Comparison of Lumenis Pulse™ 120H Moses 2.0 holmium laser versus Olympus Soltive™ thulium fiber laser for mini-percutaneous nephrolithotomy

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1 Introduction/Significance

Multiple procedural modalities for treating nephrolithiasis are available to patients with the ultimate choice dependent on stone size, location, and patient factors.[1] For over 30 years, the holmium: yttrium-aluminum-garnet (Ho:YAG) laser has been the gold standard for laser lithotripsy due to its efficiency in stone fragmentation irrespective of stone composition and its enviable safety profile.[2-5] Different energies, pulse rates, pulse durations, and work settings are utilized based on stone density and surgeon intent for fragmentation versus dusting.

Basic physical principles underlie the effectiveness of the Ho:YAG laser, which made a revolution over two decades ago.[4] Energy is transmitted through a flexible quartz fiber that varies in size from 150-1,000 micrometers making it amenable to flexible ureteroscopy. Its wavelength of 2,100 nm is effectively absorbed by water conferring a safety profile which is further bolstered by its 0.4mm depth of penetration.[7] The photothermal mechanism by which it exerts force requires direct stone contact leading to stone vaporization.[8] As a pulsed laser, holmium emits a cyclic burst of light wavelength with a corresponding omission. The average of the laser's pulses accounts for the power output. Contemporary advancements have led to utilization of higher power by taking advantage of the pulse technology. At present pulse duration can be lengthened from 350 microseconds to 1500 microseconds and utilized to reduce stone retropulsion.[2] The latest evolution of the technology includes the aptly named "Moses Technology" (now in version 2.0) whereby a short vapor bubble precedes a longer duration, high energy pulse that can conserve energy by means of travel through the vapor bubble.[9] This technology has been key in reducing stone retropulsion leading to improved ablation rates. Data has suggested that the Moses technology improves patient outcomes by reducing procedural duration and reducing fragmentation time.[10]

A newer alternative to the Ho:YAG laser is the thulium fiber laser (TFL) lithotripter, introduced in 2018.[5] It can provide greater power output from a smaller fiber core due to the diode construction with silica chemically doped with thulium ions.[3,4] This is achieved by using a 50-150 micrometer optical laser fiber core rather than mirrors to focus light energy as in the Ho:YAG.[11] Small form factor renders the fiber more adaptable in acute angle applications. The low power consumption of the TFL arises from fan cooling and plug efficiency permitting increased pulse repetition rates up to 2,000 – 2,200 Hz with pulse durations from 0.2 to 12 milliseconds.[5,11] Due to these improvements, the TFL can both fragment and dust with moderated heat generation. Moreover, the TFL is compatible with variable operating room configurations based on its standard electrical wall socket (110V) making it more accessible. Similar to the Ho:YAG laser its wavelength varies between 1,908 and 1,940 nm bestowing a higher absorption coefficient in water which grants a similar safety profile owing to higher energy density focused at the tip of the laser fiber.[2] In summation, the TFL has comparable results for stone ablation and low retropulsion with lower power consumption and less retropulsion leading to better dusting.[2,9]

Recent studies have compared specific features of each laser to standardize best practices albeit with no clear winner. Pulse profiles differ with each laser. The Ho:YAG pulse has an acute spike in voltage with a dramatic drop within 150 microseconds whereas the TFL pulse profile has an

acute upsurge that is sustained for the duration of the pulse.[5] This inherent property within the TFL allows greater dialed in variability. With regard to energy absorption the TFL has been shown to be 4-5 times more effective thus correlating with lower pulsed energies for stone ablation in the in vitro setting.[2,7,11] Lower pulsed energies in conjunction with increased pulse durations allow for less retropulsion with better dusting.[2] The TFL has demonstrable improvements in stone free rates by more readily creating fine dust than can the Ho:YAG and the Ho:YAG-MOSES in in vivo settings.[12] Not to be undone, the Ho:YAG laser has statistically higher ablation rates at slow speeds of 500 mm/min when using approximately identical energies and frequencies.[2] Data suggests that higher ablation rates are more readily obtained at high-powered settings (24W) albeit with increased risk for thermal damage.[13] Moreover, in vivo models suggest increased risk for urothelial tissue injury when using TFL in the absence or ureteral access sheaths owing to increased temperature within the collecting system.[11] At best, current in vivo and in vitro studies lack certain corollary to clinical scenarios however they do suggest an equivalency for tissue temperature damage by either laser modality via high-power low-irrigation settings.[14] When going head-to-head the Ho:YAG has shown superiority with denser calcium phosphate stones.[9] TFL may confer greater stone clearance but has also been found to increase the rate of infectious complications.[15] Other studies have concluded no significant clinical time advantage, stone free rate, complication, or patient related stone quality of life outcomes.[16] Therefore as both lasers confer safety with effectiveness, surgeon preference and institutional preference may dictate technological approach.

Studies have begun to compare TFL to high power holmium with Moses™ technology for ureteroscopy and laser lithotripsy (URSLL), however, data is lacking as to the superior laser technology for medium or large stones approached antegrade in the mini percutaneous nephrolithotomy (PCNL) setting.

Review of the existing literature reveals just two studies from India comparing Ho:YAG versus TFL for mini PCNL: A study in the Indian Journal of Urology from 2022 randomized 125 participants to holmium or TFL, however, this compared 35 watt Ho:YAG laser unit to a Russian TFL unit.[17] A second study from India published in the Journal of Endourology in 2022 was not randomized but had a matched cohort of 51 patients in each group. This also utilized a novel suction sheath limiting applicability. This study demonstrated that TFL produced a greater proportion of fragments >3 mm (36% vs 22.68%, $p = 0.002$). On subset analysis based on stone density, all outcome parameters were comparable except a shorter total operative time with TFL ($p <= 0.05$).[18] To this date, there are no RCTs completed in North America addressing this question.

2 Study Objectives

We propose a prospectively registered single institution, single surgeon randomized controlled trial to specifically evaluate the Boston Scientific Lumenis Pulse™ 120H Moses 2.0 holmium laser versus the Olympus Soltive™ Superpulsed thulium fiber laser (TFL) for medium-to-large stones in the mini PCNL setting. Maine Medical Center (Portland, ME) is unique in that we have both a Lumenis Pulse™ 120H Moses 2.0 holmium laser and an Olympus Soltive™ thulium fiber laser available concurrently in our hybrid operating room and cystoscopy suite for laser lithotripsy.

Comparison of Lumenis Pulse™ 120H Moses 2.0 holmium laser versus Olympus Soltive™ thulium fiber laser for mini-percutaneous nephrolithotomy has three specific aims:

- Evaluate the efficiency (primary outcome: total lasing time) of these two laser energy modalities for the treatment of kidney stones
- Evaluate the efficacy (secondary outcomes: Stone-free rate [SFR], retreatment rate) of these two laser energy modalities
- Evaluate the safety (secondary outcome: adverse events, need for subsequent procedures) of these two laser energy modalities

3 Patients and Methods

3.1 Study Design

3.1.1 General Design

This is a prospectively registered single institution, single surgeon randomized controlled trial to evaluate the Boston Scientific Lumenis Pulse™ 120H Moses 2.0 holmium laser versus the Olympus Soltive™ Superpulsed thulium fiber laser (TFL) for medium-to-large (1-3 cm) stones in the mini PCNL setting. This clinical trial will be registered on clinicaltrials.gov prospectively prior to the initiation of the first consent/recruitment of participants.

3.1.2 Hypothesis

Primary: Our hypothesis is that the Lumenis Pulse P120H holmium laser will have decreased lasing time compared to the Olympus Superpulsed thulium fiber laser.

All Secondary: For evaluated outcomes other than the primary, our hypothesis is that the null hypotheses will not be rejected in comparing the Lumenis Pulse P120H holmium laser and the Olympus Superpulsed thulium fiber laser.

3.1.3 Primary outcome:

The primary outcome will be total laser treatment time measured in minutes and seconds. Total laser treatment time will be total cumulative lasing time.

3.1.4 Secondary and tertiary outcomes:

Secondary outcomes will include stone-free rate, measured on low-dose noncontrast CT imaging approximately 8-12 weeks after surgery. Stone-free status will be defined as no fragments greater than 3 mm in greatest dimension on bone window. Retreatment rate will be defined as participants undergoing URSLL or repeat Mini PCNL for the same stone(s) within 90 days. It will also include total operative time measured in minutes. Operative time will start at time of instrument insertion after positioning and draping and end at instrument removal ("scope-in to scope-out" time). In the case of renal access performed by vascular interventional radiology (VIR), operative time will include procedural time attributed to renal access in the VIR suite plus scope-in to scope out time.

Safety profile and adverse events including estimated blood loss, postoperative labs if available, immediate and delayed complications (Clavien-Dindo classification I-V, see below for grading system), subsequent stone events, emergency department (ED) visits, and need for additional procedures will be measured. Length of stay (hours), same-day ambulatory discharge, subjective pain scores on the numeric rating scale postoperatively and at time of discharge, need for opioid medications at time of discharge will be captured.

Tertiary outcomes measured will be postoperative inpatient opioid utilization (morphine mEq/kg/day [MEDD]), PROMIS pain domain symptom scores at time of stent removal, nonopioid medications prescribed at discharge for pain, and outpatient healthcare resource utilization (HCRU) measured by unplanned calls to clinic for pain/discomfort, requests for refills of opioid prescriptions, and ED visits for genitourinary concerns or pain within ninety (90) days after date of surgery.

3.2 Participant Selection and Withdrawal

3.2.1 Screening and enrollment:

Patients who present for evaluation of kidney stones in the outpatient setting will be screened for eligibility for this study. Patients typically are seen in the office for initial consultation for percutaneous treatment of their kidney stones. This initial consultation is typically performed by the surgeon performing the procedure. Patients undergo evaluation and history gathering in an office examination room, and then, if determination for surgery is made, written consent is obtained at that time. Typically patients without screening lab work undergo pre-screening lab work with BMP and CBC, INR and extended spectrum type and screen prior to surgery as well as a urinalysis and urine culture for preoperative antibiotic selection. The procedure is typically scheduled for six weeks after initial office consultation. Screening for inclusion and participation in the study would occur at the time of outpatient surgical consultation. Informed consent for participation in the study would be obtained at that point if patient met all inclusion criteria

without any exclusion criteria. A standardized eligibility checklist will be utilized to ensure that patient meets all criteria.

Informed consent will be obtained at the time of consent for surgery in the outpatient urologic clinic setting. Either the PI or the research coordinator will conduct the consenting process. Consent will be in written form. A description of the study will be described verbally and will be provided in written form. Patients deemed able to consent for the surgery will have capacity to consent to participation in the study. The consent process will inform a volunteer about the study, indicate the participation is voluntary and he/she/they has the right to stop at any time. Risks will be enumerated in the informed consent form and described verbally during the consent process. All informed consent for the study will be obtained in written hardcopy form and scanned into the patient electronic medical record along with the consent for surgery and eligibility checklist. Hardcopy of the study consent and eligibility checklist will be kept in a locked research cabinet. No compensation will be provided to participants.

3.2.2 Inclusion Criteria:

- Scheduled to undergo mini PCNL for nephrolithiasis
- Stone burden (multiple stones acceptable) with largest stone 1cm – 3cm in greatest dimension on bone window of noncontrast CT within a 6 month preoperative period.
- Able to give informed consent
- Age 21 or older

Regarding stone burden inclusion criteria: We are intentionally not limiting the stone burden to single stone or restrictive stone size or single location to maximize eligibility for participation, acknowledging that this may affect secondary outcomes. The stone burden may include multiple stones in multiple locations but the largest stone should be 1-3 cm in greatest dimension of bone window on the preoperative CT scan within 6 months of evaluation.

3.2.3 Exclusion Criteria:

- Patients scheduled to undergo concurrent non-PCNL procedure such as contralateral ureteroscopy
- Inability to give informed consent
- Age less than 21
- Body Mass Index (BMI) > 45
- Pregnant patients
- Stone burden outside of inclusion criteria range
- Untreated urinary tract infections
- Uncontrolled bleeding disorders and coagulopathy
- Abnormal upper tract anatomy such as presence of ureteral strictures or complete UPJ obstruction
- Patients with urinary diversion such as ileal conduit or neobladder

- Any preexisting medical condition or situation that, in the investigator's opinion, could put the participant at significant risk, confound the study results, or interfere significantly with the participant's participation in the study
- Are currently prescribed buprenorphine or methadone, or carry active diagnosis of chronic opioid use disorder.

3.2.4 Participant Withdrawal

Participants may withdraw from the trial at any point after enrollment by contacting the research team by telephone through Maine Medical Partners Urology office, MyChart message or directly contacting the principal investigator. Prospective data already collected during participation in the study will be maintained in the database for research purposes. No new data will be collected besides reason for withdrawal. The PI may choose to remove a participant from study activities if it is deemed no longer in the participant's best interest to continue. Participants who withdraw or are removed will still receive standard-of-care follow up.

3.3 Study Procedures

Following enrollment, participants will undergo standardized Mini PCNL with plan for overnight observation <24 hours versus ambulatory discharge following the procedure pending postoperative recovery course and achievement of discharge criteria. No procedural changes will be made for study participants. The PROMIS-57 "pain interference and global pain" domains will be administered preoperatively, either at preoperative visit in the office or in the preoperative area prior to surgery (see below for PROMIS description) to collect baseline pain.

Prior to time of~~At time of~~ surgery, ~~following induction of anesthesia,~~ participants will be randomized to Boston Scientific Lumenis Pulse™ 120H Moses 2.0 Holmium or Olympus Soltive™ Superpulsed thulium laser lithotripsy in 1:1 fashion. Randomization will be done in blocks of 4 to account for changes in patient population and laser and will be done using the REDCap randomization module, using an RStudio produced randomization. Participants will be blinded but due to differences in the laser units themselves, the surgeon will not be blinded. The surgeon may switch laser modality (holmium to thulium or vice versa) at any point during the procedure at their discretion as necessary to complete the surgery. This will be recorded if it occurs, however, data analysis will be conducted on an intent-to-treat analysis. Participant blinding will be ensured by concealing the laser unit prior to induction of general anesthesia, as well as textual concealment in the electronic medical record of assigned arm and intervention received.

Mini PCNL is conducted at our institution using the Karl Storz MIP-M set which utilizes a 16/17.5fr metal sheath and 12fr rigid mini nephroscope in the prone split leg position utilizing fluoroscopic access at time of surgery by the urologist with or without endoscopic guidance from retrograde ureteroscopy. Laser lithotripsy is conducted with a 360 micron fiber with dusting, fragmentation, basketing and extraction via the "vortex" effect through the sheath techniques all utilized. Our institution has not yet adopted active suction sheaths during Mini PCNL but should

this technology become available during study activity, utilization would be applicable to all participants undergoing the procedure and usage data will be collected. Stone fragments will be sent from all participants for both chemical composition and stone microbial culture.

Laser settings will be initially defaulted to roughly equivalent settings between the holmium and TFL systems. Initial expected range of laser settings for both laser systems is 1-2 joules and 20-10 hertz (average 20 watts) as primary fragmentation settings and 0.3-0.4 joules and 70-50 hertz for dusting (average 20.5 watts), but settings may be changed during the procedure at the surgeon's discretion to best treat the stone(s). These settings are considered standard-of-care and well within the standard safe operating range for energy, frequency and peak power of both laser devices. Surgeons routinely change settings to optimize laser lithotripsy based on stone type and the observed response to laser energy. Chosen initial settings are based on routine fragmentation and dusting settings in the literature and in practice.

Pulse-width and specialized settings such as Moses™ Distance and Moses™ Contact will be utilized at the surgeon's discretion. This will be recorded using the electronic medical record with paper backup which will list the initial power setting, the number of switches made during the procedure, and joules, hertz, time, and total kilojoules utilized.

Following treatment of the stone(s), a double J ureteral stent will be placed with sizing at the surgeon's discretion. Participants will undergo standard-of-care postoperative treatment, and when meeting discharge criteria will be discharged to home. Cystoscopic stent removal will be performed in the office 7-14 days following surgery, and participants will complete the Patient-Reported Outcomes Measurement Information System (PROMIS)measures for pain intensity, behavior and interference.[19] PROMIS is a validated series of self-reporting questionnaires developed by the US Department of Health and Human Services (DHHS) to evaluate quality of life in various physical, mental and social domains. The PROMIS-57 "pain interference and global pain" domains will be utilized.

Follow-up imaging after PCNL is considered standard-of-care to evaluate for residual stone fragments and to rule out silent (painless) hydronephrosis and other postoperative complications. While exact imaging choice and timing is left to the discretion of the provider per 2012 American Urologic Association guidelines, the preferred modalities are plain film abdominal x-ray (KUB) and retroperitoneal US (RBUS) together or noncontrast CT abdomen pelvis (NCCT). The gold standard for follow-up imaging is NCCT for both accurate sizing of residual stone and anatomic detail of the kidneys as well as detection of surgical complications such as hydrothorax, effusion, hematoma etc. RBUS has been shown to overestimate the size, position and number of stones. Additionally, the Journal of Endourology has recently announced that manuscripts presenting stone-free-rates must be based on noncontrast CT scans with 2 to 3 mm cuts.[20] Other journals are expected to follow suit.

Our clinical practice has evolved with the shift toward ambulatory PCNL and mini PCNL. Traditionally patients would be observed overnight with NCCT on postoperative day 1. With an increased number of patients being discharged from the recovery room, immediate follow-up

NCCT is less common, with interval follow up imaging in the form of KUB and RBUS or NCCT occurring 8-12 weeks after surgery.

Our study protocol imaging will mimic current clinical practice and standard-of-care. For patients who are discharged without NCCT being performed while inpatient, a NCCT will be performed approximately 8-12 weeks after surgery to determine stone free status. In the event that a CT scan is performed while inpatient following surgery, follow up imaging modality will be at the discretion of the PI (i.e., a participant with a CT scan immediately postoperatively while inpatient showing no residual stone may undergo other imaging such as retroperitoneal ultrasound 8-12 weeks after surgery to assess for silent hydronephrosis). While it is possible that this imaging protocol might possibly introduce bias through heterogeneity of imaging for participants, it is a pragmatic approach that prioritizes patient safety (CT scan immediately postoperatively if necessary) while maximizing opportunity for ambulatory discharge if the patient meets criteria and reduction of radiation exposure through minimizing repeat CT scans. As the depicted follow-up imaging protocol is standard-of-care, the radiologist reading any studies performed will not be part of the research team and will not be blinded to the intervention received.

Participants will be followed for 90 days postoperatively to capture any surgical complications, subsequent stone events, emergency department visits, need for additional procedures, refills for pain medications, or telephone calls to clinic. The application of 90 day follow-up will likely be a straightforward endeavor as typically patients are followed beyond 90 days as standard-of-care. The Clavien-Dindo classification of surgical complications[19] is a widely used standardized grading system to evaluate and report surgical complications encountered (See Risks to Participants).

Stent removal typically occurs 7-14 days after the primary procedure. Follow-up imaging protocol is depicted above. Postoperative follow-up visit typically occurs the same day as imaging or shortly thereafter, with the primary surgeon (the principal investigator) in the office to review. The vast majority of these patients undergo metabolic testing for their kidney stone disease and 24 hour urinalysis and serum labs is obtained 1-3 months after primary procedure with office visit to review. This follow up is considered standard-of-care, billed normally, and research activities do not add any additional financial or healthcare resource burden. After 90 day follow up and completion of all study activities, participants may request documentation of the intervention they received.

3.3.1 Summary of standard-of-care vs research activities:

Standard-of-Care	**Research Activities**
Preoperative evaluation and counseling	
Informed written consent for procedure	
	Informed written consent for study participation
	Completion PROMIS-57 Pain interference and global pain validated questionnaire preoperatively
Preoperative urine culture and serum labs	
Preoperative antibiotics as indicated	
Perioperative anesthesia evaluation and general anesthetic plan	
Perioperative antibiotics	
Mini PCNL procedure	
	Block randomization of laser device utilized prior to~~during~~ procedure as described
Post Anesthesia Care Unit (PACU) orders	
Chest x-ray in PACU	
Ambulatory discharge vs. observation overnight	
Postoperative low dose CT abdomen pelvis while inpatient if concern for residual stone burden	
Office cystoscopy and stent removal in office 7-14 days postoperatively	
	Completion PROMIS-57 Pain interference and global pain validated questionnaire at time of stent removal
Postoperative imaging 8-12 weeks after surgery to rule out silent obstruction and evaluate residual stone burden: CT abdomen pelvis *or* Renal US if CT previously performed	
Metabolic stone workup including serum labs and 24 hour metabolic urinalysis 8-12 weeks postoperatively with follow up visit	

3.3.2 Feasibility:

The completion of this study is highly likely as a majority of study procedures are already standard-of-care and much of the data can be captured through the electronic medical record.

Participant accrual will be the primary consideration. The wide eligibility criteria will maximize patient screening and potential enrollment.

Mini PCNL is a relatively new modality at Maine Medical Center and as such, there is limited data to determine baseline screening volume for enrollment. Additionally, PCNL case volume has been skewed by the COVID-19 pandemic, where most elective PCNLs were deferred from 2020 – 2022. Review of Pre-COVID-19 PCNL case volume at our institution yielded approximately 100 annual cases, and we estimate that the approximately 25-33% of these cases would have been eligible for mini PCNL. As the study has a minimal risk profile (randomization to two accepted standard-of-care modalities), we anticipate high enrollment from screened patients.

A review of our initial 180 days of PCNL cases was performed, starting in September 2022. 10 Mini PCNLs were completed in the time interval. Accounting for ramp-up and increasing referrals, 25 Mini PCNLs are expected yearly. Assuming 100% of these patients are screened and 80% consent, 20 subjects are expected to be enrolled yearly. Accounting for 5-10% drop out rate, we conservatively anticipate the accrual period to last 36 months.

3.3.3 Risks to participants:

As both the interventions are currently FDA approved for the indication of nephrolithiasis (ICD10 N20.0) and are utilized as standard-of-care lithotrites during ureteroscopy (URS), percutaneous nephrolithotomy (PCNL) and Mini PCNL, the risks and potential complications intraoperatively and postoperatively are not unique to study participants alone.

Complications after laser lithotripsy may include infection, sepsis bleeding, pain, inflammation, tissue necrosis, perforation or death.

Complications after mini PCNL may also occur and may include infection, sepsis, bleeding, pain, inflammation, damage to adjacent structures such as lung (hemothorax, pneumothorax, hydrothorax), liver, spleen, or colon, need for secondary procedures, perforation or death.

These complications may occur regardless of participation in the research study. Management of these complications may require outpatient, inpatient care or secondary procedures.

The non-standard-of-care risks would be any event introduced by randomization. In this study, it is possible that one intervention is superior and participants could be randomly assigned to the inferior group. Additionally, participation includes the risk of protected health information (PHI) being seen by individuals who are not involved with the study. We aim to mitigate this risk with a comprehensive data safety plan (see “Data Safety Plan”).

3.3.2 Adverse Events, Serious Adverse Events, and Unanticipated Problems

The definition of Adverse Events (AEs), Serious Adverse Events (SAEs) and Unanticipated Problems (UPs) will conform to the Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP) and HHS regulations 45 CFR part 46.

DHHS/OHRP defines AEs as "any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research."

SAEs are defined as "any untoward medical occurrence that meets any of the following criteria:

- Results in death
- Is life-threatening (The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. [Explanatory text from ICH E2A])
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect [Bullets 1-5 from ICH E2A and E6]

In addition, an important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed in this definition."

UPs are defined as "in general, to include any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research);
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Protocol specific examples of AEs, SAEs and UPs:

Adverse Events (AEs)	**Serious Adverse Events (SAEs)**	**Unanticipated Problems (UPs)**
Bleeding or injury from laser lithotripsy	Bleeding requiring vascular intervention	Device malfunction or device-related adverse event
Observed pneumothorax	Pneumothorax, abscess, etc. requiring drainage	Laser product non-conformity such as laser fiber breakage
UTI	Sepsis requiring ICU level care	
Acute kidney injury	AKI requiring dialysis	
ED visit or readmission for observation (pain, UTI, hematuria, etc.)	Death	
All other Clavien-Dindo grade II complications	All other Clavien Dindo IIIb or greater complications	

Clavien-Dindo classification of surgical complications: [21]

Grade	**Definition**
Grade I	Any deviation from the normal post-operative course not requiring surgical, endoscopic or radiological intervention. This includes the need for certain drugs (e.g. antiemetics, antipyretics, analgesics, diuretics and electrolytes), treatment with physiotherapy and wound infections that are opened at the bedside
Grade II	Complications requiring drug treatments other than those allowed for Grade I complications; this includes blood transfusion and total parenteral nutrition (TPN)
Grade III	Complications requiring surgical, endoscopic or radiological intervention Grade IIIa - intervention not under general anesthetic Grade IIIb - intervention under general anesthetic
Grade IV	Life-threatening complications; this includes CNS complications (e.g. brain hemorrhage, ischemic stroke, subarachnoid hemorrhage) which require intensive care, but excludes transient ischemic attacks (TIAs) Grade IVa - single-organ dysfunction (including dialysis) Grade IVb - multi-organ dysfunction
Grade V	Death of the patient

Due to the small prospective study size, monitoring of AEs, SAEs and UPs will be conducted weekly and as issues arise by the PI or the research team. Any AEs that are possibly related to participation in the study as well as any SAEs or UPs will be documented in a secure electronic file and a report will be made to the IRB and the sponsoring institution (Maine Medical Center) promptly (within 5 days for SAEs and within 14 days for AEs or UPs). Reports will include actions the sponsoring institution and the PI is taking or plans to take to address the problem (e.g., revise the protocol, suspend participant enrollment, terminate the research, revise the informed consent document, inform enrolled participants, increase monitoring of participants, etc.).

Any device malfunction, device-related adverse events and product nonconformities that are identified will be reported to the respective device manufacturer as well as the IRB and sponsoring institution as above. The research coordinator will prepare reports that list AEs, SAEs, deaths, and disease-or treatment-specific events including device causality required for review in order to ensure good clinical care and identify any emerging trends.

Participants' electronic medical records will be appropriately marked as participating in the research trial. Urology housestaff and an attending urologist are on call 24 hours a day. The PI will be available 24/7 in case any study-related issues arise. The written informed consent as well as preoperative visit and postoperative discharge summary contain telephone contact information for the urology office and after-hours answering service. Participants will be encouraged to reach out via telephone to the office or answering service for any clinical concerns or questions regarding the study. AEs that are possibly related to participation in the study as well as any SAEs or UPs that occur after hours will be reported to the PD/PI promptly by the urology housestaff or attending urologist covering.

3.3.5 Data Safety Plan:

A minimum of PHI (protected health information) that might identify patient participation will be collected for data integrity purposes. PHI will be used exclusively for coding the data. HIPAA identifiers that will be collected include first name, last name, medical record number (MRN) and date of birth. Data will be collected in a Maine Medical Center / MaineHealth Institute for Research (MHIR) encrypted REDCap® database. All data points will be collected electronically and from abstracted from the Epic electronic medical record to the REDCap® database. Completed written consent forms will be housed in a locked cabinet in Maine Medical Partners Urology research office with access limited to key personnel.

Data fields to be captured can be found in the data dictionary and data fields forms, for a total of approximately 290 variables to be abstracted manually from free text or automated reports from the electronic medical record.

3.4 Statistical Plan

3.4.1 Sample Size Determination

The primary outcome measure is lasing time. In the prior year, patients undergoing laser lithotripsy at this institution had a lasing time of approximately 10±2 minutes. Using these parameters, a sample size of 48 participants (24 in each study arm) is needed to detect a difference in lasing time of 16% by two sided t-test with 80% power and alpha=0.05 (calculated using R version 4.3.1). To account for dropout after enrollment, as well as the potential for switching lasers mid-procedure if deemed necessary, 52 participants (26 in each arm) are planned to be enrolled in the study. This number was chosen due to preliminary estimations of case volume based on eligibility criteria that showed this to likely be the maximum number of

participants able to be enrolled in a viable study interval such that the study could still be successfully completed in a timely manner. Time is of the essence, as laser technology is rapidly changing in urology and protracted enrollment over 36 months will potentially reduce the impact the findings may have on clinical practice patterns. Based on clinical judgment we estimate a lasing time reduction of 16% (approximately 1.5 minutes when using holmium laser vs. thulium laser) may be detected at minimum in accordance with the selected sample size.

3.4.2 Statistical Methods

We will first summarize our data descriptively, both overall and after stratification by assigned study arm (Thulium laser vs. Holmium laser). Continuous variables will be shown as mean and standard deviation or median and interquartile range, as appropriate. In assessing distributions, we will use the Shapiro-Wilk or Kolmogorov-Smirnov test for normality, as appropriate. Categorical variables will be as frequency (n, %).

We will evaluate differences in lasing time (primary outcome measure) by two tailed t-test or Mann Whitney U test, as appropriate; significance will be accepted at $p<0.05$. These comparisons will be made using an intention-to-treat analysis and then explored by per-protocol analysis. We will evaluate differences in our secondary outcome measures using two tailed t-tests or Mann Whitney U tests (continuous variables) and by chi square or Fisher's exact test (categorical variables), as appropriate. Significance of these latter analyses will be interpreted after Bonferroni's correction for multiple comparisons.

As this is a randomized study, we do not anticipate any differences in key clinical, procedural and demographic variables between the two study arms. However, should potential differences be observed, we will explore differences between the two study arms using the above tests. We will then use a general or generalized linear regression model (depending on the distribution of lasing time) to adjust the difference between study arms for covariates that are significantly different ($p<0.1$) between the two study arms, as well as independently found to be associated with the primary outcome interest: lasing time.

4 Data Handling and Record Keeping

4.1 Confidentiality

All patient information taken from Epic will be stored in MaineHealth REDCap and will only be accessible to study personnel. PHI identifiers will be kept in a separate data entry form and will be marked as PHI identifiers and will be granted the extra layer of privacy that it entails.

4.2 Records Retention

The master list will be kept until data validation is completed directly prior to data analysis. All other study data will be maintained for at least 6 years following manuscript publication, following federal requirements for maintain this information.

4.3 Regulatory Binder

A regulatory binder will be maintained for this study on a password protected computer and will only be accessible while on the MaineHealth network. This will include all IRB and scientific review committee submission forms, consent forms obtained from participants, adverse event documentation, delegation of responsibilities for research staff and all other information pertinent to this study. This binder will only be accessible to research personnel.

5 Study Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the MMC IRB, the sponsor (if applicable), government regulatory bodies, and MMC IRB research compliance and quality assurance (SEQuR) of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable MMC IRB compliance and quality assurance offices.

6 Budget

The Boston Scientific Corporation Investigator-Sponsored Research (ISR) Program grant will be used to support the time and effort of a research coordinator as below. The requested budget for this trial is $54,975. Please see attached budget breakdown.

6.1 Direct Costs:

Research Coordinator time and effort: Evelyn James, Clinical Research Coordinator will assist with recruitment, perform consent of participating patients, and ensure compliance with the protocol. They will be responsible for entry and management of study data, maintenance of the database, retrospective chart review, and adherence to IRB and data management protocols. Year one will include protocol development, IRB navigation, and implementation of the study in clinic and OR, in addition to ongoing responsibilities, hence the larger time commitment in year one.

6.2 Indirect Costs:

Indirect cost type: Modified Total Direct Costs. Negotiated Clinical F&A rate for Maine Medical Center is 28.0%. Cognizant Federal Agency is DHHS, Michael Stanco, 212-264-2069.

7 Publication Plan

We aim to publish our findings in the Journal of Endourology, a peer-reviewed journal focused on endourology and robotic urology, applications and clinical outcomes with an impact factor of 2.6. Findings will be submitted to sectional, national and international conferences such as the New England Section of the American Urologic Association, the AUA itself, as well as the World Congress of Endourology (WCE). The ROCK (Research on Calculus Kinetics) Society will also be engaged as a potential venue for presentation of our findings.

Study accrual is conservatively anticipated to last 36 months and tentatively complete December 31, 2026. We estimate preliminary findings to be available April 2027 with aim for abstract submission to the World Congress of Endourology and New England Section of the AUA in April and May 2027, with manuscript completion summer 2027.

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6 Attachments

All other documents can be found in the IRBNet package in the MaineHealth IRB.