Characterization and Evaluation of New Technologies for the Management of Urinary Stones with Laser Lithotripsy. Preclinical and Clinical Research.

PhD Thesis

Programa de Doctorado en Ciencias Médicas y
Farmacéuticas, Desarrollo y Calidad de Vida

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"If I have seen a little further it is by standing on the shoulders of giants."

Isaac Newton, 1676.

On a letter to Robert Hooke, speaking about his own research in light diffraction and how his own theories built upon those of Descartes.

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To all the people who have given me love. Thanks for your support. To all the people who have made it difficult for me. Thanks for helping me grow.

Thanks to LIFE.

CERTIFICATIONS

D. David M. Castro Díaz, Professor of Urology at the Faculty of Health Sciences of the University of La Laguna,

Certifies:

That Ms. Begoña Ballesta Martínez, a graduate in Medicine, has carried out under my supervision the Research Work corresponding to the PhD: "**Characterization and Evaluation of New Technologies for the Management of Urinary Stones with Laser Lithotripsy. Preclinical and Clinical** " which has ended with the greatest use and will be presented to qualify for the degree of Doctor of Medical Sciences from the University of La Laguna. After reviewing the report, I believe that it faithfully corresponds to the results obtained, and I am satisfied with its presentation to be judged by the designated panel for its reading. And for the record and take the appropriate effects in compliance with current provisions, I extend and sign this certificate.

D. **Manuel F. Ravina Pisaca**, Associate Professor of Urology at the Faculty of Health Sciences of the University of La Laguna,

Certifies:

That Ms. Begoña Ballesta Martínez, a graduate in Medicine, has carried out under my supervision the Research Work corresponding to the PhD: "**Characterization and Evaluation of New Technologies for the Management of Urinary Stones with Laser Lithotripsy. Preclinical and Clinical** " which has ended with the greatest use and will be presented to qualify for the degree of Doctor of Medical Sciences from the University of La Laguna.

After reviewing the report, I believe that it faithfully corresponds to the results obtained, and I am satisfied with its presentation to be judged by the designated panel for its reading.

And for the record and take the appropriate effects in compliance with current provisions, I extend and sign this certificate.

Dr. Otaš Durutović, Associate Professor of the University of Belgrade, Clinic of Urology, Serbia

Certifies:

That Ms. Begoña Ballesta Martínez, a graduate in Medicine, has carried the Research Work corresponding to the PhD: "**Characterization and Evaluation of New Technologies for the Management of Urinary Stones with Laser Lithotripsy. Preclinical and Clinical** " which has ended with the greatest use and will be presented to qualify for the degree of Doctor of Medical Sciences from the University of La Laguna.

After reviewing the report, I believe that it faithfully corresponds to the results obtained, and I am satisfied with its **International Mention.**

And for the record and take the appropriate effects in compliance with current provisions, I extend and sign this certificate.

Dr. Achilles Ploumidis, MD PhD Urology Consultant at Athens Medical Centre

Certifies:

That Ms. Begoña Ballesta Martínez, a graduate in Medicine, has carried the Research Work corresponding to the PhD: "**Characterization and Evaluation of New Technologies for the Management of Urinary Stones with Laser Lithotripsy. Preclinical and Clinical** " which has ended with the greatest use and will be presented to qualify for the degree of Doctor of Medical Sciences from the University of La Laguna.

After reviewing the report, I believe that it faithfully corresponds to the results obtained, and I am satisfied with its **International Mention.**

And for the record and take the appropriate effects in compliance with current provisions, I extend and sign this certificate.

Clarification note for the panel:

Despite the present PhD Thesis is not presented as a compilation of articles but as a traditional PhD Thesis, 2 papers (1,2), and 1 abstract (3) have been published by the author Ms. Begoña Ballesta Martínez while she was a student of the Doctoral School. The rest of data presented in the current Thesis is aimed to be published in indexed journals of the field.

Begoña Ballesta Martínez, sponsored by the European Association of Urology (EAU), the European Urological Scholarship Program (EUSP) and the Section of Urolithiasis of the EAU, EULIS, completed a fellowship at an internationally prestigious research centre, the University Hospital of Patras, Greece, where non all but many of the experiments presented in the current PhD Thesis were performed there alongside the team lead my Prof. Evangelos Liatsikos and Ass. Prof. Panagiotis Kallidonis.

Other experiments were conducted at Royal Perth Hospital, Western Australia, Australia, with remote supervision of Prof. David M. Castro Díaz, Ass. Prof. Manuel F. Ravina Pisaca, Prof. Evangelos Liatsikos and Ass. Prof. Panagiotis Kallidonis.

Ethics approval for the clinical study was obtained in Patras, Greece, where it was conducted.

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HIV = Human Inmunodeficiency Virus

CT = Computed Tomography

EAU = European Association of Urology

Ho:YAG = Holmium: yttrium aluminum garnet

TFL = Thulium Fiber Laser

J= Joules

Hz= Hertz

W= Watts

HU = Hounsfield Units

AR= Ablation Rates

Fr= French

KUB= Kidney, ureter and bladder

INTRODUCTION

Classification, epidemiology and risk factors for urinary calculi

Urinary tract stones (urolithiasis) are composed of inorganic and organic crystals amalgamated with proteins (4). Diverse solutes within the urine may crystallise and form urolithiasis subsequently (4).

Urolithiasis can be classified according to size, location, X-ray features, aetiology of formation, composition, and risk of recurrence. The classification by aetiology results by diving them into those caused by infections and non-infectious causes such as genetic defects or adverse drug effects (drug stones) (5). Infection stones include magnesium ammonium phosphate, highly carbonated apatite and ammonium urate; non-infection stones include calcium oxalate, calcium phosphate, uric acid and ammonium urate; and stones caused by genetic causes include cystine, xanthine and 2,8-Dihydroxyadenine (5).

Urolithiasis is one of the most common conditions affecting nearly all populations (6). It is a worldwide problem which is known to be associated with overall health and socioeconomic burdens (4,6–9).

The prevalence rates for urinary stones formation vary from 1% to 20% according to published reports (5,10,11). The incidence of urinary calculi depends on geographical, climatic, ethnic, dietary, and genetic factors (5). Wealthy nations such as The United States of America, Canada or Sweden show high renal stone prevalence (> 10%).

A rise of more than 37% in the burden of urolithiasis has been reported in some areas during the past 20 years (10,12,13). This rise at the burden of urinary calculi rose happened in most nations or territories (8). This resulted in nearly 50% increase in the total expenditure for diagnosis of nephrolithiasis disease up to 2.1 billion US dollars from 1994 to 2000 (14). The age-standardized rates of the urolithiasis incidence and disability-adjusted life years were 1,394.03/100,000 and 7.35/100,000, respectively, in 2019. Both, the age-standardized rates of incidence and disability-adjusted life years of urinary stones fell from 1990 to 2019. It showed estimated annual percental changes of −0.83 and −1.77, respectively. Males have shown a higher burden of stone disease than females (8). The highest incidence of urolithiasis has been registered in the 55–59 age group (9). In 2019, the highest burden of urinary calculi was observed in areas with high–middle sociodemographic index, particularly in Eastern Europe, Central Asia, and Southeast Asia. The age-standardized mortality rate of kidney stones was 0.17/100,000 in 2019 (9).

Several factors have been linked to the risk of stone formation. These include (5,6,9,15–28):

- Early onset of urolithiasis (especially children and teenagers)
- Family history of stone disease
- Recurrent stone formers
- Short time since last stone episode of urolithiasis
- Brushite-containing stones
- Uric acid and urate-containing stones
- Infection stones
- Chronic kidney disease
- Certain conditions such as hyperparathyroidism
- Metabolic syndrome
- Mineral bone disorder

- Nephrocalcinosis
- Polycystic kidney disease
- Gastrointestinal diseases (i.e., jejuno-ileal bypass, intestinal resection, Crohn's disease, malabsorptive conditions, enteric hyperoxaluria after urinary diversion, exocrine pancreatic insufficiency)
- Bariatric surgery
- Increased levels of vitamin D
- Sarcoidosis
- Spinal cord injury
- Neurogenic bladder
- Cystinuria (type A, B and AB)
- Primary hyperoxaluria
- Renal tubular acidosis type I, 2,8-dihydroxyadeninuria
- Xanthinuria
- Lesch-Nyhan syndrome
- Cystic fibrosis
- Certain drugs including allopurinol/oxypurinol, allopurinol/oxypurinol, amoxicillin/ampicillin, ceftriaxone, quinolones, ephedrine, indinavir and other HIV-protease inhibitors, magnesium trisilicate, sulphonamides, triamterene, amoxicillin/ampicillin, ceftriaxone, quinolones, ephedrine, indinavir and other HIV-protease inhibitors, magnesium trisilicate, sulphonamides and triamterene.
- Anatomical abnormalities including medullary sponge kidney (tubular ectasia), ureteropelvic junction (UPJ) obstruction, calyceal diverticulum,

calyceal cyst, ureteral stricture,vesico-uretero-renal reflux, horseshoe kidney, ureterocele, environmental and professional factors, high ambient temperatures, chronic lead and cadmium exposure (5,6,9,15–28).

The data suggests a relationship between kidney stones and an increased risk of chronic Kidney disease (29). Risk factors for chronic kidney disease in stone formers are female gender, overweight, frequent urinary tract infection, struvite stones, acquired single kidney, neurogenic bladder, previous obstructive nephropathy and ileal conduit (5).

More effective and appropriate medical and health policies are needed for prevention and early management of urolithiasis (8).

Diagnosis

Standard assessment of any patient with clinical suspicion of stone disease includes a detailed medical history and physical examination(5,30). Patients with ureteric stones normally present with loin pain, vomiting, and occasionally fever(5). However, these patients with ureteric stones may also be asymptomatic (5,31). Urgent evaluation including blood and urine tests together with imaging is indicated in patients with solitary kidney, fever or when there is doubt regarding the presence renal colic (5). Nonetheless, pain relief and other emergency measures, should not be delayed by imaging assessments. Ultrasound is safe, as it avoids risk of radiation, it is reproducible and cheap. It is recommended to be used as the primary diagnostic imaging test (5,30,32,33). It can identify stones located in the renal pelvis, calyces, and pyeloureteric and vesico-ureteral junctions, if it is performed with filled urinary bladder and hydronephrosis (5). The finding of moderate or severe dilation in the upper urinary tract in patients presenting with renal colic is highly specific for the presence of any calculus, and the presence of any hydronephrosis suggests the presence of a larger stone, usually larger than 5mm (32). However, point-of-care ultrasound shows modest accuracy for diagnosing nephrolithiasis (32). For ureteric stones diagnostic accuracy shows sensitivity of 45% and specificity of 94%; and sensitivity of 45% and specificity of 88% for renal stones (34,35). Kidney-ureter-bladder radiography has sensitivity of 44% and specificity of 77% (5,36). However, it only shows radiopaque stones. Therefore, it is helpful in differentiating radiolucent and radiopaque calculi (5).

Non-contrast-enhanced computed tomography (CT) is the current gold standard imaging tool for diagnosing acute flank pain and has replaced intravenous urography (5,37). It provides information of the diameter and density of the stone. Non-contrast-enhanced CT scan can detect uric acid and xanthine stones, which are radiolucent on Kidney-ureter-bladder radiography, but Non-contrast-enhanced CT scan not indinavir stones (38). Indinavir urolithiasis are stones formed in patients receiving indinavir sulfate for the management of HIV-AIDS which are composed either of indinavir or indinavir and other substances (39). Non-contrast-enhanced CT provides additional of the stone´s features besides the location. It assesses features that will determine the treatment selection such as stone density, inner structure, skin-to-stone distance, and the rest of the anatomy (5). Low-dose CT lowers the risk of radiation (5,40–42), and achieves diagnostic accuracy close to that of standard-dose CT (43), around 93.1% and a specificity of 96.6% (44). Low-dose CT and Ultra-low-dose CT provide effective methods of identifying and characterizing urolithiasis. High diagnostic accuracy, sensitivity, and specificity are maintained with the benefit of significant radiation dose reduction compared to standard dose CT. This is of particular advantage in young patients with recurrent stones disorder (40).

Management Options for Interventional Treatment

Most patients with urinary stones present to the emergency department with typical colic symptoms. Non-obstructive urolithiasis in the renal calices usually are asymptomatic. Ureteral stones smaller than 6mm may pass spontaneously. Sufficient pain management is mandatory in acute renal colic. Medical expulsive treatment, usually with α-receptor antagonists, is recommended to support stone passage and reduces the need for analgesia (5).

In case of sepsis with obstructing stones, antibiotics and percutaneous drainage or ureteral stenting is advice urgently in order to decompress the collecting system. In those cases, definitive treatment must be delayed until sepsis is resolved (5).

The interventional treatment of urolithiasis is individualised for each patient and based on many parameters (5). The treatment choice depends on the stone features (size, number, location, morphology, shape, volume, mobility, and hardness), the anatomy of the patient and compliance of the entire pelvic-calyceal system and other characteristics of the patient such as age, pregnancy, comorbidities, treatment with blood thinners and others (5).

Currently, there is a substantial deficiency of comparative clinical data to develop enhanced algorithms using parameters other than calculi size and composition (5).

Treatment Modalities

The treatment of urolithiasis in the upper urinary tract is divided according to the location of the stone in ureteric stones and renal stones. Within the kidney, management options are divided according to location and size. Likewise, there are some special cases worth to consider separately such as the paediatric population, pregnant women, obese patients, radiolucent stones and patients with horseshoe kidney.

Ureteric Stones

Overall, stone free rates after extracorporeal shock wave lithotripsy or ureteroscopy for ureteric calculi are comparable, but larger stones achieve earlier stone clearance status with ureteroscopy (5). Only 12% of patients needed further intervention after ureteroscopy in comparison to 26% in the extracorporeal shock wave lithotripsy group in a large multi-centre non-inferiority trial which compared ureteroscopy to extracorporeal shock wave lithotripsy for ureteric stones (45).

Despite the complication rate and morbidity of ureteroscopy has dropped significantly in the current endourological era (46), compared with shock wave lithotripsy, ureteroscopy was associated with greater complication rates and longer hospital stay (47).

Ureteroscopy can be performed in patients with bleeding disorders, with a moderate increase in complications (5).

It has been demonstrated that ureteroscopy is a safe option in obese patients with body mass index greater than 30 kg/m^2. Nevertheless, in morbidly obese patients with body mass index greater 35 kg/m^2 the overall complication rates double (48).

Renal Stones

Size and location determines management algorithms for kidney stones.

Renal Stones larger than 2 cm

In 2016 the EAU Guidelines on Urolithiasis amended an algorithm which is still vigent up to date, where percutaneous nephrolithotomy is the first line option for stones larger than 2 cm if not contraindicated at any location within the kidney, being external shock wave lithotripsy and retrograde intrarenal surgery, both second option of choice (5).

Renal Stones between 1 and 2 cm

Stones measuring less than 2 cm but more than 1 cm are divided into any location within the kidney, on the one hand, and the lower calyx, on the other hand.

For those stones measuring less than 2 cm but more than 1 cm located in the lower pole, unfavourable features for external shock wave lithotripsy must be assessed before deciding treatment (5).

These unfavorable features for external shock wave lithotripsy include:

- Shockwave-resistant stones
- Steep infundibular-pelvic angle
- Long lower pole calyx (>10mm)
- Narrow infundibulum (<5mm)

If at least one unfavorable factor is present, endourology is the treatment of choice (5). If none of them is present either endourology or external shock wave lithotripsy are first treatment option equally (5).

From 2016 on those stones located at any location except the lower calyx, are recommended to be managed with either endourology i.e. percutaneous nephrolithotomy or retrograde intrarenal surgery, or external shock wave lithotripsy as first line options according to the EAU Guidelines (5). The rationale behind the change of perspective was that a systematic review and metanalysis was published by Zheng C. and collaborators in July 2015 (49) where they included 7 studies and 983 patients comparing retrograde intrarenal surgery and external shock wave lithotripsy for the treatment of renal stones measuring between 1 and 2 cm. The review resulted in higher stone free rates and lower retreatment rates for retrograde intrarenal surgery with similar complication rates. However, the analysis had important limitations. 5 out of the 7 studies included referred to lower pole stones, which is a well-established limitation of shock wave lithotripsy, and 1 out of the 2 studies not referring to lower pole was based on radiolucent stones, which is another well-established limitation of shock wave lithotripsy. The only study non rereferring neither to lower pole stones nor radiolucent stones was that published by Okan Bas and collaborators in 2014 (50). The study was a retrospective review that included 149 patients subjected to shock wave lithotripsy, retrograde intrarenal surgery or percutaneous nephrolithotomy for 1-2cm stones in the renal pelvis. The shock wave lithotripsy cohort included 52 patients. The retrograde intrarenal surgery cohort included 47 patients. Stone free rate was 86% (after 2.6 sessions) for the shock wave lithotripsy cohort and 91.4% for the retrograde intrarenal surgery cohort. Complications were registered in 7.6% patients of the shock wave lithotripsy cohort including 2 patients with renal cholic, 1 hematoma and 1 steinstrasse. Complications were recorded in 6.3% patients in the retrograde intrarenal surgery cohort. 1 patient had collective system perforation, and 2 had fevers port treatment. The study concluded that there were no significant differences between treatments. Thus, from 2016 on kidney stones located at any location except the lower calyx, can be managed with either endourology i.e. percutaneous nephrolithotomy or retrograde intrarenal surgery, or external shock wave lithotripsy as first line options according to the EAU Guidelines (5).

Renal Stones smaller than 1 cm

For stones~~,~~ smaller than 1 cm at any location within the kidney, both external shock wave lithotripsy and retrograde intrarenal surgery are first line treatment, and percutaneous nephrolithotomy is the second option of choice (5,51). Active treatment is not necessary when no indications for stone removal are present i.e. stone growth; stones in high-risk patients for stone formation; obstruction caused by stones; infection; symptomatic stones (e.g., pain or haematuria) ; stones > 15 mm; patient preference/ choice of treatment; patient comorbidity or social situation of the patient (e.g., profession or travelling) (5). Nonetheless, these recommendations are not supported by high-level evidence (52).

Special Cases

- Pediatric population

The incidence of urolithiasis in the pediatric population has risen significantly in recent years and affects 2% of children (53,54). Extracorporeal shockwave lithotripsy was recommended as the first-line treatment for kidney and proximal ureteral stones < 2 cm in the pediatric population in recent years(53). However, in the recent updates of the EAU Guidelines on pediatric urology recommend either extracorporeal shock wave lithotripsy, retrograde intrarenal or percutaneous nephrolithotomy for pelvic stones between 1 and 2 cm (55). Several studies have proved the safety and efficacy of flexible ureteroscopy in the pediatric population (56,57), and other series have compared retrograde intrarenal surgery and extracorporeal shock wave lithotripsy for the treatment of upper tract urinary stones in children (53,58). Retrograde intrarenal surgery has shown a higher single-session Stone free rate than external shock wave lithotripsy without morbidity (53).

For stones smaller than 3 mm, observation is the first option (55). For staghorn calculi, lower pole stones larger than 1 cm and pelvic stones larger than 2 cm the first line option if non contraindicated is percutaneous nephrolithotomy (55). Shock wave lithotripsy is the first recommended option for pelvic stones smaller than 1 cm and upper ureteric stones (55). Distal stones are recommended to be managed with ureteroscopy as first line treatment option (55).

- Pregnancy

Urolithiasis in pregnant women presents a complex clinical scenario requiring engagement between the patient, urologists, obstetricians, radiologists, and anesthesiologists, with as well careful consideration of the benefits and drawbacks of any diagnostic test or intervention is critical (59). Clinical decisions must be individualized. Observation is the best option for most patients (59); experience with alpha-blocker therapy in this setting remains limited. When active treatment is indicated, temporary drainage of the urinary tract with ureteral stent placement or percutaneous nephrostomy tube might be considered with frequent exchanges (59). The safety of ureteroscopy for stone removal in pregnant patients is not significantly different from the safety of that procedure in nonpregnant patients and in each cohort the complication rate is low (60). Therefore, ureteroscopic stone removal may reasonably be considered appropriate option, even first line according to some authors (60), in pregnant patients with stone disease, particularly in the second trimester (59).

- Obese patients

Body Mass Index is an independent predictor of success for shock wave lithotripsy (61). Obese patients show significantly higher stone-free rate at 3 months for retrograde intrarenal surgery compared to shock wave lithotripsy (90.4% vs 68%) and significantly higher retreatment rate for shock wave lithotripsy (36% vs 9.5%) (62). Severe obesity, which prevents targeting of the calculus is a counterindication for shock wave lithotripsy according to the EAU Guidelines (5).

- Stone density

On the one hand, the stone attenuation value is an independent predictor of the success of external shock wave lithotripsy and an useful tool for planning stone treatment (63). The Hounsfield unit (HU) is a relative quantitative measurement of radio density used by radiologists in the interpretation of images provided by computed tomography (64) .
Aouzaid and cols. found that stone free rates for stones <970 Hounsfield Units treated with shock wave lithotripsy was 96% against 38% for stones ≥ 970 Hounsfield Units (p value < 0.001) (65). Abdelbary and collaborators found stone free rates of 100% in stones <500 Hounsfield Units treated with shock wave lithotripsy, 95% in 500-1000 Hounsfield Units Stones and 44.6% in >1000 Hounsfield Units Stones (63).

On the other hand, radiolucent stones require ultrasound monitoring and/or intravenous contrast injection (66). For treatment of moderate-sized radiolucent renal stones, flexible ureteroscopy and percutaneous nephrolithotomy provide significantly higher stone free rates and lower retreatment rate compared with extracorporeal shock wave lithotripsy (66). Reduced effectiveness of extracorporeal shock wave lithotripsy is due to the fact that up to 31% of cases are unable to visualize stone by ultrasound. Stone free rates are 66.5% for radiolucent stones <2cm treated with shock wave lithotripsy versus 87% for flexible ureteroscopy (66). Retrograde intrarenal surgery has much less morbidity than percutaneous nephrolithotomy (66).

- Horseshoe Kidney

The horseshoe kidney is the most prevalent anomaly of the kidney, occurring in approximately 1:500 individuals, and a male to female ratio of 2 to 3:l. Horseshoe kidney results from a fusion of the lower poles of both right and left kidneys together with a cessation of the normal rotation lead to an abnormal ureteral course with an abnormally high insertion into the pelvis (67,68).

Despite high stone fragmentation rate per session in extracorporeal shock wave lithotripsy (63%) there is low stone expulsion rate resulting in inferior outcomes because of the anatomical features of horseshoe kidneys and the data shows that only 21% of cases in this scenario achieve stone free from a single session and 47.7% after 3 sessions (68). Therefore, the data shows very high recurrence rate in patients with horseshoe kidneys who are not rendered stone-free after extracorporeal shock wave lithotripsy (67).

Technologies in laser lithotripsy

Laser technology is one of the most important innovations introduced in endourology (69). The laser technology has revolutionized urolithiasis management in the last decades (70). New developments of endourology for urolithiasis have significantly enhanced the indications of endourology compared to extracorporeal shock wave lithotripsy (71). The new advances in retrograde intrarenal surgery and percutaneous endoscopic surgery have significantly increased the rate of primary success and lowered the complication rates (72).

Miniaturization of instruments was the cornerstone for evolution in endourology (72). New technology to access the urinary collecting system includes marker-based tracking with iPAD, laser-guided puncture, electromagnetic tracking (only experimental), and optical tracking for ultrasound-guided puncture.

Miniaturization percutaneous nephrolithotomy has been further extended and classified to Midi-PCNL (20-22fr/Large), Mini-PCNL (16-18fr/Medium), Ultra/Super-mini-PCNL (12-14fr/Small), and Micro-PCNL (8-10fr/xtrasmall) (71). Also improvements regarding stone fragments extraction (active/passive washout, purging, vacuum-cleaner-effect) have gained momentum (71).

Improvements of flexible ureteroscopy focus on digital-HD-videotechnology with post-processing software (NBI/SPIES) providing improved resolution and augmented optical field, further miniaturization of scopes to fit in smaller access sheaths, additional tip-less Nitinol baskets and graspers, and commercialization of a robotic device (Avicenna Roboflex) to enhance ergonomics during the surgery (71).

This miniaturization of instruments made laser lithotripsy the a gold standard for these modern endourology practices because of to the features of laser fibers compared with other lithotripters (73,74). Deep knowledge of laser lithotripsy including power settings for fragmentation becomes mandatory (71).

The holmium:yttrium-aluminum-garnet (Ho:YAG) laser, especially the new systems with new technologies, is widely used. It offers different effects on stones such as fragmentation, dusting, and popcorning (72). The Ho:YAG laser has been considered the gold-standard laser for lithotripsy during the past 30 years due to to its efficacy and safety profile (69). The Ho:YAG laser is a flashlamp-pumped, solid-state laser with an infrared emission wavelength of approximately 2.09 mm that operates in pulsed mode (75).

Holmium: yttrium aluminum garnet (Ho:YAG) is the gold standard device for lithotripsy, and can be safely and effectively used within the urinary for all types of stones [1, 2]. Ho:YAG is a 2.1 µm wavelength solid-state pulsed laser, highly absorbed in water. The main ablative mechanism of Ho:YAG is by photothermal effect [3]; as the energy delivered is absorbed by the stones causing its breakage [4].

By contrast, the recently introduced laser type and technology, the thulium fiber laser (TFL), is gaining in momentum and popularity in the endourology community because of its presumed better dusting capability even though robust clinical data are still lacking (69). The TFL is chemically doped with thulium ions and is excited by multiple diode lasers; the laser beam emitted has a wavelength of 1940 nm, that makes its absorption in H2O superior to Ho:YAG laser, is formed inside a thulium-doped small-diameter and long silica laser fiber (10–20 mm core diameter, 10–30 me long) (76). It then couples with another laser fiber to reach the target stone (72,76–79). It can operate within a large range of energy, frequency, and pulse shape settings (80,81).

The capacity of TFL to adjust to a very small fiber core diameter of is extremely important in the potential role of TFL for lithotripsy since the drop in the fiber core diameter to 50%, for instance, from 200mm in Ho:YAG laser to 100mm in TFL, lets the cross-sectional area of the fiber to be reduced to 25% and the density of laser energy to rise 400% (76).

However, despite the TFL is no doubt a new promising laser technology commercially available, clinical studies with robust methodology are needed in order to provide solid scientific evidence of the clinical superiority of TFL over Ho:YAG despite the in vitro ones (69,72). Randomized clinical trials comparing both laser types are still ongoing and unpublished (72). Most of the published preclinical studies found the ablation efficiency of TFL to range from 1.5 to 10 times with cleaner craters due to pulse uniformity and better stone-suctioning effect, lower stone retropulsion especially with the new muzzle brake fiber design and more durability of the laser fiber compared with Ho:YAG laser (72,82–84). In an in-vivo study, the super-pulseTFL was found superior to Ho:YAG laser ablations efficiency wise at the same pulse energy during fragmentation (2 times) and dusting (2.5 times), with 2-4 fold lower stone retropulsion (72,85). Additionally, in an in vitro study where the intraureteral/renal temperature generated by TFL during lithotripsy was compared to Ho:YAG laser at the same power settings, the TFL generated more heat at all settings tested (86). Higher temperatures with TFL, probably because of its very high coefficient of absorption in water, exceeding the threshold for tissue damage in some situations (69,86). No clinical data are available on this issue and this is a concern that really deserves more investigation to better define the safety profile of TFL (86).

Currently, TFL has not proved to be a game-changer, as it does not allow anything to be done that was not possible before its release despite promising enhanced dusting abilities compared yo Ho:YAG (69).

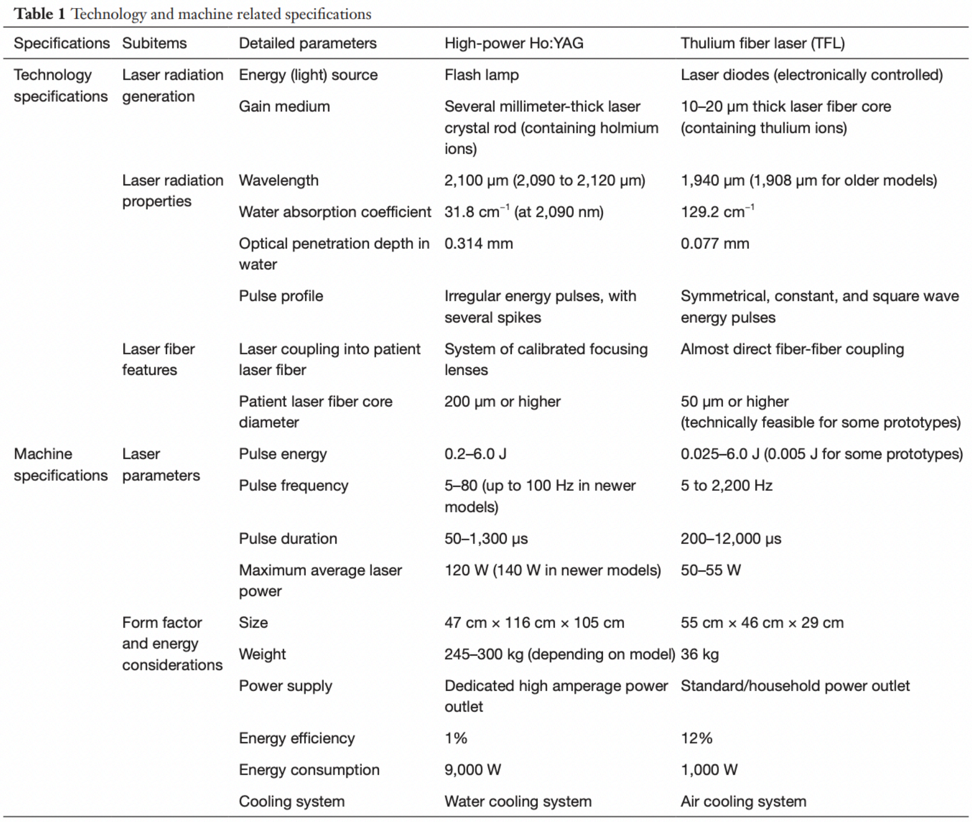


Table 1 Technology and machine related specifications

Specifications	Subitems	Detailed parameters	High-power Ho:YAG	Thulium fiber laser (TFL)
Technology specifications	Laser radiation generation	Energy (light) source	Flash lamp	Laser diodes (electronically controlled)
		Gain medium	Several millimeter-thick laser crystal rod (containing holmium ions)	10–20 µm thick laser fiber core (containing thulium ions)
	Laser radiation properties	Wavelength	2,100 µm (2,090 to 2,120 µm)	1,940 µm (1,908 µm for older models)
		Water absorption coefficient	31.8 cm^{-1} (at 2,090 nm)	129.2 cm^{-1}
		Optical penetration depth in water	0.314 mm	0.077 mm
		Pulse profile	Irregular energy pulses, with several spikes	Symmetrical, constant, and square wave energy pulses
	Laser fiber features	Laser coupling into patient laser fiber	System of calibrated focusing lenses	Almost direct fiber-fiber coupling
		Patient laser fiber core diameter	200 µm or higher	50 µm or higher (technically feasible for some prototypes)
Machine specifications	Laser parameters	Pulse energy	0.2–6.0 J	0.025–6.0 J (0.005 J for some prototypes)
		Pulse frequency	5–80 (up to 100 Hz in newer models)	5 to 2,200 Hz
		Pulse duration	50–1,300 µs	200–12,000 µs
		Maximum average laser power	120 W (140 W in newer models)	50–55 W
	Form factor and energy considerations	Size	47 cm × 116 cm × 105 cm	55 cm × 46 cm × 29 cm
		Weight	245–300 kg (depending on model)	36 kg
		Power supply	Dedicated high amperage power outlet	Standard/household power outlet
		Energy efficiency	1%	12%
		Energy consumption	9,000 W	1,000 W
		Cooling system	Water cooling system	Air cooling system

Table from Peter Kronenberg and Olivier Traxer, 2019 (87).

Pulse Modulation Technologies

At first, Ho:YAG lithotripsy devices allowed control pulse energy and pulse frequency, and consequently control the total power output, which is the result produced by these two parameters: Total Power (W) = Pulse energy (J) x Pulse frequency (Hz) (72,81,88).

The possibility of selecting pulse duration—either a short pulse or long pulse —when using laser generators changed the endourology practice (75). Short Pulse and Long Pulse are two different pulse modalities whose features go beyond than the mere duration of laser emission (75). For a Ho:YAG laser the short pulse modality displays an asymmetrical pulse shape with a steep leading slope and a trailing slope without any flat section. The long pulse modality has a pulse shape with a steep leading slope, a flat-top section and gradual trailing slope (75). These differences are a key fact in determining the interaction between the laser source and the stone: when the pulse energy is more equally distributed during the emission interval (the flat-top section), the ablation efficiency increases 1.5–2 times (89). This is even more evident with TFL as the almost rectangular flat-top pulse shape is significantly longer than in the counterpart Ho:YAG pulse. This results in higher ablation efficiency and lower retropulsion, at least in preclinical studies (82,83,85,89).

Most recently, further innovations to modulate pulse characteristics of Ho:YAG lithotripsy devices have also been introduced (81,88). These innovative laser generators bring technology capable of providing pulse modulation to enhance energy transmission (70). Taking advantage of the “Moses effect” described since 1986, the Moses™ technology (Lumenis®, Yokneam, Israel), is a modulated pulse mode that allows energy release into two peaks, the frst creates the water cavity known as the Moses effect so that the second reaches the target calculus more efectively (80,81,88,90–95). This results, at least in theory, in reduction of stone retropulsion and enhanced efficiency of laser ablation (80,81,88,90–95).

Likewise, pulse modulation technologies for Ho:YAG laser devices for endourology have become available in the market by other manufacturers such as the High-Power Cyber: Ho™ lithotripters (Quanta System, Samarate, Italy) with the Vapor Tunnel™ pulse modality, Virtual Basket™ pulse modality, and Bubble Blast™ pulse modality (96). These pulse modes transform the laser pulse transmission by creating bubbles emerging from the laser fiber tip with diverse effects on the target lithiasis (1,96,97). However, there is a significant lack of clinical robust clinical studies regarding these innovative Ho: YAG pulse modulation modalities (88).

In a randomized clinical trial comparing lithotripsy with 100W Cyber Ho laser generator in Vapor Tunnel mode versus the 35W Litho laser generator in 1 J and 12 Hz for the treatment of ureteral stones in an emergency scenario, including 210 patients (105 per arm), the Vapor Tunnel pulse modality was related to with significantly shorter dusting time, total procedural time, less total delivered energy, less retropulsion and reduced need to retrieve fragments with baskets (98).

The Virtual Basket pulse modulation technology has been related to reduced ablation time and less retropulsion when compared with regular Ho: YAG laser lithotripsy pulse modes for the management of ureteral and renal stones in a study including 160 patients (40 per cohort) (99).

When in vitro evaluating stone retropulsion in various laser pulse modes in both Moses pulse modulation modality and Virtual Basket pulse modulation mode, retropulsion was not significantly different between the laser settings at 1-mm distance in Moses pulse modulation modality, or when contacting the stone Virtual Basket pulse modulation mode (97). Laser settings and tip position may affect retropulsion in Moses pulse modulation modality and Virtual Basket pulse modulation mode (97).

Other companies have introduced pulse modulation technologies as well (100).

Choice of the appropriate pulse modality for laser lithotripsy depends on the inherent features of the laser pulse, the peak power and pulse modulation (70). According to preclinical studies, the traditional long pulse modality results in less retropulsión compared to short pulse modality, whereas the long pulse modality and Moses technology for Ho:YAG lasers have comparable retropulsion and ablation efficiency (70). Nonetheless, to date, data on clinical comparison between these pulse modulation technologies overall is insufficient. Thus, we do know not how to use the innovative laser technologies safely and efficiently in endourology for managing kidney stones (1,70).

High-Power Ho:YAG Lithotripsy

In past years, available laser lithotripters allowed maximum standard power up to 20 W, whereas the high-power options were employed for tissue ablation procedures (72). Most recently, the high-power laser lithotripters that are becoming available in the market offer a wider range of pulse energy and frequency adjustment to improve efficacy of laser lithoripsy (72). These lithotripters have exhibited outstanding results for stone fragmentation with a good safety profile when used properly (81,88).

One of the main concerns with high-power lithotripsy is keeping the intrarenal and intraureteral temperature at safe levels to avoid tissue harm. The injury can be produced indirectly through elevation of temperature of the irrigation fluid (72). Many preclinical studies are available but not much neither quality nor non quality clinical evidence. Low irrigation with high power result in high temperatures (101). Cellular injury threshold has been suggested at 43^0 C (101) and 54 °C (102).

43^0 C can be quickly reached within even 1 second, and it takes 5 seconds to return to safe temperatures (101). On another experiment testing intrarenal temperatures with Lumenis laser with settings up to 22.5W, average heating rate increased proportionally to power from 0.06°C/s at 2 W to 0.74°C/s at 22.5 W (101). Similar results were recorded in temperature when the power was the same despite the different settings (101).

Also, another study found that the damaging thermal effect with high-power Ho:YAG laser to the kidney occurs when exceeding the threshold temperature of 54 °C, under gravity irrigation. Lower power settings (up to 40 W) can be used with safety. According to this experiment the combination of ureteral access sheath and manual pump irrigation, is the safest practice regarding renal thermal damage for high-power Ho:YAG lithotripsy (102).

Another experiment showed that intrarenal temperature in pigs was safe while using Ho:YAG laser at 10 and 20W (103). Another study proved that the intrarenal temperature can rise substantially during Ho:YAG lithotripsy, but the high rate of irrigation can lower this temperature and render lithotripsy safer (104). It was also found that the absence of minimal safe irrigation (30 ml/m) may lead to result potentially harmful intrarenal temperature at a laser power as low as 5W during ureteroscopy in a study where real-time intrarenal temperature was recorded during lithotripsy using Ho:YAG laser at a powers between 5–100W and irrigation rate from 0 to 100 ml/m in an ex-vivo porcine model (105).

Our group found on another in vivo study with a porcine model no differences were observed when different fibers were utilized intrarenal temperature wise. Rising the overall power, increased the irrigation fluid temperature significantly. The smaller the volume of the pelvis, the greater the temperature increase. The presence of artificial stones was associated with the absorption of energy emitted by the laser (106).

Laser Settings and Ablation Rates with Ho:YAG laser

Ho:YAG laser lithotripsy varies as power settings (pulse energy and frequency) are modified (107). Optimal lithotripsy laser dosimetry depends on the desired outcome. Less fragmentation and retropulsion occur and small fragments are produced at low pulse energy (0.2 J) (108). Contrarily, more fragmentation and retropulsion occur with larger fragments at high pulse energy (2.0 J) (108).

Peter Kronenberg and Olivier Traxer published an in vitro study (107), low frequency-high pulse energy settings were more ablative than high frequency-low pulse energy, up to 6 times more ablative, at the same power levels ($P < 0.001$) (107). They resulted in deeper and wider stone fissures. In this study, significant linear correlations between pulse energy and fragmentation volume, fissure width, and fissure depth were found . Total power did not correlate with fragmentation measurements. Except at very low pulse energies, where the large fibre was less efficient, the diameter of the laser fibre did not affect fragmentation volumen (107). Thus, small fibres are preferable due to better scope irrigation and manoeuvrability (107). However, clinical data on the ideal laser settings for each case scenario is missing to date.

The performance of Ho:YAG laser lithotripsy is affected by many technical parameters which can be controlled by the user. Knowing and understanding these parameters allows performing a Ho: YAG laser lithotripsy procedure effectively and safely (81).

Artificial Stones Used for Research in Endourology

The great evolution of technology designed for endourological procedures has led to the need to design experimental models to improve the knowledge of new devices in order to optimise their safety and application (72,81,88,107). Many of these models are in vitro platforms to test the lasers´ properties including fragmentation rates (107,109), intrarenal temperature (106,110,111) and stone retropulsión (77,83,89,97). In order to perform trials with the laser lithotripters and laser fibers, artificial stones built from Bego™ powder or similar are used in many studies (1,102,112,113). However, our knowledge about these artificial stones is limited. Artificial stones were initially characterized by Esch and colleagues in 2010 (113). According to their data, hard artificial stones, made from a powder:water ratio of 15:3, can compare acoustically to real stones composed of calcium oxalate, and soft artificial stones, made from a powder:water ratio of 15:6, can compare acoustically to real stones composed of uric acid (113). However, there are no publications to my knowledge that measure and compare the optical properties of artificial stones to real stones. Thus, to ensure experimental accuracy the artificial stones must resemble real urolithiasis in both their acoustic and optical properties.

MATERIALS AND METHODS

Aims

The present PhD Thesis Study had the overall purpose of shedding some light in the knowledge of how new technologies for laser lithotripsy work from both clinical and preclinical assessments. The specific endpoints were set as follows:

End Points for the Preclinical Assessment

The endpoints for the in vitro experiments were:

1) To assess the bubble formation features of Virtual Basket, Bubble Blast, and Vapor Tunnel.
2) To test the stone ablation rates for the pulse modulation modalities that Quanta Cyber Ho offers, Virtual Basket, Bubble Blast, and Vapor Tunnel, using different power, energy, and frequency settings, on a horizontal experimental setting.
3) To assess the fragmentation patterns created by lasering artificial stones with the pulse modulation modalities that Quanta Cyber Ho offers, Virtual Basket, Bubble Blast, and Vapor Tunnel, using different power, energy, and frequency settings.
4) To assess the fragmentation rates created by lasering artificial stones with the pulse modulation modalities that Quanta Cyber Ho offers, Virtual Basket, Bubble Blast, and Vapor Tunnel, using different power, energy, and frequency settings.
5) To test the stone ablation rates for the pulse modulation modality of Moses Distance, and standard short and long pulse modalities on a vertical setting.
6) To characterize artificial stones used for preclinical experiments in endourology by comparing them to real stones from three perspectives;

- Radiological properties

- Spectral properties
- Hardness in terms of stone fragmentation rates.

End Points for the Clinical Assessment

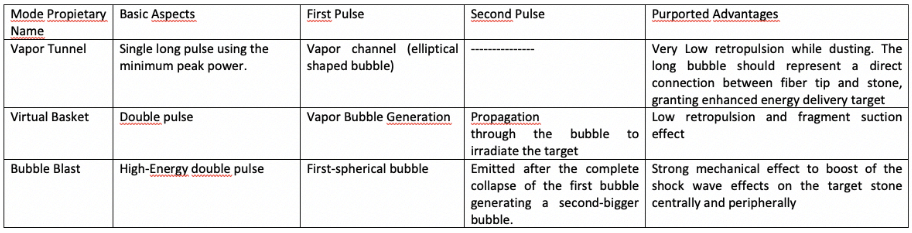
The goal for the clinical analysis was:

- To compare effectivity and safety of high and low-power settings at Ho:YAG laser lithotripsy for Retrograde Intrarenal Surgery (RIRS) in patients from a reference tertiary centre.

In vitro experiment to test the pulse modulation modes: Virtual Basket, Bubble Blast, and Vapor Tunnel.

Table 1 summarizes the features of the pulse modulation modalities as per the manufacturer (114).

Table 1: Properties of each pulse modulation mode offered by High-Power Cyber: Ho™ lithotripters (Quanta System, Samarate, Italy) according to the manufacturer (110).



Mode Propietary Name	Basic Aspects	First Pulse	Second Pulse	Purported Advantages
Vapor Tunnel	Single long pulse using the minimum peak power.	Vapor channel (elliptical shaped bubble)	---------------	Very Low retropulsion while dusting. The long bubble should represent a direct connection between fiber tip and stone, granting enhanced energy delivery target
Virtual Basket	Double pulse	Vapor Bubble Generation	Propagation through the bubble to irradiate the target	Low retropulsion and fragment suction effect
Bubble Blast	High-Energy double pulse	First-spherical bubble	Emitted after the complete collapse of the first bubble generating a second-bigger bubble.	Strong mechanical effect to boost of the shock wave effects on the target stone centrally and peripherally

Materials

Materials used were:

- The Quanta Cyber: Ho 150 W™ (Quanta System, Samarate, Italy)
- A 365 micrometers Quanta Precision Fiber™ (Quanta System, Samarate, Italy)
- Bego stone Plus Powder (Bego USA, Lincoln, RI).
- A rounded plastic mold with the dimensions: 8.5 x 8.5 x 5.5 mm
- Water
- 10 ml syringes
- Automatic mixer
- Compact Scale
- A 10:01 standard crystal tube sustained
- An iron holder was placed inside the container.
- An 8 french-84 cm guide catheter (Cook Medical, Indiana, USA)
- A16 Fr-30 cm Amplatz Renal Dilator (Cook Medical, Indiana, USA).
- An18 Fr-30 cm Amplatz Renal Dilator (Cook Medical, Indiana, USA)
- A transparent plastic container (37 x 27 x 17 cm)
- Normal saline.
- An iPhone 12 pro camera (Apple, Palo Alto, California)
- A high-speed camera, i-speed 2 (Olympus Cortp., Tokyo, Japan)

Stones

Two different stone types, hard and soft of artificial-phantom calculi were constructed with BegoStone™ powder (Bego USA, Lincoln, RI). Hard artificial stones were made with a powder to water ratio of 15:3 and soft artificial stones were made with a powder to water ratio of 15: 6 as per recommendations of the previous published studies (93,113). A rounded plastic mold with the dimensions: 8.5 x 8.5 x 5.5 mm was used to let the mixture dry. The mixture was let dry for 3 whole days. The artificial stones were then placed and left in a water container overnight before the experiment to mimic the real conditions of urinary stones. Figure 1 displays the appearance of ready-to-use built artificial stones.

Figure 1: **Sample phantom BegoStones built for all in vitro stone ablation rates assessments created before applying lithotripsy**

Bubble Formation Record

Bubble formation pattern from the distal laser fiber tip, for each of the three modes was captures with an i-speed 2 (Olympus Cortp., Tokyo, Japan) high-speed camera.

Experimental Set Up

In order to test the stone ablation rates of the innovative pulse modulation modalities known as Vapor Tunnel™, Virtual Basket™ and Bubble Blast™ which were introduced by Quanta Cyber: Ho 150 W™ (Quanta System, Samarate, Italy), an in vitro custom experimental setting was designed and built.

Figure 2 shows the custom experimental setting.

The transparent plastic container (37 x 27 x 17 cm) filled up with normal saline. A 10:01 standard crystal tube sustained by an iron holder was placed inside the container. The laser fiber was introduced through one overture of the crystal tube and fixed by the 8 french-84 cm guide catheter (Cook Medical, Indiana, USA) inside a 16 Fr-30 cm Amplatz Renal Dilator (Cook Medical, Indiana, USA). The target Bego stone was placed in the middle of the tube and secured with an 18 Fr-30 cm Amplatz Renal Dilator (Cook Medical, Indiana, USA) inserted from the other end of the crystal tube.

Settings and Measurements

The Quanta Cyber: Ho 150 W™ (Quanta System, Samarate, Italy). with a 365 micrometers Quanta Precision Fiber™ (Quanta System, Samarate, Italy) was employed for all tests. The laser lithotripsy was delivered up to a total energy sum of 3 kJ for every test. The Bego stones were then labeled and let dry at room temperature for 3 whole days.

The stone ablation rate (AR) was calculated dividing the weight difference [Artificial Stone Weight before the experiment (mg) - Artificial Stone Weight 72 hours after the experiment (mg)] with ablation time.

Time to achieve 3KJ was registered for all tests. The same laser parameters (power, pulse energy and frequency) could not be used for each cohort within the three pulse modulation modes because the manufacturer does not allow to set all parameters for all modes. For example, high-power settings are not allowed in Vapor Tunnel, and the lowest-power accepted in Bubble Blast is 12 W. In the Virtual Basket mode, the combinations of power, energy and frequency were tested as follows: 10W = 0.5Jx20Hz, 10W = 0.5Jx20Hz, 60W = 1Jx60Hz and 60W = 2Jx30 Hz. For Bubble Blast mode, the tested laser settings were 12W = 1.2Jx10Hz, 60W = 1J 60Hz and 60W = 2Jx30Hz. The setting of 10W = 0.5Jx20Hz was used using Vapor Tunnel which was the mode with least potential for adjustment of energy and frequency.

It was ensured that the laser lithotripsy configuration was precise, suitable, and homogeneous for every trial.

Regular pictures of the fragmentation patterns were also taken at the end of every test.

Statistical Analysis

SPSS v25 software (IBM Statistics, NY, USA) was used for the statistical analysis. Three trials were performed for every cohort with specific laser settings. Data are presented as median values.

In vitro assessment atone ablation rates with Lumenis Moses 120H. Vertical setting

Materials

Materials employed were:

- Lumenis® Pulse P120H holmium laser system (Lumenis Ltd, Yokneam, Israel)
- A 365 µm Moses D/F/L fiber (Lumenis Ltd, Yokneam, Israel).
- Bego stone Plus Powder (Bego USA, Lincoln, RI).
- A rounded plastic mold with the dimensions: 8.5 x 8.5 x 5.5 mm
- Water
- 10 ml syringes
- Automatic mixer
- Compact Scale
- A 10:01 standard crystal tube sustained
- An iron holder was placed inside the container.
- An 8 french-84 cm guide catheter (Cook Medical, Indiana, USA)
- A16 Fr-30 cm Amplatz Renal Dilator (Cook Medical, Indiana, USA).
- An18 Fr-30 cm Amplatz Renal Dilator (Cook Medical, Indiana, USA)
- A transparent plastic container (37 x 27 x 17 cm)
- Normal saline.
- An iPhone 12 pro camera (Apple, Palo Alto, California)

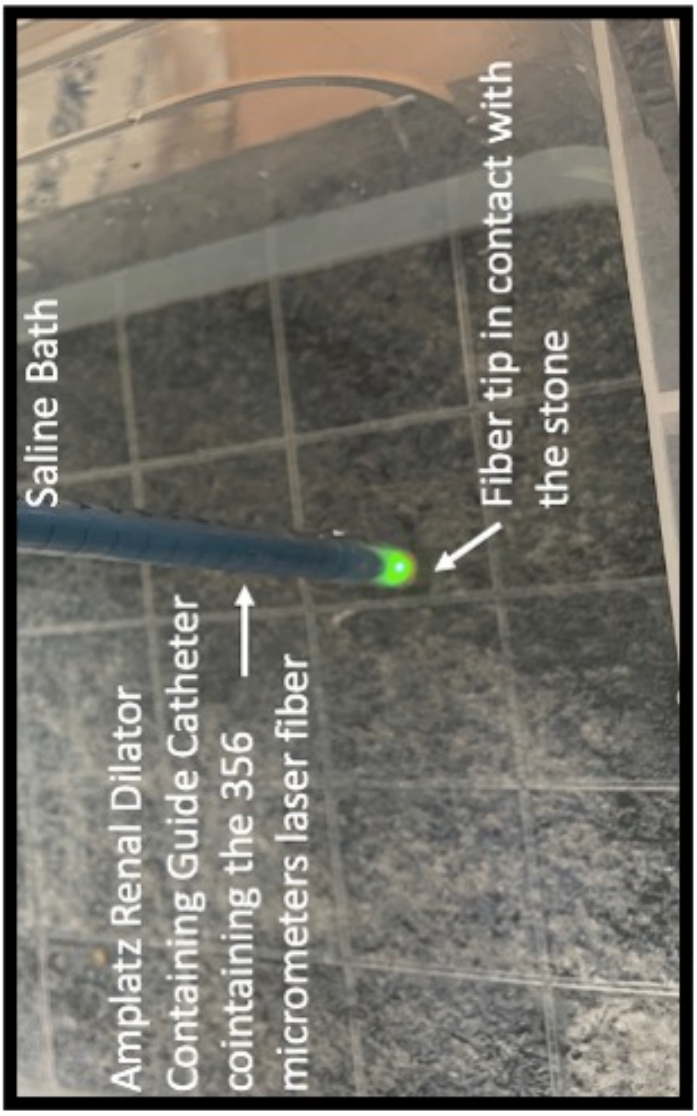
Stones

The same two types of phantom 8.5 x 8.5 x 5.5 mm stones made of BegoStone™ powder (BEGO Lincoln, RI, USA) than the ones used for the first experiment with Quanta Cyber Ho were built for this experiment. The hard stones were built from a ratio: 15 gr of powder: 3 ml water and soft stones from a ratio: 15 gr of powder: 6 ml water (113). The mixture was left dried for 3 days in a plastic mold, Then, the artificial stones were moistened by water immersion during 60 minutes before the experiment. The stones were weighted in dry conditions with an electronic compact scale.

Experimental Set Up

The experiment settings (Fig. 3) consisted of a transparent plastic container (37 x 27 x 17 cm) with a 10:01 standard crystal tube using a vertical setting to avoid retropulsion in this occasion. No active irrigation was set but all the container was filled with saline water. The laser fiber was introduced through an 8 french-84 cm guide catheter (ref: 075001. Cook Medical, Indiana, USA) inside an 18 french-30 cm Amplatz Renal Dilator (ref: 075000. Cook Medical, Indiana, USA) in the crystal tube.

Figure 3: Experiment settings: Custom experimental configuration installed in a saline filled bath where all the tests were conducted for the experiment with Lumenis Moses on a vertical setting.



Settings and Measurements

The experiments were conducted using Lumenis® Pulse P120H holmium laser system (Lumenis Ltd, Yokneam, Israel) and a 365 µm Moses D/F/L fiber (Lumenis Ltd, Yokneam, Israel).

Ablation rates in all the four pulse modality settings that the manufacturer offers were evaluated, “Short Pulse”, “Long Pulse”, and “Moses Distance”. The laser tip was positioned at 1 mm distance from the stone at Moses Distance as recommended by Winship et al (13). The power-energy-frequency combinations 10W=0.5Jx20Hz, 10W=2Jx5Hz, 60W=1Jx60Hz and, 60W=2Jx30Hz were set in order to test the stone ablation rates at high and low-power lithotripsy with high and low frequency and energy settings. Laser lithotripsy was delivered up to 3kJ of total energy for every test. All fragments were collected for weight measurement. Stone ablation rate was assessed from the formula: Stone weight before the experiment (mg) - stone weight dried for 72 hours after the experiment (mg)/lasing time. Three consequent measurements was performed for every cohort i.e. each combination of [stone type-energy and frequency settings-pulse modality]. Mesurements were made blindly i.e. researchers recording the measurements did not know the settings and pulse modality set for each experiment. Median values were assessed for the final analysis. Likewise in the previous experiment, all efforts were focused on assuring experimental accuracy, rigor and homogeneity for all the tests.

In this experiment, bubble formation for the Moses Technology was not assessed because it has been published in the literature before (92).

Statistical Analysis

Statistical analysis were made with SPSS v25 software (IBM Statistics, NY, USA). A qualitative analysis from descriptive statistics were presented in terms of means.

Characterization of artificial stones

Materials

Materials used for this experiment were:

- A GE Revolution CT® scanner (GE Medical Systems, LLC. Waukesha, WI, U.S.A) together
- The CT Gemstone Spectral Imaging (GSI) ® software (GE Medical Systems, LLC. Waukesha, WI, U.S.A)
- Gel platform bed from agar
- Lumenis® Pulse P120H holmium laser system (Lumenis Ltd, Yokneam, Israel)
- A 365 µm Moses D/F/L fiber (Lumenis Ltd, Yokneam, Israel).
- Bego stone Plus Powder (Bego USA, Lincoln, RI).
- A rounded plastic mold with the dimensions: 6mm x 6mm x 5.5mm
- Water
- 10 ml syringes
- Automatic mixer
- Compact Scale
- Real Stones from a stone bank
- A 10:01 standard crystal tube sustained by an iron holder was placed inside the container.
- An 8 french-84 cm guide catheter (Cook Medical, Indiana, USA)
- A16 Fr-30 cm Amplatz Renal Dilator (Cook Medical, Indiana, USA).
- An18 Fr-30 cm Amplatz Renal Dilator (Cook Medical, Indiana, USA)

- A 22Fr-30cm Amplatz Renal Dilator
- A rounded transparent plastic jag (10cm x 10cm x 20cm)
- Normal saline.
- An iPhone 12 pro camera (Apple, Palo Alto, California)

Stones

Ten types of artificial stones from Bego Stone Plus™ powder (BEGO Lincoln, RI, USA) were built with a ratios of powder (grams):water (ml) 15:03, 15:04, 15:05, 15:06, 15:07, 15:08, 15:09, 15:10, 15:11, and 15:12. The same 6mm x 6mm x 5.5mm mould was used to build all the artificial stones where they were dried for 72 hours. Real stones were sourced from a tertiary hospital in Perth, Western Australia.The real stones were composed of uric acid, magnesium ammonium phosphate, calcium phosphate, calcium oxalate, ammonium urate, and cystine.

Radiological Properties

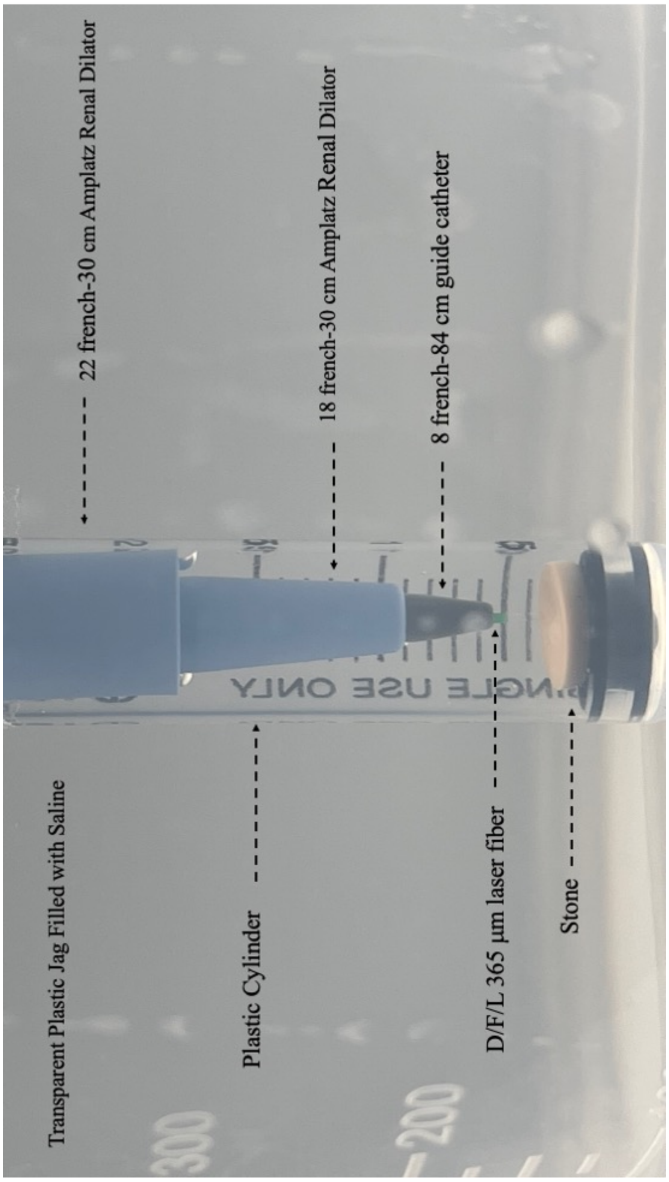
All artificial and real stones were placed in a gel platform bed and identified with codes (Figure 4). A GE Revolution CT® scanner (GE Medical Systems, LLC. Waukesha, WI, U.S.A) together with the CT Gemstone Spectral Imaging (GSI) ® software (GE Medical Systems, LLC. Waukesha, WI, U.S.A), were utilized to assess the radiological properties in terms of HU and spectral atomic numbers of all stone types. The results between artifical and real stones were then compared. The GSI software provides the effective atomic number for every stone and the density is obtained in HU, with the former being the most accurate estimate of stone composition. Spectral curves from the artificial stones' effective atomic numbers were built by the software and compared to that of real stones. The GSI software was then able to determine which type of real stone the sample was characteristically most similar to.

Figure 4: Stones disposal for the radiological characterization on computerized tomography scan. Stones were placed in a gel platform bed and identified with codes to be scanned in the Revolution CT® Computer Tomography Scan Machine (GE Medical Systems, LLC. Waukesha, WI, U.S.A).

Fragmentation Rates Assessment Set Up

In order to compare the fragmentation rates between artificial and real stones, an in vitro experiment was performed with reproducible conditions for every test. The fragmentation rate was defined as weight before laser lithotripsy minus weight after laser lithotripsy. The experiment settings (Fig. 5) consisted of a rounded transparent plastic jag (10cm x 10cm x 20cm) filled with saline water. The laser fibre was introduced through an 8Fr-84cm guide catheter (ref: 075001. Cook Medical, Indiana, USA) in an 18Fr-30cm Amplatz Renal Dilator (ref: 075000. Cook Medical, Indiana, USA) which was stabilized and fixed by a 22Fr-30cm Amplatz Renal Dilator (ref: 075000. Cook Medical, Indiana, USA) inside a plastic cylinder on a vertical setting to avoid the bias of stone retropulsion. A Lumenis® Pulse P120H holmium laser system (Lumenis Ltd, Yokneam, Israel) and a 365µm Moses D/F/L fibre (Lumenis Ltd, Yokneam, Israel) were used for laser lithotripsy.

Figure 5: Fragmentation Rates Experimental Settings for the Artificial Stones Characterization Experiment



Settings and Measurements

Laser settings of power, energy and frequency for every experiment were set at 1.5Jx20Hz=30W at the long pulse modality. Every stone was lasered for 30 seconds. The laser fibre was fixed prior to starting the experiment keeping the fiber tip at a 2mm distance from the stone. The laser settings and the time were set arbitrarily to standardize the comparison between the stones. All real and artificial stones were moistened by water immersion for 24 hours prior to the experiment to mimic the in vivo conditions of the stones. The stones were weighed when dry blindly by two researchers (B.B.M and D.M.) with an electronic compact scale 72 hours before and 72 hours after the experiment.

Statistical Analysis

Two trials were performed on each stone type, and calculated mean values were used for the final analysis. The mean values, standard deviation, spectral curves and histogram for the radiological properties assessment were provided by the GSI software. A quantitative analysis for the stones fragmentation rates experiment was performed using SPSS v25 software (IBM Statistics, NY, USA).

High-Power lithotripsy. Clinical data

Study Population and Design

A prospective Institutional Board approved database was built and analyzed. Adult patients who underwent retrograde intrarenal surgery for the management of kidney stones were included regardless of stone size, number of calculi, and location. Surgery were performed consecutively over a period of roughly 2 years. A written informed consent was signed by each patient prior to the procedure.

Patients with ipsilateral ureteral stones, cases managed by stone extraction “in toto”, and cases with other laser parameters (other than the below-mentioned parameters) were excluded from the study.

Study Arms

The patients included in the study were divided into two groups based on the laser parameters used to achieve disintegration of the stone: Group, low-power settings at dusting modality(79,93,115,116), and Group 2, high-power settings at stone “self-popping” mode .

Equipment

- Anesthesia ventilator, monitor and drugs
- Stent extraction endo grasper
- Semi-stiff with hydrophilic tip guide wire
- Dual Lumen® Ureteral Access Catheter (Cook Medical, Indiana, USA)
- Stiff guide-wire
- Semi-rigid ureteroscope (Karl Storz, Tuttlingen, Germany)
- Flex Xc ureteroscope (Karl Storz, Tuttlingen, Germany)
- 12/14Fr ureteral Access sheath (Flexor®, COOK Medical, Limerick, Ireland)
- 14/16Fr ureteral Access sheath (Flexor®, COOK Medical, Limerick, Ireland)
- Manual irrigation pump (COOK Medical, Limerick, Ireland)
- High-power Ho:YAG laser (Lumenis Pulse P120H, Lumenis Ltd, Yokneam, Israel)
- A D/F/L 200-µm laser fiber (Lumenis Ltd, Yokneam, Israel or Quanta System, Samarate, Italy)
- High-Power Quanta Ho150, Quanta System, Samarate, Italy)
- A 270 micrometers Quanta Precision Fiber™ (Quanta System, Samarate, Italy)
- A 4.8-7Fr/24-28cm double J stent
- Iodum contrast
- Normal saline irritation
- 10 and 20 ml syringes

Surgical technique

All surgeries were performed by an expert endourologist, with an expertise of more than 1000 endourological procedures. All patients underwent general anesthesia in supine position. Propofol 1,8 -2,5 mg/kg, fentanyl 1,5 µg/kg, Rocuronium 0,7-1mg/kg and paracetamol 1gr were used for Introduction of anesthesia, whereas propofol 6-7 mg/kg/h and remifentanil 3-10µg/kg/h were employed for maintenance. Once patients were anesthetized, they were placed in lithotomy position.

Firstly, if there was a previous double J catheter it was removed. Secondly, a safety guide-wire (usually semi-stiff with hydrophilic tip) was placed. A Dual Lumen® Ureteral Access Catheter (Cook Medical, Indiana, USA) was then placed through the guidewire and contrast was inserted. A second, working, stiff guide-wire was placed through the Dual Lumen Catheter, and lithotripsy was performed once reached the stone with either a semi-rigid ureteroscope (Karl Storz, Tuttlingen, Germany) or Flex Xc ureteroscope (Karl Storz, Tuttlingen, Germany) depending on the location of the stone. All cases included in the the high-power lithotripsy group, group 2, were treated following the placement of a 12/14Fr or 14/16Fr ureteral access sheath (Flexor®, COOK Medical, Limerick, Ireland).

Laser Lithotripsy

All laser lithotripsies under were performed with Ho:YAG laser.

A high-power Ho:YAG laser (Lumenis Pulse P120H, Lumenis Ltd, Yokneam, Israel and a D/F/L 200-µm laser fiber (Lumenis Ltd, Yokneam, Israel or Quanta System, Samarate, Italy) or Quanta Ho150, Quanta System, Samarate, Italy) with a 270 micrometers Quanta Precision Fiber™ (Quanta System, Samarate, Italy) were used for the laser lithotripsy with the predetermined laser settings of power, energy and frequency according to the study group. Fluid irrigation was done with manual assisted pump. At the end of the procedure, a 4.8-7Fr/24-28cm double J stent was placed once the stone was completely disintegrated as per the surgeons eye perception and a final control pyelography.

Laser Settings and Lasing Techniques

Laser settings for the two groups patients were divided into were set as;

- Group 1: Dusting Mode: 20W=40HzX0.5J (115)

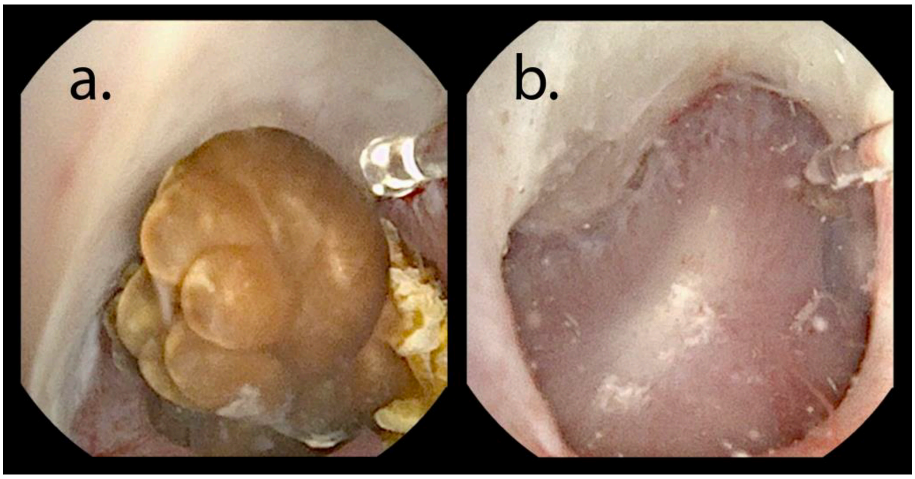
Stone Dusting is achieved using low-power (20W) with high frequency (40Hz), low energy (0.5J), and long pulse duration (79,93,115,117). The laser fiber tip should always be in close vicinity but without direct contact to the target stone, gradually “painting” its whole surface (117). Continuous activation of the laser is feasible for this technique. As a result, no big fragments are generated (79,115). Stone relocation with an endobasket stone retractor might be needed especially in cases of stones located in the lower calyx (118)

- Group 2: Fragmentation mode with settings of 60W=30-40HzX1.5-2.0J.

Stone fragmentation with higher frequency or ·stone “self-popping” technique is performed with set pulse energy between 1.5 and 2.0 J and frequency between 30-40 Hz resulting in power of 60W. For this technique the tip of the scope together with the laser fiber tip are placed in the middle of the target stone harbouring calyx. The laser fiber is activated without direct contact with the target stone. The generated power allows breakage of the stone and generated stone fragments circulate within the calyx hitting the laser (self-popping). Continuous laser activation must not exceed 10 seconds. Gentle active manual pumping during the breaks is mandatory to avoid tissue harming due to increases of the intrarenal temperature (102,106).

The procedure is considered completed when no big fragments (bigger than the diameter of the laser fiber) are visible with simple sight (Figure 6). The number of attempts depends on the size of the stone.

Figure 6: Stone "self-popping" technique a. Laser fiber set in the middle of the calyx and activated without direct contact to the stone, **b.** Affected renal calyx following 12 attempts of laser firing with 10 seconds



Perioperative Management and Follow-Up

All patients received single dose antibiotic prophylaxis with either fluoroquinolone or aminoglycosides. Follow-up imaging at 1-month after the surgery was performed with either a kidney, ureter and bladder (KUB) plain radiography and ultrasonography, or non-contrast enhanced computer tomography. The double J stents were then removed if no-clinically-significant stone fragments were seen in the imaging test.

Study variables

Study variables registered were:

Patient demography

- Age
- Gender
- Body mass index

Stone Characteristics

- Mean cumulative stone size
- Stone location

Perioperative outcome parameters

- Total operation time
- Stone disintegration time
- Fluoroscopy time
- Hemoglobin drop

- Hospital stay
- Stone Repositioning
- Insertion of ureteral access sheath
- Size of ureteral access sheath
- Complications
- Stone-free status
- Need of additional procedures

The primary-outcome variables were the operative time (time between the start of urethroscopy till the placement of urethral catheter) and stone disintegration time (time between the first activation of the laser till the end of the laser lithotripsy).

The secondary variable was the Stone free rate. The largest diameter of the stone was used for the stone size calculation. In case of multiple stones, cumulative size of the largest diameters of the stones was considered. Patients were considered stone-free if no remaining fragments were found on the follow-up imaging performed. All occurred complications were graded according to Clavien-Dindo classification (119). Furthermore, the classification of Traxer and Thomas were used to grade ureteric damage due to the insertion of ureteral access sheath (120).

Statistical Analysis

Statistical analyses were performed using SPSS v. 21.0 (SPSS Inc., 2012). Means and standard deviations (SD) were used to describe continuous variables and proportions for categorical variables. After testing the variables in univariate models, the significant variables with a P value <0.2 were included in the multiple regression analysis. P value < 0.05 was considered as statistically significant.

RESULTS

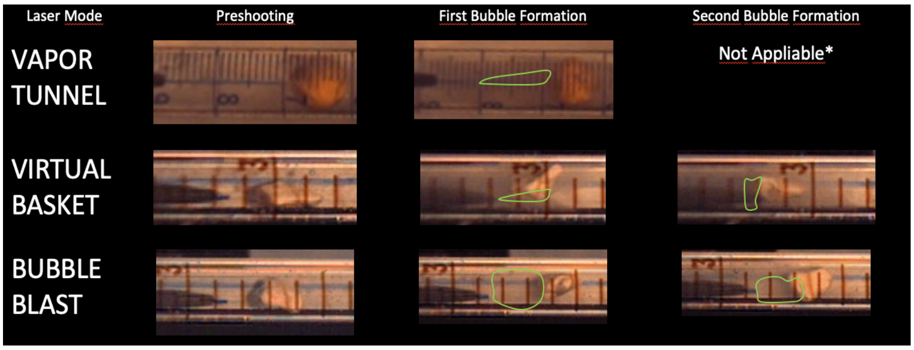
In vitro assessment of stone ablation rates with Quanta CyberHo 150W.

Horizontal setting

Assessment of the bubble formation features of Virtual Basket, Bubble Blast, and Vapor Tunnel.

Bubble formation wise with the three pulse modulation modalities offered by Quanta Cyber Ho, Table 2 displays the patterns recorded with the high speed camera employed.

Table 2: Bubble Formation for each pulse modulation mode. The table displays images of the bubble formation, and the laser tip-stone distance before shooting and after shooting. The images are captures from a high-speed camera, i-speed 2 (Olympus Cortp., Tokyo, Japan)



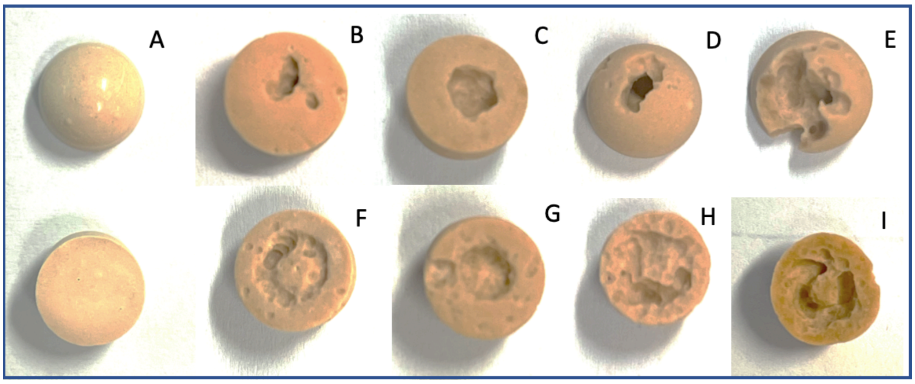
Laser Mode	Preshooting	First Bubble Formation	Second Bubble Formation
VAPOR TUNNEL			Not Appliable*
VIRTUAL BASKET			
BUBBLE BLAST			

*The Vapor Tunnel pulse modulation modality involves only one bubble formation

Assessment of the fragmentation patterns created by lasering artificial stones with the pulse modulation modalities that Quanta Cyber Ho offers, Virtual Basket, Bubble Blast, and Vapor Tunnel, using different power, energy, and frequency settings.

Figure 7 shows photographs of the soft (15:6) phantom stones before and after the tests. The Virtual Basket modality generated lots of little fragments. In 10W= 2 J X 5 Hz a generally greater cavity was created compared to 10W= 0.5 J X 20 Hz. Virtual Basket in 60W= 1 J X 60Hz lead to a deeper cavity compared to the low energy setting trials. However, the cavity generated with the Virtual Basket pulse modulating mode at 60W= 2 J X 30Hz was wider and deeper, and more fragments were generated. Overall, all the tests using the Bubble Blast pulse modulation modality generated many fragments and a flat wide cavity in the remaining stone. This cavity was shallow compared with the cavity generated in the Virtual Basket mode trials. The pattern for Vapor Tunnel was generally flat and shallow, and dust was generated instead of fragments.

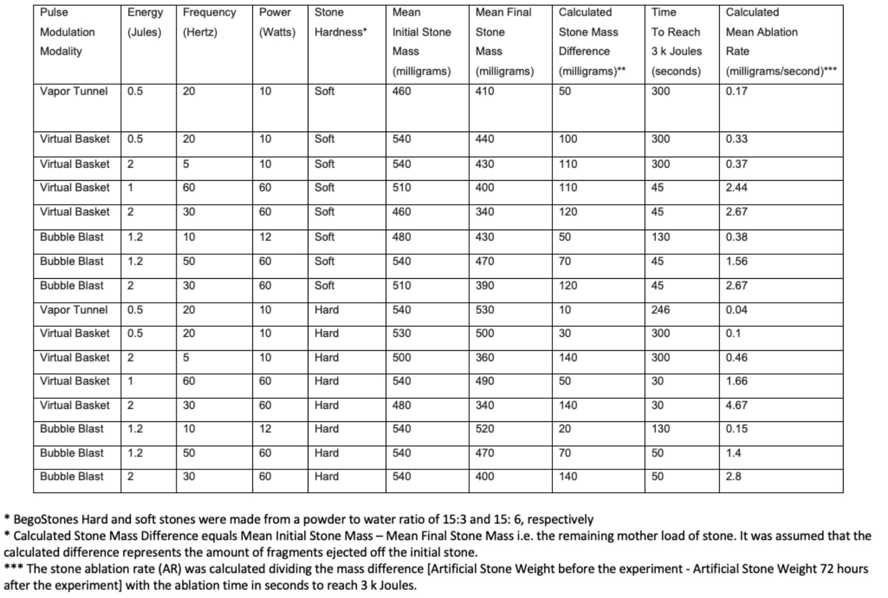
Figure 7: Soft (15:6) Phantom Stones. Before (A) and after laser lithotripsy using the following setting combination; Virtual Basket 10 W 0.5 J 20 Hz(B), Virtual Basket 10W=2Jx 5Hz (C), Virtual Basket 60W= 1Jx60Hz (D), Virtual Basket 60W= 2Jx30Hz (E), Bubble Blast 12W=1.2Jx10Hz (F), Bubble Blast, 60 W 1 J 60 Hz (G), Bubble Blast 60W= 2Jx30Hz (H) Vapor Tunnel 10W= 0.5Jx20Hz (I).



Ablation rates created by lasering artificial stones with the pulse modulation modalities that Quanta Cyber Ho offers, Virtual Basket, Bubble Blast, and Vapor Tunnel, using different power, energy, and frequency settings.

Pulse modulation affected the stone ablation rates. High-power settings were associated with higher ablation rates regardless of the stone hardness (Table 3, Figure 8).

Table 3: Data display regarding median values for 3 measurements for each trial. Median initial stone mass, median final stone mass, calculated difference, time to reach 3 k Joules of energy delivered and calculated median ablation rate for each pulse modality, stone type and, energy, frequency and power settings tested.



Pulse Modulation Modality	Energy (Jules)	Frequency (Hertz)	Power (Watts)	Stone Hardness*	Mean Initial Stone Mass (milligrams)	Mean Final Stone Mass (milligrams)	Calculated Stone Mass Difference (milligrams)**	Time To Reach 3 k Joules (seconds)	Calculated Mean Ablation Rate (milligrams/second)***
Vapor Tunnel	0.5	20	10	Soft	460	410	50	300	0.17
Virtual Basket	0.5	20	10	Soft	540	440	100	300	0.33
Virtual Basket	2	5	10	Soft	540	430	110	300	0.37
Virtual Basket	1	60	60	Soft	510	400	110	45	2.44
Virtual Basket	2	30	60	Soft	460	340	120	45	2.67
Bubble Blast	1.2	10	12	Soft	480	430	50	130	0.38
Bubble Blast	1.2	50	60	Soft	540	470	70	45	1.56
Bubble Blast	2	30	60	Soft	510	390	120	45	2.67
Vapor Tunnel	0.5	20	10	Hard	540	530	10	246	0.04
Virtual Basket	0.5	20	10	Hard	530	500	30	300	0.1
Virtual Basket	2	5	10	Hard	500	360	140	300	0.46
Virtual Basket	1	60	60	Hard	540	490	50	30	1.66
Virtual Basket	2	30	60	Hard	480	340	140	30	4.67
Bubble Blast	1.2	10	12	Hard	540	520	20	130	0.15
Bubble Blast	1.2	50	60	Hard	540	470	70	50	1.4
Bubble Blast	2	30	60	Hard	540	400	140	50	2.8

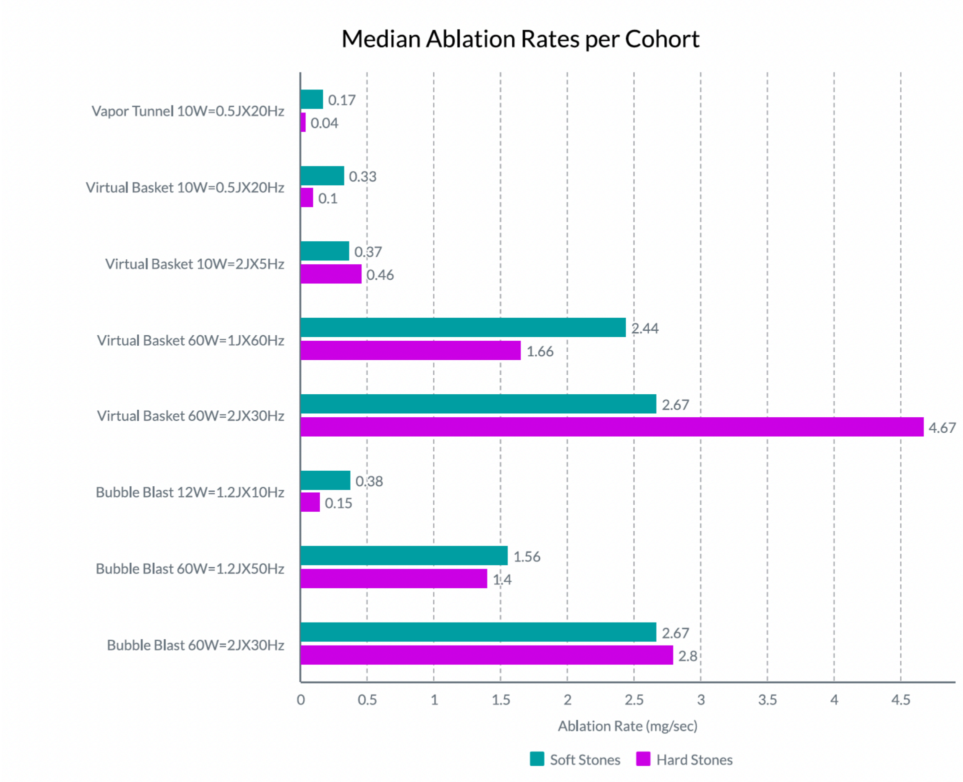
* BegoStones Hard and soft stones were made from a powder to water ratio of 15:3 and 15: 6, respectively
* Calculated Stone Mass Difference equals Mean Initial Stone Mass – Mean Final Stone Mass i.e. the remaining mother load of stone. It was assumed that the calculated difference represents the amount of fragments ejected off the initial stone.
*** The stone ablation rate (AR) was calculated dividing the mass difference [Artificial Stone Weight before the experiment - Artificial Stone Weight 72 hours after the experiment] with the ablation time in seconds to reach 3 k Joules.

The Virtual Basket, Bubble Blast and Vapor Tunnel modalities showed different records of laser activation-time to reach the target energy of 3kJ when used with the same power, energy and frequency settings. The time to reach the target energy of 3kJ was shorter with high-power laser lithotripsy also regardless of the stone hardness (Table 3).

The Virtual Basket, Bubble Blast and Vapor Tunnel pulse modulation modalities displayed different ablation rates for the equal energy and frequency settings. The greatest ablation rates were recorded using the Virtual Basket mode with 60W=2 J X 30 Hz i.e. high-power laser settings. The lowest ablation rates of all cohorts were documented with hard stones in the Vapor Tunnel pulse modulation mode.

For the identical power setting, different results were obtained for different energy-frequency laser settings and pulse modulation modality. A noteworthy improvement was noticed when using 60W = 2Jx30Hz compared to 60W = 1Jx60Hz in Virtual Basket and Bubble Blast modes for hard stones (Figure 8).

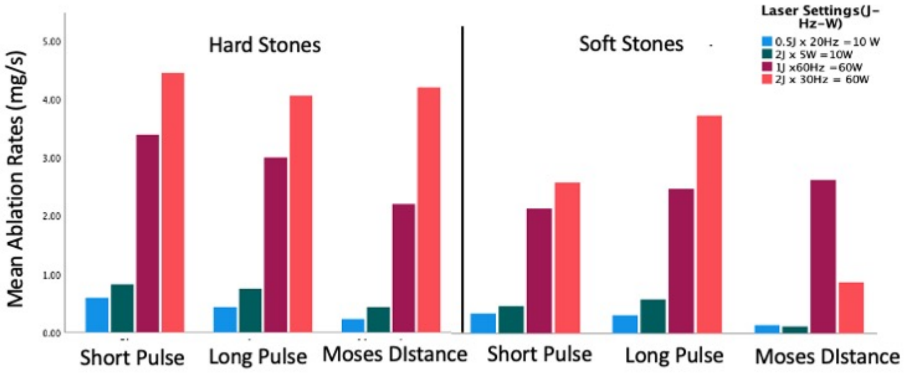
Figure 8: Stone ablation rates, that is, calculated stone mass difference/time. Median values out of three measurements per cohort are represented.



In vitro assessment stone ablation rates with Lumenis Moses 120H. Vertical setting

The time to reach the target energy of 3kJ was 5 minutes in all the 10 W trials and 50 seconds in all the 60 W trials. Moses Distance compared to non-Moses short and long traditional pulse modes seemed to result in lower ablation rates in all groups except 1J-60Hz-60W 15:3 stones, whereas Moses Distance was superior fragmentation rates wise to both short and long conventional pulses, 2J-30Hz-60W 15:3 stones where Moses Distance was inferior to both short and long conventional pulses, 1J-60Hz-60W 15:6 stones where Moses Distance was inferior to both short and long conventional pulses and 2J-30Hz-60W 15:6 stones where Moses Distance was inferior to short pulse and superior to long conventional pulse modalities (Figure 9)

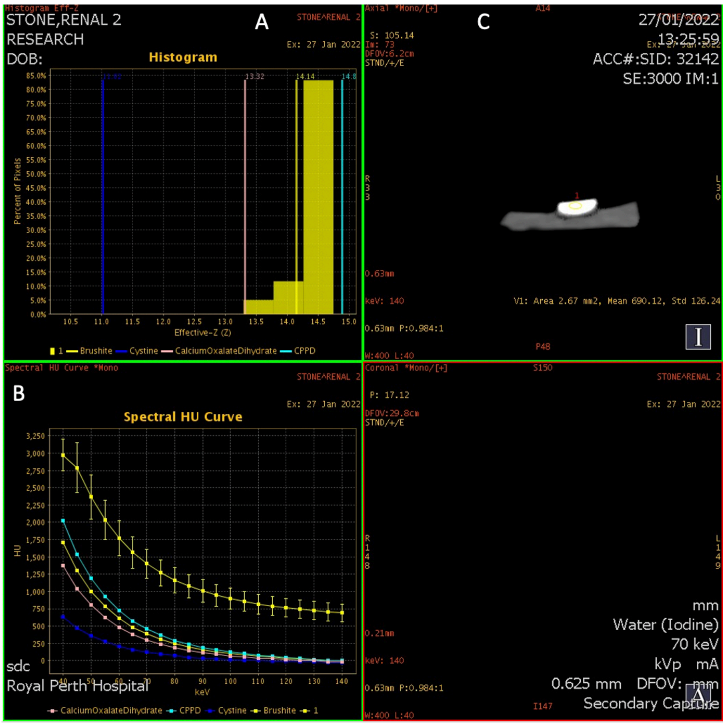
Figure 9: **Mean ablation rates (mg/s) for hard and soft stones in the second ablations rates experiment, with Lumenis 120H.**



Characterization of artificial stones

The stones were compared based on the radiological properties, spectral proeperties and fragmentation rates. Figure 10 displays an example of how data was provided by the GSI software.

Figure 10: Example of Data was provided by the GSI Software. Histogram (A), Spectral Curve (B) and Hounsfiel Units (C) were provided for every stone tested. Analysis of Monochromatic Images at 70 keV, axial. Calculation of the average effective atomic number (Z eff): quantitative analysis. The density is obtained in Hounsfield Units (C). The histogram (A) displays the distribution of the atomic number (Z) of each pixel within the area selected according to the known Z eff of various stone compositions for a quantitative analysis. The thick bar on the histogram represents the tested stone. The colored lines represent known Z eff of various stone compositions as a reference to estimate the composition of the tested stone. The thick bar on the histogram represents the tested stone. The colored lines represent known Z eff of various stone compositions as a reference to estimate the composition of the tested stone.



Regarding radiological properties in terms of HU, artificial calculi composed of 15g of Bego Powder and 3ml of water could be comparable to real stones composed of calcium oxalate and calcium phosphate. However, the rest of artificial stones tested were not comparable to real struvite, uric acid or cystine stones (Figure 11, Table 4).

Figure 11: Stones' Hounsfield Units Assessment by Computerized Tomography (CT) Scan.

A: BegoStones. 1: Artificial Stone composed by 15gr of Bego powder and 12 ml of water; 2: Artificial Stone composed by 15gr of Bego powder and 11 ml of water; 3: Artificial Stone composed by 15gr of Bego powder and 11 ml of water; 4: Artificial Stone composed by 15gr of Bego powder and 10 ml of water; 4: Artificial Stone composed by 15gr of Bego powder and 9 ml of water; 5: Artificial Stone composed by 15gr of Bego powder and 8 ml of water; 6: Artificial Stone composed by 15gr of Bego powder and 7 ml of water; 7: Artificial Stone composed by 15gr of Bego powder and 6 ml of water; 8: Artificial Stone composed by 15gr of Bego powder and 5 ml of water; 9: Artificial Stone composed by 15gr of Bego powder and 4 ml of water; 10: Artificial Stone composed by 15gr of Bego powder and 3 ml of water.

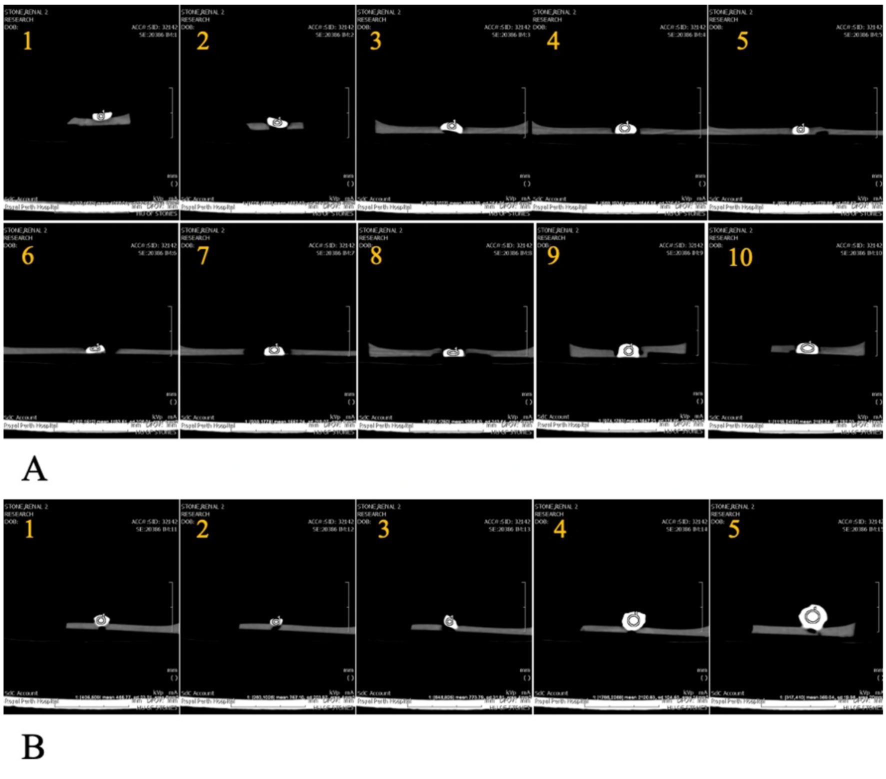


Table 4: Radiological Density in Hounsfield Units Calculated for every type of stone tested Scan, Mean Atomic Numbers and Real Stone Match as per Computed Tomography (CT) using the GSI Software.

CPPD= Calcium Pryophosphat

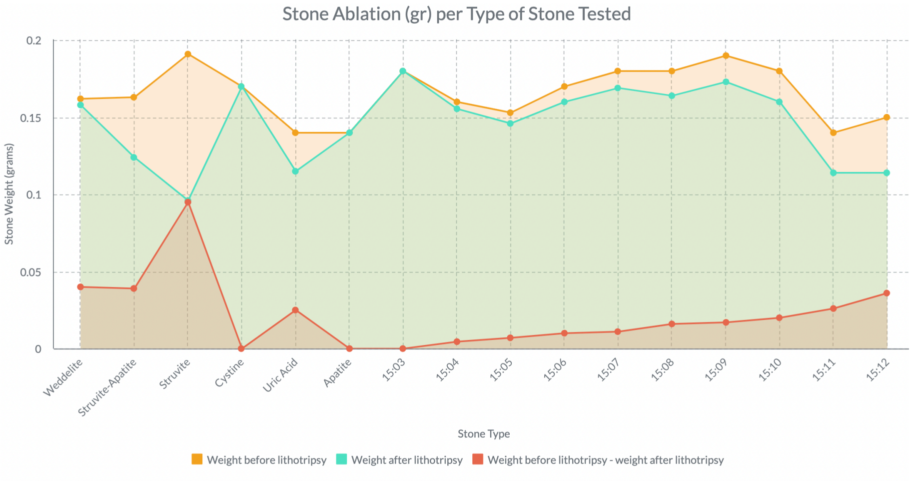
Brushite= Calcium hydrogen phosphate dihydrate

Stone Composition	Housfield Units (mean)	Range	Standard Deviation (SD)	Atomic Number mean (SD)	Real Stone with most similar Spectral Curve According to the software
Artificial Stone composed by Bego powder (gr) and water (ml) ratio of 15:12	1287	(337-1673)	372.27	690.12 (126.24)	Brushite (major) Calcium Oxalate Dihydrate (minor)
Artificial Stone composed by Bego powder (gr) and water (ml) ratio of 15:11	1587	(1028-1688)	131.13	731.12 (149.96)	CPPD (major) Brushitee (minor) Calcium Oxalate Dihydrate (minor)
Artificial Stone composed by Bego powder (gr) and water (ml) ratio of 15:10	1664	(921-2027)	254.75	797.25 (190.23)	CPPD (major) Brushitee (minor)
Artificial Stone composed by Bego powder (gr) and water (ml) ratio of 15:09	1545	(568-1934)	335.52	766.15 (216.47)	CPPD (major) Brushitee (minor) Calcium Oxalate Dihydrate (minor)
Artificial Stone composed by Bego powder (gr) and water (ml) ratio of 15:08	1278	(662-1469)	198.87	620.20 (131.96)	CPPD (major) Brushitee (major) Calcium Oxalate Dihydrate (minor)
Artificial Stone composed by Bego powder (gr) and water (ml) ratio of 15:07	1193	(402-1512)	326.01	712.20 (112.20)	CPPD (major) Brushitee (minor)
Artificial Stone composed by Bego powder (gr) and water (ml) ratio of 15:06	1552	(939-1778)	219.07	820.24 (97.84)	CPPD (major) Brushitee (minor)
Artificial Stone composed by Bego powder (gr) and water (ml) ratio of 15:05	1394	(737-1750)	313.64	765.40 (141.37)	CPPD (major) Brushitee (minor) Calcium Oxalate Dihydrate (minor)
Artificial Stone composed by Bego powder (gr) and water (ml) ratio of 15:04	1647	(974-1783)	175.86	929.41 (13.82)	CPPD
Artificial Stone composed by Bego powder (gr) and water (ml) ratio of 15:03	2182	(1118-2407)	292.03	1058.66 (87.44)	CPPD
Real Stone composed by Uric Acid	468	(405-509)	465.77	538.16 (41.81)	Uric Acid
Real Stone composed by Magnesium Ammonium Phosphate (major component) and Calcium Phosphate (major component)	757	(260-1026)	203.97	471.95 (101.14)	CPPD
Real Stone composed by Cystine	774	(646-825)	31 81	483.65 (36.68)	Cystine
Real Stone composed by Calcium Oxalate (major component) and Calcium Phosphate (minor component)	2121	(1786-2268)	104.5	999.25 (22.24)	CPPD
Real Stone composed by Magnesium Ammonium Phosphate (major component) and Calcium Phosphate (minor component)	359	(317-410)	19 96	411.14 (40.92)	Uric Acid

Artificial stones composed by 15g of Bego powder and 3ml of water, and artificial stones composed by 15g of Bego powder and 4ml of water were comparable to CPPD stones in terms of both atomic number and spectral properties. The GSI software was accurate only for uric acid stones, cystine calculi and calcium oxalate stones in terms of atomic number and spectral properties. However, it was not accurate with stones composed by struvite (Figure 11 and Table 4).

Fragmentation rate comparison demonstrated that the artificial stones composed of 15g of powder and 12ml of water were comparable to real stones composed of uric acid, and the artificial stones composed of 15g of powder and 3ml of water were comparable to real stones composed of apatite and real stones composed of cystine (Figure 12).

Figure 12: **Mean stone ablation (gr) per type of stone tested.** All stones were lasered during 30 seconds at the laser settings of power, energy and frequency of 1.5Jx20Hz=60W at the long pulse modality. Stone ablation was defined as weight before laser lithotripsy – weight after laser lithotripsy.



High-Power lithotripsy. Clinical data

174 patients were included in the analysis. 179 renal units were included in the study. 103 patients were males, and 71 patients were females. The mean age of the patients was 57.0 ± 13.5 years.

98 patients and 100 renal units underwent laser lithotripsy in dusting mode (Group 1). 76 patients (79 renal units) underwent stone "self-popping" technique (Group 2). The mean stone size was 16.4 ± 2.9 mm for the patients in Group 1, 17.4 ± 2.6 mm in group 2, (p-value = 0.018). More than 50% of the stones in both groups were localized in lower calyx (Table 5).

Table 5: Patient demographics and stone characteristics of patients treated with high-power (60W) and low-power (20W) setting.

Patient demographics	**All pts (N=174)**	**Pts treated with 60W (N=76)**	**Pts treated with 20W (N=98)**	**P value**
Age (years), mean (SD)	57.0 (13.5)	55.2 (14.2)	58.4 (12.7)	0.115
Gender, n (%)				0.241
Male	98 (56.3)	45 (59.2)	53 (54.1)	
Female	76 (43.7)	31 (40.8)	45 (45.9)	
BMI (kg/m^2), mean (SD)	24.3 (2.9)	24. (3.1)	24.0 (2.7)	0.285
Stone characteristics	**Renal units (N=179)**	**Renal units (N=79)**	**Renal units (N=100)**	**P value**
Cumulative stone size (mm), mean (SD)	16.8 (2.8)	17.4 (2.6)	16.4 (2.9)	0.018
Stone location (kidney), n (%)				0.936
Upper Calyx	18 (10.1)	8 (10.1)	10 (10.0)	
Middle Calyx	37 (20.7)	15 (18.9)	22 (22.0)	
Lower Calyx	93 (52.0)	43 (54.4)	50 (50.0)	
Renal Pelvis	31 (17.3)	13 (16.5)	18 (18.0)	

Ureteric access sheath was inserted in 94.4% of the whole study population. The 14/16Fr ureteric access sheath was more utilized in Group 2 (63.4%) compared 50.0% in Group 1. The difference in diameters between the groups was statistically significant. However, ureteral-wall severe injuries, grade 2-3 of Traxer and Thomas classification (120), were not significantly higher in any of the groups, observed in 6.7% of the whole cohort. There were no differences in developing intra or postoperative complications. Out of 20 cases with documented complications (11.2%), postoperative fever occurred in 15 patients, 3 of them developing urinary sepsis. Persistent hematuria was recorded in the remaining 5 patients managed with longer catheterization. The Stone free rate was slightly higher for the high-power lithotripsy group (84.8%) (Table 6).

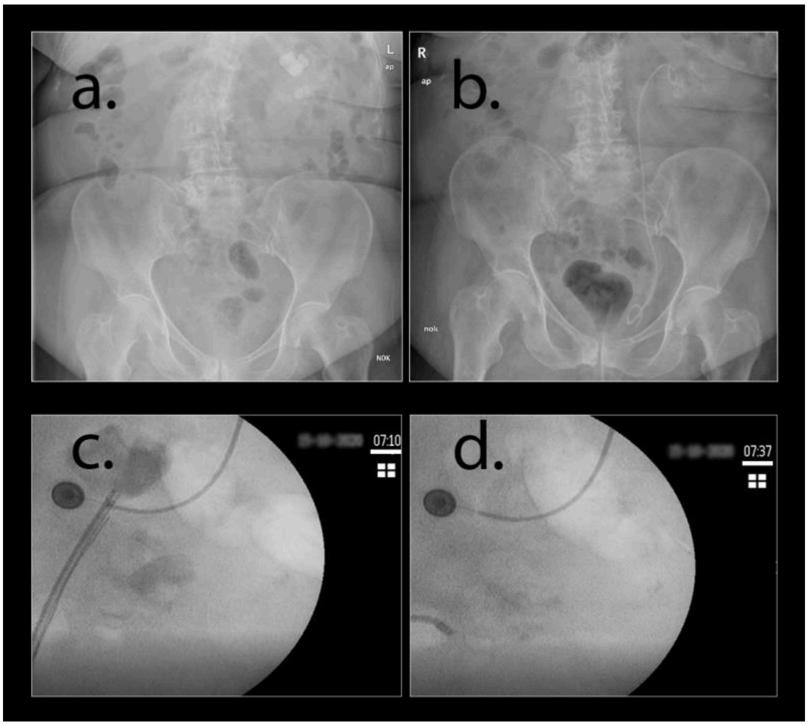
Table 6: Perioperative parameters and outcomes of patients treated with high power (60W) and low power (20W) setting.

Perioperative parameters and outcomes	All renal units (N=179)	Renal units treated with 60W (N=79)	Renal units treated with 20W (N=100)	P value
Operative time (min), mean (SD)	53.4 (18.8)	44.9 (15.5)	60.1 (18.6)	<0.001
Stone disintegration time (min), mean (SD)	25.5 (11.1)	16.5 (4.7)	32.6 (9.4)	<0.001
Fluoroscopy (min), mean (SD)	3.4 (1.0)	3.4 (1.01)	3.4 (0.97)	0.805
Hb drop (g/l), mean (SD)	0.67 (0.3)	0.7 (0.32)	0.65 (0.3)	0.249
Length of hospital stay (days), mean (SD)	1.2 (0.4)	1.2 (0.5)	1.1 (0.4)	0.14
Stone repositioning before lithotripsy, n (%)				<0.001
Not performed	140 (78.2)	79 (100)	61 (61.0)	
Performed	39 (21.8)	0	39 (39.0)	
Size of the UAS (Fr), n (%)				0.004
No UAS	10 (5.6)	0	10 (10.0)	
12/14	65 (36.3)	25 (31.6)	40 (40.0)	
14/16	104 (58.1)	54 (63.4)	50 (50.0)	
Intra and postoperative complications, n (%)	20 (11.2)	7 (8.9)	13 (13.0)	0.383
Overall complications	12 (6.7)	5 (6.3)	7 (7.0)	

Fever	5 (2.8)	3 (3.8)	2 (2.0)	
Persistent hematuria	3 (1.7)	1 (1.3)	2 (2.0)	
Sepsis				
Injury due to UAS insertion (11), n (%)				0.848
No injury	121 (67.6)	54 (68.4)	67 (67.0)	
Mild (Grade 1)	46 (25.7)	19 (24.1)	27 (27.0)	
(Grade 2-3)	12 (6.7)	6 (7.6)	6 (6.0)	
Stone-free status, n (%)				0.404
No	32 (17.9)	12 (15.2)	20 (20.0)	
Yes	147 (82.1)	67 (84.8)	80 (80.0)	
Additional treatment, n (%)				0.844
No treatment	164 (91.6)	71 (89.9)	93 (93.0)	
URS	9 (5.0)	5 (6.3)	4 (4.0)	
SWL	6 (3.4)	3 (3.8)	3 (3.0)	

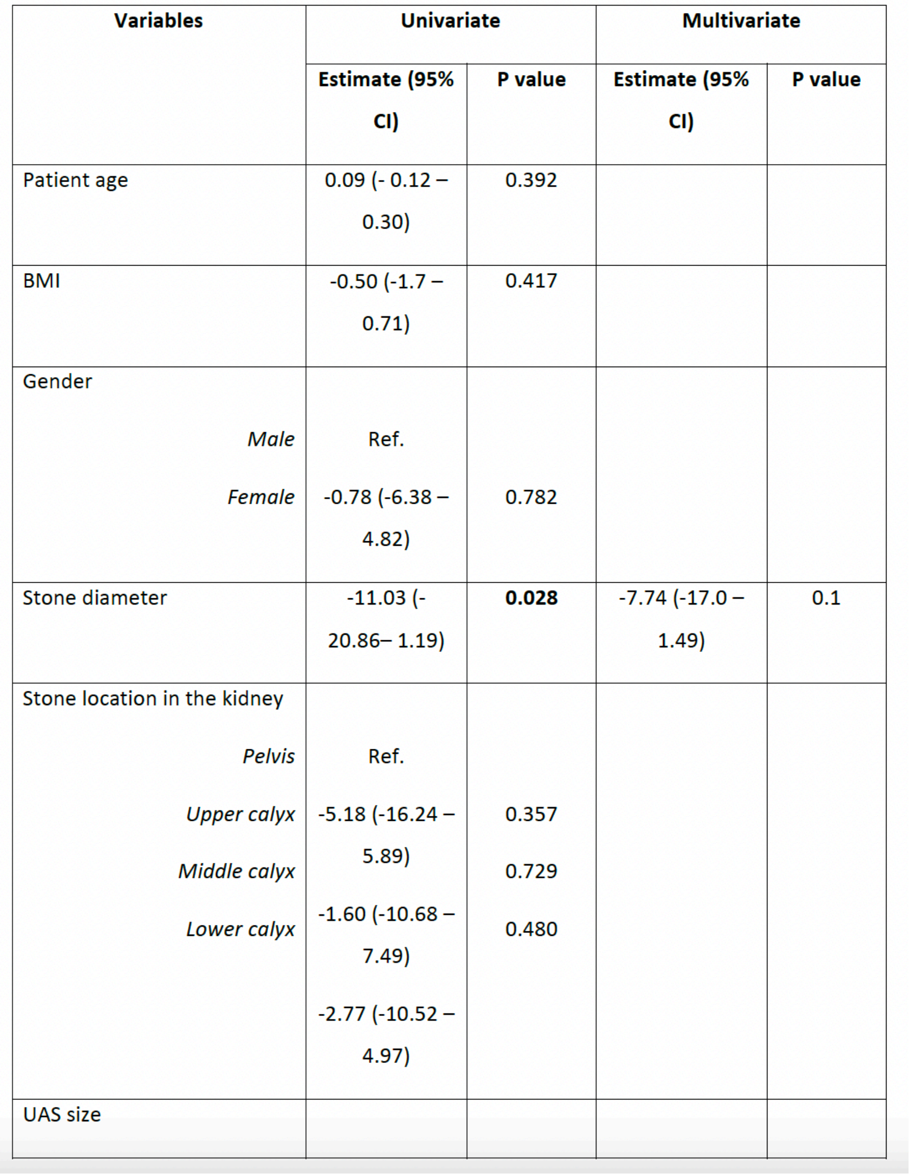
No other factor had any significant impact on the stone free rate. Nevertheless, the mean operating time and stone disintegration time were significantly better in Group 2, high-power laser lithotripsy with the "self-popping" firing technique, comprising 44.9 ± 15.5 minutes and 16.5 ± 4.7, respectively (Figure 13).

Figure 13: Retrograde intrarrenal surgery for 2.2cm stone **a.** Preoperative KUB image, **b.** Postoperative KUB image without any visible stone fragments and double J stent in place, **c.** Start of the stone disintegration at 07:10, **d.** End of the stone disintegration at 07:37 (total disintegration time 27 minutes).



On univariate analysis, the stone size, the use of 14/16Fr ureteral access sheath and stone lithotripsy with stone "self-popping" technique decreased the operative time and Stone disintegration time significantly. According to multiple regression analysis, the only factor improving both operation time for 14.1min (CI = 8.8 – 19.44) and stone disintegration time for 15.8min (CI = 13.44 – 18.2), remained laser lithotripsy using stone "self-popping" technique (Table 7 and 8).

Table 7: Factors affecting overall operative time on univariate and multiple regression analyses.

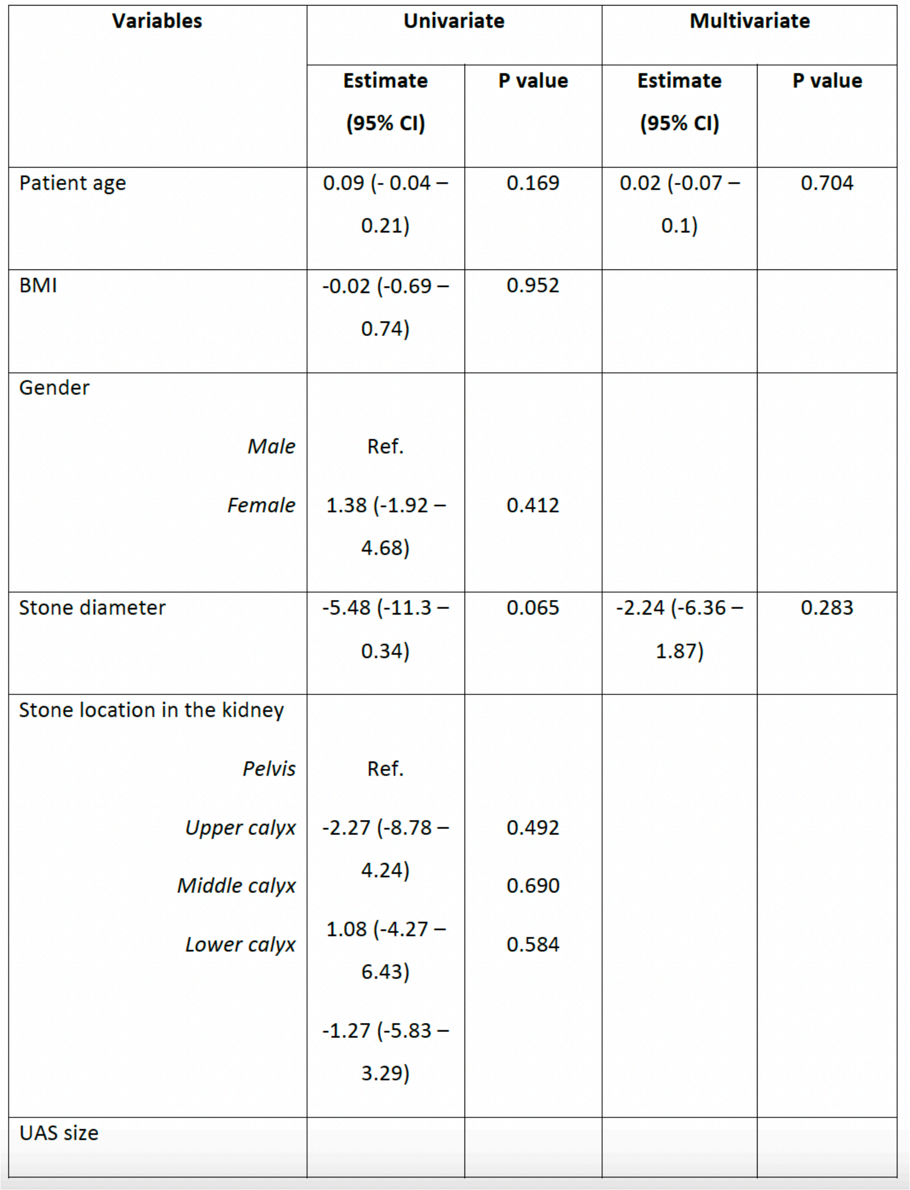


Variables	Univariate		Multivariate	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
Patient age	0.09 (- 0.12 – 0.30)	0.392		
BMI	-0.50 (-1.7 – 0.71)	0.417		
Gender				
Male	Ref.			
Female	-0.78 (-6.38 – 4.82)	0.782		
Stone diameter	-11.03 (-20.86– 1.19)	**0.028**	-7.74 (-17.0 – 1.49)	0.1
Stone location in the kidney				
Pelvis	Ref.			
Upper calyx	-5.18 (-16.24 – 5.89)	0.357		
Middle calyx	-1.60 (-10.68 – 7.49)	0.729		
Lower calyx	-2.77 (-10.52 – 4.97)	0.480		
UAS size				

No UAS	Ref.			
12/14Fr	-8.85 (-21.37 – 3.67)	0.222	-2.48 (-14.27 – 9.32)	0.679
14/16Fr	-12.21 (-24.42 – -0.02)	**0.05**	-3.74 (-15.4 – 7.93)	0.528
Laser lithotripsy mode				
Stone self-popping (High power with 60W)	Ref.		Ref.	
Dusting (Low power with 20W)	15.1 (9.96 – 20.24)	**<0.001**	14.12 (8.8 – 19.44)	**<0.001**

BMI – body mass index, UAS – ureteral access sheath, CI – confidence interval. Statistically significant outcomes are bolded.

Table 8: Factors affecting stone disintegration time on univariate and multiple regression analyses



Variables	Univariate		Multivariate	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
Patient age	0.09 (- 0.04 – 0.21)	0.169	0.02 (-0.07 – 0.1)	0.704
BMI	-0.02 (-0.69 – 0.74)	0.952		
Gender				
Male	Ref.			
Female	1.38 (-1.92 – 4.68)	0.412		
Stone diameter	-5.48 (-11.3 – 0.34)	0.065	-2.24 (-6.36 – 1.87)	0.283
Stone location in the kidney				
Pelvis	Ref.			
Upper calyx	-2.27 (-8.78 – 4.24)	0.492		
Middle calyx	1.08 (-4.27 – 6.43)	0.690		
Lower calyx	-1.27 (-5.83 – 3.29)	0.584		
UAS size				

No UAS	Ref.			
12/14Fr	-4.55 (-11.88 – 2.77)	0.222	1.92 (-3.39 – 7.23)	0.476
14/16Fr	-8.00 (-15.14 – -0.86)	**0.028**	0.69 (-4.58 – 5.96)	0.796
Laser lithotripsy mode				
Stone self-popping (High power with 60W)	Ref.		Ref.	
Dusting (Low power with 20W)	16.1 (13.78 – 18.36)	**<0.001**	15.84 (13.44 – 18.2)	**<0.001**

BMI – body mass index, UAS – ureteral access sheath, CI – confidence interval. Statistically significant outcomes are bolded.

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DISCUSSION

Endourology i.e. ureteroscopy, retrograde intrarenal surgery and percutaneous nephrolithotomy are gaining momentum in the treatment of renal and ureteral stones (5,55,72). New developments of endourology for urolithiasis have significantly enhanced the indications of endourology compared to extracorporeal shock wave lithotripsy (71). The laser technology has revolutionized urolithiasis management in the last decades (70). The present PhD Thesis Study had 4 aims with the bigger purpose of shedding some light in the knowledge of how new technologies for Ho:YAG laser lithotripsy work from both clinical and preclinical assessments.

Firstly, in vitro experiments were designed to characterize the pulse modulation modalities that Quanta Cyber Ho offers, Virtual Basket, Bubble Blast, and Vapor Tunnel, assessing the bubble formation features of each pulse modulation modality, test the stone ablation rates for these pulse modulation modalities, using high and low-power lithotripsy with different energy, and frequency settings, on a horizontal experimental setting, and assessing the fragmentation patterns created by lasering artificial stones in the experiment.

Secondly, in vitro experiments were designed to test the stone ablation rates for the pulse modulation modalities of Moses Distance, and standard short and long pulse modalities on a vertical setting in order to avoid retropulsion and assess this effect on stone ablation rates.

One the ablation rates experiments were performed, it was noticed that the artificial stones used as hard stones had only been characterized from limited perspectives, and a third group of experiments were designed to characterize these artificial stones used for preclinical experiments in endourology by comparing them to real stones from three perspectives; Radiological properties, spectral properties and hardness in terms of stone fragmentation rates.

Finally, the goal for the clinical analysis high-power lithotripsy wise in a real patient setting was to compare a high and low-power settings at Ho:YAG laser lithotripsy for Retrograde Intrarenal Surgery in terms of effectivity and safety in patients from a reference tertiary centre.

High-power laser lithotripsy was faster in all in vitro experiments and in the clinical analysis. It was related to higher ablation rates in preclinical studies. High-power laser lithotripsy was as save as low-power laser lithotripsy in the clinical analysis.

In the presented experiments, the Virtual Basket pulse-modulation modality proved the highest stone ablation rates, compared to the Bubble Blast pulse-modulation modality and the Vapor Tunnel pulse-modulation mode in high-power and low-power lithotripsy for all stones types tested.

Despite clinical trials are needed to confirm the data of basic research, the data presented in the present PhD project suggest that, in the same energy and frequency settings, the ablation rates of Moses Technology in Distance mode might be, in general, lower to non Moses short and long pulse, in a context where retropulsion is artificially controlled. These findings may not influence the clinical effectivity when compensated by the reduced retropulsion of the stone.

Artificial stones mimicking urinary calculi may be very useful for basic research in endourology. However, according to our results only stones with a gram of powder to milliliter of water ratio of 15:03 mimic hard real urinary stones in terms of HU, atomic number and fragmentation rates. 15:12 stones could mimic uric acid stones in terms of fragmentation rates.

The clinical data presented indicated that the stone “self-popping” technique using high-power laser lithotripsy at 60W (pulse energy of 1.5J and frequency of 40Hz) is a safe and effective modality for retrograde intrarenal surgery as active treatment of renal stones. In comparison to dusting mode, it resulted in significantly faster procedures (14.12min), while possessing similar stone free rates.

Virtual Basket, Bubble Blast and Vapor Tunnel are three laser pulse modulation technologies that modify the Ho:YAG laser pulse transmission through the creation of bubbles emerging from the laser fiber tip with different outcomes on the target stone. These pulse modulation technology designed for Ho:YAG laser lithotripsy result in more attraction of the stone by decreasing retropulsion; while stone dusting in Vapor Tunnel and while high and low-power lithotripsy in Virtual Basket, and the creation of a strong mechanical effect that boosts stone ablation with Bubble Blast according to the manufacturer (114). However, data on these statements are scarce. Very few clinical studies (96,99), a video (98) and some preclinical data presented on a conference (121) had provided some data on it in the time we published the paper with the data resulting from the present PhD thesis (1).

Takhar M and colleagues. provided the only in vitro data currently available for Quanta Cyber-Ho pulse modulation modes in an abstract format. They used a standard 365 micrometers fiber in two modes of energy and frequency settings, 0.5J-30Hz and 0,8 J-45 Hz, in an experiment with artificial stones in the model bladder of a simulator. The Virtual Basket modality resulted in enhanced stone stability, fewer migration and better performance using high-power settings (121).

The urological community needs more information of these technologies to learn how to use them safely and efficiently. This study provides information on the ablation rates of these three pulse modalities using an in vitro custom experimental configuration with hard and soft artificial stones. Additionally, 5 different combinations of energy and frequency and 3 settings of power were tested. As a result, the current data could provide clues on the optimal use of these new technologies and further improve the laser intra-operative laser lithotripsy.

In the trials we present, for high power-power lithotripsy at 60W, Virtual Basket showed higher ablation rates than Bubble Blast in the two tested settings and in both stone types. The highest ablation rate of all tested power, pulse energy and frequency settings was observed in Virtual Basket at 2J and 30Hz for the fragmentation of hard stones. Ablation rates for Virtual Basket and Bubble Blast improved with increasing laser power. Virtual Basket mode and Bubble Blast mode for hard stones, showed a noticeable improvement when using 60W = 2Jx30Hz compared to 60W = 1Jx60Hz. The likely explanation to this result mighy be that retropulsion is lower in hard stones because they are heavier and therefore have limited mobility compared to soft stones, but required higher energy to achieve effective fragmentation. Thus, when using higher energy (2J) at the trials with 60W (2Jx30Hz) the fragmentation rate was higher in hard stones compared to soft stones in both the Virtual Basket and the Bubble Blast modalities. Contrarily, the difference between the ablation rates for these two high-power settings tested regarding energy and frequency was not evident for soft stones. It seemed that these stones were efficiently fragmented with lower power settings. These points could correlate to the clinical practice and the use of high-power settings could provide an advantage during laser lithotripsy of hard stones.

In low-power lithotripsy (10W=0.5Jx20Hz), the Virtual Basket mode showed higher ablation rates compared to the Vapor Tunnel modality. The vapor tunnel could be efficient for dusting. The lack of higher power settings result in non taking advantage of the high-power settings. Thus, this is more appropriate for those willing to optimise the "traditional" lithotripsy -dusting.

In contrast to clinical findings of Bozzini and colleagues (98,99), our results showed a low stone ablation rate (median= 0.04 mg/sec) for the hard stones using the Vapor Tunnel mode. This may be due the fact that a dusting mode was not ideal for evaluating lithotripsy of hard stones since they usually need a higher energy peak (116). Winship et al. outlined the same problem when investigating the efficiency of dusting mode of the MOSES technology™ (93). (93). It is claimed that when dusting is clinically employed for hard stones, a completion stage of pop-dusting is required using low pulse energy (0.5–0.6 J), high frequency (20–40 Hz) and long pulse mode in a non-contact lithotripsy to pulverize the Stone (88,115). However, the settings that we used to test the Vapor Tunnel mode were included in those ranges (0.5 J-20 Hz).

In hard stones, the Virtual Basket modality at 10W=2Jx5Hz mode showed a higher ablation rate than the Bubble Blast mode at 12W=1.2Jx10Hz. According to our experiments, the Virtual Basket pulse mode is the best to use for low and high-power lihtrotripsy for specific stones, concuringly with the clinical findings of Bozzini and colleagues (99).

Sea and collaborators showed that dusting settings (pulse energy at 0.2 J at high frequency) yields small fragments whereas higher pulse energy (1-2 J) tends to produce larger fragments but at a faster ablation speed (108). The effect of each mode on stone fragment size distribution assessed qualitatively. A quantitative characterization could be addressed in further studies.

Other limitations of this and the second part (Lumenis Moses Ablation Rates with Vertical Setting) of study might be that only two stone types were built and tested. Plus, in the third part of the study was proved that the 15:06 stone might not represent soft stones in reality ablation rates wise. However, the protocol for this experiment was based on previous studies which stated that 15:06 mimic real soft stones (113). Other factors such as intrarenal pressure or irrigation flow, stone retropulsion may affect stone ablation rates in clinical conditions. Nevertheless, the experiments of this part of the study shed some light on a field where there was barely preliminary data and provided experimental data on the use of recently introduced laser pulse modulation technologies. The experimental setting was simple and reproducible. Additional studies and especially clinical studies could further strengthen the presented results. Furthermore, laser beam profiling experiments should be needed to physically characterize each of these modes with their relative intensities, pulse lengths, bubble formation features and duty cycles.

The benefits of Moses Technology® are focused on improving the main factors that limit the efficiency of the conventional Ho:YAG laser technologies, which are energy transmission through water and stone retropulsion. In theory, a more effective pulse transmission happens, saving procedural time. Nevertheless, the urology community is waiting for further data related to this promising technology in order to optimize its clinical use, overall, taking into consideration that, despite shortening the procedural time, the Moses technology has a price differential of significant increase when compared to the standard Holmium system due to higher cost of the software itself and the laser fibers

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The impact of laser pulse modulation technologies through bubble formation on stone ablation has been most widely studied across platforms with the MOSES technology™. Nonetheless, the data are contradictory. Elhiladi and colleagues showed that stone ablation volumes were significantly higher in the Moses modes compared with non-Moses (92). Black and colleagues found that, at 2 mm laser tip-stone distance, Moses Distance with low frequency and power (1 Hz, 20 W) popcorn settings results in more fragmentation than short pulse (90). However, other experiments with hard and soft stones showed that Moses modes have no significant impact on stone ablation neither in hard stones at any distance nor in soft stones at 2 mm laser tip-stone distance (93). In experiments with soft stones at 1 mm distance, Moses Distance produced significantly greater ablation than all other settings (93,109). In tests with soft stones at 0 mm laser tip-stone distance, Moses Contact produced a greater ablation than regular long-pulse mode in Winship and collaborator´s study (93), but according to Aldoukhi´s findings Moses Distance resulted in greater fragmentation (109).

All the data from in vitro studies is based on models mimicking unobstructed stones where the reduction of retropulsion enhanced stone fragmentation and shortened the procedure time.

The first numbers were published by Elhiladi and colleagues in 2017. They compared stone retropulsion in Moses and non-Moses using a high-speed camera, and stone ablation efficiency using an experimental setting that consisted in a water chamber under a motorized stage holding the fiber. They found that stone movement was decreased by 50 times at 0.8J and 10Hz ($p<0.01$). Stone ablation volumes were 160% higher in the Moses modes compared with non-Moses mode ($p<0.001$). They observed the greatest differences at low-energy, high-frequency settings such as those used when dusting a stone (92).

Regarding the fiber tip-stone distance, Ibrahim et al (95) and Winship et al (93) found that fragmentation efficiency was higher in Moses contact mode, whereas Aldoukhi and colleagues (109)found that it was higher using Moses Distance when the fiber tip was 1 mm away from the stone.

Ibrahim et al used a stone simulator model that mimics the urinary system, including bladder, ureters, and kidneys, with different calyces to compare fragmentation efficiency of the Moses mode to a conventional Ho:YAG laser. They placed the artificial stones in the lower pole of the kidney in the simulator to measure the efficiency of laser lithotripsy by procedural time and compared the degree of stone retropulsion between the different modes. They recorded a significant reduction in stone retropulsion in the Moses contact mode. They concluded that Moses Contact lead to a significant shorter procedural time during fragmentation and dusting in comparison to the regular mode (95).

Aldoukhi et al evaluated the effect of fiber tip to stone distance on fragmentation with a 3D positioning system and a 230 μm core laser fiber They tested the ablation volume positioning the fiber tip at 0, 0.5, 1, 2, and 3 mm from the stone. They measured the volume of ablation crater using a 3D confocal microscopy. For all the testes they used the energy and frequency settings 1J-10Hz over 3 minutes. They observed that ablation declined as the working distance increased with no ablation occurring at 3 mm. At 1 mm distance, the ablation crater volume using Moses Distance mode was significantly higher when compared to short pulse, long pulse and Moses Contact ($p<0.05$). Compared to all pulse modes tested, Moses Distance resulted in 28% and 39% greater fragmentation at both 0 and 1 mm working distance, respectively ($p<0.05$) (109).

Winship et al used a stage controller and three-dimensional positioning system in a spiral motion across a flat artificial stone submerged in water to compare ablation efficiency of short pulse, long pulse, Moses Contact, and Moses Distance and fiber tip degradation. The laser tip was positioned at 0, 1, and 2 mm from the stone at energy settings of 0.4 J delivered at 70 Hz until reaching 4 kJ of energy. Fiber tip degradation was recorded at 1 kJ intervals. In their experiments, the closer the laser was to the stone, the higher stone ablation was. Pulse mode had no significant impact on ablation at any distance in hard stones. In soft stones Moses Contact at 0 mm produced the greatest ablation, significantly higher than long pulse ($p<0.05$). Moses Distance at 1 mm, produced significantly greater ablation than all other settings ($p=0.025$) and was as effective as long o short pulse at 0 mm. At 2 mm distance, no pulse type demonstrated significantly different ablation. Fiber tip degradation was minimal and not significant between settings (93).

Our group presented a study where we compared the lithotripsy ablation rates using the Moses technology to conventional pulse modes within the Ho:YAG laser (122). We used the exact same materials as in the experiment performed for the present PhD and tested stone abkation rates at Conventional Short Pulse, Conventional Long Pulse, Moses Contact and Moses

Distance at the exact same settings set for this experiment 10W=0.5Jx20Hz, 10W=2Jx5Hz, 60W=1Jx60Hz, and 60W=2Jx30Hz on 15:03 and 15:06 artificial BegoStones. The difference is that we are using a vertical setting in the experiment for this PhD to avoid retropulsion, and we set a 30 degree setting for the published study. The time to reach the target energy was 5 minutes in all the 10W trials and 50 seconds in all the trials at 60W, like in this experiment. In 10W=0.5Jx20Hz for soft stones the highest mean stone ablation rates were recorded in the Long Pulse conventional modality, and for hard stones in the Moses Distance modality. The highest mean ablation rates at 10W=2Jx5Hz were recorded in Moses Distance for soft stones and the long conventional pulse modality for hard ones. In 60W=1Jx60Hz for both soft and hard stones the highest mean stone ablation rates were recorded in the long conventional pulse modality, and in 60W=2Jx30Hz the highest mean stone ablation rates were recorded in the Moses Distance mode. This is why we are testing only Moses Distance for this experiment we are presenting.

In the custom experimental settings, retropulsion was avoided and, therefore, compared retropulsion biased less ablation rates of Moses Distance to Non-Moses short and long pulse. This explains the absence of concordance between our results and the previously published papers. The translational value of our data is probably based on what laser modality should be used in order to boost efficiency in obstructed stones where retropulsion does not play a role.

Additionally, four different energy and frequency settings with two different power settings were tested while the rest of studies to date have performed their experiments with fixed settings regarding energy and frequency, and we have proved that high power lithotripsy is related to a shorter time to reach the target energy and higher ablation rates. Nonetheless, only

Moses Distance mode was tested, which may be considered a limitation. Our heterogeneous results in high power 2J-30Hz for all types of stones needs further investigations.

The aim of the third group of the experiments of the PhD was to characterize artificial stones used for in vitro and in vivo experiments for endourology. Bego Stones with Bego powder: water ratios from 15:03 to 15:12 were built and compared with real stones from the perspective of radiological properties in terms of HU, spectral properties in terms of effective atomic numbers, both using the GSI software, and hardness in terms of stone fragmentation rates with an in vitro custom experimental model with a reproducible setting.

As it has been argued, new technologies in endourology for stone treatment are gaining momentum. However, there is a lack of data on how to use these new technologies safely and effectively. Preclinical studies are very useful in order to design translational research and learn how use the new technologies optimally. During the last years, many preclinical studies using in vitro and in vivo experimental settings with artificial stones have been published for many purposes such as characterizing stone ablation rates with different pulse modulation technologies, and energy and frequency settings, the optimal laser fibre tip- stone distance, intrarenal temperatures assessment with high-power laser lithotripsy etc. However, the data regarding the properties of these phantom stones is limited.

Esch and colleagues published a paper where they proposed a simple method to build artificial stones from BegoStone Plus Powder (113).

They prepared phantom stones with a powder(gr):water(ml) ratio ranging from 15:3 to 15:6. They assessed the acoustic properties of the stones by using an ultrasound transmission technique. However, there are not papers to our knowledge that further characterize other properties of Bego stones and compare them to real stones. Esch and colleagues concluded that hard Bego stones, made from a powder:water ratio of 15:3, could compare acoustically to real stones composed of calcium oxalate. Similarly, according to our results, 15:03 Bego stones mimic real urinary stones with calcium as a major component. Nonetheless, according to Esch et al, 15:06 Bego Stones could compare real soft stones such as uric acid acoustically. On the contrary, according to our study, it is the 15:12 Bego Stones that could compare soft stones like uric acid ones in terms hardness from their fragmentation rates properties. This could be explained because they did not test the hardness but they estimated the mechanical properties of Bego Stones based on the elastic wave theory from the acoustic properties that they measured. When the 15:06 stones were lasered in our experiment, they showed lower ablation rates than uric acid or magnesium phosphate real stones. That suggests that 15:06 artificial stones are harder than uric acid or magnesium phosphate real stones.

According to our results, the Bego Stones with powder:water ratios from 15:12 to 15:04 were not comparable neither to real struvite, uric acid or cystine stones. This could be explained because HU are determined by the material per se and all the Bego Stones built were composed by the same material (water and Bego powder). However, artificial calculi composed of 15 gr of Bego Powder and 3 ml of water could be comparable to real stones composed of Calcium Oxalate and Calcium Phosphate.

Artificial stones composed by 15 gr of Bego powder and 3 ml of water, and artificial stones composed by 15 gr of Bego powder and 4 ml of water were comparable to calcium pyrophosphate stones in terms of atomic number and spectral properties.

Simmons et al performed diametral compression testing and ultrasound transmission tests to characterize the Bego Stones from their acoustic properties. They found that the tensile fracture strength and acoustic properties of these stones match a wide variety of real calculi (123).

According to Liu and Zhong, the physical properties of BegoStone are comparable to hard renal calculi such as calcium oxalate monohydrate stones. BegoStone is much denser and harder than phantom stones made of plaster-of-Paris (112). When they compared fragmentation rates on Bego Stones, paster-of-Paris Stones and real Calcium Oxalate Stones by using Shock Wave Lithotripsy, they found that BegoStone was more difficult to fragment than plaster-of-Paris phantoms, but the trends in stone comminution were similar for both phantoms. They attributed this finding to the high elastic moduli and hardness of Bego Stone (112).

In our study, 15:03 Bego stones showed similar results compared to real urinary stones with calcium as a major component from all the perspectives assessed, stone ablation and radiological properties. Nonetheless, our experiments showed that at least from the perspective of stone ablation, 15:11 Bego Stones could compare soft stones like uric acid. Perhaps not only plaster-of-Paris but also BegoStones composed with an enough amount of water (from 15:11 on) are softer and comparable to soft stones stone ablation wise.

According to our results, 15:12 to 15:04 Bego Stones were not similar neither to real struvite, uric acid or cystine stones radiological properties wise. This could be explained because HU are determined by the material per se and all the Bego Stones built were composed by the same material (water and Bego powder). However, 15:03 Bego Stones were comparable to real stones composed of Calcium Oxalate and Calcium Phosphate and not any other powder: water ratio tested.

15:03 and 15:04 artificial stones showed similar results than calcium pyrophosphate stones in terms of atomic number and spectral properties.

Stone ablation wise, the experiment was reproducible and avoided bias of retropulsion. The numbers for artificial stones followed a logic order i.e. the hardest the stones were, the less weight difference they showed before and after fragmentation meaning they broke less.

The GSI software was accurate for uric acid stones, cystine calculi and calcium oxalate stones in terms of atomic number and spectral properties. It was not accurate with stones including struvite as a major component. There are data suggesting that the software has a sensitivity and specificity for uric acid stones of 100 and 99.7%, respectively (124–130). The validity for other types of stones was not as accurate in this study. The software uses the atomic number of crystals of calcium pyrophosphate which are common in gout disease but not in renal stone formation disease.

Understanding the physical characteristics of urinary calculi and how the stone composition influences their fragmentation is key to improve the understanding on lithotripsy (131,132). The data suggests that changing the absorption of the stones at 2.12 µm leads to a change in the extent of fragmentation, whereas altering the absorption of the bulk medium has a negligible impact on fragmentation (132). Also, when studying the microstructure and mineral composition of kidney stones and their influence on the stone’s susceptibility to fragmentation, there was a significant positive correlation between the total number of shock waves required for complete stone fragmentation and the volume fraction of crystalline phase i.e. the increase in the volume fraction of crystalline phase in the stone structure reduces the stone's susceptibility to fragmentation by shock waves. BegoStones have been assessed from their optical properties as well (133). Absorption coefficients and reduced scattering coefficients of samples at 1940 nm have been evaluated from total transmittance and diffuse reflectance measurements using an Inverse Monte Carlo technique. However, comparability to real urinary calculi has not been performed yet to our knowledge. A significant amount of knowledge on new laser technologies for laser lithotripsy is based on experiments using artificial Bego Stones. The more we learn about these stones, the more we accurate we will be to design and understanding the research in this field.

A limitation of the study might be that not pure real stones, nor artificial stones softer than 15:12 were tested nor other variety of powder used to build stones. Nonetheless, the hardest stones built proved to mimic hard real stones from the perspective assessed. Likewise, despite some authors point that BegoStone is a super-hard material (112), in our study the soft stones built, from 15:11 on, showed similar ablation rates compared to soft stones in reality.

Artificial stones are used to test endourology equipment in terms of ablation rates, stone retropulsion, intrarenal temperature, laser-tissue interactions, power output per pulse, etc (1,91–93,95,101,102,106,107). According to our experiments, the 15:03 and 15:11 Bego Stones could be comparable to real hard and uric acid calculi, respectively, for most of those experiments.

The final part of the PhD Thesis was the analysis where high-power and low-power lithotripy were compared in a clinical setting. The perioperative and postoperative outcomes of 174 patients and 179 renal units undergoing retrograde intrarenal surgery with wither low-power stone dusting lase lithotripsy or high-power stone “self-popping” laser lithotripsy were analized. The overall complication and infectious complication rates were alike in both groups. Although larger calliper ureteral access sheaths were used in the high-power laser lithotripsy group, it did not result in higher ureteral-injury rate. The mean stone size for the whole cohort was 16.8 ± 2.8mm, patients in Group 2 i.e. participants undergoing high-power laser lithotripsy had larger calculi.

Multivariable linear and logistic regression analyses were performed for both primary and secondary outcome-variables. Although patients treated with stone “self-popping” technique had larger stones, they required an average of 15 minutes less to achieve successful stone disintegration, resulting in significantly shorter procedures. Additionally, a higher stone-free-rate of 84.8% in high-power laser lithotripsy with the stone “self-poping” technique compared to 80.0% in Group 1, low-power dusting, at 1-month follow-up was reported. However, the difference was not statistically significant. The proposed technique proved to be a highly effective, safe and fast procedure for the traeatment of renal stones at any location.

Longer duration of any surgery requires more drugs-administration and theoretically increases risk of developing medical and surgical complications (134,135). Endoscopic-urological procedures are not an exception (136–138). For PCNL procedures operative time between 120-179 min was associated with 4.72 times increased odds of developing severe adverse events compared to PCNL procedures lasting ≤119 min. Longer procedures ≥ 300 min were associated with even worse outcomes with an odds ratio of 17.95 (136). In an experimental porcine model, timing of the procedure and peri-procedural higher intrarenal pressure were responsible for bacterial seeding. With a retrograde instillation of E. Coli for 1 hour, pigs treated with mini-

PCNL and having longer time of IRP above 30 mmHg were showed higher positive spleen and liver tissue cultures (139).

It is well known that the risk of increasing intrarrenal pressure is more pronounced in retrograde intrarenal surgery because of worse irrigation outflow. Recently, the impact of operative time on postoperative fever, sepsis and septic shock complications following retrograde intrarenal surgery has been investigated by Ozgor et al (137). A statistically-significant longer-operative time was reported in patients developing postoperative infectious complications compared to patients without those complications. According to a multivariable analysis, the operative time of >60 min was an independent prognostic factor increasing the risk of infectious complications (OR = 2.36, P-value = 0.04) (137). Although, operation time and stone disintegration time in the analysis presented were significantly better in Group 2, they did not result in significant difference in terms of postoperative complications. Nevertheless, the present PhD argues that keeping surgeries short and avoiding their meaningless prolongation is essential for achieving good outcomes. With expanding indications of retrograde intrarrenal surgery larger stones could be treated with shorter operative times.

Laser energy is a widely adopted mean for effective stone disintegration (138). The most used laser settings are stone dusting and fragmentation. The dusting technique requires high frequency with low energy, whereas higher energy with low frequency results in fragmentation (117). According to comparative studies of these 2 techniques no significant differences in complication rates, hospital readmission or additional procedures were observed. However, utilization the dusting technique resulted in almost 40 min shorter operative time due to avoidance of stone basketing (140). Considered as a component of dusting technique, “popcorn” approach is another well-accepted modality for effective lithotripsy (141). It incorporates the use of moderate energy (1J) with moderate frequency (10-15 Hz) and results in generation of dust plus small fragments which could be extracted with the baskets. A cornerstone of the technique is to keep the laser fiber centered in the calyx allowing the stone to bounce around the fiber. This technique is particularly useful for an overall large-stone burden but with relatively small pieces (141).

The proposed stone self-popping technique is a mix of fragmentation and "popcorn" techniques. Similarly, the principles of "popcorn" technique, the fiber should be placed centrally in the calyx to allow stone circulation of the stones and its fragments. Unlike the "popcorn" technique, utilizing higher energy (1.5 – 2 J), our approach can be successfully applied to big stone pieces. In addition, higher frequency (30-40Hz) allows to fragment and ultimately to dust most of the fragments in very high speed. The aforementioned approach eliminates the need for basket or grasper use. Therefore, no additional effort nor a prolongation of the procedure is required. Another advantage of the proposed technique is that lithotripsy is performed in harboring calyx with no need to directly aim the stone. Thus, in difficult calculi to reach, the need for stones repositioning is reduced. For other laser modes, stone repositioning in the renal pelvis, particularly for lower pole stones, before starting the lithotripsy might be required to ease the procedure and minimize the damage of the scope (118). As such, relocation in the presented cohort was required in 39% of patients treated with dusting mode, all from lower calyx into the pelvis. In contrast, no additional effort was required for patients managed with stone "self-popping" technique and lithotripsy was achieved in the affected calyx.

The potential threat of intrarenal laser firing is the risk of thermal injury to the kidney The damage can occur even with 5W power and the risk increases dramatically as power increases (104,142). A balance between the intrarenal temperature, adequate irrigation and the appropriate laser firing technique are required (102,106). Our in vivo porcine-experimental studies have shown that firing of less than 10 sec together with manual pumping were sufficient for keeping the intrarenal temperature in normal range even when using high-power settings at 60W (143), and the use of constant and gentle manual pumping for active irrigation and ureteric access sheath are the safest combination to keep intrarrenal temperature at safe levels (102) i.e. additional usage of ureteral access sheath further improved the outcomes. Moreover, ureteral Access sheaths proved to control the rise of intrarenal temperature even during active-manual pumping (144,145).

In a clinical setting activating the laser with a power higher than 35-40W creates a lot of dust which significantly reduces the visibility. Thus, stopping to irrigate and check the field allows for reduction of the temperature. The aforementioned recommendations (firing < 10 sec., manual pumping, and use of ureteral access sheath) should be followed for all patients in whom RIRS with 60W laser power is intended.

Despite all efforts, several limitations were unavoidable. Only 2 laser settings of power, energy and frequency were investigated, and there was a lack of comparison with the 2 other firing modes (fragmentation and pop-dusting). The dusting technique ensured a full disintegration of renal stones with no need to use any of stone extraction devices. Likewise, no additional surgical effort was required for the self-popping technique. The above mentioned were the rationales for conducting this comparison.

In addition, in most of the cases the follow-up investigation was performed with KUB and US, and the NCCT was reserved for patients with any doubts or persisting symptoms. While the NCCT remains the most precise imaging modality for follow-up imaging, reporting of the postoperative stone free rates in the literature is mainly with KUB and ultrasound tests, and it is consistent with the present reporting. Finally, despite a statistical difference was observed for the duration of the surgeries between 2 groups, it did not affect the postoperative outcomes. Partially, this might be explained by the low number of included patients. Future randomized controlled trails are required to confirm our results and further investigate the gaps.

CONCLUSIONS

1. High-power laser lithotripsy was faster in all in vitro experiments and in the clinical analysis. It was related to higher ablation rates in preclinical studies. High-power laser lithotripsy was as save as low-power laser lithotripsy in the clinical analysis.

2. In the presented experiments, the Virtual Basket pulse-modulation modality accounted for the highest stone ablation rates, compared to the Bubble Blast pulse-modulation modality and the Vapor Tunnel pulse-modulation mode in high-power and low-power lithotripsy for all stones types tested.

3. Despite clinical trials are needed to confirm the data of basic research, our data suggest that, in the same energy and frequency settings, the ablation rates of Moses Technology in Distance mode might be, in general, lower to non Moses short and long pulse, in a context where retropulsion is artificially controlled. These findings may not influence the clinical effectivity when compensated by the reduced retropulsion of the stone.

4. Artificial stones mimicking urinary calculi may be very useful for basic research in endourology. However, according to our results only stones with a gram of powder to millilitre of water ratio of 15:03 mimic hard real urinary stones in terms of HU, atomic number and fragmentation rates. 15:11 stones could mimic uric acid stones in terms of fragmentation rates.

5. The clinical data presented indicated that the stone "self-popping" technique using high-power laser lithotripsy at 60W (pulse energy of 1.5J and frequency of 40Hz) is a safe and effective modality for retrograde intrarenal surgery as active treatment of renal stones. In comparison to dusting mode, it resulted in significantly faster procedures (14.12min), while possessing similar stone free rates.

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