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Holmium laser enucleation of the prostate: A truly size-independent method?

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Abstract

Objectives: To evaluate the impact of prostate size on functional outcomes and perioperative morbidity, we analyzed patients undergoing holmium laser enucleation of the prostate (HoLEP) for lower urinary tract symptoms (LUTS). As LUTS secondary to benign prostatic obstruction (BPO) are a chronic progressive disease, prevalence and prostate size increase with age. HoLEP is a size-independent method for surgical treatment of LUTS/BPO and can be offered in medication-refractory patients with durable long-term results and reduced perioperative morbidity.

Methods: We retrospectively collected data of 852 patients who underwent HoLEP for LUTS secondary to BPO between 2014-2018. Patients were divided into group 1 (≤60 cc), group 2 (>60 < 120 cc), group 3 (≥120 cc). Perioperative parameters, safety and short-term functional outcomes were assessed and analyzed.

Results: Patients in group 3 were significantly older and showed a significantly higher median prostate-specific antigen level. Perioperative parameters, such as enucleation time and morcellation time significantly differed in favor of smaller prostate sizes, while enucleation and morcellation speed showed favorable results for larger prostate sizes. Larger prostates ≥120 cc showed a significantly higher postoperative drop in hemoglobin. However, patients did not differ in postoperative functional outcomes or Clavien-Dindo grade ≥II complications (4.8% of all patients [41/852]). There was no difference in perioperative complications between all groups ($P = 0.760$).

Conclusion: While larger prostates take significantly longer to operate on, postoperative functional outcomes show no difference between all sizes. In conclusion, HoLEP is a size-independent and effective method for surgical treatment of LUTS/BPO in prostates ≥30 cc.

KEYWORDS
benign prostatic enlargement, BPH, holmium laser enucleation of the prostate, LUTS, medical treatment, prostate size

1 | INTRODUCTION

The term benign prostatic hyperplasia (BPH) refers to the non-malignant growth of prostate tissue, predominantly in the prostate's transitional zone and is a common cause of male lower urinary tract symptoms (LUTS) secondary to benign prostatic obstruction (BPO).[1] The prevalence of BPH increases with age: about half of the 50-60-year old male population present with the histological diagnosis of BPH upon autopsy, peaking up to 80% in men above the age of 80 years.[1,2] BPH is a histological diagnosis characterized by an unfavorable balance between stromal and epithelial cell proliferation and cell death in the prostate's transitional zone surrounding the urethra.[2] Compression of the urethra leads to bladder outlet obstruction (BOO) caused by benign prostatic enlargement (BPE), thus leading to clinically relevant LUTS secondary to BPO. In 2018 about 612 million men worldwide were affected by LUTS/BPO, with annual costs peaking up to five billion US$ for medical treatment.[3] Age is a significant predictor of BPH and subsequent LUTS and, by the year 2040, one in four Americans will be above the age of 65, leading to even higher prevalence of LUTS/BPO.[4,5] While prostate size alone may not be an unlimited predictor of LUTS, prostate volume significantly increases with age. Studies have shown that prostate volume increases up to 2.5% per year.[5] Typically, the patient seeking urological treatment for LUTS/BPO is 65 years of age or above, bringing with them an increased risk of higher prostate volume and a much more challenging approach when considering the benefits and limitations of medical or surgical treatment.[6,7]

With the introduction of holmium laser enucleation of the prostate (HoLEP), a size-independent method for surgical relief of LUTS has constantly challenged transurethral resection of the prostate (TURP) as surgical reference method.[8-10] The efficacy of HoLEP is comparable to open prostatectomy (OP), but with shorter catheterization time, hospital stay and less blood loss.[9,11] HoLEP is equally efficient when compared to TURP, and even superior regarding perioperative morbidity.[12] HoLEP may therefore be a viable treatment option even in very large prostate glands (≥120 cc).

Considering this, together with the demographic shift in Western countries, the age-dependent progression of prostate size warrants improved understanding of the influence of prostate size on feasibility and functional outcomes of surgical treatment options for LUTS/BPO.

We therefore analyzed the impact of prostate size on preoperative LUTS profile, perioperative morbidity and mortality and postoperative functional outcomes for patients undergoing HoLEP for LUTS/BPO at our tertiary referral center.

2 | METHODS

2.1 | Patient population and study design

We included 852 patients who underwent HoLEP for LUTS secondary to BPO between 2014 and 2018. A computerized database containing information about patients' prostate sizes, various clinical information, as well as perioperative data and follow-up information, was used for this study. We retrospectively analyzed this database and included patients according to the aforementioned criteria. In total, 852 patients were evaluated, in which all the information was available, and subdivided into three groups. HoLEP for LUTS/BPO was indicated in accordance with the current European Association of Urology guidelines on management of non-neurogenic male LUTS.[13] However, patients presenting with an indwelling urinary catheter (ICUD) could not partake in preoperative uroflowmetry. Additionally, patients with a higher-than-expected preoperative prostate-specific antigen (PSA) value (ie, PSA density >0.15 ng/mL/cc) were assessed for prostate malignancy or, if inflammation was the cause of increased PSA, received antibiotics before surgery. The latter, were then re-assessed before definite surgery.

Only two experienced surgeons performed all HoLEPs. We used the VersaPulse® 100 W Holmium Laser (Lumenis Ltd., Yokneam, Israel) with a frequency of 53 Hz and a power setting of 1.2 kJ. Morcellation was performed using a mechanical tissue morcellator (R. Wolf, Piranha, Knittlingen, Germany). According to our standard protocol, a 24 F three-way foley catheter was inserted after surgery and followed by 12 hours of continuous bladder irrigation with normal saline.

Prostate size was assessed with transrectal ultrasound (TRUS) and patients were stratified into three groups. Group 1 included patients with prostate sizes ≤60 cm^3 (cc) (n = 157), group 2 included patients with glands from >60 cc to <120 cc (n = 523) and group 3 included only patients with very large prostates ≥120 cc (n = 172). We performed an additional analysis, dividing patients into two clinically very relevant groups: prostate size <80 cc (group 4; n = 410) vs ≥80 cc (group 5; n = 442), that is, where OP is indicated by current guidelines.[13]

Clinical and pathological information as well as perioperative data were used to describe the patient cohorts. Perioperative complications were analyzed in all groups. They were defined as any adverse event within 30 days of surgery and classified using the modified Clavien-Dindo (CD) scale.[14]

2.2 | Statistical analysis

Statistical analysis was performed using SPSS V26.0 software (IBM SPSS Statistics, Version 26.0. Armonk, NY, USA). Results are given as median and interquartile range (IQR) for continuous variables and as percentage for categorial variables. Univariate analyses were performed using Fisher's exact test, *t* test and Mann-Whitney *U* test for categorical variables and continuous variables, respectively. All reported *P*-values were two-sided and considered statistically significant if $P < 0.05$.

3 | RESULTS

3.1 | Patient characteristics

Table 1 displays demographic parameters of our patient cohorts. In total, 852 patients underwent HoLEP for LUTS secondary to BPO. Patients significantly differed in prostate size, with a median 139 cc (IQR 124-160) in group 3 vs 83 cc (IQR 72-100) and 55 cc (IQR 50-60)

TABLE 1 Demographic parameters

Variables	Group 1 (≤60 cc) n = 157	Group 2 (>60 < 120 cc) n = 523	Group 3 (≥120 cc) n = 172	*P*-value
Prostate volume (cc)				
Median	55	83	139	**<0.001**
IQR	50-60	72-100	124-160	
Age (y)				
Median	70*	71**	73	***<0.003**
IQR	62-76	65-76	69-77	****<0.02**
BMI				
Median	25.6	26.0	26.2	0.540
IQR	23.9-28.3	24.1-27.8	24.0-29.0	
IPSS				
Median	19	19	17	**<0.05**
IQR	14-24	14-23	12-22	
QoL				
Median	4	4	4	0.722
IQR	2-5	3-5	3-4	
Q_{max} (mL/s)				
Median	11	11	11	0.941
IQR	8-15	8-15	8-15	
PVR (mL)				
Median	80	100	60	0.154
IQR	30-185	40-170	20-150	
Hb (g/dL)				
Median	15.0	14.7	14.7	0.105
IQR	14.1-15.6	13.8-15.5	13.9-15.4	
Total PSA (ng/mL)				
Median	3.2	5.5	8.9	**<0.001**
IQR	1.7-5.6	3.4-9.6	5.6-15.2	
PSA density (ng/mL/cc)				
Median	0.06	0.06	0.06	0.277
IQR	0.03-0.11	0.04-0.11	0.04-0.10	
ASA score				
≥III vs <III	30.6%	31.0%	35.5%	0.509
(%)	(48)	(162)	(61)	
IDUC	20.4%	32.5%	40.1%	**<0.002**
(%)	(32)	(170)	(69)	

Note: Bold values indicate statistically significant *P*-values ($P < 0.05$).

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; Hb, hemoglobin; IDUC, indwelling urinary catheter; IPSS, International Prostate Symptom Index; IQR, interquartile range; PSA, prostate specific antigen; PVR, post-void residual urine; Q_{max}, peak urinary flow rate; QoL, quality of life.

*group 1 vs. group 3.

**group 2 vs. group 3.

in groups 2 and 1, respectively ($P < 0.001$). Patients also differed in age, with the highest median age of 73 years (IQR 69-77) in group 3 vs 71 years (IQR 65-76) in group 2 ($P < 0.02$) and 70 years (IQR 62-76) in group 1 ($P < 0.003$). LUTS profile was significantly different between the patient cohorts (Table 1). Patients in group 3 presented with significantly lower international prostate symptom score (IPSS) of 17 points (IQR 12-22) compared to group 1 with 19 (IQR 14-24) ($P < 0.05$) with no significant difference to group 2 with 19 points (IQR 14-24). As expected, median PSA was significantly different in all three groups with the highest median of 8.9 ng/mL (IQR 5.6-14.2) in group 3 vs groups 1 and 2 with 3.2 ng/mL (IQR 1.7-5.6) and 5.5 (IQR 3.4-9.6), respectively ($P < 0.001$). Presenting with an ICUD at time of surgery was significantly more prevalent in group 3 with 40.1% vs 32.5% and 20.4% for groups 2 and 1, respectively ($P < 0.002$). Apart from that,

TABLE 2 24-h perioperative parameters and clinical outcomes 4 weeks after surgery

Variables	Group 1 (≤60 cc) n = 157	Group 2 (>60 < 120 cc) n = 523	Group 3 (≥120 cc) n = 172	*P*-values
Enucleation time (min)				
Median	27	39	40	**<0.001**
IQR	24-38	30-55	33-53	
Enucleation speed (g/min)				
Median	1.08	1.60	2.79	**<0.001**
IQR	0.92-1.45	1.10-2.22	2.04-3.77	
Morcellation time (min)				
Median	6	13	25	**<0.001**
IQR	4-9	10-18	15-35	
Morcellation speed (g/min)				
Median	5.50	5.00	4.57	0.603
IQR	4.00-7.15	3.87-6.06	3.65-5.33	
Resected tissue (g)				
Median	35	63	115	**<0.001**
IQR	25-44	50-75	88-132	
Resected tissue (%)				
Median	67	75	76	**<0.001**
IQR	53-80	63-87	65-90	
Catheterization time (d)				
Median	2.0	2.0	2.0	0.147
IQR	2.0-2.0	2.0-3.0	2.0-3.0	
Hospitalization time (d)				
Median	3.0	3.0	3.0	0.104
IQR	3.0-3.0	3.0-4.0	3.0-4.0	
Δ Hb (g/dL)				
Median	0.9*	1.2**	1.8**	* **< 0.01**
IQR	0.3-1.5	0.6-1.8	1.0-2.7	** **< 0.001**
Δ IPSS				
Median	8	8	8	0.613
IQR	4-16	2-16	3-14	
Δ QoL				
Median	2	3	2	0.455
IQR	1-4	1-4	1-4	
Δ Q_{max} (mL/s)				
Median	10	11	9	0.620
IQR	5-18	6-21	4-19	
Δ PVR (mL)				
Median	77	77	53	0.169
IQR	29-180	30-160	14-150	

Note: Bold values indicate statistically significant *P*-values ($P < 0.05$).
Abbreviations: BMI, body mass index; Hb, hemoglobin; IPSS, International Prostate Symptom Index; IQR, interquartile range; PVR, post-void residual urine; Q_{max}, peak urinary flow rate; QoL, quality of life.

patient characteristics were comparable between all three cohorts and groups 1, 2 and 3 showed no statistically significant difference in body mass index (BMI), preoperative quality of life (QoL), maximum flow rate (Q_{max}), post-void residual (PVR), preoperative hemoglobin (Hb) or PSA density prior to surgery.

3.2 | Perioperative assessment and functional outcomes

Displayed in Table 2, the analysis of the perioperative outcomes showed statistically significant differences in enucleation time and

morcellation time. We observed a significantly shorter median enucleation time of 27 minutes (IQR 24-38) for patients with smaller prostates in group 1 vs 39 minutes (30-55) and 40 minutes (IQR 33-53) in groups 2 and 3, respectively ($P < 0.001$). Median morcellation time was significantly shorter for the smaller prostates in group 1 with 6 minutes (IQR 4-9) compared to 13 minutes (IQR 10-18) and 25 minutes (IQR 15-35) for groups 2 and 3, respectively ($P < 0.001$). However, enucleation speed significantly favored group 3. We observed a median enucleation speed of 2.79 g/min (IQR 2.04-3.77) for group 3 vs 1.60 g/min (IQR 1.10-2.22) for group 2 vs

TABLE 3 24-h perioperative parameters and clinical outcomes 4 weeks after surgery

Variables	Group 4 (<80 cc) n = 410	Group 5 (≥80 cc) n = 442	*P*-values
Enucleation time (min)			
Median	32	40	**<0.001**
IQR	25-45	32-53	
Enucleation speed (g/min)			
Median	1.25	2.21	**<0.001**
IQR	0.91-1.67	1.48-2.78	
Morcellation time (min)			
Median	9	17	**<0.001**
IQR	6-12	12-25	
Morcellation speed (g/min)			
Median	5.33	4.71	0.122
IQR	4.00-6.29	3.68-6.07	
Resected tissue (g)			
Median	48	82	**<0.001**
IQR	36-60	68-107	
Resected tissue (%)			
Median	73	76	**0.019**
IQR	60-85	62-88	
Catheterization time (d)			
Median	2.0	2.0	0.186
IQR	2.0-2.0	2.0-3.0	
Hospitalization time (d)			
Median	3.0	3.0	.0124
IQR	3.0-3.0	3.0-4.0	
Δ Hb (g/dL)			
Median	1.0	1.5	**<0.001**
IQR	0.3-1.6	0.8-2.3	
Δ IPSS			
Median	8	8	0.222
IQR	3-16	2-14	
Δ QoL			
Median	3	3	0.322
IQR	1-4	1-4	
Δ Q_{max} (mL/s)			
Median	10	10	0.960
IQR	6-19	5-20	
Δ PVR (mL)			
Median	73	60	0.108
IQR	24-165	20-150	

Note: Bold values indicate statistically significant *P*-values ($P < 0.05$).

Abbreviations: BMI, body mass index; Hb, hemoglobin; IPSS, International Prostate Symptom Index; IQR, interquartile range; PVR, post-void residual urine; Q_{max}, peak urinary flow rate; QoL, quality of life.

1.08 g/min (IQR 0.92-1.45) for group 1 with $P < 0.001$ for all groups, respectively. However, there was no difference in morcellation speed. As anticipated, median total resected tissue was more in group 3 with 115 g (IQR 88-132) vs group 2 with 63 g (IQR 50-75) vs group 1 with 35 g (25-44) with $P < 0.001$ for all groups, respectively. Also, median tissue retrieval percentage was significantly higher in groups 2 and 3 with 75% (IQR 63-87) and 76% (IQR (65-90), respectively, vs group 1 with 67% (IQR 53-80) ($P < 0.001$). Table 3 shows perioperative parameters for patients divided into group 4 (<80 cc) and group 5 (≥80 cc). We observed similar results as in groups 1-3 with a median enucleation time of 32 vs 40 minutes, and enucleation speed of 1.25 g/min vs 2.21 g/min for groups 4 and 5 with $P < 0.001$, respectively. While morcellation time was significantly different between both groups, with 9 and 17 minutes for groups 4 and 5, respectively ($P < 0.001$), we observed no difference in morcellation speed. As anticipated before, resected tissue was more in group 5, with a median of 82 g vs 48 g in group 4 ($P < .001$), with a slight – albeit statistically significant – difference in relative tissue retrieval of 73% vs 76% for groups 4 and 5, respectively ($P < 0.02$). There was no difference in the length of hospital stay or catheterization time.

Hemoglobin was assessed once preoperatively, and 24 hours after surgery. There was a statistically significant difference in the overall median hemoglobin drop between the three groups with 0.9 g/dL (IQR 0.3-1.5) in group 1 vs 1.2 g/dL (IQR 0.6-1.8) in group 2 ($P < 0.01$) and 1.8 g/dL (IQR 1.0-2.7) in group 3 ($P < 0.001$) and between groups 2 and 3 ($P < 0.001$). After sub-analysis, we report a significant difference between groups <80 cc and ≥80 cc of 1.0 vs 1.5 g/dL ($P < 0.001$).

Four weeks after surgical treatment LUTS significantly improved in all three patient cohorts. Median IPSS decreased by eight points throughout all patient cohorts ($P = 0.613$). We observed a relevant improvement in QoL for all three groups with no significant difference between groups. Early functional outcomes 4 weeks after surgery showed no significant difference between all groups, with a difference in Q_{max} of 10 mL/s (IQR 5-18), 11 mL/s (IQR 6-21) and 9 mL/s (IQR 4-19), respectively ($P = 0.620$). Median PVR reduction of 77 mL (IQR 29-180), 77 (30-160) and 53 (14-150) were observed for groups 1-3, respectively ($P = 0.169$). However, we observed no difference between all groups in duration of hospital stay or catheterization time. Furthermore, in groups 4 and 5, postoperative functional outcomes improved in a similar fashion, showing no difference between both groups for improvement of IPSS, QoL, Q_{max} and PVR (Table 3).

3.3 | Perioperative complications

In total, 63 (63/852, 7.4%) patients of the entire cohort experienced at least one perioperative complication. In groups 1, 2 and 3 respectively, nine (5.7%), 41 (7.8%) and 13 (7.6%) patients had at least one perioperative complication. There was no significant

TABLE 4 Perioperative adverse events (AEs) in groups 1-3 according to the Clavien-Dindo classification. The following AEs were identified and consecutive management is given in the table

AEs	Group 1 (≤60 cc) n = 157	Group 2 (>60 < 120 cc) n = 523	Group 3 (≥120c) n = 172	*P*-value
Overall AEs; n (%)	**9** (5.7%)	**41** (7.8%)	**13** (7.6%)	0.760
Clavien-Dindo I	**4** (1.7%)	**15** (2.7%)	**3** (6.3%)	
Clavien-Dindo II	**1** (0.4%)	**1** (0.4%)	**1** (0.3%)	
Clavien-Dindo III	**4** (2.0%)	**21** (4.5%)	**6** (4.5%)	
Clavien-Dindo IV	**0** (0.6%)	**4** (0.9%)	**3** (1.8%)	
Clavien-Dindo V	**0** (0.0%)	**0** (0.0%)	**0** (0.0%)	
Clavien-Dindo ≥II vs <II	**5** (3.2%)	**26** (5.0%)	**10** (5.8%)	0.492

Grade	Complication	Management
I	Hematuria ± blood clot retention (n = 12)	(Prolonged) bedside bladder irrigation ± clot evacuation
	Acute urinary retention after catheter removal (n = 10)	Bedside re-catheterization
II	Indwelling suprapubic catheter (n = 3)	Bladder training post-surgery
III	Persistent hematuria (n = 17)	Coagulation
	Urethral flap (n = 13)	Urethral resection (transurethral resection of the prostate)
	Injury of right ureteral ostium (n = 1)	Double J-stent placement
IV	Aspiration pneumonia (n = 2)	Admission to intensive care unit
	Urosepsis (n = 2)	Admission to intensive care unit
	Stroke (n = 1)	Admission to intensive care unit
	Pulmonary embolism (n = 1)	Admission to intensive care unit
	Myocardial infarction (n = 1)	Admission to intensive care unit

Note: Bold values indicate statistically significant *P*-values ($P < 0.05$).

TABLE 5 Perioperative adverse events (AEs) in groups 4 and 5 according to the Clavien-Dindo classification. The following AEs were identified and consecutive management is given in the table

AEs	Group 4 (<80 cc) n = 410	Group 5 (≥80 cc) n = 442	*P*-value
Overall AEs; n (%)	**31** (7.6%)	**32** (7.2%)	0.329
Clavien-Dindo I	**11** (2.7%)	**11** (2.4%)	
Clavien-Dindo II	**1** (0.2%)	**2** (0.5%)	
Clavien-Dindo III	**18** (4.4%)	**13** (2.9%)	
Clavien-Dindo IV	**1** (0.2%)	**6** (1.4%)	
Clavien-Dindo V	**0** (0.0%)	**0** (0.0%)	
Clavien-Dindo ≥II vs <II	**19** (4.6%)	**19** (4.3%)	0.463

Grade	Complication	Management
I	Hematuria ± blood clot retention (n = 12)	(Prolonged) bedside bladder irrigation ± clot evacuation
	Acute urinary retention after catheter removal (n = 10)	Bedside re-catheterization
II	Indwelling suprapubic catheter (n = 3)	Bladder training post-surgery
III	Persistent hematuria (n = 17)	Coagulation
	Urethral flap (n = 13)	Urethral resection (transurethral resection of the prostate)
	Injury of right ureteral ostium (n = 1)	Double J-stent placement
IV	Aspiration pneumonia (n = 2)	Admission to intensive care unit
	Urosepsis (n = 2)	Admission to intensive care unit
	Stroke (n = 1)	Admission to intensive care unit
	Pulmonary embolism (n = 1)	Admission to intensive care unit
	Myocardial infarction (n = 1)	Admission to intensive care unit

Note: Bold values indicate statistically significant *P*-values ($P < 0.05$).

difference between all three groups ($P = 0.760$). The groups also did not differ in the severity of their perioperative complications described by the modified CD score in Table 4. We divided complications into minor (CD I) and major complications (CD II to V) ($P = 0.492$), requiring an intervention. Complications seen are listed in detail in Table 4. However, when dividing patients into groups 4 and 5, we neither found a difference in number of complications, nor in the severity of complications, defined as CD classification ≥II ($P = 0.463$; Table 5).

4 | DISCUSSION

Upon histological examination, BPH is a true hyperplastic process with an increase in cell number both in the periurethral and transitional zones of the prostate. Both stromal and glandular proliferation can be seen, with stromal nodules predominantly in the periurethral zone and glandular nodular proliferation in the transitional zone.[15] Pathophysiology of LUTS presents both a static component, characterized by prostate growth, and a dynamic component, mainly α-adrenoceptor-mediated prostate smooth muscle contraction.[16] Medical therapy of LUTS/BPO includes α_1-adrenoceptor antagonists for rapid relief of prostate smooth muscle contraction and 5α-reductase inhibitor (5-ARI) for long-term reduction of prostate size and to prevent disease progression.[13,17] While α_1-mediated smooth muscle relaxation is achieved through various medications, static obstruction is a direct consequence of BPE resulting in periurethral compression and BOO, requiring increasing voiding pressures. In addition, BPE distorts the bladder outlet, further obstructing urinary flow.[18] If at all, 5-ARI decreases prostate size by no more than 25% and preventing disease progression is challenging.[13,17]

Currently, we observe a demographic shift in Western societies, and as prostate size increases with age, bothersome LUTS will become more prevalent.[5] In light of therapeutic limitations regarding highly enlarged prostates, assessing the impact of prostate size on preoperative LUTS profile, perioperative morbidity and postoperative functional results becomes self-evident.

We found that our patient cohorts significantly differed in age, with the highest median age in group 3. Although age difference was not clinically significant, we can confirm the age-dependency of prostate size observed by various studies before.[1,5] While age and prostate size correlate, increased total prostate volume alone does not necessarily lead to LUTS, but patients presenting with significantly enlarged prostates are at a higher risk for developing LUTS.[19] Patients with prostate volumes ≥120 cc presented with significantly lower preoperative IPSS. Although patients with increased prostate size are more likely to develop LUTS, prostate size alone may not be a predictor of severity of LUTS.[19,20] Corroborating this statement, we found no difference in preoperative Q_{max}, regardless of prostate size. Additionally, we observed unsatisfying QoL scores of four points

throughout our patient cohorts without any difference between groups as well as a clinically relevant and equally dissatisfying PVR. Although a relationship between metabolic syndrome and prostate size or the risk for developing LUTS has often been proposed, we cannot support this hypothesis as we could not show any significant difference in BMI between groups.[21] However, BMI alone may not be a sufficient indicator of metabolic syndrome and has clear limitations.[21]

As anticipated, we observed a significantly higher median PSA in patients with significantly enlarged prostates.[22] While there was a significant correlation between prostate size and total PSA, we could not show any difference in PSA density between groups, supporting that PSA correlated with prostate size and was not due to other causes, thus corresponding to our previous data.[23]

While we observed no significant difference in patients presenting with an American Society of Anesthesiologists score ≥III between groups, we found an increased number of patients presenting with an IDUC prior to surgery in group 3. We can therefore confirm the findings by Roehrborn et al, who found that patients with increased prostate size where at a three-fold higher risk for developing acute urinary retention.[24]

While there was no significant difference in preoperative hemoglobin value, there was a statistical difference in 24-hour postoperative hemoglobin drop. However, there was no need for perioperative blood transfusion, thus corresponding to the data we gathered on the favorable perioperative safety profile of performing HoLEP in octogenarians.[25] As prostatic hyperplasia may be due to an unfavorable balance between stromal and epithelial cell proliferation and cell death in the prostate's transitional zone surrounding the urethra, it can be seen as similar to a neoplastic process,[2] thus making it easy to accept the idea that angiogenesis must also accompany the abnormal growth of prostatic tissue in BPH.[26] In addition, laser enucleation of larger glands results in a larger surface of the prostatic fossa, consequently influencing the amount of fluid absorption during HoLEP and increasing the risk of hemodilution over a longer period of operating time.[27,28] Together, hemodilution may well explain the increased – albeit clinically insignificant – blood loss in patients with enlarged prostates.

We report significantly prolonged enucleation time, which significantly correlates with prostate size. This corresponds well with the current body of literature and data we recently gathered on HoLEP learning curves.[28] While Elzayat et al could show that HoLEP was functionally equivalent to OP, Park et al demonstrated that HoLEP was feasible even in smallest prostates; both reported size-dependent enucleation time.[10,29] While we anticipated enucleation and morcellation time to increase with prostate size, we found that enucleation speed significantly increased with prostate size, thus making HoLEP not only feasible, but also more efficient for larger prostates. Accordingly, we found tissue retrieval percentage significantly increased with larger prostate sizes. Even though Park et al could show that HoLEP is feasible even in smallest prostates, this, together with the significantly slower enucleation speed, may show that HoLEP presents a more challenging endeavor in smaller prostates and could be the new size-independent gold standard as alternative to OP in very large glands.[9,10]

Median morcellation time was significantly longer for larger prostates. However, morcellation was performed using the same mechanical tissue morcellator (R. Wolf, Piranha, Knittlingen, Germany) for all groups. Thus, prolonged morcellation time is due to the increased amount of tissue resected, as morcellation speed remains the same between all groups.

Although surgical parameters significantly differed between our patient cohorts, all patients in our study showed significant improvement of functional outcomes after HoLEP. There was distinct improvement of IPSS, Q_{max} and PVR for all patients in our study with similar improvement in all groups.

As prostate size progresses with age and the risk for developing LUTS/BPO increases with prostate size, patients with very large prostates may often suffer from LUTS secondary to BPO for an extended period of time and therefore detrusor contractility may need to be assessed over a longer follow-up period.[5,19] However, Elshal et al could show no significant difference in short-term (30 days) postoperative functional outcomes compared to follow-up after 1 year.[30] Furthermore, QoL did not differ significantly between groups and was similarly improved after HoLEP.

Overall, 63 patients suffered a postoperative complication according to the modified CD classification. Our population had very modest perioperative complications when compared to the study by Mamoulakis et al, where overall CD classification rate was 15.7%.[14] Most of our complications were found to be CD grade III (31/63, 49.2%) with persistent hematuria or obstruction by a urethral flap requiring surgical reintervention as the most common grade III complication. There were seven CD grade IV complications, accounting for 0.8% of all complications in our patient cohort and therefore corresponding well with the complication rate of 0.7% for CD grade IV reported by Elshal et al.[30] All grade IV complications occurred in groups 2 and 3, that is, in patients with prostates >60 cc. However, there was no statistical difference in ≥grade II CD between all groups. Even though the risk of hemodilution due to a significantly larger surface of the prostatic fossa in larger glands may be higher, one of the many advantages of HoLEP includes using physiologic saline as an irrigant. Thus, we found no life-threatening transurethral resection (TUR) syndrome in our patient cohort. Even after dividing patients into groups 4 and 5 for sub-analysis, we could not detect any difference in perioperative complications between groups.

Based on our data we could show that, regardless of prostate size, HoLEP is a feasible, effective and safe surgical treatment option in LUTS/BPO even for patients with very large prostate glands (≥120 cc).

The limitations to our study surely include its retrospective design. We did not include patients undergoing other laser treatment options or TURP for LUTS/BPO in our study. Groups 1 and 3 had significantly fewer patients than group 2, limiting the power of analysis. According to guidelines, patients in group 1 presented with prostate sizes eligible for TURP, while patients in group 3 had significantly enlarged glands eligible for OP, and were at increased risk of having already had surgical intervention at an earlier stage. Also, we cannot reproduce the data by Park et al, as our analysis only included four patients with prostate sizes ≤30 cc,[10] thus limiting the power of our conclusion. Also, following up patients at a tertiary referral center is

problematic, preventing complete collection of data for more cases. However, a longer follow-up is required for complete appraisal of functional outcomes and the safety profile. Still, we could show that there are no limitations to using HoLEP even in patients with various degrees of LUTS/BPS, presenting very large prostates prior to surgery. HoLEP shows exceptionally low morbidity and non-existent perioperative mortality in our analysis. Thus, HoLEP should be considered as a minimally invasive, but functionally equivalent, alternative to OP even for patients presenting with very large prostates.

With increasing life expectancy, there is a demographic shift in Western civilizations. As prostate size progresses with age and the risk for developing LUTS/BPO increases with prostate size, patients with very large prostates often pose a much more challenging approach when considering the benefits and limitations of medical or surgical treatment. Even though larger prostates take significantly longer to operate on, HoLEP shows high efficacy and functionally equivalent postoperative outcomes especially in larger prostates, but also in prostates usually eligible for TURP. Thus, HoLEP presents a ubiquitous treatment option for LUTS/BPO, and shows that eligibility may be independent of prostate size.

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DISCLOSURE

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTION

Alexander Tamalunas: project development, data collection and analysis, manuscript writing. Thilo Westhofen: data collection and management, data analysis. Melanie Schott: data collection and management, data analysis. Patrick Keller: data collection and management, data analysis. Michael Atzler: data collection and management. Christian G. Stief: project development. Giuseppe Magistro: project development, data collection and analysis, manuscript writing.

ETHICS STATEMENT

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required. All data were collected and analyzed anonymously.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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