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Development and pilot validation of a structured training curriculum for minimally-invasive treatment of benign prostatic hypertrophy (BPH): from simulation to clinical application.

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1. SUMMARY

Lower urinary tract symptoms (LUTS) due to benign prostatic enlargement (BPE) are common in adult men and have a major impact on quality of life and healthcare costs. While surgical management of LUTS due to BPE has evolved toward minimally-invasive surgery, there is currently no structured validated training curricula for endoscopic treatment of BPE.

Mirroring the recently proposed training programs for robotic radical prostatectomy and robotic partial nephrectomy, the aim of the current research project is to develop a structured training curriculum in minimally invasive surgery for BPE, through a multi-phase program including real-case observation, preclinical simulation and modular training under the guidance of an experienced proctor.

Specifically, the project concerned three technologies:

- Green light laser anatomic photovaporization of the prostate (aPVP)
- Holmium laser enucleation of the prostate
- Transperineal laser ablation of the prostate (TPLA)

For two of these technologies (Green light and Holmium) the project has been divided into the following packages:

- Through real-cases observation in the operating theatre, definition of the key steps of the curriculum in minimally invasive and innovative treatment for BPE based on a careful analysis of the surgeon's learning curve for each surgical

procedure the most critical steps will be included in both pre-clinical and clinical modular training modules.

- At the same time of clinical observation, dynamic acquisition of the theoretical knowledge on the surgical principles of the main surgical alternatives for minimally invasive BPE treatment through a web-based e-learning platform.
- Preclinical simulation-based training on the key steps of each surgical procedure using validated surgical training simulators.
- Modular surgical training in the operating theatre, under the guidance of an experienced surgeon, to progressively acquire the practical skills and technical nuances related to each intervention in a step-by-step fashion,
- Performance of full-cases under the guidance of an experienced proctor and blind-expert based evaluation of performance by a panel of experts in the field of minimally invasive surgery for BPE.
- Taking advantage of the pre-clinical simulation training and modular surgical training, proposal of a structured training curriculum for minimally invasive treatment of benign prostatic enlargement; this task will be accomplished by defining the minimum number of times each step of each procedure needs to be reproduced by the surgeon before full-case evaluation.

For the other technology object of the study (TPLA), due to the absence of an objective parameter to assess the learning curve, the relatively novelty of this procedure in the urologic panorama as well as the simplicity in the execution of the procedure itself,

the main objective of the program was the proposal of a step-by-step guide for surgeons approaching this ultra-minimally invasive technique focusing on technical equipment, surgical aspects and post procedural facilities.
Moreover, based on both clinical and urodynamics features, as well as the occurrence of early and late complications, we evaluate the tri and pentafecta for these procedures, as metrics to assess the quality of this ultra-minimally invasive technique.

This project has brought to the development of a structured training curriculum for some of the most widespread minimally invasive procedures for the treatment of BPH, including Greenlight laser vaporization, Holmium laser enucleation, and propose a step-by-step guide for transperineal laser ablation of the prostate. As a result, during the project period, the feasibility, acceptability, and educational impact of such a curriculum in a real-life clinical setting has been evaluated, while perioperative outcomes and patient quality of life during the different phases of the program, to evaluate the safety of such a curriculum from a patient perspective, were assessed. Additionally, we evaluated the impact of the program on surgical decision-making toward the definition of a personalized treatment algorithm for patients with LUTS due to BPH according to the specific patient- and prostate-related characteristics. As a final step of the project, a multicenter European research network across different surgeons and institutions has been created, to assess the reproducibility and the clinical value of a novel ultra-minimally invasive technique for BPH.

2. INTRODUCTION

2.1. BENIGN PROSTATIC HYPERPLASIA

Benign prostatic hyperplasia (BPH) is one of the most common conditions affecting middle-aged men, due to unregulated hyperplastic growth of epithelial and fibromuscular tissues of the transitional zone of the prostate [1]. This process may lead to bladder outflow obstruction (BOO) and to lower urinary tract symptoms (LUTS), and, if not treated, to acute or chronic urinary retention, long-term alterations of the bladder detrusor muscle and chronic kidney failure. [2,3].

LUTS due to BPH are strongly associated with ageing [4,5], associated costs and burden are therefore likely to increase with future demographic changes [5,6]. In this regard, Loeb S et al. showed that prostate volume increase with age (from 2% to 2.5% per year) [7]. In the United States, studies have shown that prevalence of BPH reaches 70% in those aged 60-69 years, and more than 80% in those older than 70 years [8].

The aetiology of BPH is influenced by a wide variety of risk factors, in addition to the direct hormonal effects of testosterone on prostate tissue. Although they do not directly cause BPH, androgens are necessary in the pathogenetic pathway of BPH, since dihydrotestosterone (DHT) directly interacts with the prostatic epithelium and stroma and has direct effects on prostate stromal cells, paracrine effects on adjacent prostate cells, and endocrine effects in the bloodstream, affecting both cell proliferation and apoptosis (cell death) [9]. BPH arises as a result of the loss of homeostasis between cell proliferation and cell death, resulting in an imbalance in favour of cell proliferation. This results in increased numbers of epithelial and stromal cells in the periurethral area of the prostate which is also detectable histopathologically.

Non-modifiable and modifiable risk factors also contribute to the development of BPH. These have been shown to include metabolic syndrome, obesity, hypertension, and genetic factors. [10]

The clinical manifestation of cervico-urethral obstruction due to benign prostatic hyperplasia usually occur as lower urinary tract symptoms (LUTS).

The severity of these symptoms widely varies but tends to worsen gradually over time.

Signs and symptoms of BPH are commonly divided into:

- **Storage symptoms**, that include urinary urgency, frequency, nocturia, urge incontinence.
- **Voiding symptoms,** due to obstruction of the bladder outlet; they include urinary hesitation, intermittence, straining, weak urine flow, terminal drip, and incomplete emptying.

A smaller percentage of patients may experience urinary tract infections, acute urinary retention and haematuria.

The differential diagnoses include prostatitis, urethral stricture, urinary, neurogenic bladder, prostate cancer, and bladder cancer.

The diagnostic pathway includes collection of the patient's medical history, assessment of subjective symptoms using validated questionnaires such as the International Prostate Symptoms Score (IPSS), urinalysis, blood tests including creatinine and prostate-specific antigen (PSA) assay, physical examination including digital rectal examination (DRE) of the prostate, and ultrasonography for morphological study of the urinary tract. Other examinations that may also be necessary in the diagnostic pathway are urodynamic examinations, cystoscopy and prostate biopsy.

Treatment options for LUTS due to BPH may include either conservative, pharmacological or surgical approaches [11].

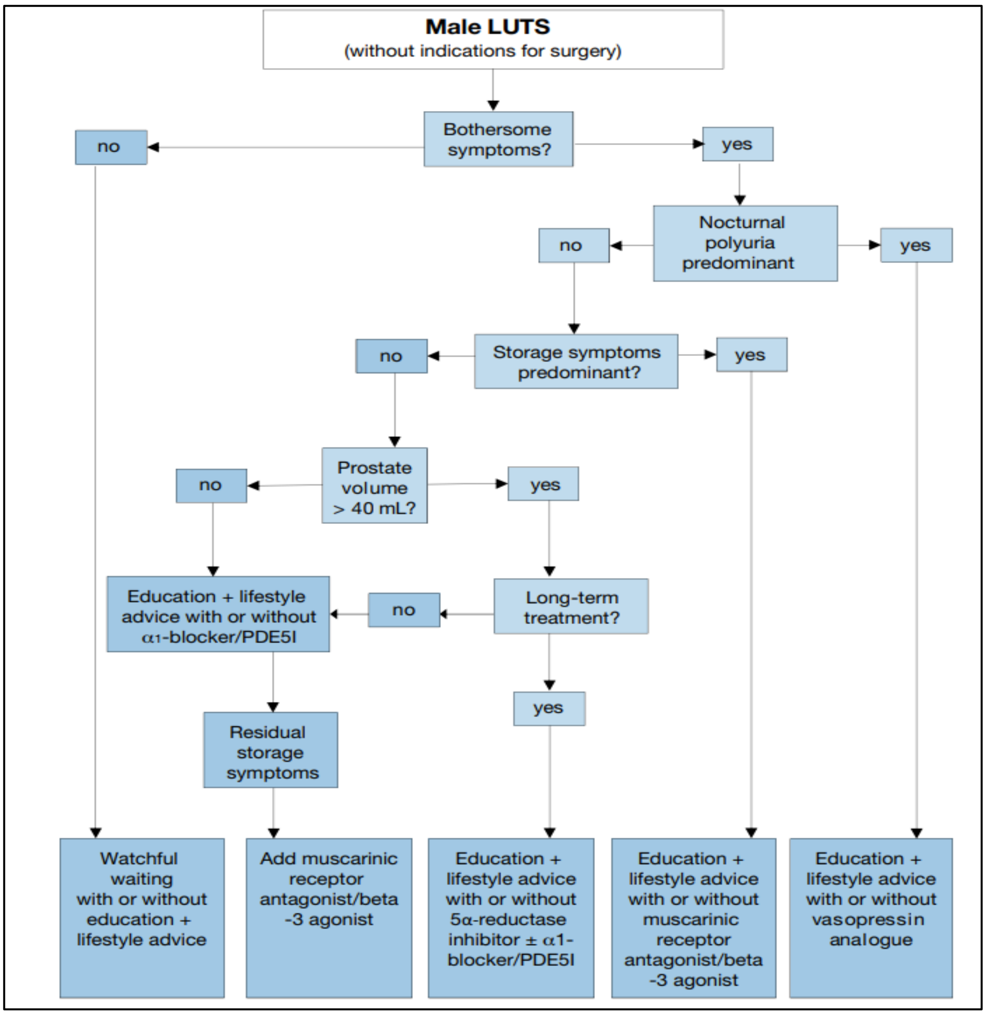


Figure 1. Algorithm for nonsurgical treatment of male LUTS: EAU Guidelines on management of non Neurogenic Male LUTS, 2022.

Lifestyle modifications are recommended for men whose symptoms are mild or mildly bothersome. These may include reducing fluid intake, avoiding or reducing intake of caffeinated beverages and alcohol, use of relaxed and double-voiding techniques, urethral milking to prevent post-micturition dribble, avoiding or monitoring the use of medications such as decongestants, antihistamines, antidepressants, and diuretics.

A pharmacological approach is recommended when the urinary symptoms burden is relevant, or the conservative approach fails. The available pharmacological options include different classes of drugs with different indications depending on the symptoms and the patient's needs. They include α-blockers, 5α-reductase inhibitors, Phosphodiesterase-5 inhibitors, muscarinic acetylcholine receptor antagonists and β3-adrenergic receptor agonists. As recommended by the last edition of European Association of Urology Guidelines all patients should be counselled about pharmacological treatment related adverse events in order to select the most appropriate treatment for each individual patient [11]. Of note, the pharmacological treatment may also have a considerable impact on the sexual sphere, in particular on the ejaculatory function, leading many patients to have low adherence rates or to discontinue the therapy [12-13]. In case of failure or intolerance to pharmacologic treatment, a surgical option can be considered.

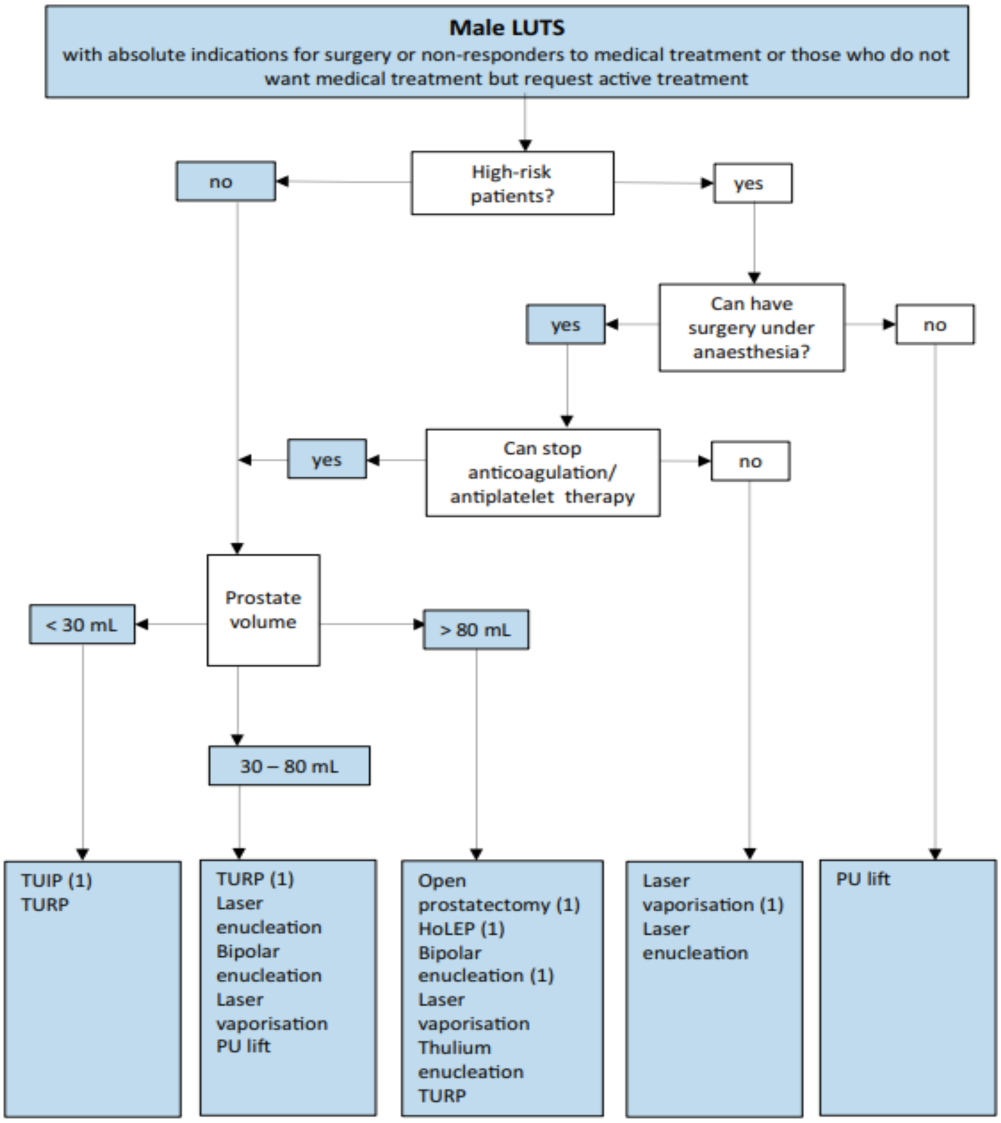
2.2.PROSTATIC SURGERY FOR BPH

Surgical treatment is one of the cornerstones of LUTS due to BPH management. Surgical options for benign prostatic hypertrophy have undergone a drastic change over the past two decades, evolving from open techniques to endoscopic techniques, including the use of laser technology, to ultra-minimally invasive surgical techniques. The choice of the right surgical technique depends on the size of the prostate, the patient's comorbidities, especially in terms of bleeding and anaesthesiologic risk, the patient's preferences, the awareness to accept the side effects associated with the procedure, the availability of the surgery, and the surgeon's experience with different surgical techniques.

European Association of Urology guidelines classify the currently available surgical options for BPH in five sections, based on the different surgical approach [11]:

- **Resection:** monopolar and bipolar transurethral resection of the prostate (M- and B-TURP), Tullium laser vaporization of the prostate (ThuVARP), transurethral incision of the prostate (TUIP);
- **Enucleation:** open prostatectomy, bipolar transurethral enucleation of the prostate (B-TUEP), enucleation of the prostate with holmium laser (HoLEP), enucleation of the prostate with thulium laser (ThuVEP and ThuLEP), enucleation of the prostate with diode laser (DiLEP); Laparoscopic Simple Prostatectomy and Robot-Assisted Simple Prostatectomy (RCT are needed)

- **Vaporization:** bipolar transurethral vaporization of the prostate (B-TUVP), vaporization of the prostate with "GreenLight" laser;
- **Alternative ablative techniques:** aquablation (AquaBeam), prostatic artery embolization (PAE), Rezum (under study);
- **Non-ablative techniques:** prostatic urethral lift (PUL), intraprostatic injections of botulinum toxin A, trifluted fexapotide and PRX302, iTIND (under study).



(1) Current standard/first choice. The alternative treatments are presented in alphabetical order. Laser vaporisation includes GreenLight, thulium, and diode laser vaporisation. Laser enucleation includes holmium and thulium laser enucleation.
HoLEP = holmium laser enucleation; PU = prostatic urethral; TUIP = transurethral incision of the prostate; TURP = transurethral resection of the prostate.

Figure 2. Algorithm for the surgical treatment of male LUTS: EAU Guidelines on management of non Neurogenic Male LUTS, 2022.

The main surgical techniques used for BPH are described below.

2.2.1. Transurethral resection of the prostate (TURP)

Represents the gold standard of treatment in moderate-to-severe LUTS and with a prostate volume of 30-80 ml (Figure 3) [11]. TURP involves the removal of prostatic tissue from the transition zone through a transurethral approach. A resectoscope is inserted through the urethra to reach the prostate and cut slices of enlarged prostate tissue with a metal loop. Prostatic tissue is then expelled at the end of the procedure and sent to histopathological analysis.

It can be performed with two techniques: with monopolar (Monopolar-TURP) or bipolar (Bipolar-TURP) instruments; although the efficacy in improving uroflowmetry parameters and reducing the symptoms burden has been proved to be similar between the two techniques, B-TURB has a higher safety profile due to lower rates of TUR syndrome [14,15]

Bleeding, clot retention, transurethral resection syndrome (mainly with M-TURP) and urinary tract infections have been reported as short-term complications. In the long term, incontinence or urinary retention, urinary tract infections, bladder neck contracture, urethral stenosis, retrograde ejaculation, and erectile dysfunction may occur.

2.2.2. Transurethral incision of the prostate (TUIP)

It is recommended in cases of moderate-to-severe LUTS and prostate volume less than 30 ml (figure 3) [11]. It involves urethral incision of the prostate to widen the prostatic urethra and thus resolve the bladder outlet obstruction without removing prostate tissue.

No case of TUR-syndrome has been recorded, the risk of bleeding requiring transfusion is negligible and retrograde ejaculation rate is significantly lower after TUIP, but the re-operation rate is higher compared to M-TURP [16,17]

2.2.3. Open Prostatectomy

Open prostatectomy, performed using the index finger and approaching the prostate from inside the bladder (Freyer's procedure) or through the anterior prostatic capsule (Millin's procedure), is the most invasive surgical method, but it is an effective and durable procedure for the treatment of LUTS/BPO. In the absence of an endourological armamentarium including a holmium laser or a bipolar system and with appropriate patient consent, OP is a reasonable surgical treatment of choice for men with prostates > 80 mL [11].

2.3. MINIMALLY-INVASIVE SURGICAL TECHNIQUES

Surgical management of LUTS due to BPH has evolved toward the concept of minimally-invasive surgery and will likely replace open surgery in the next years. Minimally invasive techniques include several technologies, including Holmium laser, Greenlight laser and Thulium laser.

2.3.1. Holmium laser

The holmium:yttrium-aluminium garnet (Ho:YAG) laser (wavelength 2,140 nm) is a pulsed solid-state laser that is absorbed by water and water-containing tissues. Tissue coagulation and necrosis are limited to 3-4 mm, which is enough to obtain adequate haemostasis. An RCT comparing HoLEP with B-TURP in patients with prostate volume > 80 mL reported shorter operation, catheterisation and hospitalisation times and lower blood transfusion rates for HoLEP but no differences in complication rates [18]. This technique requires experience and relevant endoscopic skills, especially considering that has been proven that experience of the surgeon is the most important factor affecting the overall occurrence of complications [19].

2.3.2. Greenlight laser

The Potassium-Titanyl-Phosphate (KTP) and the lithium triborate (LBO) lasers work at a wavelength of 532 nm. Laser energy is absorbed by haemoglobin, but not by water. Vaporisation leads to immediate removal of prostatic tissue. Three “Greenlight” lasers exist, which differ not only in maximum power output, but more significantly in fiber design and the associated energy tissue interaction of each. The standard Greenlight device today is the 180-W XPS laser, but most of the evidence is published with the former 80-W KTP or 120-W HPS (LBO) laser systems. Laser vaporisation of the prostate using the 180-W LBO laser (PVP) demonstrated higher intra-operative safety regarding haemostatic properties when compared to TURP. Peri-operative parameters such as catheterisation time and hospital stay were in favour of PVP, whereas operation time was in favour of TURP. Short- to mid-term results are comparable to TURP [20].

2.4. ULTRA MINIMALLY-INVASIVE SURGICAL TECHNIQUES

In recent years, several new ultra minimally invasive surgical techniques (uMISTs) have become available for BPH/ benign prostatic obstruction (BPO), potentially feasible in carefully selected patients who are not the best candidates for surgery due to comorbidities or who are intolerant of medical therapy and its potential side effects, especially in terms of sexual function and ejaculation [12-13]. uMISTs can be classified in two groups: ablative and non ablative techniques. Aquablation, prostatic artery embolization and water vapor thermal therapy (Rezum) have been introduced in the last edition of European Association of Urology Guidelines among ablative techniques, while the non-ablative group includes prostatic urethral lift, intra-prostatic injections and iTIND [11]. Of note, Rezum and iTIND are still cited as under investigation techniques. Although preliminary data in literature show feasibility, effectiveness and safety, other emerging uMISTs, such as transperineal laser ablation of prostate (TPLA) are still not cited by the European Guidelines.

2.4.1. TPLA (transperineal interstitial laser ablation)

TPLA is an ultrasound (US) guided minimally invasive procedure requiring a biplanar TRUS and EchoLaser™ system consisted of a multisource diode laser with four independent laser sources, operating at 1064 nm wavelength and a dedicated planning tool (ESI - Echolaser™ Smart Interface) with a simulation software that allows the user to plan the treatment and to place applicators in the prostate in a safe manner [21]. This EchoLaser™ application is also known as SoracteLite™. A catheter placement and local anaesthesia are needed before starting the procedure. The laser light is conveyed by the source to the tissues through 300µm quartz optical fibers with a flat tip, which are inserted percutaneously within 21G Chiba needles under transrectal ultrasound guidance. The laser light produces an ellipsoidal shape area of coagulative necrosis around the tip of the fiber (approximately 2/3 extended beyond the fiber tip and 1/3 behind it depending on the power and dose applied). A needle placement verification is required to guarantee the right safety distances from the urethra and from the bladder neck. The procedure can be planned via the Echolaser™ Smart Interface (ESI), a dedicated device that allows to establish the correct ellipsoidal shape area of coagulative necrosis on the prostatic tissue. Once the fibers are placed the energy can be delivered. The laser causes hyperthermia, denaturation and coagulative necrosis of proteins. The maximum volume treated in a session and the extent of the ablation vary according to the prostatic volume, anatomy and surgeon preference. In some cases, especially in larger prostates, a pull back of applicators (retraction of 5-10 mm along its trajectory) during the same treatment session allows the ablation of another part of the prostatic tissue not treated in the previous illumination delivering additional laser energy. Promising intra-, perioperative, and functional results have been reported by different groups [22-23]. EchoLaser ™TPLA was indeed shown to have a good safety profile and to achieve favourable short-term functional outcome as well as sexual outcomes. Yet, selection criteria for EchoLaser™ TPLA, including the ideal patient- and prostate-related characteristics, and few technical nuances regarding the procedure were found to be heterogeneous across the published series and warrant further investigation.

Figure 3. EchoLaser™ System

2.5. AIM OF THE STUDY

The aim of the project was to provide surgeons with a reference curriculum (defining the minimum number of times each step of each procedure needs to be reproduced by the surgeon before full-case evaluation) to guide the learning curve process, allowing progressive acquisition of skills across modules with growing complexity in order to guarantee patient's safety and functional efficacy. Moreover, the objective was to design a prospective observational study, which may include the creation of an international multicenter research network of high-volume referral Centers, aiming to offer a scientific framework for critical assessment of the reproducibility of the proposed curriculum and its external validation.

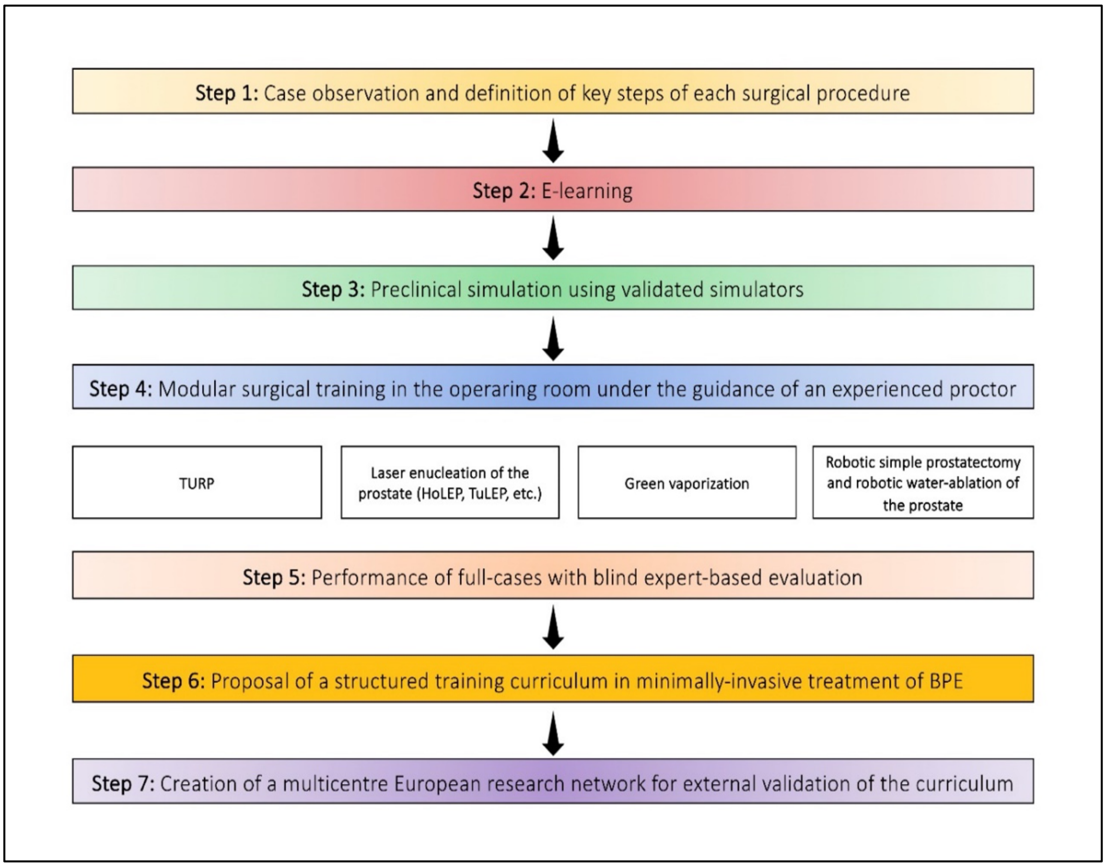


Figure 4. Overview of the main steps of the research project.

3. MATERIALS AND METHODS

3.1. ASSESSMENT OF THE LEARNING CURVE OF GREENLIGHT LASER ANATOMIC PHOTOVAPORIZATION OF THE PROSTATE

3.1.1. Design, Setting and Participants

After institutional review board approval, all data for consecutive patients who underwent PVP with 180-W XPS GL laser were collected prospectively in one international tertiary university center between 2019 and 2020. The surgeon (F.S.) who performed all surgical procedures had a prior experience with TURP (n=120) but none with laser vaporization or enucleation of the prostate.

3.1.2. Intervention: Surgical technique and step-by-step modular training program

All procedures were performed with a modular step methodology. The surgeon adopted an anatomical vaporization of the prostate described in a recently published paper [24]. A proctor (R.O) experienced in green light laser technology (> 500 PVPs) supervised all procedures. The proctor performed the aforementioned steps (totally or partially) in case the novice was not able to accomplish them safely. The surgical procedure was divided in a modular step by step training fashion. Specifically, the program included:

- **Step 1** ***creation of an irrigation channel***: creation of a working channel at 12 o' clock starting from the bladder neck to the apex. The appropriacy of the procedure included a continuous rotation of the fiber as well as the maintenance of 1–3 mm working distance.
- **Step 2** ***landmark demarcation***: demarcation of the limits of dissection at 5 and 7 o' clock from the bladder neck to the apex using the 180 W power setting. This maneuver allows for a visual guide to avoid exceeding beyond the verumontanum.
- **Step 3:** ***prostate floor tissue treatment***: once the initial groves are made, the next step is to identify the floor and to develop the capsule plane at the level of the apex. In this phase, the key point is to treat tissue with the laser fiber cap in contact with the capsule and rotating the cap and delivering energy horizontally alongside the capsular fibers. This allows to reduce the risk of capsular perforation and urinary irritative symptoms.
- **Step 4:** ***lateral lobe treatment and managing bleeding****:* The scope is rotated to direct the laser bram towards 1 o 'clock and to create a releasing incision grove, respecting the following anatomical landmarks: prostate capsule, bladder neck, and verumontanum.
- **Step 5:** ***apical treatment***: the power is lowered to 120 W to avoid thermal sphinteric trauma.

An overview of the surgical steps is reported in the figure below.

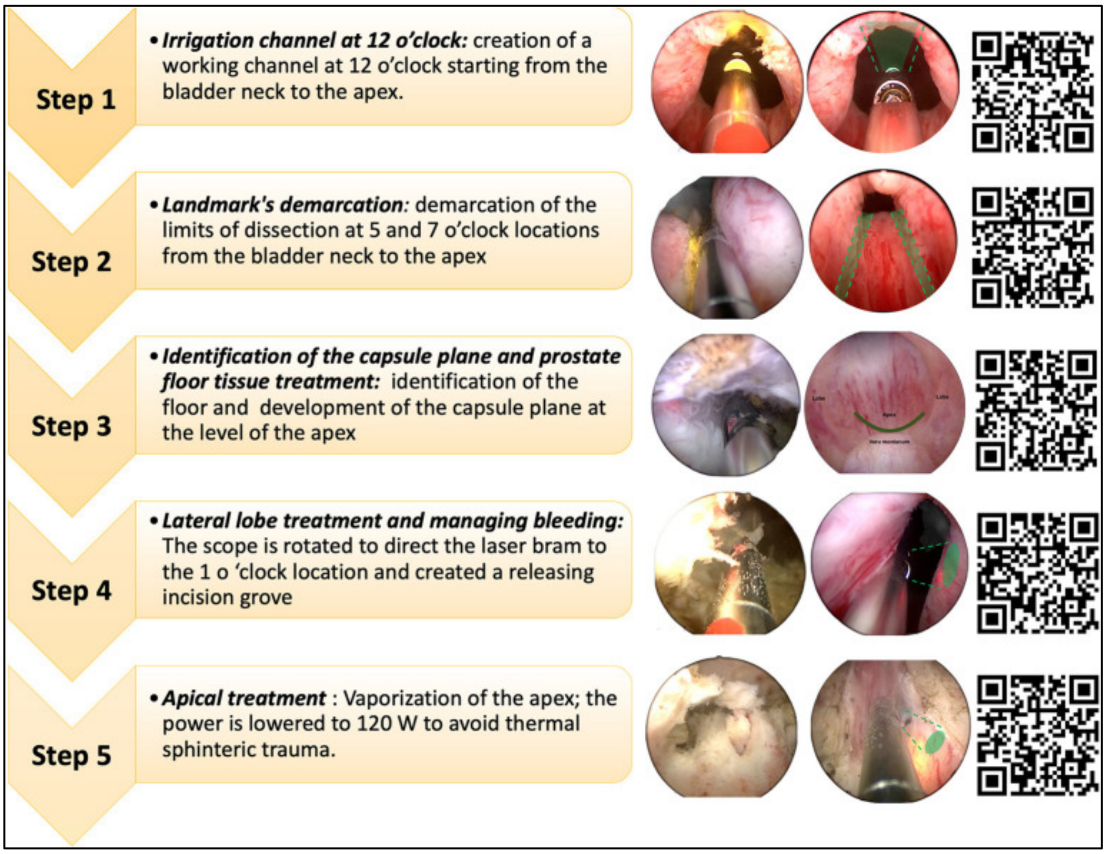


Figure 5. Surgical steps of anatomic photovaporization of the prostate (aPVP).

3.1.3. Outcome measures and statistical analysis

Surgeon experience was analyzed as a continuous variable in terms of the number of consecutive procedures performed. Given the relatively small sample size of our series, and the low number of events, we could not evaluate the learning curve for aPVP using surgical complications as the reference outcome. As such, to assess the learning curve, the amount of energy per milliliter of preoperative prostate volume was selected as reference variable to benchmark surgical performance. The rationale for choosing this primary outcome relies in its association with postoperative storage LUTS [25][26]. The primary endpoint was to identify the breakpoint at which the slope of the curve becomes less steep, reflecting a decrease in total energy/ml used.

All surgical steps were analyzed by the cumulative summation (CUSUM) method, which recognizes the importance of time and experience in clinical practice. Competency of the procedure was defined as the first turning point of the curve plateau, and proficiency was defined as the turning point at which the slope of the curve becomes less steep. Furthermore, Shewhart control charts for one-at-time data were built to evaluate how the group summary statistics deviated above or below the process centre (+2SD = alert line, +3SD = alarm line).

Linear regression was performed to estimate the relationship between the number of procedures and the improvement of surgeon energy (KJ) per ml of prostate volume usage. The relationship between the energy delivered (KJ/ml and total energy) and postoperative symptoms (post-operative and Δ-IPSS, IIEF, QoL, OABQ-SF, ICIQ-SF) was assessed with Pearson correlation. All tests were two-sided with a significance level set at $p < 0.05$.

3.2. ASSESSMENT OF THE LEARNING CURVE OF HoLEP

3.2.1. Design, Setting and Participants

After institutional review board approval, all data for consecutive patients who underwent HoLEP with 100 W Lumenis were collected prospectively in one international tertiary university center between 2019 and 2021. The surgeon who performed all surgical procedures had a prior experience with TURP (n=120) but none with laser enucleation of the prostate with Holmium laser.

3.2.2. Intervention: Surgical technique and step-by-step modular training program

All procedures were performed with a modular step methodology. The surgeon adopted an en bloc enucleation of the prostate as previously described [27]. A proctor experienced in holmium laser technology supervised all procedures. The proctor performed the steps (totally or partially) in case the novice was not able to accomplish them safely. The surgical procedure was divided in a modular step by step training fashion. Based on previously published studies evaluating the learning curve for HoLep we decided to assume 100 min of operative time as the threshold for surgical proficiency.

3.2.3. Outcome measure and statistical analysis

Data are reported, both overall and per surgeon, as median and interquartile range (IQR) for continuous variables and as absolute and relative frequency for categorical variables. The preoperative and the postoperative categorical characteristics of patients grouped by surgeon were compared through the chi-square test. Likewise, the remaining continuous variables were compared thorough surgeons by means of the Kruskal-Wallis test, according to the assumption of normal distribution. The significance level α was defined as $p\text{-value}<0.05$.

A preliminary analysis was performed on the operative time (OT) only. The Spearman's correlation coefficient was used to assess the association of OT with the chronological order of patients. Moreover, to assess the variation of OT as the number of patients increased, a CUSUM chart was obtained. At each subject, the learning curve (LC) was updated, and it was given a height by the cumulative deviation of the OT from the surgeon's median OT.

The CUSUM analysis was then extended to a multidimensional evaluation of the procedure, where the learning process was described through successes and failures. A failure was defined as the occurrence of at least one of the following events: prolonged OT intraoperative complications and conversion to TURP, surgical time more than 100 min.

The risk of surgical failure estimated preoperatively could vary considerably from patient to patient. An adjustment for this risk is therefore appropriate to evaluate the learning curve after weighting failures by patient's preoperative condition. The failure probabilities for this RA-CUSUM analysis were computed according to the logit model considering the following covariates: age, prostate volume, cardiovascular status, comorbidities, antiaggregant/anticoagulant therapy.

3.3. TPLA OUTCOMES

Transperineal interstitial laser ablation of the prostate (TPLA) represents a novel option for minimally invasive treatment of BPO; although it is still not recommended by the latest European Association of Urology (EAU) Guidelines, it has shown promising results in terms of feasibility and safety. Moreover, due to the relatively simplicity of this technology, the low number of cases to achieve proficiency as well as the difficulty to assess a tool to evaluate surgeon's dexterity (ability to put the needle into the prostatic tissue vs the respect of security distance from the benchmarks etc) we focus our analysis not on the evaluation a proctored step by step training program (as described for the other techniques) but on the proposal *of a step by step guide* for surgeons approaching this ultra-minimally invasive technique focusing on technical equipment, surgical aspects and post procedural facilities.

Moreover, we evaluate the tri and *pentafecta* achievement, defined as a combination of increase of 20% of Δq max, reduction of 20 % of ΔIPSS, increase of 20% of ΔMSHQ (trifecta), absence of early failure (acute urinary retention or fever) and late failure (indwelling catheter, surgical re-treatment or reintroduction of pharmacological therapy) (pentafecta). These parameters were used to evaluate the achievement of optimal outcomes with transperineal prostate ablation.

3.3.1. A step-by-step guide for TPLA

After Institutional Review Board approval and obtained patients' informed consent, data from all consecutive patients undergoing TPLA were prospectively collected in a specific database.

The objective of the study was to assess the early (1-month and 3-months) perioperative (surgical complications reported according to the Clavien-Dindo classification) functional and sexual outcomes (reported using the International Prostate Symptom Score [IPSS], the International Index of Erectile Function [IIEF-5] and the Male Sexual Health Questionnaire-Ejaculatory Dysfunction Short Form [MSHQ-EjD SF]) of TPLA.

3.3.2. Outpatient clinic setting for TPLA

The procedure can be performed in the outpatient clinic equipped with a surgical table with legs support (Figure 6a). The patient lies in a lithotomic position, with the surgeon between patient's legs. To best expose the perineum, the scrotum and the penis are lifted and fixed with adhesive tape. If necessary, a trichotomy is performed. Although only one surgeon is needed, technical support of a clinical specialist is advisable, especially for the first cases.

3.3.3. Technical equipment

TPLA is an ultrasound (US) guided minimally invasive procedure requiring a biplanar TRUS (in our practice, BK 5000) and a multisource solid state diode laser generator

(1064nm wavelength), with four independent channels for multi-fiber lasing approach (EchoLaser X4, Elesta s.r.l., Calenzano, Italy) (Figure 6b). The laser light is conveyed by the source to the tissues through extremely flexible quartz optical fibers with a small diameter (300 micron) and a flat tip, which are inserted percutaneously within 21G Chiba needles. The laser light produces an ellipsoidal shape area of coagulative necrosis, for a longitudinal diameter of 22,5 mm and a transversal diameter of 16 mm (2/3 extended beyond the fiber tip and 1/3 behind it). Irreversible necrosis of cells occurs for a joint action of local temperature and exposure time. Diode laser 1064nm wavelength ensure an optimal and selective laser-tissue interaction, by exploiting heme group as endogenous chromophore. Irreversible necrosis of cells occurs for a joint action of local temperature and exposure time.

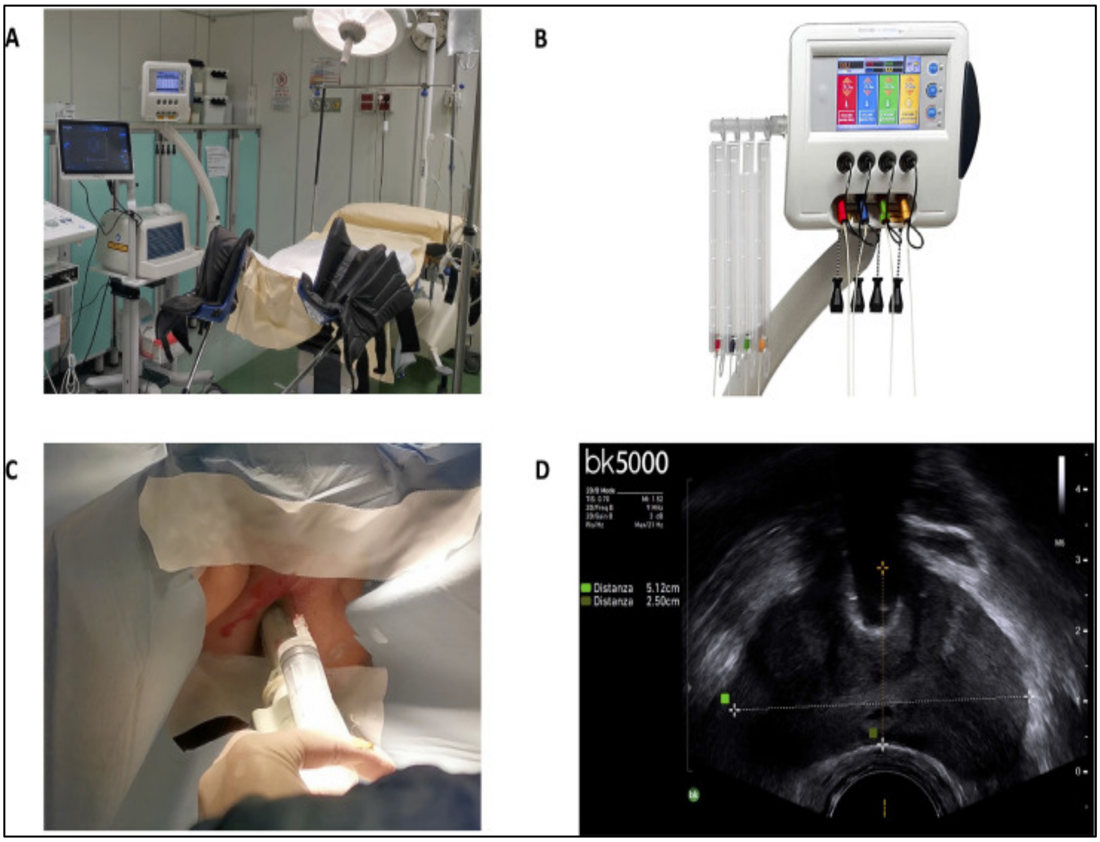


Figure 6. (a) Outpatient clinic setting. (b) Multisource solid state diode laser generator with four independent channels for multi-fiber lasing approach. (c) Perineal and periprostatic local anesthesia. (d) Transrectal ultrasound guided prostate gland measure.

3.3.4. Preliminary assessment, catheter placement and anesthesia

Routine blood testing, functional questionnaires (The International Prostate Symptom Score, IPSS; the International Index of Erectile Function, IIEF-5; Male Sexual Health Questionnaire-Ejaculatory Dysfunction Short Form, MSHQ-EjD SF) and non-invasive urodynamics data (Qmax, PVR) are collected. Endovenous prophylactic antibiotic administration is initiated within one hour before the procedure. Medical thromboprophylaxis is usually not required, except for selected high-risk patients. A three-way 18-F Foley catheter is placed with continuous irrigation, to ensure cooling of the urethral wall during lasing time, avoiding possible thermal damages.

A superficial local anesthesia of perineum skin and subcutaneous tissue is provide using lidocaine-prilocaine 5% cream and 20 ml of lidocaine 2% (Figure 6c). Benzodiazepine oral solution is used for conscious sedation. Therefore, biplanar transrectal ultrasound probe is introduced and periprostatic anesthesia at each lobe of the prostate and gland measurements are performed, as previously reported [23] (Figure 6d).

3.3.5. Step-by-step procedure

After local disinfection, two 21G transperineal needles are introduced and located in the middle of each lobe, under ultrasound guidance, with their orientation parallel to the longitudinal axis of the gland (Figure 7a). In this phase it is essential to keep the needle in line with the ultrasound probe's axis, avoiding possible misalignments, responsible for wrong needle placements. In high volume prostates (i.e. >80cc), $\geq$ 2 needles per lobe can be positioned.

A needle placement verification is required to guarantee the right security distances from the urethra (8 mm, thus preventing possible damages resulting in hematuria, storage LUTS and lumen stenosis) and from the bladder neck (around 15 mm, critical to avoid ejaculatory dysfunction) (Figure 7b). This is obtained alternating longitudinal and transversal scans, while the wrist is rotated clockwise and anticlockwise to check both prostate lobes.

The procedure is then planned thanks to the Echolaser Smart Interface (ESI), a dedicated device connected with the video output of the US system, for real-time user assistance in performing the procedure, helping to establish the correct ellipsoidal shape area of coagulative necrosis on the prostatic tissue (Figure 7c).

The stopper devices are applied to fix the needle in the desired position, preventing their intraprocedural misplacement; the 300 micrometers disposable optical fibers are then introduced.

Once the fibers are placed, the energy can be delivered. The starting power energy is 5 W, reduced at about minute 2 to 3,5 W, when a cavity starts to grow with vapor formation resulting in bubbles hyperechoic images at US (Figure 7d).

The laser causes hyperthermia, denaturation and coagulative necrosis of proteins. The maximum volume treated in a session and the extent of the ablation vary according to the prostatic volume, anatomy and receptivity of the tissue. In our experience, we use a fixed protocol to deliver laser energy, consisting in 1400 J per lobe. In case of large prostates, pulling back the needle allows the ablation of the distal part of the prostatic tissue.

Especially for the first cases it is strongly recommended to use ESI, to plan beforehand possible effects of the "pull back technique", limiting any potentially harmful treatment of the prostatic apex and urethra. Overall, the treatment plan consists in the delivery up to 3600 J, with a power of 2-3 W for a total procedural time of 30 minutes. At the end of the treatment 20 mg of Metilprednisolone EV (if not specifically contraindicated by the patient) is administered for anti-edema and anti-inflammatory purposes. An antibiotic, pain relief and gastroprotective therapy will also be established for 1 week. After an observation period of 2-3 hours in the outpatient clinic, the patient is discharged from the hospital with the urinary catheter in place, that will be removed within a week.

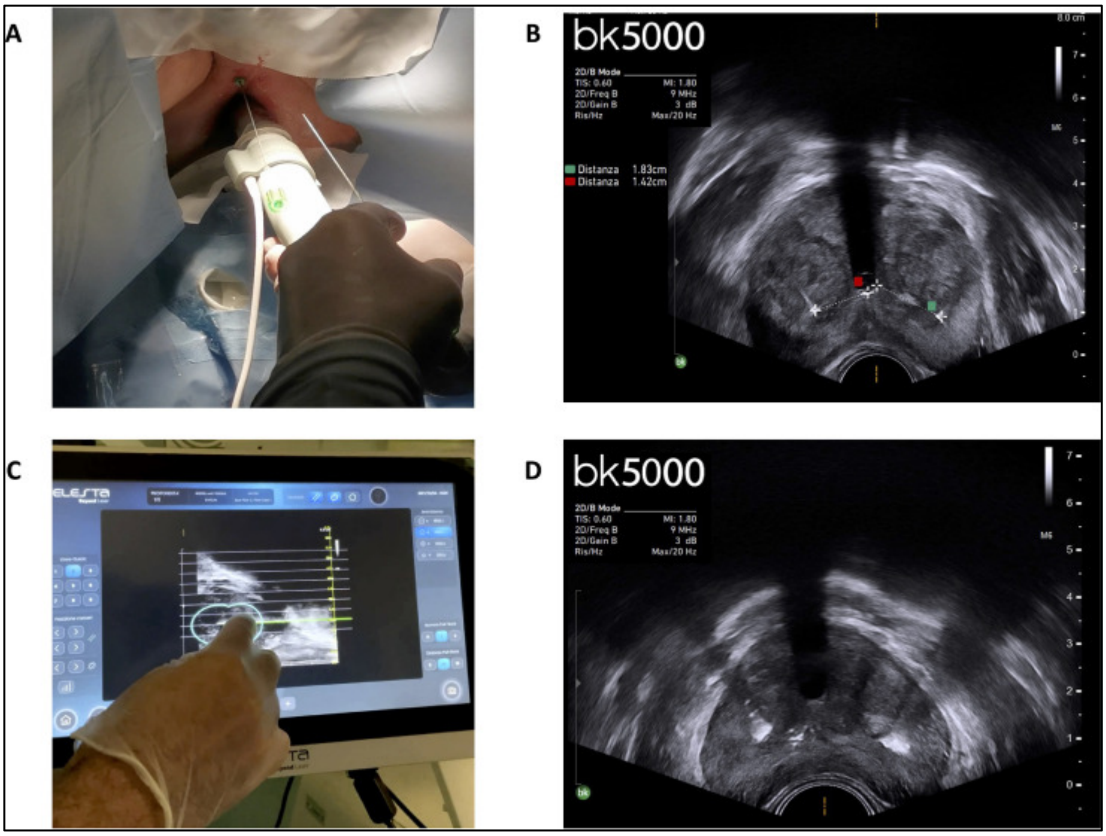


Figure 7. (a) 21G transperineal needles placement. Note the parallel orientation of the needle with respect to the ultrasound probe. (b) Ultrasound distances evaluation between needle tip and safety landmarks (urethral lumen, bladder neck, prostatic capsule). (c) Procedure planning with Echolaser Smart Interface (ESI). Thanks to this software, the operator can set treatment parameters (needle insertion angle, number and spacing of fibers, pullback etc.) and check their real time rendering, paying attention to anatomical structures to be preserved from the effect of thermal damage. (d) Ultrasound view of bubbles hyperechoic artifact images in prostate tissue resulting from vapor during cavity formation due to energy delivery.

3.3.6. Tri and Pentafecta assessment

The evaluation of trifecta was based on the following clinical factors:

- Reduction in more than 20% of ΔIPSS (assessed considering values before treatment and 6 months later);
- Increase in more than 20% of ΔQmax (assessed considering values before treatment and 6 months later);
- Increase in more than 20% of ΔMSHQ (assessed considering values before treatment and 6 months later).

Pentafecta was defined considering the following variables:

- Reduction in more than 20% of ΔIPSS (assessed considering values before treatment and 6 months later);
- Increase in more than 20% of ΔQmax, (assessed considering values before treatment and 6 months later);
- Increase in more than 20% of ΔMSHQ (assessed considering values before treatment and 6 months later);
- Absence of early failure (no acute retention within 30 days / no sepsis or abscesses requiring hospital admission).
- Absence of late failure (indwelling catheter, surgical re-treatment or reintroduction of pharmacological therapy with alpha blockers at 6 months).

3.3.7. Delphi Consensus project

The Delphi method was used to achieve consensus among a panel of experts.

A literature search on PubMed using ((TPLA) or (Transperineal laser ablation of the prostate)) AND ((BPH) OR (Benign prostatic hyperplasia) OR (BPO) OR (benign prostatic obstruction)) led to 14 articles, of which 6 were eligible after full-text screening; all studies were on Echolaser® TPLA. A different search on PubMed using ((TPLA) OR (Transperineal focal laser ablation)) AND ((PCa) OR (Prostate Cancer)), led to 24 results, of which 5 were eligible after full-text screening; one study was on Echolaser® TPLA, four on other transperineal FLA techniques.

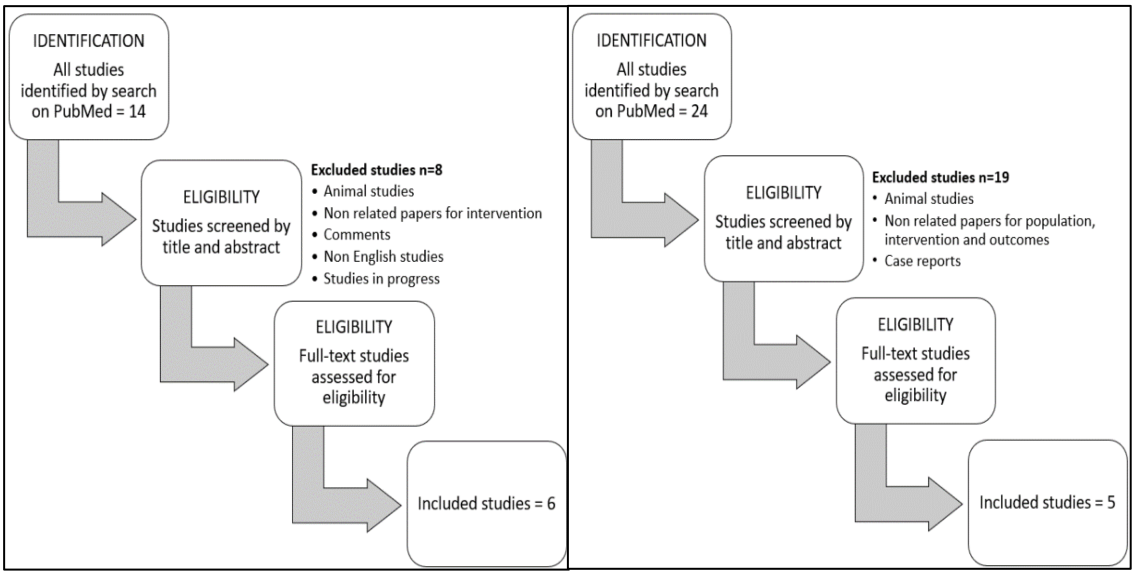


Figure 8. Illustrate flow-chart for study selection.

Panelists were selected basing on their proven experience in clinical practice and research on the topic. Online questionnaires were presented to participants in two subsequent rounds between 1st March and 31st July 2022, using online survey platform (www.welphi.com, Lisbon, Portugal). Selected topics were indications for the use of Echolaser® TPLA in the treatment of BPH and PCa, pre-procedural assessment and prophylaxis, technical aspects of the procedure, post-procedural catheterization and pharmacologic treatment, follow-up, outcomes, and general considerations about Echolaser® TPLA. Likert-Scale questions and open questions were administered to participants. For open questions, responses were analyzed to select prevailing experts' opinions. For Likert-Scale questions, in first round possible responses were 'strongly agree', 'agree', 'neither agree nor disagree', 'disagree', 'strongly disagree'; in second round they were 'strongly agree', 'mostly agree', 'mostly disagree', 'strongly disagree'. For some questions, participants have been asked to comment their responses; these comments were analyzed to highlight prevailing experts' opinions. Level of agreement or disagreement to reach consensus was set at 75% and descriptive statistics were used to determine the response rate of each topic.

Final round was performed in an online meeting on the platform Zoom® on September 26th 2022, when the results of previous rounds were presented and questions that had not yet achieved consensus were discussed, leading to final result.

A final consensus was set when agreement or disagreement were > 75%.

4. RESULTS

4.1. EVALUATION OF THE FEASIBILITY AND SAFETY OF A PROCTORED STEP-BY-STEP TRAINING PROGRAM OF GREENLIGHT LASER ANATOMIC PHOTOVAPORIZATION (aPVP) OF THE PROSTATE

A total of 60 consecutive patients were considered for the analysis. A median (IQR) follow-up of 12 months (10-13) was recorded.

4.1.1. Preoperative and intraoperative features

Patients' characteristics are reported in Table 1. Overall, the median (IQR) operative time was 43 min (38,2-52,2) min with median energy/ml of tissue delivered of 2387 KJ/ml. An overview of time and energy delivered /ml of tissue for each step (1-5) and for the whole procedure is depicted in Supplementary Table 1.

4.1.2. Perioperative and postoperative features

Overall, no intraoperative complications were recorded. Two patients (2/70, 3%) experienced early (within 30 days) postoperative complications, one was represented by clots retention requiring blood transfusion. The other case was represented by urine acute retention after catheter removal without clots, requiring recatheterization (removed after 5 days). In none of the cases a surgical revision was required. Median catheterization time was 2 days; similarly, median hospitalization time was 2 days. Functional outcomes at 3 months postoperatively are shown in Table 2.

Median ΔHb, ΔPSA, ΔQ max was 0,60 g/dl, 1,56 ng/ml, 18,5 mL/sec, respectively.

A post-operative increase (Δ) in both storage and functional symptoms at validated questionaries, as well as improvement in global satisfaction, was recorded at three months (median Δ IPSS, Δ OABQ-SF, ΔICIQ-SF, Δ QoL were 15.5, 28, 0, 3, respectively).

A significant correlation between energy delivered and reduction of storage symptoms (ΔOABQ-SH, IPSS) was detected for both the entire surgical procedures and almost all five steps (all $p < 0.05$). The only non significant correlations were found between energy/ml used in steps 4-5 and delta-OAQB ($p = 0.123$ and 0.08 respectively).

4.1.3. Evolution of intraoperative parameters over consecutive procedures

During the initial 60 cases a progressive linear drop in energy delivered/ml of prostate tissue was observed. At CUSUM analysis the learning curve reached a plateau after the 40th case, as reported in Figure 9**.** The learning curves for each step forming the overall anatomic PVP were assessed, and the plateau was reached after 37 cases for step 1, 28 cases for step 2, 41 cases for step 3, 39 cases for step 4, and 42 cases for step 5 (Supplementary Figure 1 a-e). A similar conclusion was reached also considering the total energy adopted/number of procedures, showing a progressively reduction in KJ/ml used after the first 10 cases. (Figure 10).

Multivariate regression model identified the number of consecutive procedures as the only independent predictor for lower amounts of energy per ml of prostate volume (p=0.001) (Table 3**)**.

Variables	**Median (IQR)**
Age, years	65 (62-70)
BMI, kg/m²	26 (24-27)
Qmax, mL/s	10 (8.25-11.75)
PVR, mL	82.50 (60-127.50)
PSA, ng/mL	2.90 (2.02-3.89)
IPSS	25 (21.25-30)
QoL	4 (4-5)
OABQ-SF	59.50 (50.25-65)
ICIQ-SF	0 (0-1)
IIEF-5	21 (16.25-24)
Prostate volume, mL	56.50 (43.50-78.25)

Table 1. Preoperative characteristics of patients

BMI: Body mass index; Qmax: maximum flow; PSA: prostate-specific antigen; PVR: post-void residual; IPSS: International Prostate Symptom Score, QoL: Quality of Life; OABQ-SF: Overactive Bladder Short Form; ICIQ-SF: International Consultation on Incontinence Questionnaire- Short Form; IIEF-5: International Index of Erectile Function.

Patients	**Median (IQR)**
Catheterization time, days	2 (2-3)
Hospitalization time, days	2 (2-2)
Δ Qmax, mL/s	18.50 (14-22)
Δ Hb, g/dL	0.60 (0.30-0.87)
Δ PSA, ng/mL	1.56 (0.70-2.29)
Δ IPSS	15.50 (12-20)
Δ QoL	3 (2-4)
Δ OABQ-SF	28 (17.25-31)
Δ ICIQ-SF	0 (0-0)
Δ IIEF-5	0 (0-0)

Table 2. Postoperative data

Qmax: maximum flow; HB: haemoglobin; PSA: prostate-specific antigen; IPSS: International prostate symptom score; QoL: Quality of life; OABQ-SF: overactive bladder short form; ICIQ-SF: international consultation on incontinence questionnaire-urinary; IIEF-5 international index of erectile function.

Variable	Univariate analysis				Multivariate analysis			
	Standardized Beta	p	95% CI		Standardized Beta	p	95% CI	
			Lower bound	Upper bound			Lower bound	Upper bound
Number of consecutive cases	-0,966	< 0.001	-79,57	-69,14	-0,973	< 0.001	-81,97	-67,84
ASA score	0,292	0,024	110,10	1488,51	-0,032	0,437	-313,93	137,62
Age adjusted CCI score	0,353	0,006	146,13	820,38	0,033	0,422	-65,83	155,02
BPH therapy	-0,449	< 0.001	-519,64	-162,45	-0,01	0,798	-67,48	52,11
Preoperative prostate volume (mL)	-0,475	< 0.001	-36,62	-11,27	0,025	0,557	-2,71	4,97

Table 3. Uni and Multivariate regression model for amounts of energy per ml of prostate volume

ASA: American Society of Anesthesiologists; BPH: Benign prostate hypertrophy

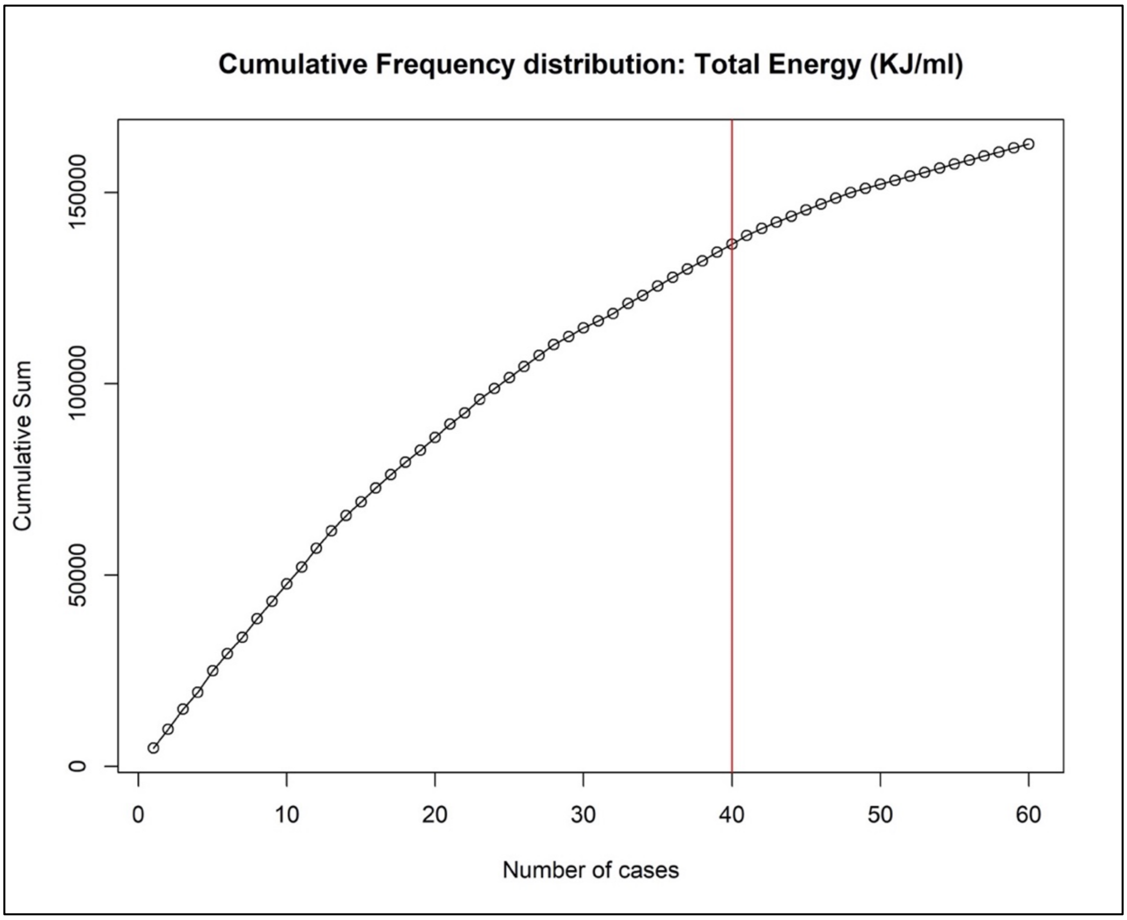


Figure 9. Cumulative summation analysis of total energy per ml of prostate volume during learning process

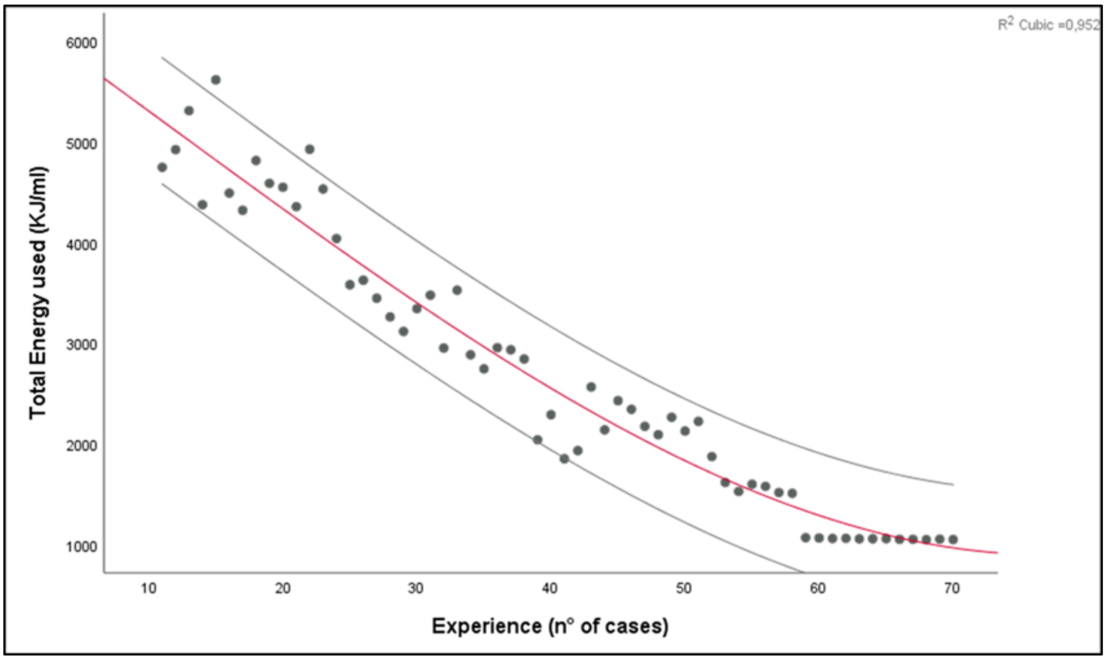
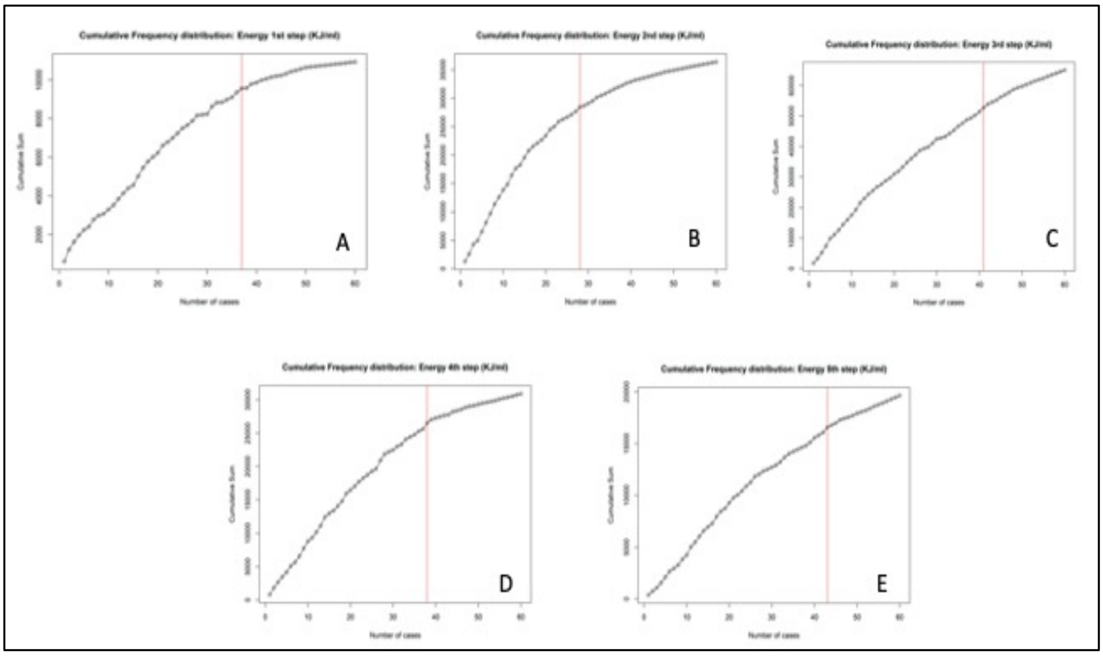


Figure 10. Linear regression: Total energy adopted /number of procedures during the learning curve

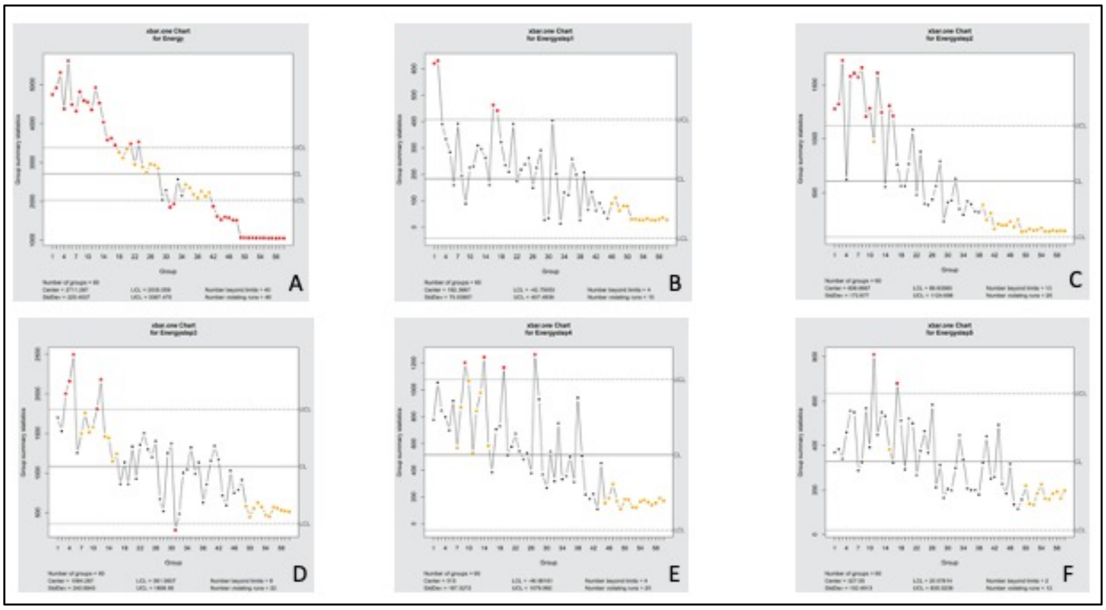
	Energy/volume of tissue, kJ/mL	**Time**, min
Overall, (median; IQR)	2387 (1541.50-3613.75)	45 (38.25-52.25)
Step 1, (median; IQR)	158.50 (40.75-261.75)	5 (3-6)
Step 2, (median; IQR)	404 (198.25-952)	10 (8-13)
Step 3, (median; IQR)	1088.50 (602-1397.25)	14 (12-17)
Step 4, (median; IQR)	491 (188-769)	9 (7-12)
Step 5, (median; IQR)	305.50 (197.50-447.50)	7 (5-9.75)

Supplementary Table 1. Intraoperative data, overall and stratified by surgical step



Supplementary Figure 1. (a-e). Cumulative summation analysis of total energy per ml of prostate volume during learning process for each step of Greenlight aPVP

aPVP= anatomical photovaporization of the prostate



Supplementary Figure 2. Swehchart charts for total (a) and step-specific (b-f) KJ/ml used during learning curve.

4.2. EVALUATION OF THE FEASIBILITY AND SAFETY OF A PROCTORED STEP-BY-STEP TRAINING PROGRAM OF A BENIGN PROSTATIC OBSTRUCTION BY USING HoLEP

A total of 128 consecutive patients were considered for the analysis. A median (IQR) follow-up of 12 months (10-13) was recorded.

4.2.1. Preoperative and intraoperative features

Patients' characteristics are reported in Table 4**.** Overall, the median (IQR) age was 71 years (48-75), 37 (30%) patients maintained anticoagulant therapy at surgery, median prostate volume was 110ml (IQR 47-132) min with median energy delivered of 143500 KJ. An overview of time and energy delivered for the whole procedure is depicted in Table 5.

4.2.2. Perioperative and postoperative features

Overall, no intraoperative complications were recorded. One patient (1/128,1%) experienced conversion to TURP for bleeding. Median operative time was 115 min (IQR 90-131). Median catheterization time was 3 days; similarly, median hospitalization time was 3 days.

Functional outcomes at 3 months postoperatively are shown in Table 6.

A post-operative increase (Δ) in both storage and functional symptoms at validated questionaries, as well as improvement in global satisfaction, was recorded at three months (median IPSS a 6 and 12 months of follow up were 6 and 5, respectively) (Table 6).

4.2.3. CUSUM analysis

The calculated Spearman's correlation coefficient for operative time is reported in Figure 11.

Specifically, assuming that the threshold time for Holep is 100 min according to the available evidence (34), the correlation coefficient is negative for surgical performance, which suggests that there is a decrease in the OT as the number of surgeries increases, but it is negligible. Since both negative coefficients is negligible it is possible to conclude that the change in the OT is minimal and at last not statistically relevant.

The CUSUM graph based on median OT only is shown in Figure 12. Curves of the operator has an oscillatory behaviour, and do not allow to clearly define phases. However, it Is possible to identify two phases, with a main peak in the curve corresponding to the 65st case. This phase of positively sloping curve is followed by a non-monotonic curve and then, after the 65th case, respectively, by a non-constant decreasing phase, representing the incapacity during the learning period to reach the plateau in the case of OT.

The RA-CUSUM graphs, which focused on surgical failures and successes, separately, but considering factors potentially affecting them, are reported in Figure 13. Considering the adjusted version of the CUSUM offers more insights in the learning process of operators, on the one hand, RA-CUSUM$^{\pm}$graphs confirm what showed by CUSUM graphs, (i.e., it is possible to divide the curve in two neatly distinct phases); on the other hand, the curve was less steep at the beginning since the probabilities of failure were tuned on the prostate' characteristics (Kruskal-Walliss test; p-value=0.1212). This means that the prostate volume, before surgery greatly affected the outcome of the operation during learning curve period. Finally, the curves suggest that the operator have reached an improvement during the 65 cases and passed the technique learning stage without reaching a true plateau.

Patient number	**128**	
AGE median (IQR)	71	(48 – 75)
Anticoagulant / Antiaggregant	37 (30 %)	
Diabetes	16 (12 %)	
Hypertension	65 (50 %)	
Charlson Comorbility	2	(1 – 3)
BMI	26	(19 – 28)
Prostate volume (ml) median (IQR)	110	(47 – 132)
CV indwelling	49 (38 %)	
PSA ng/ml median (IQR)	4,2	(0.3 – 6.2)

Alphalythic therapy	70 (55 %)
5 – ARI therapy	8 (6,25 %)
Combinated therapy	32 (25 %)

Table 4. Preoperative features

	Energy Delivered (Joule)	Irradiation time (min)	Morcellation time (min)	Operative time (h:mm)	Conversion to TURP
Median	143500	60	17	115	1
IQR	(9200-169625)	(20-84,5)	(3-25)	56-155	0,80%

Table 5. Intraoperative features

	IPSS Baseline	IPSS 6 month	IPSS 12 month
Median	22	6	5
IQR	(7-25)	(2-8)	(0-6,25)
Delta (IQR)	-	16 (29-13)	17 (9-20,25)

Table 6. Postoperative functional outcomes

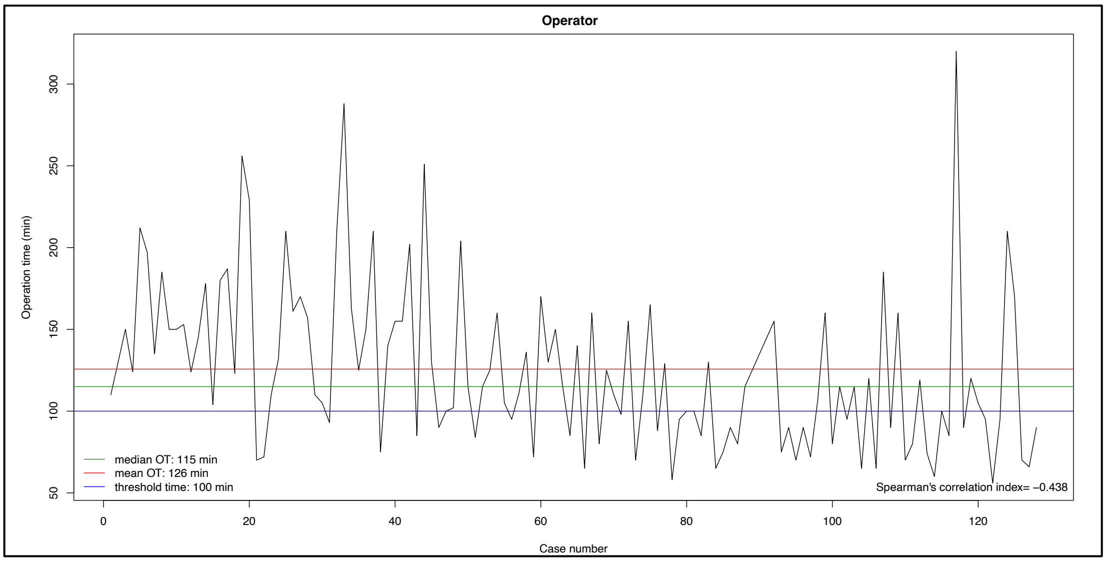


Figure 11. Operative time on number of surgeries

Figure 12. T Cumulative summation analysis of total energy during learning process for each case

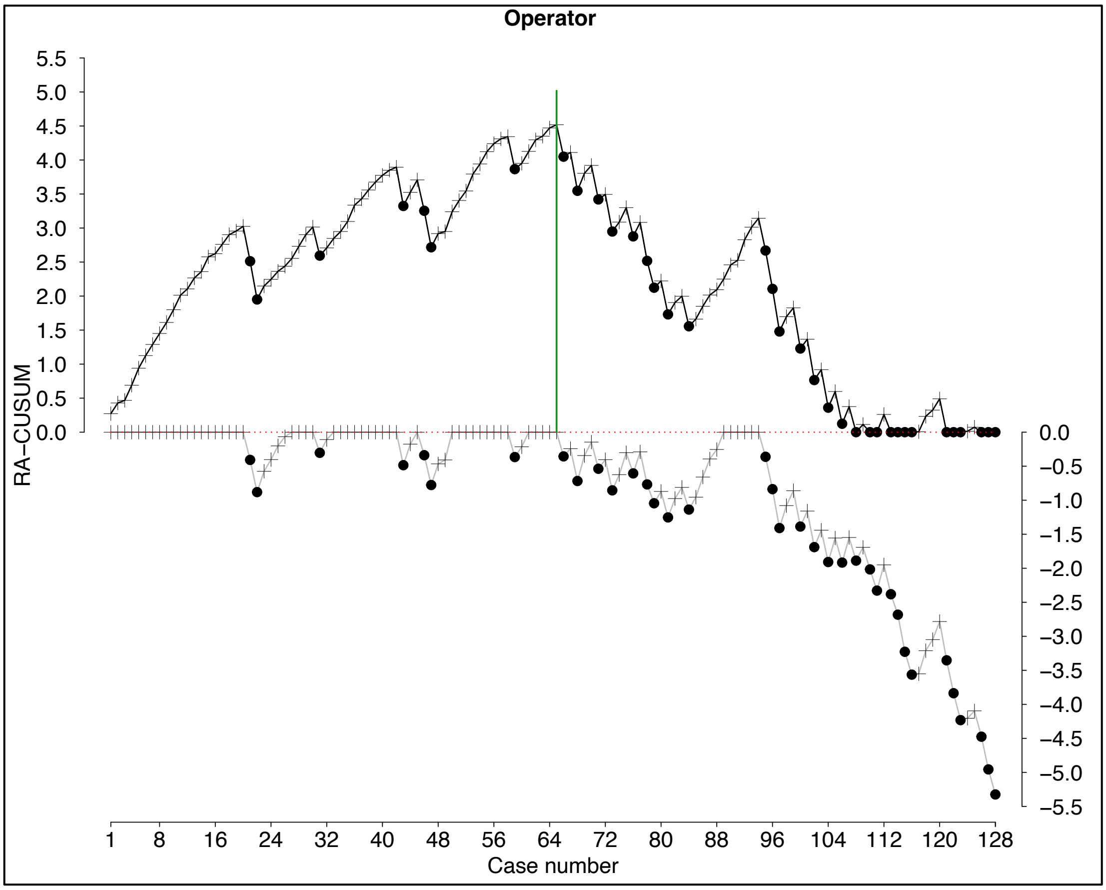


Figure 13. The RA-CUSUM graphs, which focused on surgical failures and successes, separately, but considering factors potentially affecting them

4.3. DEVELOPMENT OF A STEP-BY-STEP MINIMALLY INVASIVE TREATMENT OF A BENIGN PROSTATIC OBSTRUCTION BY USING A TRAANSPERINEALLY INTERSTITIAL LASER ABLATION (TPLA) OF PROSTATIC TISSUE

Transperineal interstitial laser ablation of the prostate (TPLA) represents a novel option for minimally invasive treatment of BPO; although it is still not recommended by the latest European Association of Urology (EAU) Guidelines, it has shown promising results in terms of feasibility and safety. Nevertheless, data in literature are still scarce regarding the best indications, functional outcomes, and patient-reported outcomes after TPLA.

Moreover, due to the relatively simplicity of this technology, the low number of cases to achieve proficiency as well as the difficulty to assess a tool to evaluate surgeon's dexterity (ability to put the needle into the prostatic tissue vs the respect of security distance from the benchmarks etc) we focus our analysis not on the evaluation a proctored step by step training program (as described for other techniques) but on the proposal *of a step by step guide* for surgeons approaching this ultra-minimally invasive technique focusing on technical equipment, surgical aspects and post procedural facilities.

Moreover, we evaluate the tri- and pentafecta achievement, defined as a combination of increase of 20% of Δq max, reduction of 20 % of ΔIPSS, increase of 20% of

ΔMSHQ (trifecta), absence of early failure (Acute urinary retention or fever) and late failure (indwelling catheter, surgical re-treatment, or reintroduction of pharmacological therapy) (pentafecta). These parameters were used to evaluate the achievement of optimal outcomes in transperineal prostate ablation.

4.3.1. Results of the procedure

Overall, 30 patients underwent TPLA at our Institution between April 2021 and December 2021. The clinical characteristics of the patients included in our cohort are shown in Table 4, while the perioperative and functional outcomes of TPLA at a short-term follow-up in Tables 4-5. The median prostate volume at TRUS was 42 ml (IQR 40-53). Four patients had an indwelling catheter before TPLA. The median time to complete the procedure was 31.5 min (IQR 28-37). All patients were discharged within 8 hours of hospital stay (median 6.4h; IQR 5.9-7.2). One patient required hospitalization for pelvic discomfort and was discharged on postoperative day 1. The catheterization time was 7 days in all but one patient (who removed the catheter two weeks after the procedure). An objective improvement in the postoperative flowmetry indexes and quality of life was recorded for all patients (Table 1).

No perioperative Clavien-Dindo grade ≥2 was recorded.

The ejaculatory function was preserved in all patients.

Patients characteristics	N=58
Age (years); median (IQR)	67 (60-76)
Preoperative PSA (ng/ml); median (IQR)	1.86 (0.82-2.97)
Prostate volume (ml); median (IQR)	48 (40-70)
Alpha-blockers n(%)	24 (41.4)
5-ARI (%)	7 (12)
Combined therapy n(%)	14 (24.1)
Patients with indwelling catheter	6 (10.3)
Patients with antiaggregant/ anticoagulant therapy	11 (18.9)
Operative data	Min and/or hours
Operative time (min); median (IQR)	31.5 (28-37)
Postoperative length of stay (hours); median (IQR)	6.4 (5.9 – 7.2)
Catheterization time (days); mean ± SD * ** 1 case required a prolonged catheterization time (95 days)*	9 (12)
N. of fibers; median (IQR)	2 (2-2)

Table 7. Preoperative and operative data. IQR: interquartile range; BMI: body mass index; CCI: Charlson Comorbidity Index; PSA: prostate specific antigen; 5-ARI: 5-alpha reductase inhibitors.

Functional outcomes	Preoperative	3 month	6 months
Qmax (ml/s); median (IQR)	9.05 (6.875-11)	15.0 (9.0-21.0)	12 (9.2-15.7)
∆ Qmax (ml/s) (%)	-	5.95 (39.7)	2.95 (24.6)
PVR (ml); median (IQR)	100 (50-150)	50 (30-92.5)	50 (20-65)
∆ PVR (ml); (%)	-	-50 (100)	-50 (100)
IPSS; median (IQR)	20 (16-25)	11.0 (8.0-16.25)	9.0 (6.0-14.0)
∆ IPSS; (%)		-9 (81)	-11 (122)
QoL; median (IQR)	4.0 (3.0-5.0)	2.0 (1.0-3.0)	2.0 (1-3)
IIEF-5; median (IQR)	18.0 (8.0-24.0)	19.5 (8.25-25.0)	20 (10.0-24.0)
∆ IIEF-5; (%)	-	1.5 (7.7)	2 (10)
MSHQ-EjD 3 item; median (IQR)	3.0 (1.0-8.0)	6.0 (4.0-11.0)	9.0 (5.0-13.0)
∆ MSHQ-EjD 3 item; (%)	-	3 (50)	6 (66)

Overall, trifecta and pentafecta were in 42 % 35 % of patients in the analytic cohort, respectively. Considering the trifecta outcome measures, 16/57 (28%) patients had a failure in q max improvement, 8/57 (14%) reported a failure in IPSS reduction, 19/57 (33%) did not experienced an improvement in MSHQ > 20%, while for 3 patients it was not possible to assess these outcomes due to the need for a catheter replacement. Moreover, 5/57 (9%) patients had more than one item not respecting the criteria to achieve trifecta, while for only one patient all the items for trifecta failed. Considering the pentafecta, 6 patients (10%) experienced an early failure and in all cases were acute retention post catheter removal. In addition, 11/57 (19%) of patients reported a late

Table 8. Pre and postoperative functional outcomes. Four patients with an indwelling catheter before surgery were excluded from preoperative analysis. Two patients experienced postoperative acute urinary retention, an indwelling catheter was replaced, and they were excluded from the postoperative data analysis. Qmax: maximum flow rate; IIEF-5: international index of erectile function 5 items; QoL: Quality of life; IPSS: International Prostate Symptom Score; Male Sexual Health Questionnaire-Ejaculatory Dysfunction (MSHQ-EjD)

failure; of these, 3/57 (5%) were due to the impossibility to remove the catheter with the need for other treatment, while 8/57 (14%) of patients required alfa blocker at 6 months. Notably, the percentage of tri and pentafecta achievement slightly increased considering a subgroup of patients > 60 years, prostate <80 ml and moderate symptoms, reaching 75 and 70 % respectively. This concept might be reinforced what highlighted in the Delphi consensus regarding indications and potential benefits o such surgical procedures; in fact, the most benefit might be in young patients with moderate symptoms in patents with desire to preserve ejaculation.

4.3.2. Transperineal Laser Ablation of the Prostate (TPLA) as a treatment for Benign Prostatic Hyperplasia (BPH): the results of a Delphi Consensus project.

Forty Italian and international experts were invited and agreed to participate. Response rate was 80% (32/40) in first round and 77.5% (31/40) in second round. 28/32 (87.5%) participants were urologists and 4/32 (12.5%) interventional radiologists.

Most respondents (80%) recommended Echolaser® TPLA for the treatment of BPO in case of prostate volume < 40 cc in patients who do not want to undergo drug therapy or do not fully respond to it, if urodynamics confirms a normal bladder pressure.

The consensus agree that the procedure can be used for prostate volume between 40 and 80 cc (90%), which is considered the ideal volume for the treatment, and for prostate volume > 80 cc (80%) delivering a more extensive treatment. Further, Echolaser® TPLA can be carried out for the treatment of BPO in presence of a hyperplastic median lobe (>75%).

All experts considered Echolaser® TPLA favorable in both young patients who want to preserve sexual function, especially anterograde ejaculation (100%), and high-risk patients with comorbidities (100%), thanks to local anesthesia, short operation time, low rate of treatment-related complications and short hospitalization. The procedure can be convenient in patients under anti-coagulant or anti-platelet drugs (96%), but their suspension is recommended before the treatment according to the patient's hemorrhagic and thrombotic risk (77%).

A pre-operative post-void residual > 300 cc can be reduced using Echolaser® TPLA (>75%). The procedure is helpful in both patients with voiding and storage urinary symptoms (80%) and patients with chronic urinary infections that complicate BPO (>75%). Instead, it is not recommended in case of patient's history of chronic prostatitis and ultrasound evidence of multiple prostatic calcifications (>75%).

Echolaser® TPLA can lead to a permanent catheter removal in patients with an indwelling bladder catheter (77%), usually from 7 days to one month after the treatment.

Before the treatment, a urine culture is recommended in all patients (84%). Performing a urodynamic examination is suggested only in catheter-carrying patients (>75%), while in elderly and comorbid patients is not considered necessary (>75%). Instead, a pre-procedural urethroscopy is not advised (>75%).

Experts believe an antibiotic therapy before the treatment must be administered (80%).

Experts would rather visit a center with good experience on Echolaser® TPLA before doing it in their hospitals or clinics (83%). Moreover, they prefer that a company Application specialist (84%) and/or an expert physician (87%) supports them during the first procedures, while there is no need for support when they master the technique (>75%), usually after 5-10 treatments.

The planning software to plan and simulate the treatment before the laser is on is considered useful (77%) and allows the shortening of learning curve, especially in placing the needles correctly (84%). When the software (Echolaser Smart Interface) gives the indication to insert more needles it is advised to follow the recommendation rather than use only one needle and perform multiple reinsertions (>75%).

Furthermore, applying a positioning aid such as a template or a grid can be helpful (>75%).

Anesthesia must be performed (77%). Lidocaine should be administered locally to skin and periprostatic tissues (>75%). The use of sedatives during the procedure is still controversial.

To avoid damage on the urethra, it is recommended to use a cooling catheter (3-way Foley) during the procedure (87%). For the same purpose, it is important to respect the safety distances, positioning the optic fiber far away from the urethra rather than close to it (>75%).

The planned dose can be delivered at the power of 3 Watt (83%), but it can be increased up to 5 Watt to get a faster treatment (>75%).

The pull-back technique is suggested depending on the prostate size (90%) and the number of pullbacks also depends on its size and shape (>75%). When realized properly, this technique can improve the outcome of the procedure (84%).

Echolaser® TPLA is an outpatient treatment (84%). Patients can be discharged the same day of the procedure (77%), after 2-4 hours on average. It is recommended to maintain the catheter after the treatment in catheter-carrying patients (94%) for 7-15 days and to place a catheter in other patients (93%) for 7-10 days, to antagonize prostate inflammation and reduce the risk of acute urinary retention (AUR).

Regarding pharmacological treatment after the procedure, antibiotics are recommended for the first 5-7 days, corticosteroids and non-steroid anti-inflammatory drugs (NSAIDs) for a period that depends on how long the patient maintains the catheter (usually 7-15 days) (>75%). Moreover, experts suggest the use of alpha-blockers in the first weeks after the treatment, until symptoms relief generated by Echolaser® TPLA starts manifesting (>75%).

The more common treatment-related complications observed are irritative and obstructive urinary symptoms, dysuria, AUR, infections, hematuria, and qualitative variation in seminal fluid. The less common ones are prostatic abscesses, colliquative necrosis and bleeding; one expert reported a hypotensive shock occurred during the treatment.

The best parameters to assess the efficacy of Echolaser® TPLA are International Prostatic Symptoms Score (IPSS), uroflowmetry parameters and PVR (>75%). These elements should be evaluated during first follow-up, recommended 1-3 months after the procedure (>75%), and subsequent ones (>75%).

A consistent symptoms relief is expected 1-3 months after the treatment (>75%) and the maximum effect after 3-6 months (>75%).

According to their experience, experts confirm that Echolaser® TPLA preserves anterograde ejaculation (94%) and reduces or zeroes incontinence risk if compared to other treatments (87%).

Based on low complication rate, transperineal approach of Echolaser® TPLA is considered safer than transurethral approaches of other techniques (81%). Furthermore, for the treatment of BPH experts prefer an organ sparing technique like Echolaser® TPLA, whose therapeutic intent is to eliminate symptoms while preserving tissue, rather than more aggressive approaches (>75%).

Echolaser® Product Manual is considered well-written and complete (93%).

5. DISCUSSION

Minimally invasive treatment for BPH is an extremely current and ever-changing research field [28].

The reason for this constant search for improvement and evolution is aimed at guaranteeing the best functional outcomes while minimizing the side effects of treatment (medical or surgical) and allowing a rapid recovery [13-29]. In this scenario, during the last two decades, surgical treatment for BPH has evolved from open techniques to endoscopic techniques, including the use of laser technology, to ultra-minimally invasive surgical techniques (uMISTs) including, Aquablation, Urolift, Rezūm, temporary implantable nitinol device (TIND) and prostatic artery embolization (PAE) [11].

While surgical management of LUTS due to BPH has evolved toward the concept of minimally-invasive surgery and will likely replace open surgery in the next years, there are currently no structured validated training curricula for endoscopic treatment of BPH, especially for novice surgeons approaching new technologies. As such, given the impact of surgeon's experience on variability in perioperative outcomes after urological surgery [19], standardized training of future surgeons is a key unmet need to ensure patient safety throughout the surgeon's learning curve.

In recent years, under the umbrella of the European Association of Urology (EAU), structured training curricula have been proposed and validated for specific urological surgical procedures, including robotic radical prostatectomy [30] and robotic partial nephrectomy [31].

Moreover, the experience and skill of the operator are undoubtedly necessary to achieve these results. As such, given the impact of the surgeon's experience on variability in perioperative outcomes after urological surgery, training and assessment methods in surgical specialties become a clinical priority, as demonstrated by the continuous need for clear structure and reproducible models present in different urological fields [32-34].

Mirroring these programs, the current research project has aimed to develop a structured training curriculum in minimally invasive and innovative surgical techniques for BPH (including Holmium laser, Greenlight laser, and TPLA) through a multi-phase program including real-case observation, preclinical simulation, and modular training under the guidance of experienced proctors. This has led to the acquisition of skills and competencies that have allowed the transition to the clinical phase of learning and have proved to be fundamental in the context of a surgical training curriculum for a novice surgeon.

5.1. GREENLIGHT LASER LEARNING CURVE ASSESSMENT

Our study fills a priority gap in the literature by proposing a framework to allow surgeons with basic endoscopic experience to gain proficiency in a more complex procedure such as aPVP. In this regard, our study provides several key findings to contextualize the role of proctored training programs for minimally invasive treatment of BPH.

The first key finding of the study is that a step-by-step training program for aPVP is feasible and safe for a surgeon with no prior experience in endoscopic enucleation of the prostate if properly mentored. Our program allowed the surgeon in training to achieve proficiency while ensuring optimal patient outcomes. Importantly, while previous studies evaluating the learning curve of Greenlight vaporization/enucleation of the prostate relied on stronger endpoints such as surgical complications to benchmark surgical performance [35], we could not use such outcomes in our study due to the relatively low sample size and a low number of events. As such, we relied on the amount of energy delivered to the prostate as a potential surrogate of the efficacy of surgery, being associated with the risk of persistent LUTS in the postoperative period [25, 26]. A progressive reduction of the amount of energy delivered on the prostate was recorded with increasing surgeon's experience; of note, in our study as well as in previous experiences, the amount of energy delivered was associated with the degree of persistent burdensome LUTS after surgery [25, 26]. Our analysis highlighted that the amount of energy delivered on the prostate plateaued after 40 cases. Interestingly, the results of the multivariable analysis point to surgeon's experience as a key determinant of the amount of energy delivered on the prostate as well as the overall operative time.

Our study confirms the opportunity to achieve favorable outcomes even by less experienced surgeons, if appropriately mentored through a structured step-by-step program. In this regard, future efforts should be focused on implementation of such training pathway through the integration of simulation-based exercises specifically designed for PVP [36].

Lastly, a key finding of the study is that, at CUSUM analysis, the steps requiring more cases to achieve proficiency by the surgeon in training in terms of energy delivered were the 4 and 5th steps, suggesting that such critical steps are those requiring a more careful mentoring and monitoring of the surgeon's technical performance to ensure optimal patient outcomes during the training period. From a surgical perspective, this finding might be explained by a higher degree of difficulty in respecting the anatomical landmarks (including prostate capsule, bladder neck, and verumontanum) during the lateral lobe treatment, as well as the need to avoid thermal sphincteric trauma during apical treatment.

5.2. HoLEP LEARNING CURVE ASSESSMENT

Our results, as previously reported by other authors, HoLEP is quite difficult for novice surgeons and has a steep learning curve [37]. Considering the clear technical difficulty of the procedure, more evident in the case of a beginner, proctorship in the learning curve of the Holep takes on an even more significant role. Other experiences have already highlighted these aspects and demonstrated that the learning curve can be overcome faster with mentorship [38]. Moreover, supporting the mentor approach to learning, a multicenter study by Robert et al showed that over 50% of surgeons who were learning laser enucleation without a mentor did not eventually employ the technique and did not finish the training course [37].

According to the detailed , enucleation of the median lobe can might be an option at the beginning of the learning curve. Laser failure occurred when the threshold was not achieved and in one patient because it was converted to TURP. Despite the initial results, if 65 cases are probably not enough to overcome the learning curve (despite the threshold have been proposed by some HoLEP users), this number is probably sufficient to give surgeon the impetus to continue with this technique. Furthermore, it does suggest that more closely supervised training programs may help new users delive efficiency and patient safety. Our results emphasize that HoLEP is quite difficult for beginners and has a steep learning curve.

5.3. TPLA

Although TPLA represents a promising minimally-invasive option with several indications, it is still not currently recommended by Guidelines [11] and may have specific limitations that should prompt cautious and judicious use in clinical practice [39]. In particular, the clinical improvements reported with this technique might be still inferior to those obtained by gold standard (recommended) resective or enucleative techniques. Nonetheless, TPLA appears promising for several reasons: it avoids general anesthesia, it can be performed in the office with local anesthesia (with or without sedation), and it has been shown to achieve favorable outcomes on LUTS in well-selected patients with a low risk of perioperative morbidity and sexual dysfunction. In this regard, the percutaneous placement of the needles and the navigation system during TPLA allows maintenance of a safe distance from the bladder neck (fundamental for antegrade ejaculation) and the urethral lumen (paramount for limiting irritative symptoms and hematuria and preventing urethral stenosis). Moreover, TPLA allows very predictable tissue ablation and has a higher safety profile and a lower rate of postoperative dysuria in comparison to transurethral interstitial laser coagulation of the prostate.

Our results support a linear direct relationship between the adoption of a step-by-step guide for TPLA and the probability of Trifecta and Pentafecta achievement. Specifically, the estimated probability of Trifecta and Pentafecta accomplishment was 42 and 35/%., respectively. Notably, the percentage of tri and pentafecta achievement slightly increased considering a subgroup of patients > 60 years, prostate <80 ml and moderate symptoms, reaching 75 and 70 % respectively. This concept might be reinforced what highlighted in the Delphi consensus regarding indications and potential benefits o such surgical procedures; in fact, the most benefit might be in young patients with moderate symptoms in patents with desire to preserve ejaculation.

According to the need for an international multicenter European research network aiming to assess the reproducibility and clinical value of training programs in the field of minimally-invasive surgery for BPH, a Delphi Consensus process was used to achieve consensus on TPLA regarding preoperative indications, preprocedural assessment, intraprocedural features and postoperative management. Based on their experience, experts believe that the transperineal approach is safer than the transurethral one, and that TPLA represents a safe procedure for improving LUTS due to BPH maintaining ejaculatory function without the need for hospitalization.

6. CONCLUSIONS

The learning curve in urologic surgery has a critical impact on surgical outcomes and has been widely described in the literature.

This project has brought to the development of a structured training curriculum for some of the most widespread minimally-invasive procedures for the treatment of BPH, including Greenlight laser vaporization, Holmium laser enucleation and transperineal laser ablation of the prostate.

As a result, during the project period, the feasibility, acceptability, and educational impact of such a curriculum in a real-life clinical setting has been evaluated, while perioperative outcomes and patient quality of life during the different phases of the program for different minimally invasive surgical procedures were assessed whit the ultimate aim to evaluate the safety of such curricula from both patient and surgeon perspective. After this preliminary clinical phase, we evaluated the impact of the program on surgical decision-making toward the definition of a personalized treatment algorithm for patients with LUTS due to BPH according to the specific patient- and prostate-related characteristics.

As a final step of the project, a multicenter European research network across different surgeons and institutions has been created, to assess the reproducibility and the clinical value of a novel ultra-minimally invasive technique for BPH.

In a future perspective, these results could be an integral part of training for surgeons wishing to perform this kind of surgery.

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