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ORIGINAL ARTICLE

Holmium laser enucleation of prostate *versus* minimally invasive simple prostatectomy for large volume (≥120 mL) prostate glands: a prospective multicenter randomized study

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ABSTRACT

BACKGROUND: The aim of this study was to compare the perioperative and functional results between laparoscopic and robot-assisted simple prostatectomy (LSP and RASP) and Holmium laser enucleation of prostate (HoLEP) in prostate volumes ≥120 mL. The primary endpoint was to investigate and compare minimally invasive techniques in the management of large prostate gland volume, and the secondary endpoint was to evaluate the frequency and type of postoperative complications according to Clavien Dindo Classification.

METHODS: This multicenter study was conducted on male patients with LUTS associated with BPO candidates for surgical treatment. The surgery approach choice in relation to the prostatic volume ≥120 mL was HoLEP or minimally-invasive simple prostatectomy (LSP or RASP). All patients were prospectively randomized into three groups, according to a simple computed randomization: HoLEP, LSP and RASP groups. During the follow-up, all patients underwent post-operative control at 1, 3, 6, 12 and 24 months from the surgical procedure.

RESULTS: One hundred ten male patients were randomized in three homogeneous groups: 36 in LSP, 32 in RASP and 42 in HoLEP group. During the follow-up (mean 26.15 months), despite the significant improvement compared to baseline results, no significant differences were shown, between the groups in terms of functional and perioperative outcomes. The only statistically significant data was reported for catheterization time, that resulted longer in the LSP group than RASP and HoLEP groups (P=0.002). Furthermore, MISP resulted in longer hospitalization, and lower rate of patients with new-onset irritative symptoms.

CONCLUSIONS: This prospective randomized study is the first to compare extraperitoneal LSP, RASP and HoLEP in the treatment of LUTS secondary to benign prostatic hyperplasia for prostate volumes ≥120 mL. Our findings confirm the safety and efficacy of MISP, demonstrating its equivalence in functional outcomes and perioperative morbidity in comparison to HoLEP.

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For a century, open simple prostatectomy (OSP) has been the standard surgical treatment for non-neurogenic lower urinary tract symptoms (LUTS) associated with urethral obstruction due to benign prostatic hyperplasia (BPH).[1, 2] Today, as recommended by the European Association of Urology (EAU) and American Urological Association (AUA) Guidelines, OSP is still considered the standard therapy for large prostate glands (>80 mL).[1, 2] However, this procedure has been reported to be associated with perioperative complications and long hospitalization.[3-6] For these reasons, endoscopic and minimally invasive approaches have been proposed and introduced with the aim of reducing the morbidity related to open surgery. In prostates larger than 80 mL, these alternative procedures are mainly represented by laser endoscopy,[7, 8] laparoscopic and/or robot-assisted simple prostatectomy (LSP/RASP).[9, 10] These two last minimally-invasive simple prostatectomies techniques have to be considered still under current investigation and reserved for patients included in clinical trials. In 1996 Gilling *et al.* described the first Holmium laser enucleation of prostate (HoLEP) and over the years, several changes have been made in the endoscopic technique,[11] representing nowadays a widespread approach for prostate >80 mL. The LSP was described firstly in 2002 by Mariano *et al.* and over the years it has been developed and studied with encouraging results, representing a valid option for large prostate adenomas.[12, 13] In 2008, the feasibility of RASP was demonstrated by Sotelo et al.,[14] and it has been progressively adopted for its potential advantages over the standard open procedure.[15]

The aim of this prospective randomized study was to compare the perioperative and functional results between minimally invasive techniques (LSP and RASP) and the HOLEP approach in prostate volumes ≥120 mL. The primary endpoint was to investigate and compare effectiveness and safety of these minimally invasive techniques in the management of large prostate gland volume, and the secondary endpoint was to evaluate the frequency and type of postoperative complications according to Clavien Dindo Classification.[16]

Materials and methods

Study design

The study design has the following characteristics: prospective, multicenter, randomized, non-blinded, observational clinical trial. This prospective multicenter study was conducted from January 2016 to July 2018, on male patients with LUTS associated with BPH candidates for surgical treatment. The surgery approach choice in relation to the prostatic volume ≥120 mL was HoLEP or minimally-invasive simple prostatectomy (LSP or RASP) with extraperitoneal access as originally described by Millin.[12, 17] All the patients were enrolled from three centers: Sapienza ICOT (Latina, Italy), Vittorio Emanuele Hospital (Catania, Italy) and San Donato Hospital of Arezzo (Arezzo, Italy). All surgeries were performed by 3 experienced surgeons (one for each center with an experience of more than 75 procedures of HOLEP; LSP and RASP). All patients were candidates for prostate surgery in accordance with the symptoms and criteria defined by the EAU Guidelines. The inclusion criteria were: 1) recurrent acute urinary retention (AUR); 2) recurrent gross hematuria; 3) recurrent urinary tract infections (UTIs) resulting from an elevated post-void residual (PVR) urine volume; 4) bilateral hydronephrosis with renal functional impairment; and moderate-to-severe voiding symptoms secondary to BPH refractory to medical therapy; 5) International Prostate Symptom Score (IPSS) of >15; 6) maximum urinary flow rate (Qmax) of <12 mL/s; and 7) prostate size evaluated by preoperative transrectal ultrasonography (TRUS) and/or by prostate multiparametric magnetic resonance imaging (mpMRI)≥120 mL. Exclusion criteria included bleeding disorders, prostate cancer, neurogenic LUTS, and previous urethral or prostatic surgery (Supplementary Digital Material 1: Supplementary Table I).

The study was conducted in accordance with the Ethical Principles for Medical Research Involving Human Subjects (World Medical Association, The Declaration of Helsinki Principles, 2000) and was approved by the local medical ethical committee of the hospital (ASL LT N. 2016/ MURO UNIV 48569). All the subjects enrolled provided written informed consent for study participation.

All the patients were prospectively randomized into three groups, according to a simple computed randomization:[18]

• patients undergoing HoLEP with YAG laser (Versa-Pulse by Lumenis; Yokneam, Israel) 100-W and 550 nm end-firing flexible quartz laser fiber with subsequent morcellation of the enucleate adenoma (according to Gilling's technique);[11]

• patients undergoing LSP through an extraperitoneal transcapsular approach known as Millin's technique;[17]

• patients who underwent RASP using the Da Vinci Si/Xi system (Intuitive Surgical; Sunnyvale, CA, USA) using an extraperitoneal transcapsular approach sec. Millin.[12, 17]

The analysis of data was also conducted after a subdivision of the entire population into two main groups and comparing the first group of patients undergoing to HoLEP and the second group of patients (LSP and RASP) undergoing a minimally invasive surgical approach named MISP (minimally-invasive simple prostatectomy).

Surgical techniques

Endoscopic technique - HoLEP

After preoperative antibiotic prophylaxis (cefazolin 2 g i.v.), spinal or general anesthesia is induced and then the patient is placed in a lithotomy position. The enucleation technique is performed in all patients according to Gilling technique using Holmium YAG laser (Versa-Pulse by Lumenis) 100-W and 550 nm end-firing flexible quartz laser fiber.[11] With a 26 Fr Iglesias resectoscope with continuous flow (Karl Storz; Tuttlingen, Germany), urethrocystoscopy and identification of the ureteral hosts are carried out. The procedure begins with 2 longitudinal incisions (at 5 and 7 o'clock) that start from the bladder neck to the lateral margins of the veru-montanum and reach the prostate capsule to enucleate the middle lobe and then the lateral ones. The apical ends are joined together through a transverse incision above the veru-montanum. Enucleation of the lateral lobes involves an anterior commissurotomy. The anterior commissurotomy is reunited with the posterior ones. After identifying the cleavage plan between adenoma and prostate capsule at the apex of the adenoma, the plan is developed in a retrograde way in order to cleave the adenoma and dislocate it in the bladder. Hemostasis and regularization of the prostate capsule and control of the integrity of the ureteral meatus. Then morcellation of the prostate adenoma previously allocated in the bladder. Positioning of three-way bladder catheter type Dufour 20 ch with cuffed balloon in the prostate lodge.

Extraperitoneal minimally-invasive technique

After preoperative antibiotic prophylaxis (cefazolin 2 g i.v.), general anesthesia is induced and the patient is then prepared in a lithotomy position. To access the preperitoneal space, an incision is performed under the umbilicus. In order to reach the Retzius space, the perivesical fascia is digitally detached and with a balloon dissector (Covidien PDB1000; Medtronic, Dublin, Ireland) the extraperitoneal space is created.

Pneumoperitoneum induction

RASP is performed using the DaVinci Si/Xi Surgical System robot (Intuitive Surgical) with the positioning of first 12 mm/8 mm trocar (Robot Si or Xi respectively) for zero-degree robotic optic in the subumbilical incision. Three 8 mm robotic trocars (two on the left and one on the right) and further tow ones on the right (1×5 mm and 1×12 mm) is positioned for the assistant on the table. Robot docking. Position of monopolar scissors on the right with subsequent replacement with needle driver, and a bipolar Maryland and a prograsp forceps on the left.

LSP is performed using 3D Storz laparoscopic system (Karlo Storz) and positioning first 12 mm Hasson trocar under the umbilical for zero-degree laparoscopic optic. Other 4 trocars, 3 of 5 mm and 1 of 12 mm are inserted in a fan shape (as for extraperitoneal radical prostatectomy). The Harmonic Scalpel Ultracision (Ethicon Endosurgery, Cincinnati, OH, US) was used in all procedures.

Exposition of the anterior wall of prostate and the endopelvic fascia using monopolar scissors and/or Ultracision scalpel (Ethicon Endosurgery); using scissors and electrocoagulation, a transversal incision is performed on the anterior wall of the prostate capsule for 4-5 cm to identi-

fy the prostate adenoma (as originally described by Millin). At this time, the adenoma is bluntly dissected with the tip of scissors or Ultracision scalpel (Ethicon Endosurgery) from the anterior prostate capsule. The dissection continues on the lateral faces. The adenoma is then dissected from the bladder neck. Finally, the adenoma is dissected from the posterior side. In case of very large adenoma, it is divided and removed in two steps. The dissection of the apex was always performed maintaining the integrity of the veru-montanum which remains in the same place. Hemostasis is controlled using bipolar or monopolar energy. In order to facilitate the re-epithelialization of the prostatic fossa and for a better control of hemostasis, the trigonization of the prostatic fossa is performed using two V-lock 2/0 sutures 3 stitches between the sacral lip of the bladder neck and posterior surgical capsula. A catheter is introduced, and the balloon is inflated into the prostate lodge. The prostatic capsule is reconstructed with 2/0 V-lock running or interrupted sutures. Paravesical drainage is left in the pelvic area, and the adenoma, placed in an endobag, is removed passing through a mini-Pfannenstiel incision.

Preoperative data

For each patient the following preoperative data were evaluated: age, Body Mass Index (BMI), medical and surgical history, use of anticoagulants, International Prostate Symptoms Score (IPSS), Quality of Life (IPSS-QoL) and International Index of Erectile Function 5 (IIEF-5), presence of indwelling catheter, blood chemistry tests (prostate specific antigen [PSA] and hemoglobin [Hb]) prostate volume by trans-rectal ultrasound (TRUS) and/or prostate multi-parametric magnetic resonance imaging (mpMRI), uroflowmetry parameters (Qmax and Qave), and bladder post void residual volume (PVR).[19, 20] Twenty-one enrolled patients underwent a preoperative prostate biopsy for suspicion of prostate neoplasia which resulted negative. Surgery was performed at least 3 months after the biopsy procedure. Nieneteen patients underwent preoperative urodynamic study in consideration of indwelling catheter due to acute urinary retention (AUR), and/or urinary urgency with or without urge incontinence during the preoperative evaluation. All patients with neurogenic LUTS were excluded from this study.

Peri- and postoperative data

For each patient the following variables were evaluated: overall and effective operating time, estimated blood loss, postoperative Hb (at 3 h), hospitalization time, catheterization time, postoperative prostate volume, weight of the removed adenoma, histopathological examination and perioperative complications according to Clavien-Dindo Classification. During the follow-up, all patients underwent postoperative control at one month from procedure and then at 3, 6, 12 and 24 months with uroflowmetry, PVR, IPSS-QoL, IIEF-5, PSA, evaluation of retrograde ejaculation and urinary incontinence.

Data analysis

The sample size calculation assumed that men randomly assigned to MISP should have clinical outcomes equivalent to those who were randomized to HOLEP. For primary outcomes, differences in IPSS score of no more than 2.5 points and no more than 4 mL per sec for Qmax were hypothesized as suggesting equivalence. These hypotheses were based on the minimally clinically important differences in the literature and on discussions with urologists about clinically relevant cutoffs. Using the two-sided log-rank test, this study had 80% power to detect a difference of 0.934 and assuming SDs of 9 mL per sec for the Qmax and 5 units for the IPSS, the target sample size for patients needed to complete the 24-months follow-up was 53 per group. This sample size provided 85% power to show equivalence for Qmax and just over 90% power for IPSS, at a two-sided α of 5%. Assuming a total sample size of 106 subjects.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 25.0 (SPSS Inc.; Chicago, IL, US). P values <0.05 were considered statistically significant. The *t*-test was used for the comparison between means of independent groups and 2-tailed *t*-test for paired samples with 95% confidence

intervals was used for comparison of continuous variables between dependent samples. The relation between the prostate volume and the considered parameters was analyzed using linear regression and Pearson's Correlation Test.

Results

The study was conducted on a total of 110 patients divided into three groups: HoLEP with 42 patients, LSP with 36 patients and RASP consisting of 32 patients. All patients completed the 24 months follow-up. The patients were collected as follows: Sapienza ICOT Latina performed 19 HoLEP, 14 LSP and 3 RASP, Vittorio Emanuele Hospital of Catania performed 14 HoLEP, 14 LSP and 12 RASP, and San Donato Hospital of Arezzo performed 9 HoLEP, 8 LSP and 17 RASP. No conversion to open surgery occurred. The two groups of patients who underwent minimally invasive surgical procedures (LSP and RASP) were considered together as a single main group, named MISP. This MISP group was possible, given the statistical homogeneity between LSP and RASP groups after considering all the preoperative variables (P>0.05; Table I).

Peri- and postoperative results

As reported in the Table II, the analysis of data showed a lower but not significant overall operating time in LSP group compared to the RASP group (P=0.082), and the same result was observed when compared to the HoLEP group (P=0.071). An opposite fashion, although not statistically significant, was observed analyzing the effective operating time (excluding the time related to morcellation for HoLEP and docking for RASP) between the three techniques (P=0.175). The estimated blood loss was statistically comparable between LSP and RASP (P=0.058), and the Hb drop did not reveal significant differences between the three techniques (P=0.271).

On histopathological examination, 96% of patients were affected by benign prostatic hyperplasia and the mean weight of prostate adenoma removed was comparable among the groups of patients treated with MISP (P=0.231) and HoLEP (P=0.122). The residual prostate volume, assessed by trans-rectal prostate ultrasound three months after surgical procedure was comparable between the techniques, and a significant reduction of prostate volume was reported (P=0.141; drop of prostate volume P<0.0001). The remaining 4% of patients' histology examination resulted in unspecific chronic prostatitis (2%), high-grade prostatic intra-epithelial neoplasia (1%), and granulomatous prostatitis (1%).

The catheterization time was statistically longer in the LSP group than in the RASP one (P=0.011), and for MISP was higher when com-

TABLE I.—*Preoperative data.*

Variables	LSP	RASP	P value	HoLEP	MISP	P value
Patients, N.	36	32		42	68	
Age, yo (SD)	64.27 (7.21)	69.35 (6.19)	0.263	68.21 (6.09)	66.41 (7.49)	0.531
BMI, (SD)	21.82 (2.98)	20.3 (3.09)	0.111	23.48 (3.34)	21.1 (2.59)	0.284
Previous surgery, N. (%)	8 (22.2)	6 (18.7)	0.371	9 (21.4)	14 (20.5)	0.462
Indwelling catheter, N. (%)	9 (25)	7 (21.8)	0.213	11 (23.8)	16 (23.5)	0.388
Tot. vol. of prostate, mL (SD)	143.84 (31.32)	149.44 (35.15)	0.372	142.21 (30.14)	146.94 (30.67)	0.212
Vol. prost. adenoma, mL (SD)	134 (28.9)	129.37 (26.58)	0.089	128 (27.9)	132.14 (28.78)	0.145
Previous prost. biopsy N. (%)	10 (27.7)	9 (28.1)	0.413	11 (26.19)	19 (27.9)	0.292
PSA, ng/mL (SD)	5.59 (3.47)	5.23 (2.85)	0.119	5.64 (3.27)	5.47 (2.97)	0.678
Qmax, mL/sec (SD)	7.11 (1.77)	7.24 (2.31)	0.352	7.05 (1.88)	7.19 (1.28)	0.18
Qave, mL/sec (SD)	4.12 (2.11)	3.72 (1.08)	0.613	4.02 (1.04)	3.99 (0.94)	0.394
PVR, mL (SD)	132.35 (31.32)	126.06 (22.25)	0.103	130.13 (33.53)	128.64 (26.49)	0.097
Hb, g/dL (SD)	13.84 (1.32)	15.12 (1.9)	0.214	14.44 (1.18)	14.08 (1.4)	0.193
IPSS, (SD)	23.42 (2.82)	24.3 (1.87)	0.227	24.15 (3)	23.9 (1.85)	0.365
IIEF-5, (SD)	14.18 (2.65)	13.21 (2.23)	0.198	14.07 (2.61)	13.55 (2.19)	0.259
QoL, (SD)	3.85 (0.78)	3.83 (0.73)	0.311	3.89 (0.83)	3.84 (0.91)	0.798

LSP: Laparoscopic simple prostatectomy; RASP: robot-assisted simple prostatectomy; HoLEP: holmium laser enucleation of the prostate; MISP: minimally invasive simple prostatectomy; PVR: post-void residual volume; Hb: hemoglobin; IPSS: International Prostate Symptom Score; IIEF: International Index of Erectile Function; QoL: quality of life (of IPSS-QoL); PSA: prostate specific antigen, BMI: Body Mass Index, SD: standard deviation.

TABLE II.—*Peri and postoperative outcomes.*

Variables	LSP	RASP	P value	HoLEP	MISP	P value
Patients, N.	36	32		42	68	
Total operative time, min (SD)	126.55 (21.01)	138.47 (22.46)	0.082	134.32 (20.58)	133.56 (20.31)	0.071
Effective operative time, min (SD)	110.41 (17.32)	107.12 (31.35)	0.213	103.08 (15.54)	108.12 (23.42)	0.175
Estimated blood loss, mL (SD)	269.57 (88.53)	219.41 (67.49)	0.058	/	/	/
Drop Hb, g/dL (SD)	1.43 (0.45)	1.22 (0.31)	0.132	1.14 (0.27)	1.31 (0.39)	0.271
Post-operative prost. vol, mL (SD)	18.37 (6.35)	20.03 (6.14)	0.137	19.4 (7.12)	19.64 (6.32)	0.141
Drop prost. vol, P value	<0.0001	<0.0001	/	<0.0001	<0.0001	/
Removed prost. adenoma, g (SD)	125.89 (23.14)	127.31 (20.43)	0.231	124.18 (19.16)	126.34 (22.22)	0.122
Catheterization time, days (SD)	5.39 (1.22)	4.14 (0.81)	0.011	2.32 (0.64)	4.72 (1.03)	0.002
Length of stay, days (SD)	4.72 (0.71)	3.84 (0.53)	0.056	2.24 (0.32)	4.25 (0.64)	0.003
Qmax*, mL/sec (SD)	19.2 (2.72)	19.45 (1.89)	0.124	20.01 (2.21)	19.31 (2.23)	0.206
Drop Qmax, P value	<0.0001	<0.0001	/	<0.0001	<0.0001	/
Qave*, mL/sec (SD)	7.78 (1.12)	8.01 (1.21)	0.192	7.91 (1.24)	7.81 (1.15)	0.214
Drop Qave, P value	<0.0001	<0.0001	/	<0.0001	<0.0001	/
PVR*, mL (SD)	35.78 (15.45)	31.21 (16.63)	0.351	35.47 (14.89)	33.85 (16.18)	0.09
Drop PVR, P value	<0.0001	<0.0001	/	<0.0001	<0.0001	/
Drop PSA, ng/mL (SD)	2.98 (1.87)	3.09 (2.01)	0.205	3.11 (2.64)	3.05 (2.47)	0.994
IPSS*, (SD)	8.41 (2.12)	8.09 (2.41)	0.215	8.26 (2.08)	8.35 (2.04)	0.863
Drop IPSS, P value	<0.0001	<0.0001	/	<0.0001	<0.0001	/
QoL*, (SD)	1.66 (0.31)	1.69 (0.52)	0.111	1.71 (0.64)	1.67 (0.58)	0.201
Drop QoL, P value	<0.0001	<0.0001	/	<0.0001	<0.0001	/
IIEF-5*, (SD)	16.41 (2.37)	15.51 (2.61)	0.097	16.63 (2.42)	16.32 (2.24)	0.185
Drop IIEF-5, P value	<0.0001	<0.0001	/	<0.0001	<0.0001	/
Complication Clavien-D.<IIIa, N. (%)	5 (13.8)	4 (12.5)	0.278	6 (14)	8 9 (11.7)	0.311
Complication Clavien-D.≥IIIa, N. (%)	2 (5.5)	1 (3.1)	0.413	2 (4.7)	3 (4.4)	0.327
Urethral stricture, N. (%)	1 (2.7)	1 (3.1)	0.522	2 (4.7)	2 (2.9)	0.212

*Results observed at three months of follow-up.
LSP: Laparoscopic simple prostatectomy; RASP: robot-assisted simple prostatectomy; HoLEP: holmium laser enucleation of the prostate; PVR: post-void residual volume; Hb: hemoglobin; IPSS: International Prostate Symptom Score; IIEF: International Index of Erectile Function; QoL: quality of life (of IPSS-QoL); MISP: minimally invasive simple prostatectomy; PSA: prostate specific antigen, BMI: Body Mass Index, SD: standard deviation.

pared to HoLEP group (P=0.002). The hospitalization time was statistically higher in the MISP group than in the HoLEP one (P=0.003). No significant difference between the groups was shown about peri and postoperative complications. All the collected data are summarized in Table II.

According to Clavien-Dindo Classification, 6 complications of grade I and 2 of grade IIIb, which required endoscopic intervention under general anesthesia to remove bladder clots, were recorded in the HoLEP group. In the MISP group there were 8 grade I complications, one of grade II with the need for blood transfusion, and two of grade IIIb with subsequent endoscopic surgery to evacuate the bladder clots. No significant differences were observed between the two treatment groups complications.

The mean follow-up was 26.15 months. During this period 4 cases of urethral stricture (2 cases after MISP and 2 ones after HoLEP) were reported (P=0.212) and no cases of new-onset postoperative erectile dysfunction were found. At first urological evaluation, at one month after the procedure, 4 patients in the HoLEP group, 5 in the LSP and 4 in the RASP one reported mild stress urinary incontinence treated and solved by pelvic floor rehabilitation at 90 days postoperatively. One month after surgery, in the HoLEP group a higher percentage of patients with new-onset irritative symptoms (burning/pain, urgency and increased urinary frequency not associated with urinary tract infection) was recorded than MISP group (33.3% *vs.* 13.2%; P=0.02), All these symptoms were solved, by medical therapy, at the 3 months. No ejaculation preservation technique was adopted, and retrograde ejaculation was recorded in all patients.

At three months, a statistically significant improvement in uroflowmetry values when compared to the preoperative data was shown for all the three surgical groups (P<0.0001). However

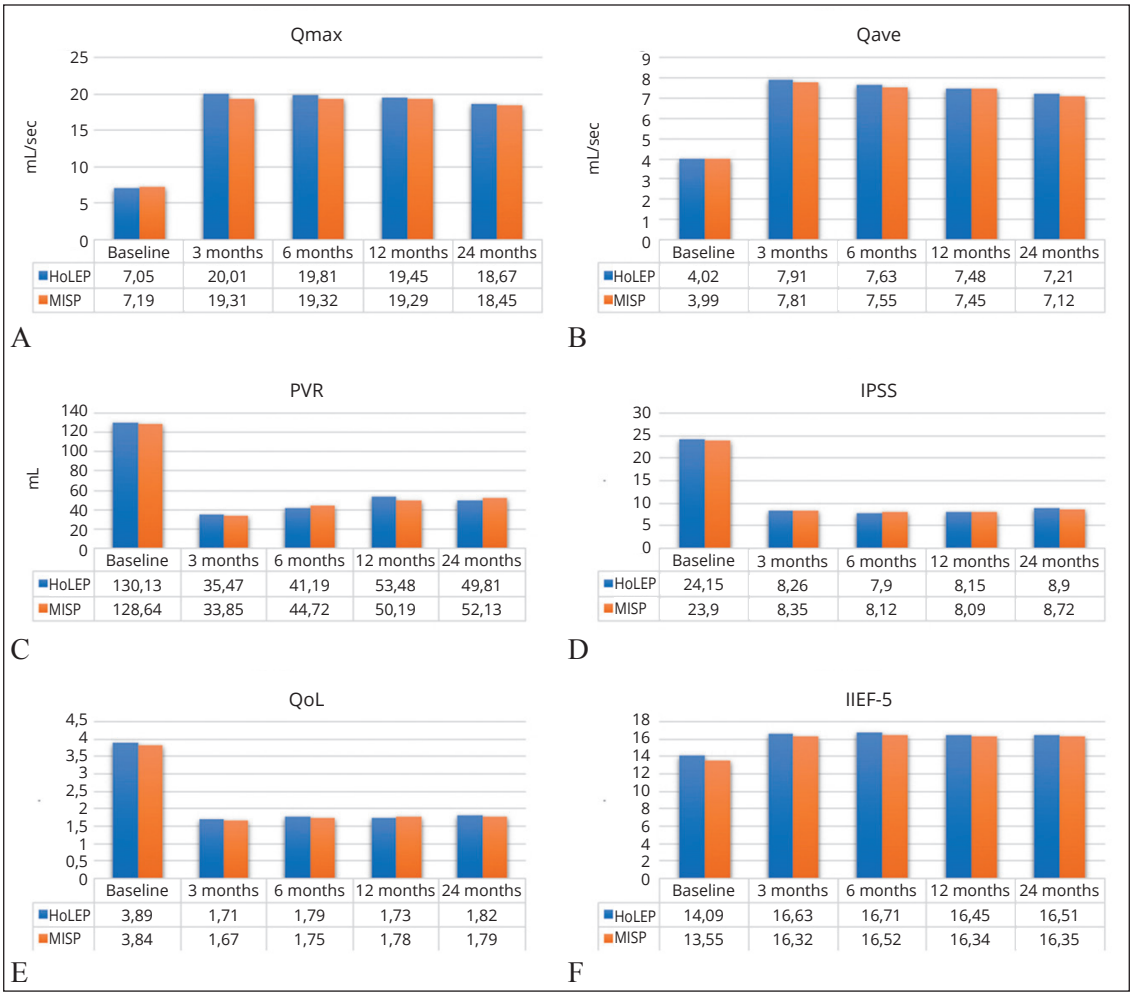

Figure 1.—A-F) Preoperative and postoperative results at 3, 6, 12 and 24 months.
HoLEP: Holmium laser enucleation of the prostate; MISP: minimally invasive simple prostatectomy; PVR: post-void residual volume; IPSS: International Prostate Symptom Score; QoL: quality of life (of IPSS-QoL); IIEF: International Index of Erectile Function.

no statistically significant difference was observed between the three groups in the comparison of the postoperative results even at 6, 12 and 24 months (P>0.05). At 24 months of follow-up the functional results did not show significant changes compared with the data at 3 months (P>0.05) (Figure 1A, B). The same result was obtained at 3 months about PVR, with a significant reduction compared to the basal PVR values in both groups (P<0.0001), and without any difference between the two surgical approaches (P=0.09). At 6, 12 and 24 months there were no significant changes compared to the 3 months postoperative results (P>0.05) (Figure 1C). At three months of follow-up, there was a significant improvement in the IPSS score compared to the preoperative data in both groups (P<0.0001) without significant postoperative difference between the approaches (P=0.863). These results were maintained through the follow-up time at 6, 12 and 24 months of follow-up without significant differences (Figure 1D). At the same time, a significant improvement of QoL and IIEF-5 scores was observed compared to baseline results (P<0.0001) without significant differences between the techniques (P>0.05). At 12 and

24 months the results obtained were confirmed without significant changes compared to the values at 6 months and between the two surgical approaches (P>0.05) (Figure 1E, F).

After three months, a significant drop in PSA was found in both groups compared to baseline values (P<0.0001) without significant differences in postoperative values between the two surgical approaches (P=0.994).

In both groups, a statistically significant positive correlation was also found between the volume of the prostate adenoma and the operative time (HoLEP r: +0.863; MISP r: +0.866; P<0.0001), drop of hemoglobin (HoLEP r: +0.599; MISP r: +0.773; P<0.0001) and estimated blood loss (HoLEP r: +0.877; MISP r: +0.762; P<0.0001) without significant differences between the two groups and between LSP and RASP.

Discussion

In recent literature several studies showed the feasibility and safety of the minimally invasive approaches and HoLEP technique in the treatment of LUTS secondary to BPH with prostate volume ≥80 mL.[1, 2, 7, 14, 21-23] In the current study we analyzed the data of 110 male patients enrolled from three experienced Italian centers. The MISP extraperitoneal approach was compared to Holmium laser enucleation of prostate (HoLEP) for BPH≥120 mL. To date, this study represents the first prospective and randomized investigation to compare these three techniques in patients with prostate volume ≥120 mL. As demonstrated, the most significant advantages of minimally invasive approach are represented by a reduced risk of blood transfusion and the estimated blood loss, reduction in catheterization time, length of stay, faster postoperative recovery, better aesthetic result, despite a longer operating time when compared to OSP.[21-25] The robotic approach when compared to laparoscopy seems to guarantee a little reduction in catheterization time and hospitalization length.[14, 26] To date, the EAU and AUA guidelines considers the minimally invasive approach still under investigation, requiring further long-term randomized studies, especially in comparison with endoscopic laser techniques. HoLEP has been established as a surgical technique with long-term functional results comparable to open approach and with better peri and postoperative complications reported outcomes (blood loss, catheterization time, length of stay and postoperative recovery) despite its longer operating times.[1, 2, 7, 9] However, this technique is characterized by the need for a longer learning-curve and specific instruments not always available.[27] Today several studies compare mini-invasive and endoscopic techniques, such as HoLEP, in the treatment of BPH associated with prostate volumes ≥80 mL, with the aim to demonstrate the non-inferiority of the minimally invasive approach.[28, 29] With this aim, we compared the laparoscopic/robot-assisted technique (according to Millin technique) to HoLEP in patients with prostate glands ≥120 mL in order to investigate whether a greater volume could impact perioperative and functional outcomes. Our results highlight how, both techniques are comparable in terms of peri and postoperative outcomes and when evaluating complications, in accordance with data reported in the literature.[21-25] Comparable results were obtained in terms of blood loss, blood transfusion rate, total operative times and surgical complications in accordance with the Clavien-Dindo Classification. When analyzing the operative times, although without significant differences, the overall surgical time was lower in LSP group than RASP and HoLEP ones, but, considering the effective operative time, HoLEP and RASP groups showed better results. This data can be explained giving the comparability of mean preparation time of operating field, port-placement and therefore robotic docking with the time required for morcellation in the HoLEP group (RASP=31.35 min; HoLEP=31.24 min).[22, 26]

As already reported in literature, the HoLEP showed a significant lower length of stay and shorter catheterization time when compared to RASP and above all compared to the LSP groups.[14, 15, 27-32] During follow-up (26.15 months) both approaches were associated to statistically comparable long-last functional results, such as urinary flow parameters (Qmax and Qave), PSA drop, IPSS-QoL, IIEF-5, new

urinary incontinence rate, complications rate with need for surgical re-intervention and retrograde ejaculation. The incidence of postoperative urethral strictures was comparable between the two groups (MISP and HoLEP), without a statistically significant difference. Both groups reported an incidence rate lower than 6%, in accordance with the EAU Guidelines.[1] As already shown by Baldini *et al.*, at one month after the procedure, the HoLEP group recorded a greater and significant incidence of urinary irritative disorders, solved at consultation at 3 months than minimally invasive approach. It was probably due to the effect of laser energy at the prostate capsule as already described in literature.[33]

Therefore laparoscopic/robot assisted approaches can be considered interesting options for experienced surgeons who have completed at least their learning curve in minimally invasive radical prostatectomy.[23] It is mandatory to consider the surgical experience of the center and the costs, especially with regard to robotic approach. In relation to this last aspect, the literature shows how both approaches (MISP and HoLEP) can have a favorable economic impact, especially when compared to the open technique, also considering robotic surgery (RASP). Matei *et al.* reported a cost of 3840 euros for each robotic procedure, lower than the open approach (5000 euros), mainly due to the high volume of robotic procedures performed, the reduction of costs is related to the length of stay and postoperative complications.[31, 34] The laparoscopic approach, however, appears to be associated with lower costs than robotics with an effective cost per procedure of 1799 euros as reported by Brunaud *et al.*.[35] Salonia et al. reported a cost of 2356 euros for HoLEP procedure, therefore lower than open approach despite the higher costs related to the initial operating room equipment. It is important to consider that the laser device can also be used for other pathological conditions such as upper and lower urinary tract urolithiasis, stenosis and other bladder/kidney diseases.[36] The growing interest and availability of the DaVinci Robot systems in the world, and the little difference in terms of actual costs between the robotic and laparoscopic approach (in high-volume centers), has led to a reversal of the trend over the years. To demonstrate this, among the growing number of works in literature, the multicenter study by Autorino *et al.* evaluated 1330 consecutive cases of MISP (LSP and RASP) carried out between 2000 and 2014 in twenty-three American and European centers. Although until 2014 most of the procedures were performed laparoscopically (N.=843; 63.4%), from 2013 there was an inversion of the relationship, between laparoscopic and robotic procedures, in favor of the latter for a total of 487 RASP performed.[24] Another consideration, regarding the minimally invasive approach, is the possibility to treat, during the same procedure, also concomitant diseases such as bladder diverticula, inguinal hernias and bladder lithiasis.[23] Our results provide a further demonstration of the safety and efficacy and non-inferiority of minimally invasive techniques compared to HoLEP.

Limitations of the study

This study certainly has the limit of the sample size, and the lack of a direct costs analysis per procedure being an objective outside of this study. Further studies are therefore necessary in order to recognize in the guidelines the minimally invasive approach as a valid alternative to endoscopic techniques for the treatment of LUTS associated with urethral obstruction due to prostate volumes ≥120 mL. The strength of the study is to represent the first prospective, randomized investigation to compare MISP and HoLEP in terms of outcomes and complications for prostate volume larger than 120 mL, a step forward the limit of 80 mL.

Conclusions

This prospective randomized study is the first to compare extraperitoneal MISP (laparoscopy and robot assisted) and HoLEP in the treatment of LUTS secondary to benign prostatic hyperplasia for prostate volumes ≥120 mL. This study confirms the efficacy and safety of minimally invasive simple prostatectomy, demonstrating its non-inferiority when compared to HoLEP in terms of functional outcomes and postoperative complications.

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