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Patterns and Predictors of Optimal Surgical and Functional Outcomes after Holmium Laser Enucleation of the Prostate (HoLEP): Introducing the Concept of "Trifecta"

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Purpose: The present study sought to provide reproducible and patient-oriented metrics to assess the rate of "successful" outcomes (Trifecta) following holmium laser enucleation of the prostate (HoLEP). Clinical and surgical predictors of failure to achieve Trifecta were investigated.

Materials and Methods: We queried our prospectively collected database of all patients treated with HoLEP between March 2017 and January 2021. Trifecta was defined as the contemporary presence of: (1) no postoperative complication within 3 months; (2) no urinary incontinence at 3-months follow-up; and (3) 3-month postoperative max flow-rate >15 mL/s. Cases were grouped according to Trifecta achievement. All surgical procedures were carried out by a single surgeon. Surgical experience was divided into two different eras according to the number of procedures conducted (surgical era). Multivariate logistic regression analysis was performed to assess predictors of Trifecta failure.

Results: Overall 305 patients were included. Of these, 192 patients (63.0%) achieved Trifecta. Preoperative patient-related features were comparable between the two groups, except for a higher post-void residual (PVR) in non-Trifecta patients (median 180 *vs.* 130 mL, p=0.003). A significant proportion of Trifecta patients (88.5%) were treated in the second surgical era and in 126 (65.6%) cases an en-bloc enucleation was performed. Multivariate analysis confirmed PVR ≥250 mL, first surgical era and standard three-lobes enucleation technique as independent predictors of Trifecta failure.

Conclusions: In our experience the rate of "successful" HoLEP, defined according to our newly introduced Trifecta metric, was 63.0%. We demonstrated that surgical strategy together with rising experience and baseline PVR are key elements to forecast the outcomes.

Keywords: Benign prostatic hyperplasia; Holmium; Lasers; Prostatectomy

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INTRODUCTION

Holmium:YAG laser enucleation of the prostate (HoLEP) is considered one the main surgical treatments for benign prostatic hyperplasia (BPH) according to the latest European guidelines on non-neurogenic male LUTS (lower urinary tract symptoms) [1] and laser technologies [2]. In 1998 HoLEP was firstly introduced in its classical three-lobes technique [3]. Soon thereafter the 'en-bloc' techniques progressively emerged due to several theoretical advantages such as a faster identification of the surgical capsule, a shorter operative time and better sphincter preservation [4]. Nevertheless, HoLEP remains a challenging procedure requiring a relevant endoscopic experience [5] and can be burdened by a non-negligible postoperative urinary incontinence (UI) rate [6,7].

The concept of "success" in surgical procedures is crucial, in any field, and needs standardization to (1) assess the effectively patients' postoperative benefits, (2) evaluate the surgical quality within centers and operators, and (3) perform reliable comparisons among techniques [8]. Inspired by the literature on radical prostatectomy [9], the concept of Trifecta has been recently extended to other surgical fields, including laser treatments for BPH [5,10,11]. Nonetheless the concept of Trifecta applicated to HoLEP scenario is still controversial. The reasons mainly dwell on the narrow reproducibility of the available metrics and the limited clinical adherence on what "success" means from patient perspective.

However, a tool as the Trifecta still has a sense in the contemporary state of art but should respond to a question "a priori", when HoLEP come as a treatment option: How many chances do I have to reach the optimal outcomes without jeopardize patient's quality of life? In other words, the "right" Trifecta should be evaluated prior the surgery and adjusted for the baseline patient's features and expectations.

To address this clinical unmet need, we sought to assess the rate of Trifecta achievement after HoLEP according to a new clinical definition, relying on our single center prospective dataset. Clinical and surgical predictors of failure to achieve Trifecta were also investigated.

MATERIALS AND METHODS

1. Ethics statement

The present study protocol was reviewed and approved by the Institutional Review Board of Florence University Hospital (Reg. No. FI-2543). Informed consent was submitted by all subjects when they were enrolled. Informed consent was obtained from all individual participants included in the study. All the procedures were in accordance with the ethical standards of the Institutional and National Research Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

2. Population data

After internal review board approval was obtained, we prospectively collected data on all patients treated with HoLEP between March 2017 and January 2021. Inclusion criteria were: (1) Symptomatic BPH not responsive to medical therapy; (2) Preoperative max flow rate (Qmax) at non-invasive uroflowmetry <15 mL/s and/or post-void residual (PVR) >100 mL; (3) Prostate volume >60 mL; (4) Negative digital rectal examination. History of previous acute urinary retention (AUR), indwelling catheter at surgery, high comorbidity burden and antiplatelet/anticoagulant therapies were not considered exclusion criteria. In case of clinical suspicious prostate cancer (PCa), multiparametric MRI was performed to rule out any possible concomitant PCa. All procedures were carried out by a single operator following the standard three-lobes or the en-bloc technique according to surgeon's preference [12]. The overall number of cases was divided within the first 50 procedures (first surgical era) and the subsequent ones (second surgical era), as surrogate of the surgical experience.

All patients underwent a preoperative laboratory and imaging analysis including uroflowmetry with PVR urine examination, prostatic-specific antigen (PSA), and abdominal ultrasound. Clinical evaluation and symptoms were assessed using validated questionnaires: The International Prostate Symptom Score (IPSS) questionnaire, the International Index of Erectile Function (IIEF), the International Consultation on Incontinence Questionnaire–Urinary Incontinence (ICIQ-UI), the Overactive Bladder questionnaire (ICIQ-OAB) and the Quality of Life (QoL) index were used.

Postoperative complications were recorded using the

modified Clavien–Dindo classification scale [13] and divided in "early" and "late" since they occurred before or after the 30th postoperative day.

All patients were assessed at 1-, 3-, 6-, 12-month postoperatively and therefore annually with uroflowmetry, PVR urine examination, PSA and creatinine measurement and symptomatologic assessment (using the above-mentioned questionnaires). At the third month of follow-up Patient Global Impression of Improvement (PGI-I) scale was also submitted to the entire study population.

UI was defined as any involuntary urine leak including postvoid dribbling, regardless the number of pads used.

3. Trifecta definition

Trifecta achievement was defined as the contemporary presence of: (1) no postoperative complications within 3 months; (2) 3-month postoperative Qmax >15 mL/s; and (3) no UI at 3-month evaluation. According to this definition, the overall population was therefore divided according to Trifecta achievement.

4. Statistical analysis

Categorical, continuous parametric and not-parametric variables were reported as frequencies and proportions, number (%) or as median and interquartile range (IQR), respectively. Before proceeding, we performed kurtosis and skewness analysis to assess if our continuous variables had a normal distribution. Based on the results of this additional analysis we opted to maintain the form of median (IQR) as more reliable for the present study. Unpaired t-test, Mann–Whitney and Pearson's chi-square tests were used to compare variables, as appropriate. Surgical eras were used as surrogate proxy of surgical experience. Patients groups (Trifecta and non-Trifecta) were stratified according to PGI-I scale (from 1-very much better to 7-very much worse) to investigate whether the Trifecta definition meets the achieving of patients clinical expectations. To

Table 1. Preoperative characteristics of patients reaching versus not-reaching the Trifecta

Variable	*Non-Trifecta* (n=113, 37.0%)	*Trifecta* (n=192, 63.0%)	p-value
Age (y)	70 (67–76)	69 (64–74)	0.13
BMI (kg/m^2)	26 (23.7–28.1)	26.1 (24.4–28.5)	0.73
CCI age adjusted	3 (1–4)	3 (1–4)	0.43
ASA score	2 (1–3)	2 (1–3)	0.21
ACs/APs therapy at surgery	25 (22.1)	24 (12.5)	0.005
AUR			0.99
Overall	51 (45.1)	87 (45.3)	
Single/multiple episodes	24 (21.2)	31 (16.1)	
Indwelling catheter	33 (29.2)	45 (23.4)	
Prostate volume (mL)	110 (80–130)	100 (75–130)	0.39
Creatinine serum level (mg/dL)	1 (0.9–1.2)	0.9 (0.9–1.1)	0.91
HB blood level (g/dL)	14 (13.1–15.2)	14.9 (13.7–15.3)	0.34
Q-max (mL/s)	8.2 (7.0–10.0)	8.7 (7.3–10.3)	0.47
PVR volume (mL)	180 (100–300)	130 (100–250)	0.003
PSA serum level (ng/mL)	5.6 (2.8–8.7)	4.8 (2.5–7.3)	0.25
IPSS score	24 (21–28)	24 (21–27)	0.63
IIEF-5 score	18 (12–22)	18 (10–21)	0.70
OAB-q score	44 (25–55)	39 (27–53)	0.76
ICIQ-sf score	0 (0–0)	0 (0–0)	0.42
QoL score	4 (3–5)	4 (4–5)	0.34

Values are presented as median (interquartile range) or number (%).
AC: anticoagulant, AP: antiplatelet, ASA: American Society of Anesthesiologists, AUR: acute urinary retention, BMI: body mass index, CCI: Charlson Comorbidity Index, HB: hemoglobin, ICIQ-sf: International Consultation on Incontinence Questionnaire-Short Form, IIEF: International Index of Erectile Function, IPSS: International Prostate Symptom Score, OAB-q: Overactive Bladder questionnaire, PSA: prostatic-specific antigen, PVR: post-voiding residual, Qmax: max flow rate, QoL: Quality of Life.

evaluate possible predictors of Trifecta failure, univariate and multivariate logistic regression analysis (MVA) were performed using significant clinical and surgical variables. Statistical analysis was carried out using SPSS® 27.0 (IBM Corporation, Armonk, NY, USA). All tests were two-sided with a statistical significance set as $p<0.05$.

RESULTS

Overall, 305 male patients were included. According to our definition, 192 patients (63.0%) achieved the Trifecta. Preoperative patients' characteristics, divided according to Trifecta achievement, are depicted in Table 1. Patients were almost comparable between the two cohorts except for a higher proportion of patient with ongoing antiplatelet or anticoagulant therapy at surgery (26.8% *vs.* 12.5%; p=0.005) and higher PVR (median 180 mL [IRQ 100–300 mL] *vs.* 130 mL [IQR 100–250 mL]; p=0.003) within the non-Trifecta group.

Intraoperative features were reported in Table 2. Median operative time, lasing time, enucleation time, morcellation time, and amount of energy delivered did not differ between the two groups (all p>0.05). A significant higher proportion of patients was treated by using the en-bloc (65.6% *vs.* 46.0%) or a standard three-lobes technique (54.0% *vs.* 34.4%) within the Trifecta and non-Trifecta group, respectively (p=0.003).

Postoperative outcomes are summarized in Table 2. At 3-month follow-up, the symptomatologic scores, using the validated questionnaires, were mainly comparable among the two groups except for median IPSS value, being lower among Trifecta patients (6 [IQR 1–8] *vs*, 9 [IQR 2–12], p=0.04). Median postoperative Q-max was found significant higher in those patients in which Trifecta was achieved (22.2 mL/s [IQR 19.2–27 mL/s] *vs.* 18 mL/s [IQR 13–21 mL/s]; p<0.001). Within non-Trifecta group, 40 patients (35.4%) Clavien–Dindo ≤2 and 4 patients (3.5%) Clavien–Dindo >2 early complications were recorded. Delayed complications occurred in 5 patients (4.4%). After stratifying for surgical experience, we found that a higher percentage of patients reaching the Trifecta were treated within the second surgical era (88.5% *vs.* 11.5%; p=0.001).

The distribution of Trifecta and non-Trifecta patients according to the 3-month PGI-I scale showed a significant higher proportion of Trifecta cases among the very-much better rank (grade 1 of the PGI-I scale) compared to the counterpart (90 *vs.* 28 patients within Trifecta and non-Trifecta group, respectively). On the contrary, the proportion of Trifecta over non-Trifecta patients decreased within the higher ranks of the PGI-I scale (p=0.002) (Fig. 1).

Univariate analysis showed that surgical era, preoperative PVR volume, surgical technique, and on-going antiplatelet/anticoagulant therapy were significantly associated with Trifecta outcome. At MVA, 1st surgical (odds ratio [OR], 1.87; 95% confidence interval [CI], 1.25–2.26; p=0.001) preoperative PVR volume ≥250 mL (OR, 1.21; 95% 1.10–1.31; p=0.02) and three-lobes surgical technique (OR, 1.66; 95% CI, 1.54–2.13; p=0.001) were found independent predictors of Trifecta failure (Table 3).

DISCUSSION

Minimally invasive treatment for BPH patients significantly evolved in the last decades also due to the introduction and rising spread of laser technology [2]. Nowadays, HoLEP is considered as one of the main surgical options for symptomatic patients with an increasing number of procedures conducted every year worldwide [14]. The Trifecta tool was developed with the intent to objectively measure the concept of surgical "success" and has progressively gained attention within the radical prostatectomy and partial nephrectomy fields [9,15-19]. More recently, this concept has been transferred into laser treatment of BPH. In particular, Robert et al [5] employed this tool for the assessment of HoLEP learning curve defining the Trifecta as a complete enucleation and morcellation within 90 minutes, without any conversion to standard TURP, and acceptable stress and difficulty. Stress and difficulty of the procedure were subjectively assessed by the surgeon, using a visual analogic scale, and were considered acceptable when under 5/10.

Therefore, the Pentafecta formulation, adopted for the Greenlight Laser enucleation of prostate, included further postoperative parameters as the absence of complications and stress urinary incontinence at 3 months after surgery [10,11].

In the present study we proposed a novel metrics to define "successful" HoLEP. Unlike previous experiences, we adopted a definition focused on what patients may perceive as "success" following surgery for BPH maintaining, at the same time, objectively measurable parameters. As such we included: (1) 3-month Q-max

Table 2. Surgical, postoperative and functional outcomes of patients reaching *vs*. not-reaching the Trifecta

Variable	*Non-Trifecta* (n=113, 37.0%)	*Trifecta* (n=192, 63.0%)	p-value
Surgical outcomes			
Enucleation technique			0.003
Three-lobes	61 (54.0)	66 (34.4)	
En-bloc	52 (46.0)	126 (65.6)	
Overall operative time (min)	100 (67–120)	97 (65–115)	0.23
Enucleation time (min)	52 (35–60)	45 (32–55)	0.24
Morcellation time (min)	24 (16–35)	23 (16–32)	0.17
Lasing time (min)	38 (32–47)	34 (29–40)	0.21
Energy delivered (kJ)	131.3 (103.2–162.6)	120.1 (100.9–140.3)	0.48
Surgical era			
≤50 procedures	78 (69.0)	22 (11.5)	0.001
>50 procedures	35 (31.0)	170 (88.5)	
Postoperative and functional outcomes			
Catheterization time (d)	3 (3–3)	5 (4–5)	<0.001
Hospitalization time (d)	4 (4–6)	4 (3–4)	<0.001
Q-max (mL/s)	14 (13–20)	22 (19–27)	<0.001
PVR volume (mL)	30 (8–50)	30 (0–50)	0.68
PSA (ng/mL)	0.9 (0.63–1.00)	0.9 (0.68–1.60)	0.17
IPSS	9 (2–12)	6 (1–8)	0.04
IIEF-5	17 (12–20)	18 (11–20)	0.81
OAB-q	15 (13–19)	13 (13–16)	0.06
ICIQ-sf	2 (0–4)	0 (0–0)	0.02
QoL	1 (0–2)	1 (0–1)	0.13
PGI-I			0.002
1 (very much better)	28	90	
2 (much better)	27	60	
3 (a little better)	43	38	
4 (no change)	12	4	
5 (a little worse)	2	0	
6 (much worse)	1	0	
7 (very much worse)	0	0	
CD complication			-
Early events	44 (38.9)	-	
CD ≤2	40 (35.4)		
CD >2	4 (3.5)		
Late events	5 (4.4)	-	
CD ≤2	2 (1.8)		
CD >2	3 (2.7)		
UI at 1-mo follow-up	31 (27.4)	9 (4.7)	<0.001
UI at 3-mo follow-up	22 (19.5)	-	-
Follow-up (mo)	18 (9–29)	17 (9–27)	0.35

Values are presented as number (%), median (interquartile range), or number only.
CD: Clavien–Dindo, ICIQ-sf: International Consultation on Incontinence Questionnaire-Short Form, IIEF: International Index of Erectile Function, IPSS: International Prostate Symptom Score, OAB-q: Overactive Bladder questionnaire, PGI-I: Patient Global Impression of Improvement, PSA: prostatic-specific antigen, PVR: post-voiding residual, Qmax: max flow rate, QoL: Quality of Life, UI: urinary incontinence, -: not available.

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Table 3. Univariate and multivariate logistic regression analysis for the predictors of "Trifecta *failure*"

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
1st surgical era (*vs.* 2nd surgical era)	1.51 (1.29–1.71)	0.01	1.87 (1.25–2.26)	0.001
Preoperative PVR volume ≥250 mL (*vs.* <250 mL)	1.23 (1.11–1.33)	0.01	1.21 (1.10–1.31)	0.02
Three-lobes enucleation technique (*vs.* En-bloc)	1.54 (1.45–2.11)	0.01	1.66 (1.54–2.13)	0.001
On-going ACs/APs at surgery	3.11 (0.27–7.20)	0.53	-	-

AC: anticoagulant, AP: antiplatelet, CI: confidence interval, OR: odds ratio, PVR: post-voiding residual, -: not available.

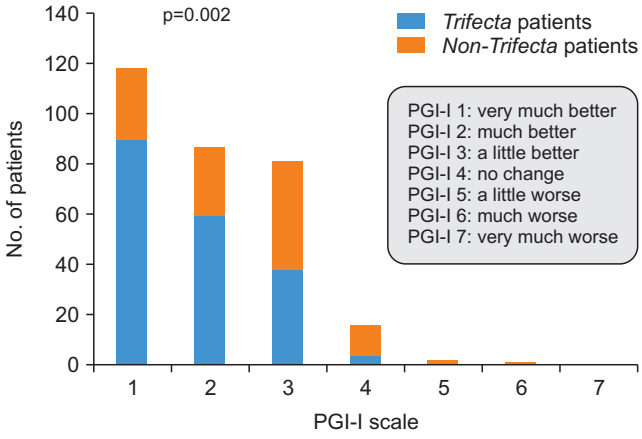

Fig. 1. Distribution of Trifecta and non-Trifecta patients according to 3-month postoperative Patient Global Impression of Improvement (PGI-I) scale.

>15 mL/s to assess the obstructive relief; (2) absence of postoperative complications at 3 months to exclude possible late events and (3) absence of UI at 3-months follow-up as major detrimental affection of the quality of life.

In particular we want to point out that We decided to include flow-max rate as surrogate outcome to assess the obstructive relief instead of the score improvements at the validated questionnaires since it is a more objective parameter which may be hardly affected by external biases. Moreover, we opted 15 mL/s as a reasonable threshold to capture the realistic rate of Trifecta achievement in the vast majority of patients despite a percentage of patient having chronic AUR at diagnosis.

Interestingly, we found that 192 patients (63.0%) achieved the Trifecta status. Our first finding confirms the reliability of the proposed metric to patients' expectations. Indeed, Trifecta patients significantly matched with the most satisfied ranks on the PGI-I scale while the proportion of non-Trifecta patients increases within the less-improved ranks of the scale (Fig. 1). Furthermore, after stratifying for surgical experience, the vast majority of Trifecta patients were treated in the second surgical era showing that, once the learning curve has been overcome, the rate of "successful" procedures consistently increases. Of note, for the first time, we compared Trifecta achievement within surgical techniques. Of note, almost two-third of Trifecta patients were treated with en-bloc HoLEP. These findings were confirmed at the MVA. First surgical era (*vs.* second surgical era) and three-lobes surgical technique (*vs.* en-bloc) independently predicted Trifecta failure (OR. 1.87; 95% CI, 1.25–2.26 and OR, 1.66; 95% CI, 1.54–2.13, respectively). We believe that the surgical benefits embodied into the en-bloc technique effectively explicate this result. In fact, as shown in previous investigations, removing the adenoma en-bloc may reduce the risk of developing false planes, enhancing at the same time the likehood of complete enucleation [20,21]. In addition, the early apical release performed at our institution at the time of en-bloc HoLEP may have further contributed to such finding. In particular, this step is crucial to preserve the sphincter competence and emerging evidence highlighted that it may determine a significantly reduction in postoperative incontinence rates [22-24].

Another key finding is related to the predictive value of preoperative PVR as independently associated with Trifecta failure. In particular, patients with preoperative PVR ≥250 mL are at higher risk of unsuccessful outcomes following HoLEP, as compared to their counterparts (OR, 1.21; 95% CI, 1.10–1.31; p=0.02). This evidence has significant clinical implications since the proper identification of such patients' category may require further functional evaluation, such as preoperative urodynamic assessment and eventually addressing toward bladder rehabilitation therapies in preparation of the surgery. Jaeger et al [25] analyzed the outcomes of patients with chronic urinary retention (PVR >300

mL) submitted to HoLEP and found that, despite the vast majority were catheter-free at one-month postoperatively, the median Q-max remained substantially weak proving a possible negative inference of a certain grade of detrusor underactivity in such cohort. Nevertheless, although the relationship between BPH and detrusor underactivity remains unclear, several studies has demonstrated a positive impact of vesical stimulation in improving voiding symptoms after surgical treatments for BPH [26-28].

Finally, albeit the rate of patients with on-going anticoagulant/antiplatelet therapies was significantly higher in *not*-Trifecta group (22.1% *vs.* 12.5%, p=0.005), it did not show independent correlation with Trifecta failure at MVA. We believe that the observed benefit of HoLEP in providing accurate hemostasis in such patient category determined this finding. Indeed, thanks to its physics characteristics, such as the chromophore of water and minimal tissue depth penetration, holmium laser is able to achieve quick vaporization and coagulation of tissue without the disadvantage of deep tissue penetration [29].

The present study is not devoid of limitations. First, it relies on a monocentric, single surgeon experience. As such the current findings may not be applicable to all center- or surgeon-related scenario. Second, the threshold adopted for each of the parameters and related timeframes have been arbitrarily selected. Third, preoperative urodynamic study was not routinely performed in those patients showing higher PVR. Each of these factors may have introduced statistical bias, ultimately undermining reliability of reported findings.

Acknowledged these limitations, this is the first experience introducing the concept of Trifecta beyond the learning curve of HoLEP embracing reproducible and objective metrics while maintaining patient-oriented outcomes. Moreover, it evaluated the possible inference of the surgical technique in achieving the optimal outcomes. Whether confirmed by larger investigations, these results may contribute to the current HoLEP literature, significantly deepening the knowledge on surgical technique, improving preoperative counseling and ultimately maximizing postoperative outcomes.

CONCLUSIONS

Our newly introduced Trifecta metric has shown to be a valid tool to assess the surgical quality and goals achievement within the HoLEP field, relying on reproducible and patient-oriented metrics. The present study provided meaningful insights to predict Trifecta failure and, based on our experience, initial surgical experience, three-lobes surgical approach and preoperative PVR ≥250 mL were independently associated with this outcome. Further experiences, including external validation, are expected to corroborate these findings.

Conflict of Interest

The authors have nothing to disclose.

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Author Contribution

Conceptualization: AAG, Andrea Minervin, AT. Data curation: AAG, FDM, MS, LM, SG, Andrea Cocci, RT. Formal analysis: AAG, FDM, RT, Andrea Mari, Andrea Cocci. Writing–original draft: AAG, FDM. Writing–review & editing: AAG, Andrea Mari, Andrea Cocci, Andrea Minervin, RT.

Data Sharing Statement

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

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