body Mass Index
CAD	Coronary Artery Disease

Chapter 1

1 Introduction and Literature Review

To understand the role of a new surgical tools in the treatment of urolithiasis, it is important to review the increasing burden of this condition across the globe and the potential clinical impact the technology may impart on the condition. The epidemiology and pathophysiology of stone disease will first be reviewed. Next, the clinical presentation and treatment approaches will be described to provide context when considering the importance of laser lithotripsy in stone management. In the final section, a description and comparison of the laser lithotripsy technologies is depicted and how they differentiate.

1.1 Epidemiology of Urolithiasis

Kidney stone disease is a common condition around the world with an estimated lifetime prevalence between 1 to 15% [1]. The prevalence of stones will vary according to age, gender, race and geographic region. Multiple reports have documented varying prevalences' for each geographic region including: 7-13% in North America, 5-9% in Europe and 1-5% in Asia [2]. An analysis based on the updated United States National Health and Nutrition Examination Survey (NHANES) from 2007-2010, reported that 19% of males and 9% of females will be diagnosed with nephrolithiasis by the age of 70 years [3].

A study done in Rochester, Minnesota from 1950 to 1974, documented a stable incidence for the female population (36 per 100,000/year) over a 25-year period, while in contrast, the incidence increased from 78 per 100,000/year to 123.6 per 100,000/year for males with an estimated male to female ratio of 3:1 [4].

Among females the peak incidence is bimodal occurring at the age of 20 (2.5 per 1000/year) and 70 years old. For male patients, the incidence starts to rise at 20-years of age and will peak between 40 to 60 years (3 per 1000/year [1,5].

An update from the epidemiology nephrolithiasis study done in Rochester, Minnesota from 1970 to 2000, documented an increase in the incidence of symptomatic stones for females and a decrease for males, changing the male to female ratio from 3:1 to 1.3:1 [6].

1.1.1 "Time-related" Increase in Prevalence

Several international reports have documented a global phenomenon of increases in the prevalence and incidence of kidney stone disease [7]. In 1994, one of the first prevalence assessments done by Stamatelou et al. from the NHANES II & III (1976-1994), documented a kidney stone prevalence of 1 in 20 persons in the United States [8]. In addition, the authors reported an increase in prevalence from 3.8% in 1976-1980 to 5.2% from 1988-1994 (p<0.05).

An updated study based on the NHANES 2007-2010, continued to report an increasing prevalence [3]. There was a documented increase from 1 in 20 to 1 in 11 persons in a period of 15 years in the United States. The increase in prevalence was noted in all ages, gender, and ethnics groups. Specifically, a relative increase of 63% (6.3% in 1988-994 to 10.3% in 2007-2010) in stone prevalence was observed and the mean annual incidence of nephrolithiasis increased 1% annually between 1997 to 2012 (206 to 239 per 100,000 population) [9].

The Urologic Diseases in America Project documented 2 million outpatient visits for a diagnosis of urolithiasis in the year 2000 [10]. The outpatient hospital visits increased 40% from 1994 to the year 2000, in addition, physician's office visits increased by 43%.

In a study performed in Ontario, Canada using the Ontario Health Insurance Plan (OHIP) and the Canadian Institute for Health Information (CIHI) Discharge Abstract Database, there was an increase in the number of procedures performed for kidney stones from 1991 to 2010 [11]. The rate of procedures performed per year increased steadily from 85 to 126 per 100,000 population. The reported overall ratio of male to female patients that underwent kidney stone procedures was 1.7:1. Although this study could not calculate incidence or prevalence of stone occurrence, the increase in procedures would nevertheless suggest an increasing burden of stone disease in this Canadian population.

1.1.1.1 Economics of Kidney Stone Treatment

The global increase in the prevalence of kidney stones has been associated with an increase in costs of nephrolithiasis treatment. Direct costs related to diagnosis, treatment and prevention are already substantial and projected to reach an estimated of 4.1 billion US dollars by 2030 [12]. This estimation is based on the 1.83 billion dollars spent in 1995 in contrast to 2.1 billion dollars spent in the year 2000 on nephrolithiasis treatments in the USA [10]. Indirect costs resulting from time off from work and the impact on patients' quality of life are not as easily quantifiable but also significant.

1.1.2 Variables that May Influence Urolithiasis Development

Multiple factors have been associated with the development of kidney stones including:

- *Age:* The prevalence for kidney stones varies according to age and appears to increase as one gets older. In a study based on the NHANES 2007-2016 data set, the was a documented linear increase in prevalence with age, the increase was prominent in males as shown in Table 1 [13]. The bimodal distribution in females with an increase after 60 years-old, appears to be related to a fall in estrogen levels (menopause) which is associated with enhanced renal calcium absorption and reduced bone resorption [4,14].

Table 1. Age-related Kidney Stone Prevalence

Age-related kidney stone prevalence (2007-2016) [13]	*Male*	*Female*
20-39 years-old	5.1%	5.8%
40-59 years-old	11.5%	9.8%
60-79 years-old	18.8%	9.2%
≥80 years-old	19.7%	10.6%

- *Sex:* There was a documented increase in the incidence of symptomatic stones from the 1970s to the 2000s for females, in contrast to a decrease incidence for males; shifting the male to female ratio from 3:1 to 1.3:1 over 30 years (p=.006) [6]. The female incidence increased from 43.2 (±14.0) to 68.4 (±12.3) per

100,000/year and the male incidence decreased from 155.1 (±28.5) to 105.0 (±16.8) per 100,000/year.

- *Race*: In 1994, Soucie et al. documented a difference in prevalence of stones between white males, African Americans, Hispanic and Asians in the United States [15]. The highest prevalence was for white males followed by Hispanics (70%), Asians (63%) and African Americans (44%). Among females, the prevalence was the lowest for Asians (55%) in comparison to white females, followed by African American (88%) and Hispanics (88%). In comparison to white males and females the adjusted odds for stone by race was: for African Americans 0.40 and 0.61; for Hispanics 0.66 and 0.85; and for Asians 0.56 and 0.54 respectively. Scales et al., documented a similar trend in urolithiasis prevalence among races in the 2007-2010 NHANES study [3].

- *Ethnicity:* Based on a study performed at a Kidney Center in Toronto Canada, 1280 consecutive individuals were included to compare the Relative Risk (RR) of idiopathic calcium nephrolithiasis between ethnicities in the same geographical area [16]. In contrast to Canadians of Europeans descent, the risk for calcium nephrolithiasis was higher for ethnic groups from the Middle East [Odds Ratio (OR) 3.8, 95% Confidence Interval (CI) 2.7-5.2], West Indies (OR 2.5, 95% CI 1.8-3.4), West Asia (OR 2.4, 95% CI 1.7-3.4) and Latin America (OR 1.7, 95% CI 1.2-2.4). Maloney documented a similar incidence of metabolic abnormalities between white and non-white stone formers in the same geographic area, suggesting that dietary and environmental factors are as important as ethnicity [17].

- *Geography:* Variation in the prevalence and incidence of urolithiasis has been documented worldwide and throughout the same country. This variability could be related to seasonal temperatures, genetics, water availability and dietary habits [2]. In the United States, the stone prevalence increased 60% for those men living in the southern regions in contrast to those living in northern regions (Prevalence ratio 1.60, 95% CI 1.49-1.72) [15]. Similar findings were also documented for women (Prevalence ratio 1.45, 95% CI 1.31-1.61). There was also variability from western and eastern regions, with a higher prevalence noted in the west.

1.1.3 Risk Factors for Urolithiasis

- *Family History:* A positive family history of kidney stones confers a 2.5 times increased risk of stone formation (RR 2.57, 95% CI 2.9-3.02) [18,19]. This risk could be explained due to a combination of genetic predisposition, environmental factors and/or life-style choices such as diet [1].

- *Obesity:* An increase in body size, body mass index (BMI) and waist measurements are related to an increase in stone formation [20]. Weight gain after early adulthood (>15.9 kg after 21 years of age), is related with a RR of 1.39 (95% CI 1.14-1.70; p=.001) for stone formation in comparison to those with no changes in weight. A BMI of 30 kg/m^2 or higher, had an associated RR of 1.33 (95% CI 1.08-1.63; p<.001) in comparison to an individual with a BMI of 21-22.9 kg/m^2. In addition, a waist circumference greater than 109.2 cm, was associated with a RR of 1.48 (95% CI 1.13-1.93; p=.002) in comparison to men with a waist circumference of 86.4 cm.

- *Medical / Systemic Conditions:* Primary hyperparathyroidism, gout, diabetes mellitus, sarcoidosis, distal (type 1) renal tubular acidosis, medullary sponge kidney, inflammatory bowel disease and cystinuria, have been associated with an increased risk of stone formation via variable metabolic mechanisms [1,21,22].

- *Fluid Intake:* A high intake fluid has an inverse relationship with stone formation and has been documented by multiple investigators to have a protective effect (RR 0.71 95% CI 0.52-0.97) [18]. A prospective study compared the effect of fluid intake and stone recurrence in idiopathic first-time stone formers [19]. A urine output less than 1 liter per day had higher prevalence of stone recurrence (27% vs 12%).

1.2 Stone Composition & Classification

Stones are formed from multiple chemical components and are classified from their principal mineral-based composition (Table 2). Calcium based stones account for the majority (75-80%) of urinary stones, and stones are often broadly divided into calcium-containing and non-calcium-containing subtypes [23–25]. Stones can also be classified based on their X-ray appearance which is closely related to the amount of calcium they contain and is outlined in Table 3.

Calcium oxalate will encompass 60% of calcium-based stones, followed by mixed calcium oxalate and calcium phosphate [23–25]. Calcium oxalate composition can be subdivided into monohydrate (whewellite) and dihydrate (weddellite). The microscopic crystal appearance or "shape" for calcium oxalate monohydrate is an "hourglass" and "tetrahedral or envelopes" for calcium oxalate dihydrate. Calcium phosphate stones can be further classified into apatite (basic calcium phosphate) and brushite (calcium hydrogen phosphate dihydrate), up to 50% of calcium-based stones will contain calcium phosphate as a component. The microscopic apatite crystals shape is "amorphous or powder-like" and brushite will be "needle-shaped" or "rosettes".

The most common non-calcium-based urinary stones are struvite (magnesium-ammonium-phosphate), uric acid and cystine stones which accounts for approximately 5-15%, 5-10% and 1-2.5%, of stones respectively [23–25]. Several epidemiology studies, document uric acid composition as the predominant non-calcium-based stone type [23–25]. Uric acid stones are related to an acidic urine pH and/or hyperuricosuria state. Uric acid crystals appear as "parallelograms or rhomboids".

Struvite stones are mostly related to recurrent urinary tract infections and the crystals have a characteristic shape of "coffin-lid or rectangular" [23–25]. Struvite formation occurs when ammonia is increased, urine pH is elevated and the solubility of the phosphate decreases. This occurs in chronic recurrent urinary tract infections by urease-producing organism (*Proteus sp, Klebsiella sp, Ureaplasma urealyticum*).

Cystine stones are related to a genetic disorder in the amino acid transporter that prevents cystine reabsorption resulting in its precipitation in the collecting system [23–25]. Cystine crystals are "hexagonal" shaped. Other types of urinary stones can be medication or drug-related (e.g., indinavir, triamterene, and many others) or related to genetic disorders such as xanthine stones. These stone compositions are typically quite rare.

Stone composition can have important clinical relevance. Certain stone types maybe harder to break and therefore this knowledge may influence clinical decisions around preferred treatment options. As an example, the hardest composition of stones include calcium oxalate monohydrate, brushite and cystine stones, which are relatively resistant to Shock Wave Lithotripsy (SWL) fragmentation [26].

Table 2. Stone Composition Classification

Calcium based composition [23–25]	Calcium Oxalate Monohydrate (Whewellite)
	Calcium Oxalate Dihydrate (Weddellite)
	Calcium Phosphate (hydroxyapatite)
	Brushite (Dicalcium phosphate dihydrate)
Non-calcium-based composition [23–25]	Uric Acid
	Struvite (magnesium-ammonium-phosphate)
	Cystine
	Drug-related stones (triamterene, antiretroviral)
	Xanthine and 2,8-Dihydroxyadenine (DHA)

Table 3. X-Ray (KUB) Stone Classification

Radiopaque	***Mildly Radiopaque***	***Radiolucent***
Calcium Oxalate Monohydrate	Struvite	Uric Acid
Calcium Oxalate Dihydrate	Cystine	Xanthine
Calcium Phosphate		Drug-related Stones

Information based on References [25,27]

1.3 Clinical Presentation of Kidney Stone Disease

A large percentage of urinary calculi are asymptomatic and are detected incidentally on abdominal imaging for other clinical indications. Asymptomatic renal stones have been reported in 10% of a screened population [25]. Boyce et al. reported a prevalence of 7.8% for asymptomatic stones in a consecutive cohort of 5,047 patients that underwent a non-contrast computed tomography (NCCT) [28].

Patients with symptomatic stones or renal obstruction, will classically develop unilateral flank pain of sudden onset (acute renal colic), with no relation to a precipitating factor nor will it alleviate with postural changes [29]. Renal colic will often present as a vague pain initially and evolve to episodes of more intense and severe pain. Nausea and vomiting can be present due to stimulation of the celiac plexus. Recurrent urinary tract infections, especially with urease-producing organisms such as *Proteus mirabilis* or *Klebsiella pneumoniae*, may also be a sign of urinary stone development and should warrant investigations to rule out renal stone formation [23]. Urolithiasis can also result in urinary obstruction and present as acute or chronic renal insufficiency [30].

1.4 Nephrolithiasis Management

1.4.1 Acute Medical Management

In an emergency setting, one of the key aspects of management is to exclude the presence of systemic sepsis due to obstruction of the urinary system and the presence of acute urinary infection [27,29]. In the scenario of obstructive uropathy and acute urinary infection, the need for urgent drainage or decompression is necessary via retrograde ureteric stent placement or percutaneous nephrostomy tube insertion. Other scenarios that require urgent management include: anuria, unilateral obstruction in a solitary functioning kidney, inability to maintain oral intake due to vomiting and refractory pain.

For patients who are clinically well, ambulatory management is preferable. Non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen are effective against renal colic pain and have at least equivalent analgesic efficacy to opioids without the addictive potential and significant side-effects.

In the context of nephrolithiasis, there are several indications for definitive treatment which will be discussed in the following section (1.4.3). Medical expulsive therapy with alpha-blocker medication can be utilized to increase the likelihood of spontaneous stone passage, this therapy is mostly recommended for distal ureteric stones without an urgent indication for surgical intervention [26,27].

1.4.2 Conservative Management

Observation can be an option for non-obstructing kidney stones such as those located in the calyces. A prospective trial supported annual observation for lower pole stones <10 mm in size [31]. One third of the patients had an interval growth and 11% required active treatment but no intervention was needed in the first 2 years of follow-up. In a systematic review of asymptomatic renal stones undergoing active surveillance; spontaneous passage was documented in 3-29%, related symptoms in 7-77%, interval stone growth in 5-66% and required surgical intervention in 7-26% of patients [32].

1.4.3 Definitive Management

There are several indications for surgical treatment for kidney stones. The most recent European Urological Association (EAU) Guidelines on Urolithiasis [26,27], recommended definitive management in the following scenarios: stone interval growth, stone size >15 mm, stones <15 mm if observation is not an option, patients with higher risk of stone formation, obstruction, infection, symptomatic stones (pain, hematuria), comorbidity and social situation or patient choice (profession or travel).

The preferred treatment modality will vary according to the size or stone burden in the kidney and the location of the stone inside the collecting system. The available treatment options in the modern era for kidney stones are SWL, ureteroscopy (URS) and percutaneous nephrolithotomy (PCNL). In the following table (Table 4), we delineate and summarize the treatment modalities according to the EAU and American Urological Association (AUA) guidelines [26,27,33,34].

Table 4. EAU & AUA Guidelines for treatment of Kidney Stones

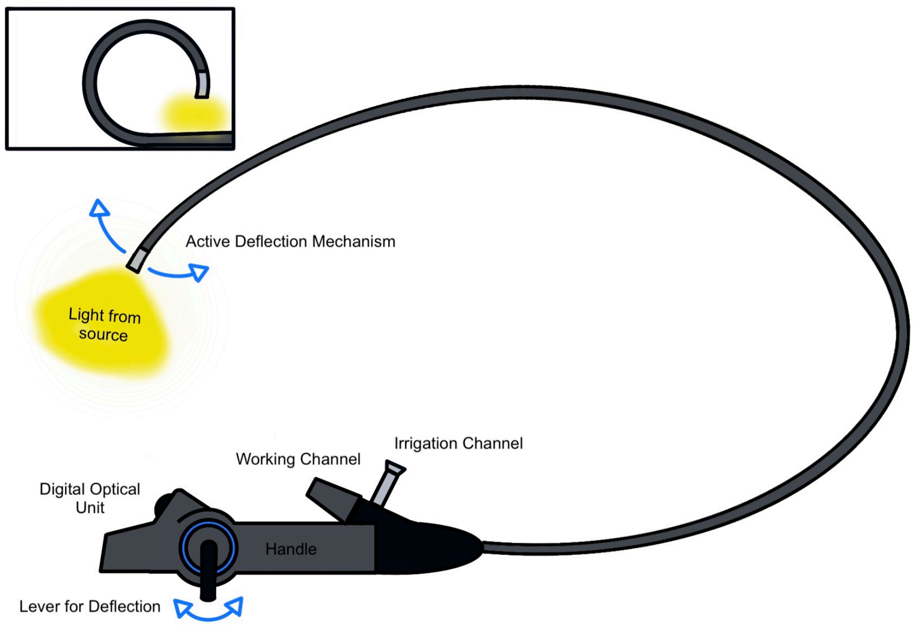
Location	**Size**	**EAU** [26,27]	**AUA** [33,34]
Upper Calyx Middle Calyx Renal Pelvis	>20 mm	1. PCNL 2. URS	PCNL
	10-20 mm	SWL / URS / PCNL	SWL / URS
	<10 mm	1. SWL or URS 2. PCNL	SWL / URS
Lower Pole	>20 mm	1. PCNL 2. URS	PCNL
	10-20 mm	SWL / URS / PCNL	1. SWL, URS 2. PCNL
		[+]URS or PCNL	
	<10 mm	1. SWL / URS 2. PCNL	SWL / URS

[+]*Use if unfavorable factors for SWL are present: steep infundibular-pelvic angle, long calyx, long skin-to-stone distance, narrow infundibulum and SWL resistant stone (whewellite, brushite, cystine). PCNL: Percutaneous Nephrolithotomy, URS: ureteroscopy, SWL: shockwave lithotripsy.*

1.4.3.1 Flexible Ureteroscopy

Flexible URS also referred to as Retrograde Intrarenal Surgery (RIRS), is one of the most common treatment modalities utilized to treat kidney stones according to the aforementioned indications. It involves the insertion of a flexible ureteroscope through the urethra, bladder, ureter and into the renal collecting system in a retrograde fashion. The components of a flexible ureteroscope includes an optical system (fiberoptic or digital), deflection mechanism and a working channel [35]. Active deflection of the ureteroscope allows the surgeon, due to the maneuverability of the scope, to navigate the entire collecting system via a retrograde approach. The working "channel" allows the introduction of the intracorporeal energy or flexible lithotripter technology to disrupt the stone [25,35]. A flexible ureteroscope and its components is shown in Figure 1.

Figure 1. Flexible Ureteroscope Diagram (Digital)



1.5 Intracorporeal Lithotripsy

The technologies available for intracorporeal lithotripsy include electrohydraulic (EHL), laser lithotripsy, ultrasonic technology and ballistic lithotripters [25]. These technologies can be classified into flexible probes (EHL, laser) and non-flexible probes (ultrasonic and ballistic). The flexible lithotrites are needed for stone disruption when using flexible ureteroscopes.

1.5.1 Electrohydraulic Lithotripsy

The technology has been used to treat urinary tract stones since the 1950s, invented by Yutkin in 1955, an engineer at the University of Kiev [36]. The EHL utilizes two concentric electrodes that produces an electric discharge in a liquid medium ("underwater spark plug") [25,36,37]. The spark discharge creates an explosive formation of a plasma channel and vaporization of the surrounding water. The expanding plasma bubble produces a hydraulic shockwave followed by a cavitation bubble. Consequently, the rapid collapse of the bubble results in a secondary shockwave (symmetrical collapse) or high-pressure multiple microjets (asymmetrical collapse) that produces stone fragmentation.

The main disadvantage of the EHL is the inability to control the destructive plasma discharge which can result in collateral damage to surrounding soft tissues. Multiple enhancements and miniaturization of the probes improved the safety of this technology, but the complication rate remains high (6-17%) [25,36–38]. The described complications are ureteral perforation, hemorrhage due to mucosa erosion, inflammation, and strictures. For these reasons, EHL is not recommended for use within the ureter [33,34].

The use of EHL is associated with the production of larger fragments than other modalities which decreases the stone clearance and results in widely variable stone-free rate (SFR) ranging between 67-98% [25,38]. In addition, it is less effective for stones of harder composition and larger stones (>1.5 cm).

With the significant limitations associated with EHL, “Light Amplification by Stimulated Emission of Radiation” (LASER) technology has evolved to become the most effective and safest intracorporeal lithotripter and it is the current standard for URS and flexible nephoscopy [26,39]. This technology will be described in more detail in the next section.

1.6 L.A.S.E.R. Technology in Urology

The use of LASER as a modality for intracorporeal lithotripsy, was first described in 1968 using a ruby laser [40]. Mulvaney et al. reported successful stone fragmentation which was enhanced when fluid surrounded the stone. Despite the ability to produce stone disruption, heat production was significant causing thermal injury to surrounding tissues and making it unsuitable for clinical use [41]. The CO_2 laser has the ability to directly “burn through the stone” however, the inability to transmit the energy through silica fibers needed for use with an endoscope made this energy source unsuitable. Due to the limitations with the application of these wavelengths, attention was turned to pulsed-wave lasers instead of continuous-wave lasers for stone fragmentation [42].

In the 1980’s multiple laser technologies were introduced. The FDA approved the Neodymium:YAG (Nd:YAG) Laser in 1984, the Argon Laser in 1987 and the Potassium-Titanyl-Phosphate (KTP) Laser in 1988 for the use in urology [43]. These lasers were only beneficial in highly selected soft tissue ablation scenarios and were not useful for lithotripsy or urinary calculi.

In 1992, Douglas and colleagues evaluated the potential benefit and usefulness of Holmium:yttrium-aluminium-garnet (Ho:YAG) laser in urologic surgery in an animal model [44]. Their results showed this wavelength had both cutting and hemostastic properties. They concluded that the Ho:YAG was a reliable, solid-state laser with “excellent and precise” cutting abilities with hemostatic control for endoscopic soft tissue procedures.

In 1995, preliminary clinical results with the Ho:YAG laser proved it to be a versatile tool for intracorporeal lithotripsy with a 65% rate of successful fragmentation of stones in the era of electrohydraulic and ultrasonic lithotripters [45]. In 1996, a prospective study involving 79 laser procedures was performed (retrograde ureteroscopy for ureteral stones and fragmentation of calyceal stones remote form nephrostomy tract during a percutaneous approach) [46]. Complete stone fragmentation was documented in 85% of the cases. The advantages were the ability to fragment even the hardest stones (calcium oxalate monohydrate and cystine) and its multipurpose use, including the capacity to cut, coagulate, ablate, enucleate and vaporize tissues [46,47].

1.6.1 Physics & the Stone Fragmentation Process

The laser energy fragmentation process begins when the photons are absorbed by the calculus or fluid surrounding the calculus [42]. The ablation effect created by pulsed lasers is a relationship between a photo-thermal mechanism and a photo-acoustic/photo-mechanical process.

1.6.1.1 Photo-thermal Mechanism

The photothermal effect is the conversion of the laser energy into heat by the absorption of the laser light [42,48]. In intracorporeal lithotripsy, the absorption of the energy by the water molecules within the stone contribute to fragmentation. The heat is accumulated during the laser pulse producing local destruction and removal of irradiated volume before the heat is conducted to surrounding tissues with an end-effect of melting, carbonization or chemical decomposition of the calculus.

In addition, the conversion into heat and water vaporization, produces a vapor bubble which has minimal mechanical effect on tissues but parts or divides the water creating a vapor channel ("Moses effect") allowing direct deposition of the remaining portion of the laser light in the stone surface [42,48,49].

Vaporization, melting and chemical decomposition are the consequences of a photo-thermal mechanism which is related to heat production rather than stress-related mechanism [42,48]. This will be characteristic of long-pulsed lasers (10-1000 μseconds).

1.6.1.2 Photo-acoustic / Photo-mechanical Mechanism

The photo-acoustic or photo-mechanical mechanism refers to the generation of a shockwave as a "primary mechanism" to fragment or disrupt urinary tract stones [42,48]. The conversion of laser energy into mechanical energy results in the formation of stress waves that propagate at the speed of sound. A spherical cavitation bubble is produced in a fluid environment that rapidly expands symmetrically to a maximum size and then collapses violently. The collapse of the bubble generates a strong shockwave or acoustic emission directed to the stone.

The shockwave characteristics will depend on the shape and geometry of the cavitation bubble created by the generated plasma emission [42,48]. The bigger and more symmetrical the bubble is, the stronger the shockwave disruption effect will be. If the pulse width (length) is longer, more energy goes into generation of the cavitation bubble and the generated bubble will be asymmetric. This will be beneficial because the collapse of the bubble will happen at different intervals of time, producing multiple shockwaves from a single cavitation bubble. A continuous-wave laser will impact in the collapse of the bubble, in contrast to a pulsed-wave laser, which will take advantage of this effect.

For lasers with a short-pulsed duration (1-10 μseconds) or in the nanosecond range (e.g., Q-switched Nd:YAG, pulsed-dye), optical breakdown occurs [42,48]. Optical breakdown refers to plasma formation and expansion, shockwave generation, cavitation formation and bubble collapse (acoustic emission) as primary mechanisms of calculus disruption. Ho:YAG can develop optical breakdown but the acoustic emission is weaker than short-pulsed lasers, however the principal effect of Ho:YAG is photothermal.

1.6.2 Current Laser Technology

Multiple publications have demonstrated the superior effectiveness of the Ho:YAG over other laser technologies for intracorporeal lithotripsy [48]. The Ho:YAG laser can fragment all type of stones and has become the gold-standard for URS according to the EAU guidelines [26].

Ho:YAG lasers have improved dramatically since their introduction in urology. High-power (150 watts) and multi-core (multiple optical cavities) lasers were introduced resulting in the ability to control the pulse frequencies at wider ranges, as well as the pulse width or length. These technological advancements increased the efficiency of Ho:YAG lithotripsy and ablation rates, as well as decreasing operative times [50].

In 2005, Fried et al. introduced a new laser lithotripsy technology based on the chemical element Thulium [51]. Further refinement of the technology introduced the Thulium Fiber Laser (TFL), which offers a wider range of frequencies and theoretically faster ablation rates in comparison to the Ho:YAG [50].

Holmium (*Holmia*, Latin name for Stockholm) and Thulium (*Thule*, place located furthest north in ancient Greek and Roman literature referring to Scandinavia) are catalogued as two earth-rare elements [52]. They are predominantly found as tri-valent ions in nature and in industrial applications as lasers, both have specific emission of wavelength near-infrared range.

The following sections will discuss the technical details as well as the advantages and disadvantages of each laser technology.

1.6.2.1 Wavelengths & Optical Depth Penetration

The Ho:YAG and TFL energies are highly absorbed in water. The Ho:YAG has a radiation wavelength of 2,120 nm and has an absorption coefficient of alpha=31.8 cm^{-1} at

20º Celsius degrees [47]. In contrast, the TFL has a radiation wavelength of 1,940 nm nearer to the peak absorption of water and has an absorption coefficient of alpha=129.2 cm^{-1}. The alpha values refer to the optical water penetration depth of each laser technology, which are 0.314 mm for the Ho:YAG and 0.077 mm for the TFL.

The energy of the laser beam passing through water will be reduced based on exponentiation of the mathematical constant *e* (Euler's number) for a non-linear optical penetration [47]. The Ho:YAG laser energy will be reduced to 37% of its total power after traveling its optical penetration depth (0.314 mm). In contrast, the TFL energy will have been reduced to 1.7% of its total power over the same distance. At 1 mm, the Ho:YAG will have been reduced to 4% against 0.00024% for the TFL. The TFL optical penetration depth is four times less than the Ho:YAG, theoretically providing a higher safety profile.

1.7 Holmium: YAG Laser

The Ho:YAG laser operates via a flashlamp-pumped (Xenon or Krypton) solid-state configuration (YAG crystal rod) chemically doped with Holmium ions inside an optical cavity [52]. The laser pulsation is the light emitted by the flashlamp interacting with the Holmium ions and producing new photons with an infrared wavelength of 2,120 nm. These photons are reflected inside the optical cavity mirrors (reflective mirrors at each end) and multiplicated depending on the desired pulse energy. The pulsed laser energy is tightly focused or collimated to exit the cavity when the laser is activated via a fiber laser.

The Ho:YAG generator requires a water-cooling system, which translates into a larger physical footprint, due to heat produced (wasted energy) inside the optical cavity (the flashlamp light emission has broad spectrums) [52]. The maximal temperature range of the laser crystal cavity limits the power and frequency of each generator. The solution for high power Ho:YAG lasers was using multiple optical cavities allowing generators to reach greater than 50 watts.

The infrared wavelength of the Ho:YAG is highly absorbed in liquid water producing a rapid formation of a vapor bubble after a pulsed emission. [48,49,53] The optical penetration depth is limited to 400 μm. The laser has a pulsed mode, 0.2-6.0 Joules pulse energy with 250-1500 μs pulse duration, 5-80 Hz pulse rate and an average power up to 120 watts [48,49,52,53].

The Ho:YAG delivers the energy via a low hydroxyl silica optical fibers and are available in multiple diameters, with the smallest fiber diameter measuring 200 micrometers in size. The key components of the laser fiber are a core, cladding and a jacket. The silica core transmits the laser light energy efficiently via internal reflection, the cladding is outside the core and has a low index of refraction and the jacket surrounds the fiber (outer coating) to protect the delicate glass components [54]. An *in-vitro* study reported that the smallest size of stone fragments is achieved by the smaller diameter fibers (272 micrometers) [55]. There are several explanations for this observation including: the smaller fibers deliver the energy to a smaller surface area on the stone thereby decreasing the probability for large fragments to detach from the initial stone. In addition, smaller fibers also create a higher energy density, resulting in more power per surface area leading to quicker fragmentation and smaller resultant fragments [52,55].

1.7.1 Current "Gold-Standard"

The Ho:YAG was reported more than 30 years ago and has been the gold-standard for endoscopic laser lithotripsy for the last 20 years [45,46]. Since its introduction, several technological improvements in the Ho:YAG generators and optical cavities have provided better ablation efficiency. In the early days of Ho:YAG systems, only the pulse energy (limited to 2 J) and pulse frequency (limited to 15 Hz) could be controlled in low-power systems.

More recently, high-power systems have improved and enhanced the pulse energy and pulse frequency allowing for the "dusting" technique of urinary stones. A "dusting" technique is utilized to pulverize the urinary stone into dust and to promote a better SFR. The benefits of this approach are to avoid extraction of stone pieces with an endoscopic basket [54]. Additionally, the ability to control the pulse width (length) and pulse shape, results in less stone retropulsion and decreased fiber burn back [47]. Movement of the stone away from the fiber during laser lithotripsy is termed retropulsion and fiber burn back refers to laser fiber-tip degradation during the lithotripsy and can have a significant effect on the efficacy and efficiency of laser lithotripsy.

1.7.2 “Moses” Effect and Vapor Channel

In 1986, Isner and colleagues, described that ultraviolet and infrared focused beam laser irradiation to myocardial tissues caused a formation of “dynamic optical cavities”, creating vapor tunnels serving as a pathway for transmission of the laser [56,57]. The vapor tunnels enabled transmission of the laser energy over longer distances in a liquid environment and this phenomenon was called the “Moses Effect”. This described the “parting of the seas” or liquid environment to allow for the laser energy to reach its target more effectively.

This was applied to the Ho:YAG laser, which created a rapid vaporization following activation of the laser, producing vapor pressure which expanded into a vapor bubble due to laser light absorption in water. This vapor bubble has minimal mechanical effect on tissues and rather parts or divides the water creating a vapor channel/tunnel allowing direct deposition of the remaining energy of the laser light onto the stone surface (photo-thermal mechanism) [42,47,58]. This allows for improved concentration of the laser energy onto the stone surface, thereby increasing lithotripsy efficiency and decreasing retropulsion.

1.7.3 Advantages and Limitations

The advantages of the Ho:YAG laser includes the ability to fragment urinary stones of all known compositions, its applicability with flexible endoscopes, minimal tissue penetration and high safety threshold damage to surrounding tissue due to its abortion in water (high absorption water coefficient) [46,47].

The main inherent limitations of the Ho:YAG laser, despite its technological advancements, in the current era are the following:

- The generator is prone to misalignments of the mirrors inside the optical cavity due to external shocks or impacts that can permanently damage the generator resulting in costly equipment repairs
- Large laser generators (physical footprint) due to required water-cooling systems
- Required high power energy outlet of 220 Volts
- Limited size of the fiber laser diameter to 200 μm, which can impact the ureteroscope flexibility and limit the navigation to areas of the renal collecting system
- Limited dusting efficiency due to the pulse frequency and pulse energy restrictions by the optical cavities' energy power output
- Dusting capabilities with certain stone compositions are not ideal, leading to larger than desired stone fragments
- Retropulsion of stones during laser application, necessitating the need to chase stones fragments, thereby reducing efficiency and efficacy

1.8 Thulium Fiber Laser

The TFL operates via an electronic modulated laser diode-pumped configuration. The laser diodes are capable of high and constant peak power [47,52,59,60]. A long (10-30 meters) 10-20 μm silica fiber chemically doped with Thulium ions is excited by the diode laser. The TFL can operate in a continuous mode or adopt a super-pulsed mode (50 μs to 12000 μs pulse duration). The TFL is theoretically more efficient because the spectrum of the emission (laser diode) matches the Thulium ions producing less heat in comparison to the Ho:YAG (flash-lamp produces a broad light spectrum emission). Consequently, less energy is wasted, and less heat is produced inside the generator. The cooling can be performed by an air system (fan ventilation) even at a high-power mode (>50 watts) with variable frequencies (~2000 Hz). The fiber laser technology provides a simpler focusing of the laser beam and can transmit the high energy via smaller fibers (150 micrometers).

The infrared wavelength of 1,940 nm (closer to liquid water absorption peak) produces a four-fold higher absorption coefficient compared to the Ho:YAG. The TFL has 0.025-6.0 Joules pulse energy, 50 to 12000 μseconds pulse duration, 1-2000 Hz pulse rate and an average power up to 60 watts. Due to the TFL absorption coefficient being four-fold higher than the Ho:YAG laser, a higher ablation efficiency can be expected at equivalent pulse energies [52,59,60]. In Table 5, a comparison of the characteristics of the Ho:YAG and TFL is shown.

Table 5. Comparison of Ho:YAG and TFL Features

	Ho:YAG Laser	***Thulium Fiber Laser***
Light source	Flashlamp (Xenon / Krypton)	Laser Diode
Solid-State core	Yttrium-Aluminum-Garnet (YAG) Crystal + Holmium ions	10-20 µm Silica Fiber + Thulium ions
Wavelength	2,120 nm	1,940 nm
Optical penetration depth	0.314 mm	0.077 mm
Laser fiber diameter (µmeters)	≥ 200	≥150
Cooling system	Water-cooled	Air-cooled
Power supply	High amperage outlet	Standard outlet
Pulse profile	Irregular + energy spikes	Symmetrical
Operation mode	Pulsed	Pulsed/Continuous
Pulse energy (Joules)	0.2-6.0	0.025-6.0
Pulse width (µseconds)	50-1,300	200-12,000
Maximum power (Watts)	120	50-60

The low pulse energy and high frequency rate increases dusting abilities with the TFL, which also reduces stone retropulsion and increases the ablation efficacy of the laser [52,59,60]. Hardy et al. published preliminary results comparing the dusting mode between the Ho:YAG and TFL and noted the TFL had a higher stone ablation rate and produced smaller stone fragments under the same laser settings in an experimental model [60].

1.8.1 Laser Characteristics

1.8.1.1 Pulse Frequency

As previously mentioned, the TFL can reach a higher frequency of up to 2,200 Hz in comparison to Ho:YAG optical cavities, which is limited to 30 Hz because of the heat-energy produced by the flashlamp [47,52,61]. The majority of the white light produced by the flashlamp does not contribute to laser operation and is transformed into heat. To overcome this problem, Ho:YAG laser manufacturers introduced technology to allow for synchronous operation of multiple optical cavities or cores for a higher power. This technology increased the pulse frequency, but the wall-plug efficiency decreased to less than 1%. Higher frequencies can be achieved with the TFL (laser diodes) with a wall-plug efficiency of 12%.

1.8.1.2 Pulse Energy

The TFL offers pulse energy up to 6 Joules, similar to the most powerful Ho:YAG laser generators [47,61]. The main difference, is the possibility to use minimal pulse energies up to 0.025 J while the Ho:YAG is limited to a minimum pulse energy of 0.2 J. These low energies can be relevant when performing a dusting technique and reducing stone retropulsion.

1.8.1.3 Pulse Width and Profile

The TFL can be set to short-pulse (200 μsec) or long-pulse durations (1000 μseconds) as the most recent Ho:YAG lasers but is also able to reach longer pulse durations of 12,000 μsec [47,60,61]. Interestingly, Hardy and colleagues documented a technical limitation regarding pulse energy and width with TFL system used in their study. The TFL was unable to produce high pulse energy with short-pulse duration as the Ho:YAG can [47,60,61]. This might be more relevant when fragmentation of stone is desired instead of a dusting technique.

The long-pulse width can cause carbonization (charring) of the stone surface. This is secondary to the photothermal effect and its undesirable because limits the ablation efficiency and increases fiber-tip degradation [59]. Blackmon et al. described the charring of stone increases as the pulse width increases and was evident with pulse durations 1000-20,000 μseconds [62]. However, carbonization also occurs with Ho:YAG [51].

The pulse profile of the Ho:YAG is irregular with an initial energy spike and a rapid decline in power, whereas the TFL has a symmetrical (almost squared) wave providing constant peak power throughout the wave duration [47]. The initial spike is responsible for the cavitation bubble expansion and might be partially responsible for the higher retropulsion seen with Ho:YAG lasers [61].

1.8.2 Laser Fibers

The configuration of the TFL (chemically doped 10-20 µm silica fiber) provides the advantage of smaller laser fibers (150 µm diameter) which translates into better irrigation flow, improved instrumentation deflection (flexibility) and less stone retropulsion [52].

1.8.3 In-Vitro Experience

It has been described that the TFL is more efficient than Ho:YAG laser as a treatment for urinary stone disease, even at equal settings, including pulse energy and frequency [63]. The key *in-vitro* studies are summarized below:

- Andreeva et al. documented a faster laser ablation rate for the TFL in a controlled *in-vitro* environment using human uric acid and whewellite stones [64]. The ablation rate in fragmenting mode was twofold faster for uric acid stones with the TFL laser. Whereas in the dusting mode TFL was threefold faster for whewellite and 2.5-fold faster for uric acid stones in comparison to the Ho:YAG laser.

- Panthier and colleagues demonstrated higher ablation volumes for the TFL in an *in-vitro* study using BegoStone® phantoms (hard and soft stones) with the same laser settings for both the TFL and Ho:YAG [65]. With a dusting setting (0.5 J / 15Hz) the TFL resulted in four and two-fold higher ablation volumes for hard and soft stones respectively. With a fragmentation setting (1 J / 15 Hz) the TFL demonstrated three and two-fold higher ablation volumes for hard and soft stones.

- Chiron et al. documented 2- and 5-times faster ablation speed, for fragmentation and dusting respectively with the TFL laser [66]. The study was performed using an *in-vitro* model with a 50W TFL and a 30W Ho:YAG, and measured ablation volume with a single pulse and speed after 2 minutes of ablation. The TFL ablated volume was 3 times higher. Further details are described in Table 6.

- Chew et al. described more efficient disruption and smaller dust particles with the TFL [67]. The study was performed with BegoStone® ($5mm^3$) with 120W Ho:YAG and commercially available 50W TFL. Fragmentation and dusting were analyzed after delivering 0.5 KJ and 2 KJ. Fragmentation and dusting to <1mm particles was significantly faster for the TFL. Following the delivery of 0.5 KJ fewer particles sized bigger than 2 mm remained with the TFL. With the delivery of 2 KJ of energy, 40% dust (<0.5 mm) was produced with the TFL compared to 24% with the Ho:YAG. The authors concluded that TFL produces smaller dust and fragments, thus making dusting as well as fragmentation and basketing more efficient. Further details are described in Table 6.

- Coninck et al. reported that TFL produces the double the amount of dust than a high-power 120W Ho:YAG with Moses technology [68]. In this *in-vitro* study, uric acid stones were dusted for two and half minutes using a 200-micrometer fiber laser and the same laser settings (0.2 J / 80 Hz). The weight of stone dust produced by the Ho:YAG was 69 ± 32 mg and 138 ± 25 mg for TFL.

Table 6. In-Vitro Studies Comparison

	Chiron et al. [66]		***Chew et al.*** [67]	
Laser	Ho:YAG	TFL	Ho:YAG	TFL
Laser Power (W)	30	50	120	50
Stones	BegoStone®		BegoStone®	
Laser Settings	-	-	0.8 J / 10 Hz 0.3 J / 70 Hz	0.6 J / 30 Hz 0.1 J / 200 Hz
Time (mg/s): *-Fine Dusting* *-Dusting* *-Fragmentation*	 - 0.25 0.98	 0.57 1.32 1.99	 - 0.46±0.09 1.78±0.4	 - 1.05±0.08 2.23±0.22

The better dusting effect and rapidity of fragmentation with the TFL may be explained by its higher water absorption coefficient wavelength relative to the Ho:YAG, producing a more efficient fracture of the stone and micro-explosions. The "micro-explosions" mechanism refers to the water trapped in pores or fissures inside the stone close to the surface, that will vaporize creating high pressures which produce mechanical stress on the stone [42,60]. The "micro-explosion mechanism" is related to the photo-thermal mechanism produced by superheating the stone with an additional photo-mechanical effect [42].

1.8.3.1 Dusting Mode

An *in-vitro* study performed by Keller et al., reported the TFL is capable of producing dust from calcium oxalate monohydrate, calcium oxalate dihydrate, uric acid, calcium phosphate, struvite, brushite and cystine stones [69]. Human urinary stones (>90% purity) were disrupted at 0.05 J / 320 Hz (200 µsec pulse width) with a total delivered energy of 2400 J. The TFL was able to disintegrate the included stones into particles smaller than 500 µm and these were observed to spontaneously evacuate from irrigation. Interestingly, calcium oxalate monohydrate stones had a mean maximal width of 254 µm (179-380 µm) and tended to preserve their original lamellar morphology when viewed with electron microscopy. As well, calcium phosphate stones had preserved organizational structure with spherical particles [69,70].

1.8.3.2 Retropulsion

Retropulsion leads to inefficient fragmentation as fragments must be "chased" to completely fragment them. A higher retropulsion threshold refers to less movement of the stone while lasering. The TFL retropulsion threshold is up to four times higher when compared to Ho:YAG at equal pulse energies [64,71,72]. Retropulsion will become evident with the Ho:YAG at 0.2 J, while TFL retropulsion is apparent at 1 J (higher energy). This can be related to the more constant and prolonged peak power, and profile pulse with longer pulse duration with the TFL laser. In contrast, Knudsen et al. documented an equivalent retropulsion of the TFL to the 120 W Ho:YAG with Moses mode [71].

1.8.3.3 Fiber Burn Back

Fiber tip degradation can be seen at high pulse energy levels and decreases with longer pulse durations. This phenomenon is potentially hazardous as it might result in laser fiber fragments breaking off within the patient or cause damage to the tip of the endoscope. When the core diameter of a fiber laser is divided by two (small diameter fiber, 200 µm fiber → 100 µm fiber), the energy density (photons) will be increase by 4 [73]. The increase in energy density in smaller caliber laser fibers is related to an increased fiber-tip degradation.

In an *in-vitro* study performed with a BegoStone® phantom and 200 µm fiber lasers, the tip of the fiber was placed in contact with the stone and the burn back was measured after 1 KJ of energy [71]. The burn back was lower for the TFL in dusting (0.1 J / 200 Hz), low power (0.8 J / 8 Hz), medium power (1 J / 16 Hz) and high-power settings (2 J / 30 Hz, 0.1 J / 600 Hz, 6 J / 10 Hz) compared with the Ho:YAG laser. Furthermore, an *in-vitro* study performed by Andreeva et al., documented a pronounced fiber burn back with Ho:YAG laser, especially at high output power (>30W) [64].

The TFL offers the advantage of providing low energy pulses, long-pulse durations (up to 12,000 µsec) and uniform distribution of the energy. To counteract the decrease in pulse energy, a higher frequency is possible with the TFL which compensates by producing improved ablation efficiency and speed [52].

1.8.4 Clinical Experience

The first reported clinic experience with the TFL was described by Martov et al. in Russia in 2018 [74]. Fifty-six patients with upper and lower urinary tract stones were included. Twenty-four patients underwent treatment by RIRS and the size of the upper urinary tract stone was 0.6-1.8 cm. The authors reported 100% stone fragmentation with 47.7% requiring additional stone removal techniques. The mean stone disruption time was 19 minutes and at follow-up (4-6 weeks), one patient was found to have a residual symptomatic stone.

The first TFL case series performed in North America was reported by Carrera et al. and included 118 treated urinary stones mostly commonly treated by RIRS (76.3%) [75]. The mean operative time was 59.4 ± 31.6 minutes, and a ureteral access sheath was used in 71.1% of procedures. Dusting technique was the preferred treatment (67.1%) with mean total laser time of 10.8 ± 14.1 minutes, mean frequency of 228 ± 299 Hz and mean pulse energy of 0.2 ± 0.3 J. No signs of ureteral thermal injuries were observed. The limitations of the study were the lack of a control group and patient randomization for direct comparison to other laser platforms. They concluded the TFL was able to ablate numerous types of stones with a safety profile comparable to the Ho:YAG.

Corrales et al. reported an initial clinical experience in the first 50 patients from Tenon hospital in Paris [76]. Forty-one patients were treated for renal stones. The median renal stone volume was 1800 (IQR 682-2760) mm^3 with a median stone density of 1200 (IQR 750-1300) HU. The median pulse energy was 0.3 (IQR 0.2-0.6) J with a median pulse frequency of 100 (IQR 50-180) Hz. The median laser-on time was 23 (IQR 14.2-38.7) minutes. Two complications were noted in the group of renal stones, but none were related to the TFL. This report is also limited by the lack of a comparison group. The authors concluded the TFL is a safe and effective modality for lithotripsy during RIRS while keeping in the suggested setting of 15-30 Watts of laser power output (e.g., 0.5 J X 30 Hz = 15 W). Their dusting results were similar to the findings of the initial experience of Enikeev et al., higher dusting efficiency was noted using higher pulse frequencies [77].

Taratkin and colleagues developed a prospectively collected RIRS study using the TFL [78]. One hundred and fifty-three patients with a stone volume of 279 (IQR 139.4-615.8) $mm^3$and stone density of 1,020 ± 382 HU were included. The median laser-on time was 2.8 (IQR 1.6-6.6) minutes and a median total energy for stone ablation of 4 (2.1-7.17) kJ. The median ablation efficiency was 13.3 (IQR 7.3-20.9) J/mm^3 and median ablation speed of 1.7 (IQR 1.0-2.8) mm^3/s. The authors conclude the TFL was a safe and efficient tool in lithotripsy regardless of the stone composition or density. They also comment that stone retropulsion was minimal and visibility was good during the URS procedures as graded on a Likert scale.

Ghazi et al. compared a 100W Ho:YAG and 60W TFL from a prospectively collected data, with fixed dusting settings (24 watts) in Rochester New York [79]. Thirty-one patients were included in each group. The TFL had a shorter laser-on time (533.6 VS 380.6 seconds, *p*=.015) and a faster median ablation speed (1.19 VS 4.1 mm^3/s, *p*=.003). The median ablation efficiency was lower for the TFL (12.5 VS 21.2 J/mm^3, *p*=.02).

A comparison between clinical prospectively collected studies is shown in Table 7.

Table 7. Comparison of Clinical Experience Studies with Thulium Fiber Laser

<table>
<tr><th colspan="2"></th><th colspan="2">Enikeev 2020
[77]</th><th>Carrera 2020
[75]</th><th>Corrales 2021
[76]</th><th>Taratkin 2021
[78]</th><th>Ghazi 2021
[79]</th></tr>
<tr><td colspan="2">n</td><td colspan="2">40</td><td>86</td><td>50</td><td>153</td><td>31</td></tr>
<tr><td colspan="2">Stone Volume (mm³)</td><td colspan="2">883
(606-1664)</td><td>>500</td><td>1800
(682-2760)</td><td>279 (139-615)</td><td>1150±2254.8</td></tr>
<tr><td colspan="2">Stone Density (HU)</td><td colspan="2">880±381</td><td>>900</td><td>1200
(750-1300)</td><td>1020
(250-1900)</td><td>845.6±371</td></tr>
<tr><td colspan="2">TOT (min)</td><td colspan="2">24±10.9</td><td>59.4±31</td><td>59.4±31</td><td>-</td><td>-</td></tr>
<tr><td rowspan="2">Laser Settings</td><td>J</td><td>0.5</td><td><u>0.15</u></td><td>0.2±0.3</td><td>0.3</td><td>-</td><td>0.4</td></tr>
<tr><td>Hz</td><td>30</td><td><u>200</u></td><td>228±299</td><td>100</td><td>-</td><td>60</td></tr>
<tr><td colspan="2" rowspan="2">Laser-on time (seconds)</td><td colspan="2">219 (90-330)</td><td rowspan="2">10.8±14.1</td><td rowspan="2">23 (14.2-38.7)</td><td rowspan="2">162 (96-396)</td><td rowspan="2">380.6 (340-698)</td></tr>
<tr><td colspan="2"><u>372 (96-414)</u></td></tr>
<tr><td colspan="2" rowspan="2">Ablation Speed (mm³/s)</td><td colspan="2">5.5 (1.5-8.7)</td><td rowspan="2">-</td><td rowspan="2">1.16 (0.8-2.1)</td><td rowspan="2">1.7 (1.0-2.8)</td><td rowspan="2">4.1 (1.1-4)</td></tr>
<tr><td colspan="2"><u>8.5 (3.6-19)</u></td></tr>
<tr><td colspan="2" rowspan="2">Ablation Efficiency (J/mm³)</td><td colspan="2">2.7 (1.8-9.8)</td><td rowspan="2">-</td><td rowspan="2">18.6 (9.5-26.1)</td><td rowspan="2">13.3 (7.3-20.9)</td><td rowspan="2">21.2 (5.8-28.3)</td></tr>
<tr><td colspan="2"><u>4.8 (2.6-11.3)</u></td></tr>
<tr><td colspan="2">SFR (%)</td><td colspan="2">92.5</td><td>78.9</td><td>-</td><td>89</td><td>68</td></tr>
</table>

Values display in median (IQR) or mean ± SD. TOT: Total operative time, IQR: Interquartile range, SD: standard deviation, SFR: stone-free rate.

1.8.4.1 Randomized Experience

Ulvik and colleagues documented the results of a prospective randomized controlled trial (RCT) of 60W TFL versus a low power 30W Ho:YAG for URS with laser lithotripsy

[80]. Sixty patients were randomized to each group including ureteral and renal stones. After a single URS procedure for a stone located in the kidney, the renal SFR at 3 months was higher for patients treated with the TFL using NCCT (86% vs 49% for the Ho:YAG, p=.001). The operative time was shorter for the TFL (49 minutes compared to 57 minutes, p =.008) but the mean laser-on time was similar 13 (IQR 6-17) minutes for the TFL and 13 (IQR 4-19) minutes for the Ho:YAG (p = 0.9) with a mean total energy of 3.5 (IQR 0.9-5.1) vs 4.2 (IQR 0.6-6) KJ (p = 0.4).

Recently, Haas et al. reported a single center RCT comparing a 120W high-power pulse-modulated Ho:YAG with "Moses 2.0" technology versus the super-pulsed 60W TFL [81]. One hundred and eight patients were randomized with ureteric and renal stones measuring 3-20 mm. No difference in URS time was noted when subdivided based on stone size, stone hardness [>1,023 or <1,023 Hounsfield Units, (HU)] or stone location. A comparable SFR was noted for both lasers at 4-8 weeks using different imaging modalities (X-ray, ultrasound and NCCT). Median laser-on-time was similar (Ho:YAG 4.8 VS TFL 5.1 minutes, p =.3); however less energy (Ho:YAG 3.1 VS 4.3 kJ, p=.046) was demonstrated for stone disruption as well as improved ablation efficiency in favor of the Ho:YAG laser (p =.009). The authors describe that similar starting laser settings and modifications were left to each surgeon's discretion, which may have influenced results given that optimal TFL settings are still not entirely known.

1.8.4.2 Multicenter Clinical Experience

1.8.4.2.1 Propensity Score-Matched Data

A recent retrospective, multicenter, non-randomized study based on the Flexible Ureteroscopy Outcomes Registry (FLEXOR), compared the 120W high-power pulse-modulated Ho:YAG and the super-pulsed 60W TFL from different high-volume centers around the world [82]. The overall cohort included 508 patients in the Ho:YAG and 1567 patients in the TFL that underwent flexible URS. After the propensity score matching (PSM), the cohort included 284 equivalent patients based on stone size, stone density.

In the entire cohort, the median laser-on time was significantly longer for the Ho:YAG [21 (IQR12-33) vs 17 (IQR 10-27) minutes; p<.001] but median operative time was similar [60 (IQR 35-95) vs 56 (IQR 39-80) minutes; *p*=.11). SFR was defined as the absence of fragments >2mm and was significantly higher for the TFL group (90% vs 62%, p<.001) based on X-ray and ultrasound mostly.

In the PSM cohort, pure dusting was performed in 6% for Ho:YAG and 28% for TFL, which contributed to stone basket extraction in 89% against 43% respectively. The median laser-on time [Ho:YAG, 23 (IQR 14-34) vs TFL, 20 (IQR 12-40) minutes; *p*=.45] and median operative time were similar [Ho:YAG, 57 (IQR 40-82) vs TFL 60 (IQR 36-90) minutes, *p*=.45] and did not differ significantly. The SFR was higher for the TFL (85% vs 56%, p<.001). Significantly more patients in the TFL group received a postoperative NCCT for SFR analysis (28 for Ho:YAG vs 236 for TFL). Despite this, the SFR numbers were higher in the TFL group but did not differ significantly (TFL 79% vs Ho:YAG 57%, *p*=.15).

The regression analysis documented significantly higher odds of rendering the patient stone-free with the TFL (OR 39.3, 95% CI 12.0-154; *p*<.001) and with the use of a ureteral access sheath ≥8 Fr (OR 11.8, 95% CI 2.32-63.7; *p*=.003). Higher Laser-on time, multiple stones, larger stone diameter and the use of disposable ureteroscope resulted in significantly lower odds of being stone-free.

1.8.4.2.2 Meta-analysis Data

A meta-analysis performed by Chua et al. included 15 comparative studies (6 randomized controlled studies, 5 prospective clinical studies and 4 retrospective cohort studies) [83]. Three of the RCTs were complete, 2 were abstracts and 1 was ongoing at the time of the analysis. In the pooled analysis, there was a marked heterogenicity and inter-study variability related to the different methodology of the studies, limiting the usefulness of the meta-analysis findings.

The overall pooled effect for operative time and laser-on time was shorter for the TFL group (SMD=-1.19, 95% CI -1.85 to -0.52, *p*=.52 and SMD=-1.67, 95% CI -2.62 to -0.72, *p*=.002), but the variability was high (I^2=98% and I^2=98%). Subgroup analysis for TFL against Moses Technology had no difference, but TFL against Ho:YAG without

Moses Technology was in favor for the TFL ($p<.00001$). Trying to address the inter-study variability, a sensitivity study that included only RCTs was performed on both operative time and laser-on time, both remained in favor of the TFL group (SMD=-2.02, 95% CI -3.48 to -0.57, $p<.00001$; $I^2=98\%$ and SMD=-3.32, 95% CI -5.25 to -1.39, $p<.00001$; $I^2=99\%$).

The SFR was not significantly different between the groups (RR 1.09, 95% CI 0.99-1.20, $p=.08$; $I^2=77\%$). In subgroup analysis when compared to Ho:YAG without Moses Technology, a significantly higher SFR was noted for the TFL cohort (RR 1.11, 95% CI 1.01-1.23, $p=.04$; $I^2=80\%$). To address the inter-study variability, an analysis including the 6 RCTs was performed which documented no difference between groups for SFR (RR 1.04, 95% CI 0.99-1.10, $p=.11$; $I^2=27\%$).

1.8.5 Optimal Laser Settings

Multiple laser settings have been proposed for the TFL based on stone location and whether dusting or fragmentation is desired [84]. Currently, the advice has been to keep the total laser energy or power output to under 50 watts in the bladder, 25 watts in the kidney and less than 10 watts in the ureter; to deliver the laser energy efficiently on the stone and to limit damage to surrounding structures or thermal injuries [76,77,84]. These limits were found to be safe and efficacious in prospective studies [77,84]. In Table 8, we summarize the TFL settings used for laser lithotripsy in the most recent studies. However, there is a lack of consensus or standardization regarding the optimal initial settings for the TFL, and large variations in the utilized TFL laser settings exist worldwide [85].

Table 8. Reported TFL settings

Authors	Energy (J)	Frequency (Hz)	Laser Power (W)*	Modality
Enikeev et. al [77]	0.5 0.15	30 200	15 30	*Dusting* *Dusting*
Kronenberg et. al [72]	0.1- 0.2	150	15- 30	*Dusting*
Corrales et. al [76]	0.2-0.6	50-180	10-100	*Dusting*
Carrera et. al. [75]	0.2 ± 0.3	228 ± 299	45-150	*Dusting*
Ulvik et. al [80]	0.4 0.8	6 20	2 16	*Fragmenting* *Dusting*
Hass et. al [81]	0.8 0.3	8 80	3 24	*Fragmenting* *Dusting*

**Laser Power Output (Watts) or Energy Output refers to the total energy/power output with the utilized/specified laser settings and it is calculated multiplying energy pulse by frequency pulse, e.g., 0.5 J X 30 Hz = 15 W*

1.8.6 Safety

Both Ho:YAG and TFL laser energy generate heat during the process of intracorporeal lithotripsy [61]. The laser energy property of being highly absorbed in water provides the advantage of causing minimal collateral damage to the surrounding tissues when used correctly. The wavelength of the TFL is closer to the liquid water absorption coefficient than that of the Ho:YAG, resulting in a lower optical penetration in tissue in favor to the TFL, providing a theoretically higher safety profile [47,61].

Multiple concerns have been raised with respect to potential thermal effects of the TFL, although this is a subject of some controversy. With the higher TFL water absorption, it has been theorized that higher temperatures may still be generated, and the potential exists for thermal injury to nearby tissues.

1.8.6.1 Temperature

Andreeva and colleagues demonstrated in an *in-vitro* ablation model, that there were no temperature differences recorded in the inlet and outlet chamber irrigation fluid readings for both lasers (TFL and Ho:YAG) at equal power settings [64]. No significant difference was noted in the maximum rise of water temperature either.

An *in-vitro* kidney-ureter model was used to assess the intraluminal increase in temperature during lithotripsy for a simulated impacted proximal ureteric stone [86]. A temperature probe was placed 2 mm from the laser fiber and a low-power Ho:YAG, high-power Ho:YAG and TFL were compared. At 3.6, 10 and 30 watts of energy output, the TFL increased the intra-ureteral fluid temperature higher in comparison to both the Ho:YAG lasers. At 30 watts, the TFL exceeded temperatures above 43º C, considered the safe threshold limit for tissue damage.

Molina et al. performed an ex vivo porcine study comparing the rise in temperature with the 120W Ho:YAG versus the TFL while dusting (Ho:YAG 0.3 J / 70 Hz and TFL 0.1 J / 200 Hz) or fragmentation (0.8 J / 8 Hz for both) in the ureter [87]. Equivalent temperatures rise during dusting (35.8 VS 40.6 ºC, p=.064) was documented but higher temperatures were noted during TFL fragmentation (30 VS 33.3 ºC, p=.004). None of the recorded temperatures in their experiments reached the threshold for thermal injury. The TFL is capable of much higher frequency settings, not only causing increased thermal temperature but also leading to more extreme movement of the fiber making it more challenging for the operator to ensure precise laser fiber placement on the stone and potentially leading to inadvertent contact with surrounding tissues and subsequent injury. In this study however, histological analysis did not show any evidence of thermal tissue injury.

1.8.6.2 Post-operative Complications.

Data from the two RCTs documented a low overall post-operative complication rate (Clavien-Dindo I-II) [80,81]. No evidence of strictures or persistent hydronephrosis at 3 months of follow-up was noted [80]. In the RCT from Haas et al. 3 patients required unplanned URS due to obstructive ureteral fragments, the rest of the complications were classified as low-grade [81]. Two clinical prospective studies reported a complication rate of 10-15% due to urinary tract infections, classified as Clavien Dindo I-II complications [77,78]. The multicenter study from the FLEXOR worldwide database, documented 3.6% (*n*=9) of patients with sepsis in the TFL against zero in the Ho:YAG [82]. The authors discussed that the higher incidence of sepsis could be multifactorial and related to infected stone in combination with a lower use of ureteral access sheaths in comparison to the Ho:YAG group.

A case report noted the incidence of a renal artery pseudoaneurysm following TFL lithotripsy [88]. A 24-year-old male with a history of recurrent urinary stone disease, underwent URS for 6 mm left renal pelvic and 7 mm upper pole stone. The TFL was used at 0.4 J / 40 Hz (16 W) and 2 J / 20 Hz (40 W), at institutional standardized settings. The patient had a normal initial post-operative course but then presented to the emergency department on postoperative day 20 where a CT angiography documented a 10 X 7 mm left renal artery pseudoaneurysm (early branching segment) that required selective renal embolization by interventional radiology. The authors highlighted the use of a higher-energy settings (total energy output of 40 W) than what is now currently recommended as a potential factor in the pseudoaneurysm formation. In addition, the high energy paired with a renal pelvic stone location, could have increased the risk further due to the close proximity of the laser fiber to the renal vasculature. Limiting the TFL settings to the recommended total energy (<25 W) appears to be of utmost importance reducing the risk of postoperative complications.

1.9 Thesis Rationale

The search for a new lithotripter technology was driven by the aforementioned inherent limitations of the Ho:YAG laser. A more efficient laser lithotripter may shorten laser-on and total operative time, could result in benefits related to reduced anesthesia time, including less morbidity to the patient, risk of peri-operative complications and cost-savings related to shorter operative room time and fewer disposable instruments. With the production of smaller stone fragments, use of the TFL could be associated with a greater chance of rendering the patient stone-free, and reducing the need for additional treatments. It might also permit the treatment of larger stones with URS that may have previously required a more invasive approach such as PCNL.

Multiple *in-vitro* studies have demonstrated improved dusting capabilities using the TFL, related to the physical properties of this laser. Nevertheless, *in-vitro* studies have inherent limitations as they cannot control for many important variables and may not reflect clinical reality. Recently published clinical studies have found discordant results regarding the efficiency of TFL and there have been only a small number of prospective trials to date. Considering these factors, a comparative prospective RCT was proposed to assess potentially clinically meaningful parameters.

1.10 Research Question (*Hypothesis*)

The clinical research question (H_1) was to assess if the TFL lithotripter is more efficient and faster at stone ablation than the Ho:YAG laser for upper urinary tract stones treated by flexible ureteroscopy. The H_0 hypothesis would be that there is no difference among the laser lithotripter technology.

We aimed to compare both laser technologies in a prospective and random study design from a single, high volume endourology treatment center.

Chapter 2

2 Material and Methods

The purpose of this clinical study was to evaluate a new laser lithotripter technology, TFL, compared to the "gold standard" Ho:YAG laser, regarding clinical efficiency for renal stone disruption.

2.1 Study Design

A single center, randomized, prospective controlled trial was conducted following approval from the Western University Research Ethics Board (ID: 120805) and Lawson Health Research Institute (ReDA #12294). Patients from a single institution were invited to participate if the following selection criteria were met: age greater than 18-years-old, scheduled to undergo elective flexible ureteroscopy for single or multiple upper urinary tract (calyceal, renal pelvic or uretero-pelvic junction) calculi diagnosed by preoperative NCCT with a stone burden up to 20 mm. Patients with ureteral stones were not considered for inclusion in this trial. The complete list of inclusion and exclusion criteria are displayed in Table 9.

Table 9. Inclusion and Exclusion Criteria

INCLUSION	EXCLUSION
• >18-year-old • Elective Flexible Ureteroscopy • Kidney or UPJ stone (NCCT)	• Stone density < 600 HU • Stone size < 8 mm or > 20 mm • Prior upper tract reconstruction *(urinary diversion, ureteral reimplantation, pyeloplasty)* • Urinary Tract Anomalies *(solitary kidney, horseshoe kidney, ectopic kidney, mal-rotated kidney, duplex collecting system, UPJ obstruction)*

UPJ: Uretero-pelvic junction, HU: Hounsfield Units

Patients with larger renal stones (>8mm) and higher stone density (>600 HU) were selected to accentuate any potential differences between the TFL and Ho:YAG laser technologies.

Eligible patients who met the inclusion criteria, were invited to participate prior to the surgical procedure. An explanation of the study in an oral and written format (Letter of Information) was provided and questions were answered to their satisfaction. If the patient agreed to participate in the study, consent was obtained, and the patient was then enrolled in the study.

2.2 Sample Size and Randomization

A power calculation estimated a required sample size of 44 patients (22 in each group). This is based on *in vitro* data which demonstrated that the TFL is 5 times faster at stone ablation than the Ho:YAG laser (1.32 mg/sec VS 0.25 mg/sec in dusting mode - 0.1 J / 200 Hz), with an α error value of 0.05 and desired power of 80 [66–68]. We planned to enroll 66 patients to allow for a 33% chance of exclusion secondary to patients who might withdraw or be lost to follow-up.

The randomization schedule was based in blocks of four (for 1:1 randomization). The group randomization was concealed in consecutive numbered and sealed envelopes. Once the patient agreed to participate, a unique ID study number was assigned, and the randomization envelope was then opened revealing the laser lithotripsy technology group immediately before the surgical procedure. No blinding was planned for the patients and if they had the desire to know their treatment allocation, it was shared with them. We did not believe sharing this information with the patients would have any impact on the primary or secondary outcomes. Likewise, blinding of the surgeons was not feasible given their need to operate the laser platforms which have clearly different features from one another and cannot be concealed.

2.3 Methodology

All surgical procedures were performed at St. Josephs Health Care (London ON, Canada), under general anesthesia as outpatient procedures. The URS was performed in a similar fashion by four fellowship-trained endourologists but the exact intraoperative technique including the laser settings, was left to the discretion of the surgeon. It should be noted that surgical trainees, including both residents and fellows may have been involved in the performance of some portions of the procedures, however their exact role was not documented.

2.3.1 Surgical Technique

A systematic cystoscopy with a 16 French (Fr.) flexible cystoscope (Digital CYF-HD 16 Fr.; Olympus, Tokyo, Japan) is performed, as an assessment of the lower urinary tract including urethra, bladder and configuration of the ureteric orifices. Once the desired ureteric orifice is identified, it is cannulated with a PTFE-coated stainless steel (Bentson, 0.035”, 145 cm; Cook Medical) or PTFE-coated nitinol with hydrophilic tip guidewire (Sensor™, 0.035”, 150 cm; Boston Scientific) under endoscopic and fluoroscopic guidance up to the renal pelvis.

Following the cannulation with the working guidewire, a routine intramural ureter dilation was performed with an Amplatz 8/10 Fr (8/10 Dilator/Sheath Set, 70/35 cm, Boston Scientific). A flexible ureteroscope (Digital URF-V2 8.4 Fr. or Fiberoptic URF-P6R 7.9 Fr.; Olympus, Tokyo, Japan. Single-Use LithoVue™; Boston Scientific, Marlborough, MA) was advanced over the guidewire and once in the collecting system, the guidewire was removed. Ureteral access sheaths were not routinely used but employed at the discretion of the treating urologist. Once the stone was identified, laser lithotripsy was performed with the allocated (randomized) laser technology (EMPOWER H65 Holmium:YAG Laser 65W or SOLTIVE SuperPulsed TFL Laser 60W; Olympus, Hamburg, Germany) using 200- or 272-micrometer laser fibers. Basket extraction of stone fragments was not performed in any patient. All patients had a double-pigtail ureteric stent placed at the conclusion of the procedure.

The initial laser settings used for stone disruption (“dusting” was the preferred technique) were 0.8 J at 5 Hz for the Ho:YAG laser group, increasing up to 8-15 Hz depending on surgeon preference and stone characteristics. No standardized initial settings were used for the TFL lithotripsy due to lack of worldwide consensus and were left to the surgeons’ discretion [85]. The total power output was limited to 25 watts in the collecting system (most common settings used: 2 J at 10 Hz = 20 watts). Both lasers were used in a short-width pulse mode.

2.4 Study Outcomes and Variables

Our aim was to evaluate the TFL technology in comparison to the Ho:YAG laser, regarding its efficiency for stone disruption. The laser efficiency was measured based on laser time, energy used and disrupted stone volume.

The primary outcome was to evaluate the difference between laser-on time for stone disruption, total utilized laser energy, ablation efficiency (J / mm^3), ablation speed (mm^3 / s) and total operative time.

The secondary outcomes were to evaluate the SFR at 3 months after the URS using NCCT imaging and the post-operative complication rates.

2.5 Variables and Data Collection

Patient data was collected under the patient's unique ID study number and stored in the Data Collection Form under the following sections: demographics, past medical history, urolithiasis characteristics, intraoperative & laser data, discharge, follow-up data and postoperative complications. The Master List with personal identifiers was kept safe in a secure environment at the center.

Study data were collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at Lawson Health Research Institute version 13.7.12 [89,90]. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

2.5.1 Demographic and Past Medical History Data

Data related to the patients' demographics included age, sex, weight and height was documented. Past medical history included comorbidities, urinary tract anomalies and prior history of urolithiasis. Comorbidities including coronary artery disease (CAD), hypertension, diabetes mellitus, obesity surgical procedures (gastric bypass, gastric sleeve etc.), gout, hyperparathyroidism, surgical bowel resection and recurrent urinary tract infections history were recorded. Furthermore, in the presence of a prior history urolithiasis, laterality and required surgical procedures were documented, as well as previous metabolic workup and stone composition if known.

2.5.2 Urolithiasis Data

The characteristics of the treated stone(s) were based on pre-operative NCCT from the Agfa Healthcare Picture Archiving and Communication System (PACS). Laterality, number of stones and location in the upper pole, middle, lower pole or renal pelvis was recorded. The size of the stone or stones (from largest to smallest) was detailed by calculating stone volume using the generic ellipsoid formula (length X width X height X 0.523). The stone burden was the cumulative stone or stones maximum diameters. The density of the stone was calculated systematically using the ellipsoid region of interest tool of the largest stone from the NCCT and measured in mean HU. In addition, the presence or absence of hydronephrosis was assessed in the NCCT imaging.

2.5.3 Intraoperative and Laser Data

The intraoperative data included date of the surgical procedure, American Society of Anesthesiologists (ASA) physical status score, type of flexible ureteroscope (fiberoptic, digital or single-use), location of the calculi under direct vision, ureteric dilation, use of ureteric access sheath and the size of the ureteric stent placed. The Total Operative Time (TOT) was recorded from the initial placement of the working guidewire until the final positioning of the double pigtail ureteric stent post-ureteroscopy.

Based on the allocated laser technology, the laser parameters were recorded during the URS. The energy, frequency, total power output, total utilized laser energy and laser-on time were recorded from the screen of the laser machine. Changes in the laser settings during the procedure were recorded and the preferred surgeon settings were registered for each procedure. In addition, the size and style tip (straight versus ball tip) of the laser fiber were documented.

The total laser energy (recorded in Joules) was defined as the energy utilized for total disruption of the stone. The ablation efficiency (J / mm^3), defined as the energy needed to ablate 1 mm^3 of stone volume, was calculated by dividing the total laser energy over the stone volume (determined pre-operatively). The ablation speed (mm^3 / s) was calculated by dividing the stone volume over the laser-on time for lithotripsy [91].

2.5.4 Discharge, Follow-up and Postoperative Data

The patients were booked as one day procedures, unless a peri-operative complication was noted, and hospital admission was necessary. The date of the first postoperative clinic visit was documented, as well as the date of the removal of the ureteric stent.

Postoperative complications were acknowledged up to 30 days based on the Clavien-Dindo Classification system [92].

Three-month post-operative SFR was determined by NCCT and classified according to the instituted criteria system from the Endourological Society and Journal of Endourology: Grade A or *absolutely stone free* (no stones on CT scan), Grade B or *relative stone free* (<2mm fragments), and Grade C or *fragments relative stone free* (2.1 – 4mm fragments) [93,94]. Patients catalogued as having residual fragments (not stone-free) based on the previous classification, the maximum diameter of the fragment or cumulative maximum diameters of multiple fragments were recorded.

2.6 Statistical Analysis

Descriptive statistics were used to present demographic and urolithiasis variables. The data is presented in central tendencies (mean, median, quartiles 1-3 or IQR) depending on the distribution of the variable based on the Kolmogorov-Smirnov and Shapiro-Wilk normality test. Continuous variables between groups were compared using Mann-

Whitney U test or Student T-test, if they approached the normal distribution. Categorical variables were compared using a Chi-squared test.

The primary outcome variables of laser-on time, ablation speed and ablation efficiency were compared between groups using Mann-Whitney U test (non-parametric). Student T-test was used to compare TOT because it approached a normal distribution. The results were reported with mean, median and IQR. Statistical significance was set a 2-tailed p values $< .05$. The secondary outcome (stone-free rate at 3 months) was compared between groups using a Chi-squared test.

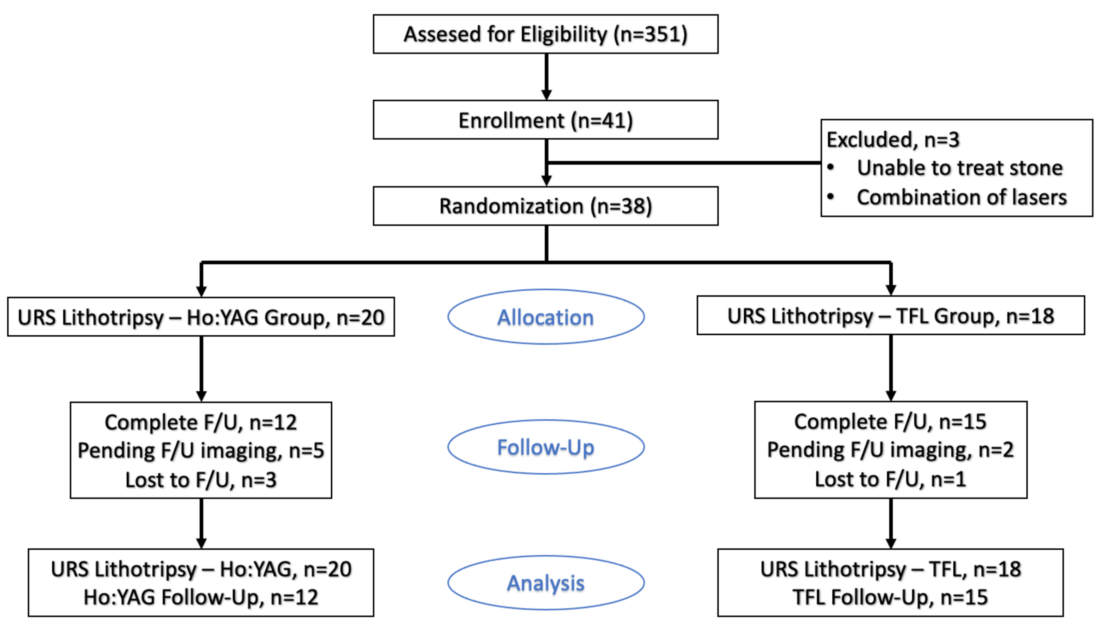
The statistical analysis was performed using IBM SPSS 25 Statistical Software Package (IBM Corp. Released 2017. IBM SPSS Statistics for Macintosh, Version 25.0. Armonk, NY: IBM Corp.).

Chapter 3

3 Results

In June 2022, the prospective recruitment of patients was initiated. During the study period 351 patients were assessed. Forty-one patients agreed to participate, met the inclusion criteria, and were enrolled in the study. Three patients were excluded due to the inability to treat the stone and/or use of both laser technologies. Thirty-eight patients were randomized, 18 were allocated in the TFL group and 20 in the Ho:YAG group for the preliminary analysis. Participant flow is shown in the Consolidated Standards of Reporting Trials (CONSORT) diagram in Figure 2. To date, we have available 3-month follow-up information from 27 patients, including postoperative NCCT imaging for postoperative stone-free rate analysis. It should also be noted that recruitment continues to fulfill the enrollment goal of 22 patients in each study arm.

Figure 2. CONSORT Diagram



URS: ureteroscopy, F/U: follow-up.

3.1 Demographics and Urolithiasis

The demographic variables of both groups are presented in Table 10. The mean age was 62 (IQR 52-72) years and 58.2% (*n*=24) were females. In the Ho:YAG group, seventy percent of patients had a prior history of urolithiasis. Two patients had a prior metabolic evaluation revealing primary hyperparathyroidism and hyperoxaluria respectively. Nine patients had prior stone composition results available with calcium oxalate monohydrate being the most common stone type. In the TFL group, 66.7% had a history of urolithiasis. Calcium oxalate monohydrate was the most common stone composition, noted from 8 patients who had available data. Three had a prior metabolic evaluation which identified hypocitraturia. There were no significant differences in any of the demographic characteristics between the two groups and the groups appeared well balanced.

Table 10. Demographic Characteristics

Variable	*Ho:YAG (n=20)*	*TFL (n=18)*	*p value*
Age, ***years-old*** ***mean, median (IQR)***	62.7, 64.5 (53-73.5)	60.8, 63.5 (49.5-74)	.673
Sex, ***n (%)***			
Female	13 (65)	11 (61.1)	.804
Male	7 (35)	7 (38.9)	
BMI, ***kg/m²*** ***mean, median (IQR)***	28, 28 (25.6-31)	28.9, 28 (25.7-33.9)	.564
Comorbidities, ***n (%)***			
CAD	0	1 (5.6)	
Hypertension	2 (10)	5 (27.8)	.707
Diabetes	3 (15)	2 (11.1)	
Dyslipidemia	4 (20)	2 (11.1)	
History Urolithiasis, ***n (%)***	14 (70)	12 (66.7)	.825
History of M. Abnormalities, ***n (%)***	2 (10)	3 (16.7)	.653
Prior stone composition, ***n (%)***			
Whewellite (>50%)	4 (20)	6 (33.6)	
Uric Acid (>50%)	2 (10)	1 (5.6)	
Struvite	1 (5)	1 (5.6)	
Calcium Phosphate	1 (5)	0	
Brushite	0	1 (5.6)	
ASA, ***n (%)***			
I	1 (5)	1 (5.6)	
II	8 (40)	7 (38.9)	
III	11 (55)	9 (50)	
IV	0	1 (5.6)	

IQR: interquartile range, BMI: body mass index, CAD: coronary artery disease, M. Abnormalities: metabolic abnormalities, Whewellite: calcium oxalate monohydrate, ASA: American Society of Anesthesiologists score

The stone characteristics of the included patients are presented in Table 11. In both groups, URS was performed to treat a solitary stone in more than two thirds of the patients and the most common location was the renal pelvis. No statistical difference was documented between groups regarding the urinary stone characteristics and the groups appeared to be well balanced. The mean surgically treated stone burden for Ho:YAG group and TFL group was 13.8 and 14.7 mm (p=.459), with a median stone volume of

603.8 and 624.9 mm^3 (p=.745) and a median stone density of 1092 and 1200 HU (p=.446), respectively.

Table 11. Urolithiasis Characteristics

Variable	*Ho:YAG (n=20)*	*TFL (n=18)*	*p value*
Side, ***n (%)***			
Right	12 (60)	7 (38.9)	.330
Left	8 (40)	11 (61.1)	
Number of stones, ***n (%)***			.7
1	16 (80)	14 (77.8)	
2	3 (15)	2 (11.1)	
3	1 (5)	2 (11.1)	
Location, ***n (%)***			.385
Upper calyx	0	1 (6.5)	
Mid calyx	0	1 (6.5)	
Lower calyx	6 (30)	4 (20.3)	
Renal pelvis	10 (50)	9 (50)	
Lower calyx + Renal pelvis	4 (20)	3 (16.7)	
Stone burden, ***mm*** ***mean, median (IQR)***	13.8, 15, (11-16)	14.7, 14.5 (11-20)	.459
Stone volume, ***mm³*** ***mean, median (IQR),***	696.5, 603.8 (271.9-1101.8)	725.2, 624.9 (415.7-760.7)	.745
Stone Density, ***HU*** ***mean, median (IQR)***	1101.9, 1092 (887.5-1288.5)	1160, 1200 (966.5-1323.2)	.446

IQR: interquartile range, HU: Hounsfield Units

3.2 Data Related to Surgical Procedure

Six patients (15.7%) underwent a concomitant surgical procedure (3 had bilateral URS, 2 had a cystolithopaxy and 1 underwent a contralateral percutaneous nephrolithotomy). One patient required balloon dilation of the ureteric orifice and the rest underwent routine dilation with an Amplatz 8/10 Fr. dilator. In three patients, a ureteral access sheath was placed (10/12 Fr) to improve irrigation and visibility during the procedure, no basket extraction of stones was performed.

The median total power output for the Ho:YAG group was 6.4 (IQR 6.4-11) watts, the most common used setting was 0.8 Joules (90%) and 8 Hz (60%). The energy varied from 0.8-1.5 Joules and frequency from 5.0-15 Hz. A 200 µm ball-tip laser fiber was used in 80% of the cases, and a 272 µm straight-tip laser fiber was used for the remainder of the cases.

The median total power output for the TFL group was 20 (IQR 13.7-20) watts and the most used setting was 2 Joules and 10 Hz (66.7%). The energy varied from 0.8-2 Joules and the frequency from 5.0-40 Hz. A 200 µm ball-tip laser fiber was used in 88% of the cases, and a 150 µm ball-tip laser fiber was used for the remainder of the cases. In Figure 3, the pulse energy and pulse frequency using during the URS procedure, are shown individually, and separated by laser group. In Figure 4, the laser settings (pulse energy/frequency) used during the URS is displayed.

Figure 3. Pulse Energy & Frequency Used in Ureteroscopy

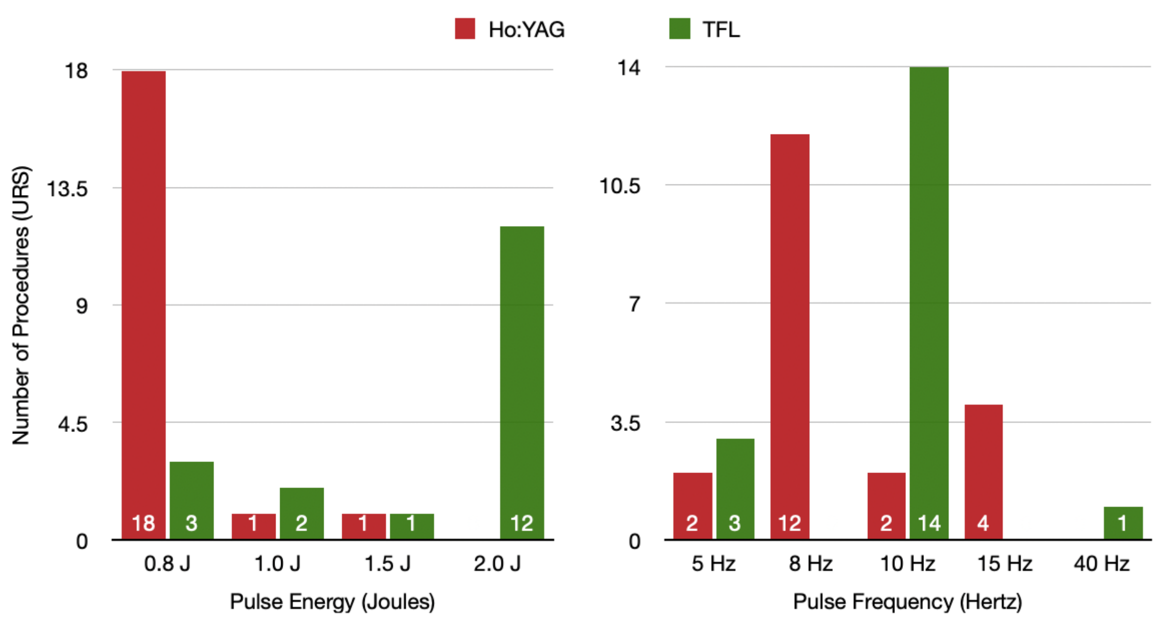
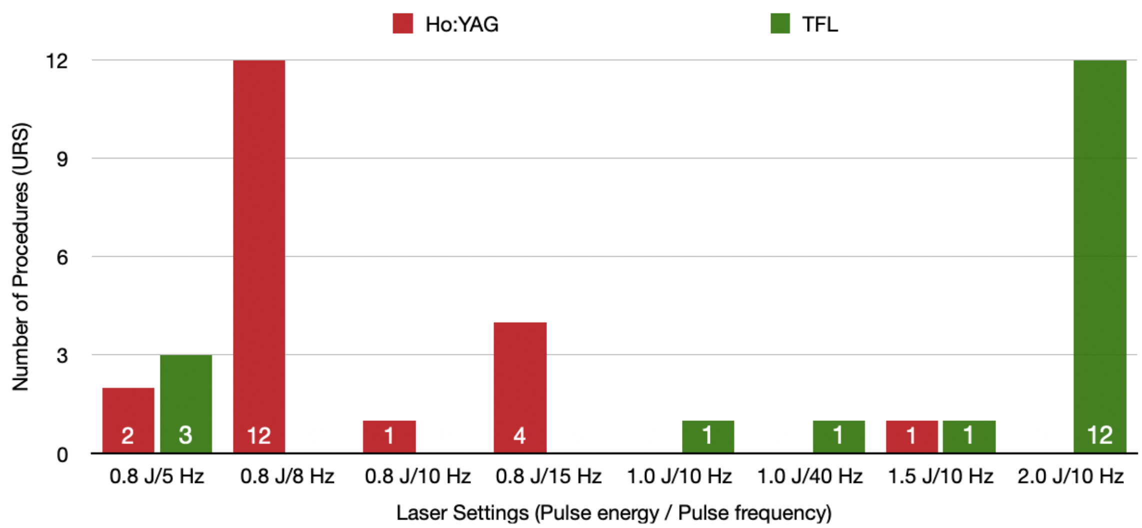


Figure 4. Pulse Energy/Frequency Setting Used in Ureteroscopy



3.3 Primary Outcomes

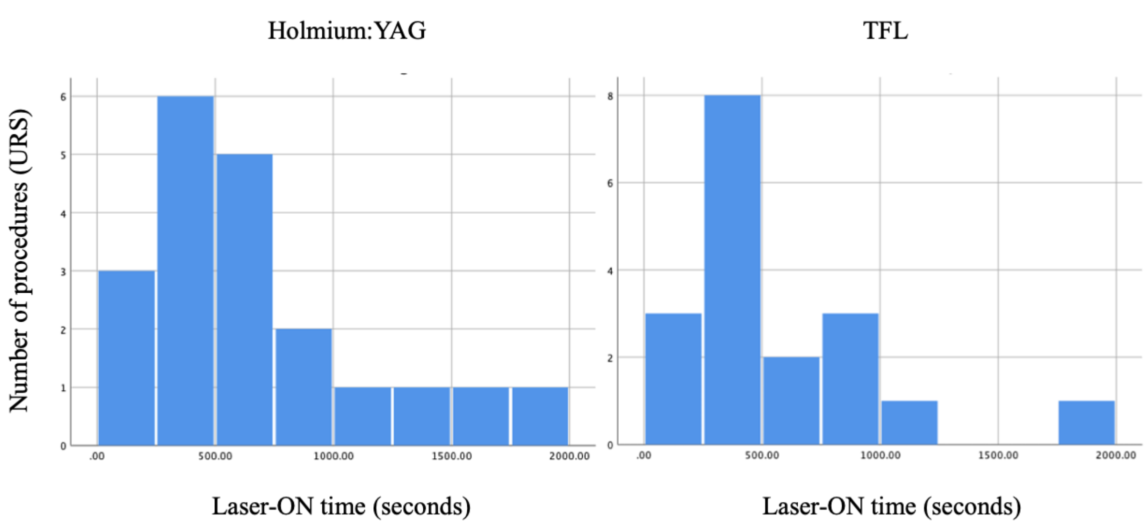
The preliminary comparison between groups documented no statistical difference in laser-on time, total laser energy, ablation speed, ablation efficiency or TOT. Interestingly, trends towards TFL group were observed for multiple primary outcome variables including: shorter laser-on time (378 VS 537 seconds, Histogram is shown in Figure 5), shorter TOT (36 VS 37 minutes), decreased Total Laser Energy (6173 VS 7764 Joules), improved ablation efficiency (10.9 VS 11.6 J/mm^3) and increased ablation speed (1.34 VS 1.08 mm^3/second). Laser related variables and statistical comparisons are fully described in Table 12.

Table 12. Laser-related Variables

Variable	*Ho:YAG (n=20)*	*TFL (n=18)*	*p value*
Total Operative Time *mean (IQR), minutes*	37 (25.2-46)	36.2 (22.7-51.7)	.849
Laser-ON Time *median (IQR), seconds*	537.5 (333.7-972.2)	378.5 (262.3-931.2)	.330
Total Energy *median (IQR), Joules*	7764.5 (3191-11780)	6173 (4786-8447)	.745
Ablation Speed *median (IQR), mm^3 / second*	1.08 (0.6-1.6)	1.34 (0.9-1.6)	.745
Ablation Efficiency$^+$ *median (IQR), Joules / mm^3*	11.6 (6.1-18.6)	10.9 (8.6-14.7)	.745

$^+$ *Lower value refers to an improved ablation efficiency. IQR: interquartile range.*

Figure 5. Laser-ON Time Histogram



Histogram comparison of Laser-ON Time for Ho:YAG and TFL. X-axis: number of ureteroscopies, Y-axis: time in seconds. Median Laser-ON time for Ho:YAG was 537 and 378 seconds for TFL, *p*=.330

3.4 Secondary Outcomes

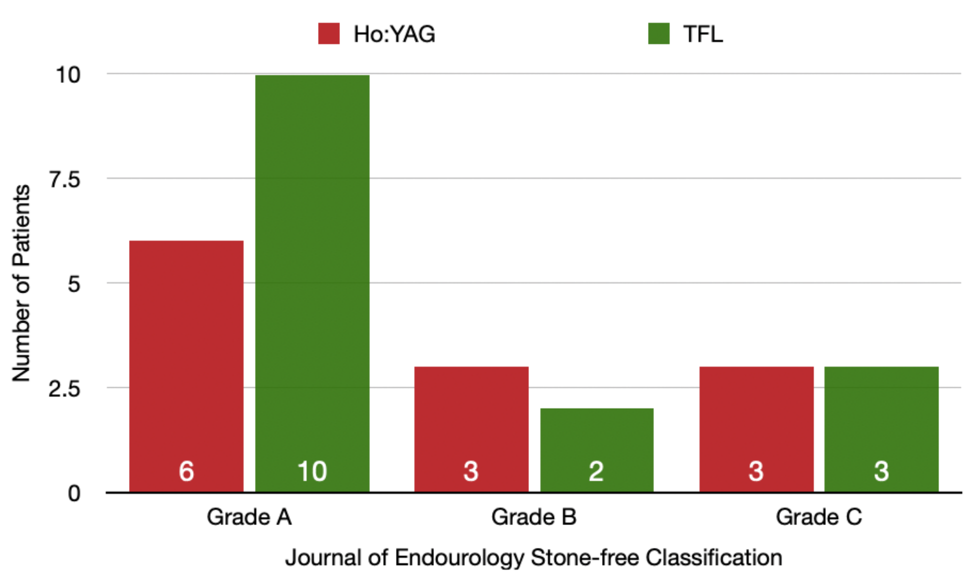
Twelve patients in the Ho:YAG group and 15 in the TFL group completed their 3 month follow up including NCCT imaging to evaluate the stone-free rate status. In the Ho:YAG group, 6 (50%) patients were completely stone-free (Grade A). Similarly, in the TFL group, 10 (66%) patients were completely stone-free. The stone-free classification is fully described in Table 13 and Figure 6. A chi-square test showed there was no significant association between the stone-free rate and the randomized laser lithotripter at 3 months of follow-up, x^2 (2, n=27) =.877, p=.645

Table 13. Stone-Free Rate based on NCCT imaging at 3 months

Stone-free Classification*	***Ho:YAG (n=12)***	***TFL (n=15)***	***p value***
Grade A *Absolute Stone-free*	6 (50%)	10 (66.7%)	.645
Grade B *Relative Stone-free (≤2mm)*	3 (25%)	2 (13.3%)	
Grade C *Fragments Relative Stone-free (2.1-4 mm)*	3 (25%)	3 (20%)	

**Based on the Stone-free classification from the Journal of Endourology, Endourological Society.*

Figure 6. Stone-Free Rate based on NCCT imaging at 3 months



No intra-operative complications were documented. There was one postoperative complication (< 30 days) reported in the Ho:YAG group, a urinary tract infection managed with oral antibiotic therapy (Clavien-Dindo grade II).

3.5 Follow-up Data

Postoperative stone analysis was available in 14 patients. Eight patients (44%) in the TFL group had stone composition available. Calcium oxalate monohydrate was the most common primary composition (>50%) in 5 patients (62%), followed by calcium oxalate dihydrate (*n*=1), calcium phosphate (*n*=1) and uric acid (*n*=1) in the remainder. In the Ho:YAG group, six patients (30%) had stone composition available. Two patients had primarily calcium oxalate monohydrate, 2 had calcium oxalate dihydrate, 1 brushite and 1 struvite.

Chapter 4

4 Discussion

This thesis reports the results of a prospective, randomized trial comparing the ablation efficiency of renal stones using the Ho:YAG laser versus the novel Super pulsed TFL. Preoperative stone density (>600HU) and burden (8-20mm) was standardized to reduce potential differences in treatment groups, with relatively larger and denser renal stones being specifically selected to emphasize any potential differences in the laser technology.

The preliminary results documented comparable outcomes for both Ho:YAG and TFL groups, with no statistical differences identified for TOT, laser-on time, total energy, ablation speed and ablation efficiency. However, there was an observed trend in favor of the TFL group for multiple primary outcome variables. Importantly, we have not yet recruited fully to our calculated sample size, thus the statistical significance of the trends we are observing remain to be determined.

4.1 Laser Efficiency

In recent years, laser lithotripsy efficacy and efficiency has been measured by the total energy utilized to ablate the urinary stone, the lasering time and the ablated volume. In 2021, the concept of the required energy (Joules) to ablate 1 mm^3 of stone volume (J/mm^3) and the ablation speed (ablated stone volume per second) was further investigated by Ventimiglia et al [91]. In their clinical study using a 35W Ho:YAG for 30 consecutive patients that underwent RIRS, the documented mean ablation efficiency was 19 (IQR 14-24) J/mm^3 for a median stone volume of 1599 mm^3 with a median density of 1040 HU. The ablation speed was 0.7 (IQR 0.4-0.9) mm^3/seconds. Regarding a high-power Ho:YAG laser efficiency, Mekayten et al. performed a comparison using a 120W against a 20W Ho:YAG laser for kidney stones with a mean 1038 HU density and a mean volume of 383 mm^3 [95]. The mean ablation efficiency was 17 and 13 J/mm^3 respectively. The efficiency was worse (higher value) for the high-power laser because of the higher utilized total energy but the laser-on time decreased by half with the high-power laser in contrast to the low-power laser.

An i*n-vitro* study developed by Panthier and colleagues, analyzed the ablation efficiency of a 30W Ho:YAG for 3 different stone types [96]. For calcium oxalate monohydrate stone, 24 Joules were required to ablate 1 mm^3 of stone, for cystine and uric acid were 7.6 and 2.5 Joules respectively.

In comparison to our findings, for a median stone volume 624 mm^3 and stone density of 1200 HU, the TFL had an ablation efficiency of 10.9 J/mm^3 and an ablation speed of 1.34 mm^3/s. This could be related to the better delivery of laser energy to the stone as well as the low pulse frequency used. As documented by Mekayten, a high frequency (0.4 J / 60 Hz = 24 watts) can increase the total energy and could translate in a less efficient laser energy delivery to the stone, the wasted energy transforms in heat that could increase the temperature of the surrounding water and potentially damage the surrounding mucosa. In Figure 7 and Table 14, we compare the ablation efficiency and speed from clinical studies.

Figure 7. Comparison of Ablation Efficiency and Ablation Speed among Clinical Studies

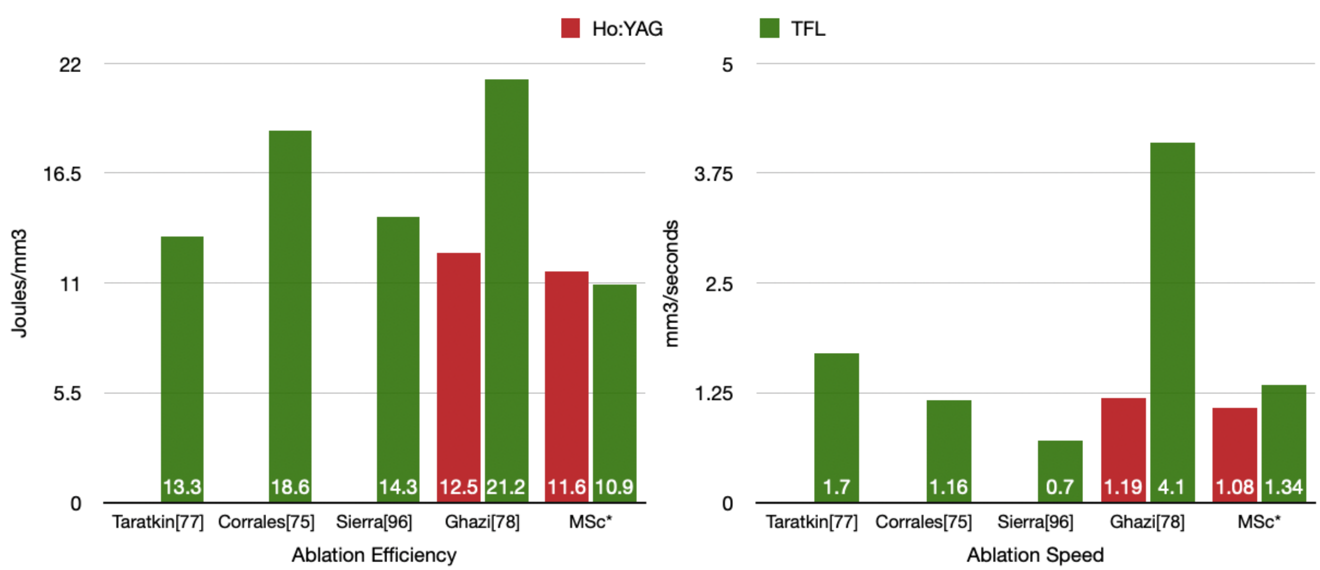


Table 14. Comparison of Ablation Efficiency among Clinical Studies

Study (year), design	Lasers	n	Stone Volume *(mm³)*	Stone Density *(HU)*	Laser-on time *(seconds)*	Total Energy *(Joules)*	Ablation Efficiency *(J/mm³)*	Ablation Speed *(mm³/s)*
Taratkin [78] (2021), PCD	*TFL*	153	279 *(139-615)*	1020 *(250-1900)*	162 *(96-396)*	4000 (2100-7200)	13.3 *(7.3-20.9)*	1.7 *(1-2.8)*
Corrales [76] (2021), PCD	*TFL*	50	1800 *(682-2760)*	1200 *(750-1300)*	1300 *(852-2322)*	-	18.6 *(9.6-26.1)*	1.16 *(0.8-2.1)*
Sierra [97] (2022), PCD	*TFL*	50	1125 *(294-4000)*	950 *(725-1125)*	1582 *(1020-3420)*	-	14.3 *(7.8-24.7)*	0.7 *(0.4-1.2)*
Ghazi [79] (2021), PCD	*TFL*	31	1150 *(±2254)*	845 *(±371)*	380 *(340-698)*	11719 *(2887-18558)*	21.2 *(5.8-28.3)*	4.1 *(1.1-4)*
	Ho:YAG	31	1088 *(±1612)*	803 *(±302)*	533 *(115-618)*	8156 *(3260-10157)*	12.5 *(5.8-16.6)*	1.19 *(0.4-1.4)*
Haas [81] (2023), RCT	*TFL*	39	202 *(77-371)*	998 *(726-1203)*	216 *(102-438)*	2500 *(1400-5600)*	1.8 *(1.1-3.2)*	-
	Ho:YAG	30	197 *(59-521)*	1059 *(808-1286)*	162 *(72-372)*	1200 *(500-4700)*	1.5 *(0.7-2.2)*	-
Preliminary Findings, RCT	*TFL*	18	624 (415-760)	1200 (415-1323)	378 (262-931)	6173 (4786-8447)	10.9 (.6-14.7)	1.34 (0.9-1.6)
	Ho:YAG	20	603 (271-1101)	1092 (887-1288)	537 (333-972)	7764 (3191-11780)	11.6 (6.1-18.6)	1.08 (0.6-1.6)

Data is presented in mean (±SD) or median (IQR). PCD: prospective collected data, RCT: randomized controlled trial, SD: Standard Deviation, HU: Hounsfield Units.

4.1.1 Pulse Frequency and Frequency Threshold

Aldoukhi et al. assessed in an *in-vitro* study, the frequency threshold for stone ablation using a high-power Ho:YAG (120W) laser [98]. Long pulse and pulse modulation technology were assessed at 0.5 J at 1-40 Hz and the area of the stone crater (ablated volume) reached a plateau in size in the same location, after 5 pulses (threshold) with no further increase in size in the subsequent pulses or with increasing the pulse frequency. The authors explain that moving the laser fiber over the stone (painting the stone) plays an important role and exceeding the ablation frequency threshold in the same or single stone location results in minimal increase in ablation volume, wasting energy and time. These findings could explain that a high pulse frequency is not always the most efficient method to disrupt a urinary stone. This also demonstrates the importance of surgical technique and experience which can also heavily influence results.

4.1.2 Pulse Frequency and Temperature

Intracorporeal laser lithotripsy technology generates heats during the stone ablation because of the delivered energy. The heat is highly absorbed by water due to physical properties of the laser technology, which limits the damage to surrounding tissues when used correctly.

The application of high pulse frequency during laser lithotripsy has raised concerns about potentially deleterious effects. A potentially significant clinical issue relates to a pronounced rise in temperature (as seen with Ho:YAG [99]). The clinical effect of these findings have been conflicting. Rather than the high frequency causing a direct thermal effect, it is also possible that the dusting technique simply impairs the surgeon's vision due to the "snowstorm" effect [100]. This then leads to less precise laser fiber placement and increasing the risk of damaging the urothelium on that basis.

Interestingly, Belle et al. documented no increase in temperature above the threshold for tissue damage (>43 ºC) and nonsignificant changes in temperature at 20 watts of power output (2 J / 10 Hz) when comparing Ho:YAG versus the TFL in a model [86]. This could reinforce the use of low-power settings with the TFL and it is in keeping with the recommended range of 25 watts within the kidney [84]. In our study, the most used setting for stone disruption with the TFL was 2 J / 10 Hz, providing adequate ablation results, yet staying below the 25 watts threshold.

The photothermal mechanism of the TFL can cause carbonization or charring of the stone surface during the lithotripsy [51]. This phenomenon can affect the ablation efficiency and increase the fiber-tip degradation. Rapid evaporation of the water due to the contact of the laser fiber-tip and the stone surface, leaves no path for excess heat to diffuse causing charring of the stone [61]. Blackmon and colleagues documented TFL carbonization of the stone surface in pulse lengths of 1-20 milliseconds and pulse frequencies above 100 Hz [59,62]. The carbonization can be reduced by shortening the laser pulse length and pulse energy [51]. In addition, Kim and colleagues documented this effect can happen more frequently with calcium phosphate stones [101].

4.2 Comparison of *In-vitro*, Clinical Data and Preliminary Results

Since 1995, Ho:YAG laser technology has been the gold-standard for intracorporeal lithotripsy and has undergone multiple technological improvements trying to overcome inherent physical limitations associated with the wavelength. The physical properties of the optical cavities inside the Ho:YAG, provide a limited dusting capability of the stone related to the pulse energy and frequency. This could result in a lower stone-free rate and the use of ancillary tools as baskets to extract the stone pieces which might increase the operative time. In addition, a higher stone retropulsion, will cause the surgeon to chase the stones to destroy it successfully decreasing the efficiency of the procedure.

The introduction of multiple optical cavities and pulse modulation have dramatically improved its efficiency in comparison to regular pulse Ho:YAG lasers. Nevertheless, these limitations persist, and represent the main reason to further develop other technological advances. The TFL has proven its ablation efficiency in multiple *in-vitro* studies. Regarding clinical evidence, it is still scarce and with conflicting results which will be discussed in further detail.

In-vitro data have documented faster ablation speed, as well as higher ablated volume for the TFL in comparison to the Ho:YAG laser. Chiron et al. and Chew et al. [66,67], described 2-5 times faster disruption speed for fragmentation (1.99 vs 0.98 mg/s) and dusting (1.32 vs 0.25 mg/s) technique using similar laser settings. In addition, delivering the same amount of total energy produced a higher amount of stone dust (40% vs 24%) and smaller dust particles making more efficient during stone disruption [67,68].

The first clinical experiences published by Carrera et al. in North America and Corrales et al. in Paris, included 86 and 41 patients respectively who underwent RIRS [75,76]. Stone characteristics included a mean stone volume of 560-1500 mm^2 and 1800 mm^3 with median density of 1200 and 900 HU respectively. The volume and density are equivalent to our cohort but higher in the Corrales et al. study. The laser-on time was 10.8 (mean) and 23 (median) minutes for each study, the laser-on time was shorter in our study (median 6.3 minutes). Their findings could be related to the higher stone volume and the used energy settings (< 0.5 J / 50-300 Hz) for dusting with a high pulse frequency.

In a report from a prospectively collected RIRS database using the TFL, Taratkin et al. included 153 patients with a stone volume (279, IQR 139.4-615.8 mm^3) and stone density (1,020 ± 382 HU) equivalent to the included cohort in our study [78]. In the subgroup analysis of harder/denser stones (>1000 HU), the median laser-on time was shorter (162 vs. 378 seconds) but the median treated stone volume (351 vs. 624 mm^3) was smaller than in our study. Consequently, the median ablation speed was faster (2.1 vs.1.34 mm^3/s) but the ablation efficiency was lower than our study (11.5 vs. 10.9 J/mm^3). A lower value in the ablation efficiency is more desirable because it represents the use of less energy (Joules) needed to disrupt 1 mm^3 of stone. These findings could also be related to the relatively smaller ablated stone volume and/or the laser settings. Unfortunately, the laser settings utilized were not described in Taratkin's study limiting the ability to compare our results; however, we believe they likely utilized comparatively lower pulse energy and higher frequencies.

A comparison of the Ho:YAG (100W) against TFL in RIRS was prospectively analyzed in Rochester, New York with 31 patients in each group [79]. Fixed dusting settings were utilized for both lasers (0.4 J / 60 Hz = 24 watts). The stone volume was similar to our study, but the density was approximately 200 HU less than our included patients. Interestingly, a statistical difference was noted in laser-on time (mean Ho:YAG 533.6 vs TFL 380.6 seconds, p=.015) and ablation speed favoring the TFL (1.19 vs 4.1, p=.003). The median total energy (8156 vs 11719 kJ, p=.05) and median ablation efficiency (12.5 vs 21.2 J/mm^3, p=.02) was better for Ho:YAG. The delivered total energy with TFL was higher in less laser-on time, thus resulting in a worse ablation efficiency for the TFL. This is contradictory to our findings, because our laser-on time and total energy were lower than Ho:YAG. This observation could be related to the laser settings used and the total energy output (24 watts versus 20 watts in the present study).

Ulvik et al. recently published an RCT comparing Ho:YAG and TFL for both ureteric and renal calculi. They included a similar number of patients with renal calculi as we plan to recruit (39 patients in Ho:YAG and 36 in TFL group) [80]. In addition, for the renal calculi included the overall stone burden and volume were comparable to our preliminary patient cohort. Their study demonstrated that the total operative time was statically significant in favor of the TFL (49 VS 57 minutes, p=.008) for both locations (ureter, kidney). However, no differences in laser-on time and total laser energy were reported, consistent with our preliminary findings. The authors believe the difference in TOT could be related to a superior endoscopic vision and less retropulsion which translated to less frequent breaks in laser application (lost treatment time) to optimize the endoscopic view. Another reason that could explain the observed outcomes is the use of similar initial settings for both laser technologies (0.8 J / 20 Hz as maximum). Ulvik and colleagues discussed that their selection of laser settings were related to safety concerns regarding temperature increases with higher pulse frequencies.

One of the main criticisms to the Ulvik et al. study is the comparison involved a low-power Ho:YAG laser system (Dornier 30 Watts) against the TFL which might bias results in favor of the TFL. Even though high pulse frequencies and pulse modulation are the benefit from the high-power Ho:YAG systems, these settings were not standard to Ulvik's study. The utilized laser settings by Ulvik and colleagues are feasible with a low-power Ho:YAG system but these systems lack the pulse modulation mode found in high-power systems which may make them more efficient.

Furthermore, Aldoukhi et al. described the frequency threshold for stone ablation using high-power Ho:YAG systems [98]. After 5 pulses, no further increase in the crater size was documented at the same location of the stone. This could explain that high pulse frequency is not always the most efficient method for ablation. Nevertheless, pulse modulation technology has been proven to have lower TOT and fragmentation/dusting time than regular mode in high-power lasers [102]. In addition, this technology has the advantage of reducing retropulsion during the surgical procedure. *In vitro* and clinical experience with the TFL has have been shown to be associated with less retropulsion than Ho:YAG systems [64].

A RCT conducted by Haas et al. compared a high-power Ho:YAG (120W with Moses Technology 2.0) against a 60W TFL [81]. This single-institution randomized trial included both ureteric and renal stones and the same starting laser settings were used for each laser. The median URS time for renal stones was 22 (IQR 15-34) minutes for Ho:YAG and 18 (IQR 14-25) minutes for TFL (*p*=.18). The planned methodology of the study had a significance cutoff of 6 minutes difference in URS time between groups, which was not reached in the results. In addition, the study documented no difference in either URS time (measured instead of TOT), overall laser-on time or either measure subdivided by stone hardness for renal stones. Also, the ablation speed was not statistically different between groups. The authors remarked the total energy (3.1 VS 4.3 kJ, *p*=.046) and ablation efficiency (1.6 VS 2.4 kJ/mm3, *p*=.009) significantly favored the Ho:YAG group, which differs from our preliminary results.

As previously discussed, the optimal TFL settings are unknown. This may have contributed to an improved ablation efficiency for the Ho:YAG in the Haas et al. study. As well, the increase in pulse energy/frequency were left to the surgeons' discretion; this could have biased the total utilized energy and ablation efficiency for the TFL. Interestingly, the documented improved ablation efficiency of the Ho:YAG did not translate to an improved shorter URS procedure time.

In our preliminary results, we did not encounter any problems with endoscopic vision and ablation of the stones was adequate, especially for cystine and uric acid stone compositions using a dusting technique. It was anecdotally noted that calcium phosphate stones were more difficult to ablate with the TFL, which corresponds with previous *in vitro* data demonstrating that calcium phosphate stones retain their crystalline structure following TFL ablation [69,70].

4.3 Stone-free Rate

Our stone-free rate results at 3 months of follow-up were similar among groups. Sixty-six percent of the patients in the TFL were stone free (zero fragments) compared with 50% in the Ho:YAG group. The comparison was not statistically significant, and it could be related to the fact that only 27 patients have completed their 3-month follow-up. In comparison with the previously discussed RCTs our findings are somewhat discordant; however, we are limited in our ability to directly compare our results given that most RCTs employed a variety of post-operative imaging modalities with differencing accuracies for detecting residual stone fragments.

Ulvik and colleagues, documented that more patients were significantly rendered stone-free following TFL [80]. For renal stones, the SFR, defined as no fragments bigger than 3 mm, was 86% for the TFL in comparison to 49% for the Ho:YAG, p=0.001. When zero fragments was considered as definition, it was 66% for the TFL and 33% for the Ho:YAG, p=.005. The SFR assessment was done with NCCT at 3 months follow-up.

The overall SFR for Haas et al. RCT was not statistically different between groups (Ho:YAG 85% vs. TFL 77%, p=.3); when examining only renal stones there was no statistically significant difference either (Ho:YAG 74% vs. TFL 71%, p=.8) [81]. One of the limitations regarding SFR was that this was primarily measured with plain X-rays and renal ultrasound, which has significantly lower accuracy. NCCT is considered the gold standard to determine stone free rate and was employed in our current study.

The recent retrospective, multicenter, non-randomized study based on the FLEXOR worldwide registry, documented a higher SFR in the overall cohort and PSM cohort favoring the TFL [82]. The SFR was defined as the absence of fragments >2mm and was significantly higher in the overall cohort for the TFL group (90% vs 62%, p<.001) based on X-ray and ultrasound mostly. In the PSM cohort, the SFR was higher for the TFL (85% vs 56%, p<.001). Patients with postoperative NCCT for SFR analysis were 28 in Ho:YAG and 236 in the TFL group, the SFR numbers were higher in the TFL group but did not differ significantly (TFL 79% vs Ho:YAG 57%, p=.15), probably related to the low NCCT sample size. The authors documented significantly higher odds of rendering the patient stone-free with the TFL technology (OR 39.3, 95% CI 12.0-154; p<.001).

4.4 Clinical Significance

The preliminary findings of the study documented several trends that favored the TFL in comparison to the Ho:YAG but no statistical significance was noted. The laser-on time, total operative time, total energy, the ablation efficiency, and the ablation speed were better for the TFL in the setting of a higher median stone burden, stone volume and stone density. The laser settings used could have impacted these results. The use of high energy and low frequency per pulse, let the operator surgeon deliver the laser energy directly to the stone and avoid a "wasting" of energy when the fiber moves faster due to higher pulse frequencies. This can result in better laser efficiency (lower value), lower total laser energy and shorter laser-on time. In addition, avoiding a waste of energy could decrease the rise in the temperature and limit thermal injuries to the urothelium. This also decreases the risk of inadvertent laser injury to the surrounding mucosa with increased laser movement observed at higher frequencies. There was no impairment of the endoscopic vision in any of the URS procedures in our study due to bleeding, "snowstorm effect" from stone fragments, or other intraoperative complications during this study but this was not objectively measured. In the same way, no URS procedure had to be stopped related to laser related complications. None of the patients who completed three-month follow-up post-operative NCCT were noted to have residual hydronephrosis of post-operative stricture formation.

In our study, the median TFL laser-on time was 378 against 537 seconds of the Ho:YAG. The time difference of 159 seconds with the TFL could be used to treat 213 mm^3 of extra stone volume in similar time, based on the preliminary findings. This extra laser-on time may be clinically significant and allow for the expansion of the application of URS to treat patients with larger and more complex stones who were previously felt to not be appropriate candidates for URS. Obviously, these findings are preliminary, recruitment fulfillment for our study is needed to complete our analysis. In addition, further multi-centered studies would also be required to validate these results.

The ability to treat stones with shorter operative times and with less delivered energy could expand the indications to treat larger and more complex urinary stones using a retrograde endoscopic approach and avoid a more invasive procedure as PCNL. As documented by Ordon and colleagues, the rate of kidney stone treatment has increased in individuals older than 64 years-old [11]. This age group is associated with a higher rate of comorbid and chronic diseases such as obesity, metabolic syndrome, heart disease and diabetes mellitus. Choosing the least invasive approach (RIRS) offers significant advantages for patients with increased age, frailty, and medical comorbidities. As the prevalence of urolithiasis continues to increase and our patient population continues to age and become more medically complex, it is imperative that our surgical technologies continue to evolve to better care for these patients.

4.5 Limitations

Our study does have several limitations which should be noted. The study was designed as a single center study which may limit its wider applicability. Larger, multi-centered trials will be required in the future to fully assess the clinical performance of the TFL laser over a broader range of patient characteristics and surgeon expertise. In addition, while URS is performed in a standardized fashion by all four surgeons at our center, the exact technique was left to the individual surgeon's discretion which may introduce bias and influence the results. This is specifically relevant to the laser settings utilized, as this may have a significant impact on the efficacy of laser lithotripsy. Also of importance, as a teaching institution trainees of varying skill sets may have been involved in some aspects of the procedures which may have particularly influenced laser and operating times. Unfortunately, trainee involvement was not specifically recorded or measured so we are unable to determine how it may have influenced the results. However, we feel that this offers a more "real-world" assessment of clinical laser performance as URS with laser lithotripsy is a commonly performed procedure and both laser technologies are likely to be utilized by urologists in both teaching and non-teaching centers with a variety of training in Endourology.

Currently, there is lack of consensus or standardization regarding the optimal initial laser settings for the TFL, and large variations in the TFL laser settings utilized have been reported worldwide [85]. This could create underperformance of the TFL considering its physical properties and demonstrated *in-vitro* efficiency [47,60,61,67,68]. Of note, the present study employed an older version Ho:YAG laser platform, which does not have the pulse modulation with Moses Technology. Furthermore, the biochemical stone analysis was not available in all patients because it is dependent on the patient straining their urine and collecting stone fragments for analysis. Given the small sample size it was not possible to analyze any correlation between stone composition and laser efficiency.

4.6 Future Directions

Our primary goal is to fulfill our recruitment to completely assess potential differences between the laser technology's efficiency and speed. The preliminary findings documented an interesting trend towards TFL regarding TOT, laser-on time, total energy, ablation speed and ablation efficiency. As previously mentioned, a more efficient laser could expand URS indications for larger stones (>20 mm), even in scenarios were PCNL might traditionally be considered the first option.

Further investigations regarding TFL laser technology are needed. The optimal initial laser settings for stone ablation remain to be established. Furthermore, documenting the ablation efficiency for different types of stone compositions in different clinical scenarios may also affect laser performance and should be further investigated.

Chapter 5

5 Conclusions

The present study compares the Ho:YAG and TFL technology in a more realistic clinical scenario, where the pulse-modulated Ho:YAG might not be widely available in all centers. Our preliminary results suggest similar outcomes between the two laser technologies for routine URS in patients with renal stones sized 8-20 mm.

Interestingly, several parameters are trending in favor of the TFL technology being more efficient. This might be clinically significant to expand indications for URS to treat patients when a more invasive approach is contraindicated. Nevertheless, recruitment fulfillment is necessary to determine if statistical significance will be reached.

Larger, multi-centered randomized controlled trials will also be required in the future to fully evaluate for clinically meaningful differences between the Ho:YAG and TFL laser technologies. The comparison is valuable, to further asses how the new TFL technology is best integrated into our current arsenal of laser technology to allow for the best care of our patients.

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	Dr. John Denstedt Masters of Surgery Research Excellence Award 2022

Publications:

1. Gonzalez-Cuenca E., Razvi H. Thulium Fiber Laser: game changer or marketing hype? Rev Mex Urol. 2023;83(1):pp. 1-11. https://doi.org/10.48193/revistamexicanadeurologa.v83i1.1013
2. Basulto M., Gonzalez E. CASE REPORT: Endoscopic Treatment of a Ureteric Stone in a Paraperitoneal Ureteroinguinal Hernia. AUANews. May 2023.
3. Sánchez-Núñez JE, González-Cuenca E, Fernández-Noyola G, González-Bonilla E, Rosas-Nava JE, Corona-Montes VE. Oncological and functional results after

robot-assisted radical prostatectomy in high-risk prostate cancer patients. Cir Cir 2022; 90(S1): pp. 1-7. https://doi.org/10.24875/CIRU.20001371

4. González-Cuenca E., Medrano-Urtecho H. M., Corona-Montes V. E., Maldonado-Ávi-la M., Rosas-Nava J. E. Recurrent ureteropelvic junction obstruction following primary treatment: prevalence, associated factors and laparoscopic treatment. Rev. Mex. Urol. 2020;80(3): pp. 1-8. https://doi.org/10.48193/revistamexicanadeurologa.v80i3.613
5. Enrique Corona-Montes V, Gonzalez-Cuenca E, López L, Eduardo Sánchez-Núñez J, Gaston R. Robot-Assisted Radical Cystectomy with Intra-Corporeal Neo-Bladder [Internet]. Modern Approach to Diagnosis and Treatment of Bladder Cancer. IntechOpen; 2021. Available from: http://dx.doi.org/10.5772/intechopen.98973
6. Corona-Montes VE, González-Cuenca E, Fernández-Noyola G, Olarte-Casas MA, Bobadilla-Salazar D, Medrano-Urtecho HM, Asimakopoulos AD. Primary lymph-node staging with ^{68}Ga-PSMA PET in high-risk prostate cancer: pathologic correlation with extended pelvic lymphadenectomy specimens. Urol Oncol. 2021 Aug;39(8):494.e1-494.e6. https://doi.org/10.1016/j.urolonc.2020.10.074