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# Predictors of re-intervention after greenlight laser photoselective vaporization of the prostate: multicenter long/mid-term follow-up experience

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## Abstract

**Aim:** Greenlight photoselective vaporization of the prostate (PVP) is considered a safe alternative to transurethral resection of the prostate (TURP) in men with lower urinary tract symptoms (LUTS) and a prostate volume of 30-80 mL for the comparable short- and mid-term results. Long-term re-treatment rate is still being debated.

**Methods:** We retrospectively reviewed greenlight PVP procedures in a multi-institutional database from September 2011 to December 2019 collecting data on patients requiring re-intervention with a follow-up period of at least 12 months.

**Results:** Among 867 patients with a median follow-up period of 32.5 months (interquartile range: 20.0-49.0 months), 35 patients (4%) required re-intervention. Patients requiring re-intervention had a prostate volume  $\geq$  100 mL in 28.6% of cases ( $P = 0.002$ ). Preoperative urethral stricture and incidence of early complications were more frequent in the re-treatment group ( $P = 0.027$  and  $P = 0.006$ ). In the re-treatment group, 22 patients required an endoscopic intervention for bladder neck or prostatic fossa contracture (2.5% of the study population). The remaining 13 patients in the re-treatment group underwent TURP or PVP for LUTS relapse (1.5%). In the univariate and multivariate logistic regression models, only prostate volume  $\geq$  100 mL ( $P = 0.003$  and  $P = 0.010$ ), preoperative urethral stricture ( $P = 0.013$  and  $P = 0.036$ ), and occurrence of early complications ( $P = 0.008$  and  $P = 0.024$ ) correlated with re-intervention.

**Conclusion:** Greenlight PVP has good functional long/mid-term results. The presence of preoperative urethral stricture and the occurrence of early complications correlate with the risk of late re-treatment. In patients with prostate  $\geq$  100 mL, the enucleation technique may be superior to vaporization in terms of lower long-term risk of re-intervention for LUTS relapse.

**Keywords:** Greenlight laser, long-term results, re-intervention

## INTRODUCTION

Benign prostatic obstruction (BPO) causing lower urinary tract symptoms (LUTS) is present in up to 80% of men over the age of 80 and in up to 50% of men over the age of 50, resulting in significant economic burden and potentially negative impact on the quality of life<sup>[1]</sup>. Pharmacological management with alpha 1-blockers or combination therapies (alpha 1-blockers + 5-alpha-reductase inhibitors or alpha 1-blockers + muscarinic receptor antagonists) is the first-line treatment. Surgical treatment is indicated in the case of pharmacological management failure or discontinuation<sup>[2-4]</sup>. Nowadays, despite the availability of several laser technologies (holmium, greenlight, diode, and thulium), monopolar or bipolar transurethral resection of the prostate (M- or B-TURP) is considered the first-line treatment for patients with moderate-to-severe LUTS and a prostate volume of 30-80 mL, due to the absence of long-term surgical randomized controlled trials on laser treatments<sup>[2]</sup>. The longer catheterization time and hospital stay, with a higher risk of hemorrhagic complications in transurethral resection of the prostate (TURP) series in comparison to laser series<sup>[5]</sup>, are increasing the use of lasers in the treatment of BPO. Some limitations preventing further spreading of holmium laser enucleation of the prostate (HoLEP) and thulium vapoenucleation of the

prostate (ThuVEP) are a long learning curve and the need for further materials regarding morcellation. The 180-W LBO crystal Green Light Xcelerated Performance System (XPS)<sup>TM</sup> (American Medical System-AMS, Minnetonka, Minnesota) and the new 532 nm wavelength, metal-capped and liquid cooled irrigated fiber (Moxy TM fiber) with its different and versatile uses [standard photovaporization (PVP), anatomical PVP, and greenlight enucleation of prostate (GreenLEP)] have allowed us to overcome these drawbacks<sup>[6,7]</sup>. Current guidelines consider greenlight laser as an alternative to TURP in men with moderate-to-severe LUTS and a prostate volume of 30-80 mL, in light of their comparable short- and mid-term results<sup>[3,7]</sup>. Moreover, some evidence is emerging supporting the use of greenlight laser also for large volume prostates and in men on anticoagulation or with high cardiovascular risk<sup>[8-11]</sup>. According to the current literature, the major limitation of greenlight is the absence of long-term follow-up ( $\geq 36$  months) data to evaluate the outcome, the rate of re-intervention, and patient satisfaction. For these reasons, we decided to review and update our large multicenter cohort of patients who have undergone greenlight laser treatment in order to analyze the long-term re-treatment rate and risk factors for treatment failure.

## METHODS

We retrospectively reviewed all cases undergoing standard or anatomical greenlight laser photoselective vaporization of the prostate for lower urinary tract symptoms secondary to BPO, using the 180-W XPS GL system, in a multi-institutional, prospectively collected database performed in 20 Italian centers from September 2011 to December 2019, and collecting data on patients developing LUTS relapse requiring re-intervention (TURP or greenlight PVP) with a follow-up period of at least 12 months. Surgeons with consolidated experience in greenlight PVP performed all considered procedures. Informed consent was obtained from all individual participants included in the study. This study was approved by the institutional research ethical committee and all related procedures were conducted in accordance with the Declaration of Helsinki. Patients with all the following data were considered in the statistical analysis: age, prostate volume evaluated with trans-rectal ultrasound (TRUS), use of antiplatelet and anticoagulant medications, LUTS therapy and history of catheterization or retention, PSA level, IPSS, maximum urinary flow (Qmax), operative time, lasing time, catheterization time, hospital stay, and complications. The Clavien-Dindo classification was used to describe reported complications and divided into early (30 days) or late (> 30 days) complications<sup>[12,13]</sup>. Postoperative frequency and urgency were considered as complications when they prompted additional medical examination or when reported by patients affecting the Patient Global Impression of Improvement scale (PGI-I)<sup>[14]</sup>. The presence of any degree and type of incontinence (stress or urge incontinence) reported by the patients and impairing their quality of life was defined as urinary incontinence. All patients underwent an outpatient clinic evaluation after at least 6 and 12 months and then annually with IPSS, Qmax, PSA level, and the PGI-I scale. Follow-up was calculated as the time from surgery to the last visit. Patients with a history of prostate cancer, neurogenic bladder disease, and previous prostate surgery, as well as those who underwent GreenLEP or contemporary treatment of bladder stones, including incidental bladder tumors, were not considered in this study.

### Statistical analysis

Quantitative variables were summarized as median and interquartile range (IQR). Qualitative data were summarized as frequency and percentage. After stratification according to reintervention performance, the Chi-square and the Mann-Whitney *U* tests were used to test the statistical significance in proportions and median differences. We relied on univariable and multivariable logistic regression models to test main predictors of reintervention. Multivariable logistic regression models included covariates that were statistically significant at univariable analysis. All tests were two-sided, and the level of statistical significance was set at  $P < 0.05$ . Analyses were performed using the R software environment for statistical computing and graphics (version 4.0.5; <http://www.r-project.org/>).

**Table 1. Values are n (%) or median interquartile range. Patients' preoperative and intraoperative characteristics**

	No re-intervention n = 832	Re-intervention n = 35	Overall n = 867	P value
Age (years)	68.0 (63.0-75.0)	70.0 (64.0-74.0)	68.0 (63.0-75.0)	0.696
Prostate volume, TRUS (mL)	60.0 (45.0-75.0)	65.0 (45.0-100.0)	60.0 (45.0-75.5)	0.236
Antiplatelet/anticoagulant therapy				0.535
None	485 (58.3%)	20 (57.1%)	505 (58.2%)	
Antiplatelet	239 (28.7%)	9 (25.7%)	248 (28.6%)	
Anticoagulant	91 (10.9%)	4 (11.4%)	95 (11.0%)	
Unknown	17 (2.0%)	2 (5.7%)	19 (2.2%)	
BPH/LUTS therapy				0.808
None	131 (15.7%)	6 (17.1%)	137 (15.8%)	
Alpha-blockers	404 (48.6%)	19 (54.3%)	423 (48.8%)	
5-ARI	48 (5.8%)	1 (2.9%)	49 (5.7%)	
Combination	249 (29.9%)	9 (25.7%)	258 (29.8%)	
Indwelling catheter history	118 (14.2%)	9 (25.7%)	127 (14.6%)	0.059
Operative time (min)	55.0 (40.0-75.0)	55.0 (40.0-65.0)	55.0 (40.0-75.0)	0.778
Lasing time (min)	25.0 (18.0, 34.0)	24.0 (17.0, 38.0)	25.0 (18.0, 34.0)	0.978
Catheterization time (days)	1.0 (1.0, 2.0)	2.0 (1.0, 2.0)	1.0 (1.0, 2.0)	0.841
Postoperative stay (days)	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)	0.529
Early complications	352 (42.3%)	23 (65.7%)	375 (43.3%)	0.006

TRUS: Trans-rectal ultrasound; LUTS: lower urinary tract symptoms; 5-ARI: 5 alpha-reductase inhibitors.

## RESULTS

Among 885 patients with at least 12 months of follow-up, 18 patients with postoperative urethral stricture (2%) were excluded from the analysis. In total, 867 patients with a follow-up of at least 12 months and all the required data for inclusion were considered for analysis. With a median follow-up period of 32.5 months (IQR: 20.0-49.0 months), 35 patients (4%) required re-intervention for LUTS relapse in our database. All preoperative data are reported in Table 1. The median prostate volume of the study population was 60.0 mL (IQR: 45.0-75.5 mL), including 102 patients (11.8%) with a prostate volume  $\geq$  100 mL. No statistical differences were found between the two groups in terms of age, use of antiplatelet and anticoagulant medications, LUTS therapy, and history of catheterization or retention [Table 1]. Patients requiring re-intervention had a prostate volume  $\geq$  100 mL in 28.6% of cases vs. 11.1% in the no re-treatment group ( $P = 0.002$ ). Interestingly, preoperative urethral stricture was more frequent in patients undergoing re-intervention (17.1% vs. 6%,  $P = 0.027$ ). Intra- and peri-operative data were similar; however, patients requiring reoperation had a higher incidence of early complications [Table 1]. Despite the higher incidence of early complications in the re-treatment group, the type of complications was similar between the two groups [Table 2]. The three most frequent early complications in the treatment failure group and the no re-treatment group were burning urination (25.7% and 15.3%), urgency (17.1% and 11.5%), and postoperative urinary retention (14.3% and 8.5%). In addition, the incidence of late complications was higher in the re-intervention group, as reported in Table 2. In the re-intervention group, 22 out of 35 patients (62.8%) required a surgical endoscopic intervention for *de novo* lower urinary tract symptoms linked to bladder neck or prostatic fossa contracture. In particular, bladder neck and prostatic fossa contracture were more frequent in the patient group undergoing re-intervention (37.1% vs. 0.7% and 25.7% vs. 0.6%, respectively,  $P < 0.001$ ). Contrariwise, no patients required surgical intervention for these complications in the control group because these did not affect urodynamic patterns. In fact, the Qmax and the PGI-I were better in patients not requiring re-intervention [Tables 2 and 3]. The remaining 12 patients (1.4% of the study population) in the re-treatment group underwent a second PVP or a TURP for LUTS relapse after surgery.

**Table 2. Type of complications**

Complications	Clavien-Dindo grade	No re-intervention n= 832	Re-intervention n = 35	Overall n = 867	P value
<b>Perioperative</b>					
Prostatic capsule perforation	IIIa	6 (0.7%)	0 (0.0%)	6 (0.7%)	0.614
<b>Early (&lt; 30 days)</b>					
Fever < 38 °C	I	15 (1.8%)	1 (2.9%)	16 (1.8%)	0.650
Fever > 38 °C	I	23 (2.8%)	1 (2.9%)	24 (2.8%)	0.974
Burning urination	I	127 (15.3%)	9 (25.7%)	136 (15.7%)	0.096
Frequency	I	66 (7.9%)	2 (5.7%)	68 (7.8%)	0.633
<i>De novo</i> urge	I	96 (11.5%)	6 (17.1%)	102 (11.8%)	0.313
Urge incontinence	I	54 (6.5%)	4 (11.4%)	58 (6.7%)	0.252
Stress incontinence	I	38 (4.6%)	3 (8.6%)	41 (4.7%)	0.274
Hematuria	I	24 (2.9%)	1 (2.9%)	25 (2.9%)	0.992
Retention	I	71 (8.5%)	5 (14.3%)	76 (8.8%)	0.238
UTI	II	10 (1.2%)	1 (2.9%)	11 (1.3%)	0.391
Blood transfusion	II	4 (0.5%)	0 (0.0%)	4 (0.5%)	0.681
MACE	IVb	6 (0.7%)	1 (2.9%)	7 (0.8%)	0.167
<b>Late complication</b>					
Stress incontinence	I	26 (3.1%)	1 (2.9%)	27 (3.1%)	0.929
Bladder neck/prostatic fossa contracture requiring reintervention	IIIb	0 (0%)	22 (62.8%)	22 (2.6%)	< 0.001
BPH recurrence requiring surgical reintervention	IIIb	0 (0%)	13 (37.2%)	13 (1.4%)	< 0.001
<b>Patient global impression of improvement</b>					
I		401 (51.5%)	11 (34.4%)	412 (50.9%)	
II		291 (37.4%)	11 (34.4%)	302 (37.3%)	
III		62 (8.0%)	6 (18.8%)	68 (8.4%)	
IV		16 (2.1%)	3 (9.4%)	19 (2.3%)	
V		5 (0.6%)	0 (0.0%)	5 (0.6%)	
VI		3 (0.4%)	1 (3.1%)	4 (0.5%)	

Interestingly, there were no differences in PSA changing and IPSS between the two groups at the follow-up visit [Table 3]. At the univariate and multivariate logistic regression models only prostate volume  $\geq 100$  mL ( $P = 0.003$  and  $P = 0.010$ ), preoperative urethral stricture ( $P = 0.013$  and  $P = 0.036$ ), and occurrence of early complications ( $P = 0.008$  and  $P = 0.024$ ) were associated with re-intervention [Table 4].

## DISCUSSION

Despite the great interest in greenlight treatment for BPO, few data are available on long-term follow up and even fewer on failure predictors. These aspects depend on the novelty of this technology. The last development of greenlight was the 180-W XPS launched in 2010. The Goliath Trial, designed at the beginning of the greenlight 180-W XPS experience in 2011, with 128 patients and 2 years of follow-up, described non-inferiority compared to TURP, with 9% re-treatment rate vs. 7.6% in the TURP group<sup>[15]</sup>. In this study, the mean prostate volume was  $48.6 \pm 19.2$  mL. However, these data have been overcome by some retrospective papers. Ajib *et al.*<sup>[16]</sup> described a re-intervention rate of 2.6% at 12 months for bladder neck contracture and a re-intervention for LUTS relapse of 0.5%, 0.7%, and 4.8% at 12, 24, and 48 months, respectively. In a previous paper from our database, we reported 24 patients out of 813 (3.1%) requiring re-intervention with a median follow-up period of 17.7 months (IQR: 12-25.8 months)<sup>[17]</sup>.

**Table 3. Main outcomes after photoselective vaporization of the prostate**

Outcome	Baseline	6 months	12 months
PSA ng/mL, median (IQR)			
No re-intervention (n = 832)	2.7 (1.6-3.9)	1.3 (0.7-2.1) (n = 439)	1.2 (0.7-2.0) (n = 501)
Re-intervention (n = 35)	2.4 (1.3-4.3)	2.0 (0.7-3.7) (n = 10)	1.3 (0.6-3.6) (n = 17)
Overall (n = 867)	2.6 (1.6-3.9)	1.3 (0.7-2.1) (n = 449)	1.2 (0.7-2.0) (n = 518)
P value	0.767	0.346	0.647
Qmax mL/s, median (IQR)			
No re-intervention (n = 832)	8.7 (7.0-10.9)	19.4 (16.6-24.0) (n = 650)	19.8 (16.9-24.0) (n = 533)
Re-intervention (n = 35)	7.0 (5.0-9.8)	18.0 (16.0-20.9) (n = 21)	18.0 (14.4-19.5) (n = 19)
Overall (n = 867)	8.7 (7.0-10.6)	19.4 (16.0-23.5) (n = 671)	19.6 (16.5-23.8) (n = 552)
P value	0.012	0.048	0.004
IPSS, median (IQR)			
No re-intervention (n = 832)	23.0 (19.0-27.0)	7.0 (5.0-10.0) (n = 624)	5.0 (3.0-8.0) (n = 539)
Re-intervention (n = 35)	23.5 (20.0-27.8)	8.0 (6.2-10.0) (n = 26)	5.0 (4.0-8.0) (n = 23)
Overall (n = 867)	23.0 (19.0-27.0)	7.0 (5.0-10.0) (n = 650)	5.0 (3.0-8.0) (n = 562)
P value	0.457	0.129	0.603

IQR: Interquartile range; Qmax: maximum urinary flow.

**Table 4. Univariate and multivariate logistic regression**

	Univariable		Multivariable	
	Odds ratio (95% CI)	P value	Odds ratio (95%CI)	P value
Age	1.00 (0.96-1.05)	P = 0.843	-	-
Prostate volume $\geq$ 100	3.22 (1.43-6.73)	P = 0.003	2.77 (1.22-5.86)	P = 0.010
Antiplatelet/anticoagulant therapy	0.90 (0.44-1.79)	P = 0.765	-	-
BPH/LUTS therapy				
None	-	-	-	-
Alpha-blockers	1.03 (0.42-2.87)	P = 0.956	-	-
5-ARI	0.45 (0.02-2.76)	P = 0.471	-	-
Combination	0.79 (0.28-2.40)	P = 0.660	-	-
Indwelling catheter history	2.09 (0.91-4.42)	P = 0.064	-	-
Preoperative urethral stricture	3.24 (1.17-7.67)	P = 0.013	2.74 (0.97-6.63)	P = 0.036
Early complications	2.61 (1.31-5.50)	P = 0.008	-	-

LUTS: Lower urinary tract symptoms; 5-ARI: 5 alpha-reductase inhibitors.

In this further analysis of our updated, multicenter experience, the rate of re-intervention for bladder neck contracture or LUTS relapse is 4% (35 out of 867 patients) with longer follow-up (median, 32.5 months, IQR: 20.0-49.0 months; minimum, 12 months). In detail, only 1.4% (12 patients) underwent a second PVP or a TURP for LUTS relapse. Recently, the Global Greenlight Group published data from 3627 patients who

underwent greenlight PVP with a median follow-up of 6 months, and the authors reported a re-treatment rate of 1.5% and an incidence of bladder neck contracture of 1.93% in 569 patients at 5-year follow-up<sup>[8]</sup>, in line with our results. Unfortunately, in all cited articles, the authors performed only a descriptive analysis, without analyzing risk factors for treatment failure. In our database analysis, apart from a descriptive analysis of results, we analyzed the possible risk factors of treatment failure after greenlight PVP. In the univariate and multivariate logistic regression models, three factors correlated with re-intervention: preoperative urethral stricture ( $P = 0.013$  and  $P = 0.036$ ), incidence of early complications ( $P = 0.008$  and  $P = 0.024$ ), and prostate volume  $\geq 100$  mL ( $P = 0.003$  and  $P = 0.010$ ) [Table 4]. The correlation between the incidence of early complications (burning urination, urgency, and urinary retention) and the risk of re-treatment due to LUTS relapse may correlate with inefficacious vaporization due to inadequate adenoma removal with excess energy absorption by the prostatic tissue, a factor which might have an inflammatory and irritating effect. Obviously, this is a hypothesis not confirmed by our data in this analysis. In fact, operative and lasing time as well as PSA changing at 12 months are similar in the two groups ( $P = 0.778$ ,  $P = 0.978$ , and  $P = 0.674$ , respectively). However, in a recent paper of our group, where we analyzed risk factors of postoperative acute urinary retention after greenlight laser procedures, lower lasing time, adenoma volume  $< 40$  mL, IPSS  $\geq 19$ , and 5 alpha-reductase inhibitors (5-ARI) assumption were associated with a higher risk of postoperative acute urinary retention, implying that an inefficacious vaporization and an inflammatory component may play a role<sup>[18]</sup>.

A further evaluation is necessary for patients with prostate volume  $\geq 100$  mL. In a recent analysis of ours regarding functional results in patients with large prostate volume, the re-intervention rate in the  $\geq 100$  mL group was 3.5% vs. 2.3% in the group with prostate volume  $< 100$  mL with a mean follow-up of 25.0 months (IQR: 16.5-35.0 months)<sup>[10]</sup>. In the literature, the re-intervention rate of patients undergoing greenlight PVP for large prostate volume is reported as 15.2% by Laine-Caroff (with a median follow-up of 54 months)<sup>[19]</sup>, 13.2% by Meskawi *et al.*<sup>[20]</sup>, 6% for 200 mL prostate and 9% for 100-200 mL in a multi-institutional series<sup>[21]</sup>, 2.9%<sup>[22]</sup>, 1.2%<sup>[23]</sup>, and no re-treatment at 12 months reported by Altay *et al.*<sup>[24]</sup>. In these papers, larger prostate volume, low energy density, and a lower PSA reduction at 6 months after surgery<sup>[20]</sup> or low energy density<sup>[23]</sup> are reported as risk factors for treatment failure.

Despite the good functional results associated with low morbidity, in these vaporization series, a large prostate is a consideration which should be made concerning the enucleation technique. In a recent nationwide database, including 58,346 patients (38,308 TURP and 20,038 HoLEP), the authors reported a higher reoperation rate in the TURP group (4.50%) than in the HoLEP group (1.27%) ( $P < 0.01$ ) with mean follow-up durations of 51.6 and 47.6 months, respectively<sup>[25]</sup>.

These data are in line with a randomized trial comparing greenlight PVP vs. B-TURP vs. HoLEP in large prostate (80-150 mL), with 3 years of follow-up and a re-treatment rate of 6.7%, 9.7%, and 0%, respectively<sup>[26]</sup>. The authors postulated that pure enucleation may guarantee longer functional results than vaporization or resection techniques. The experience in GreenLEP reported by Ferrari *et al.*<sup>[27]</sup> with a study population of 120 patients, a median prostate volume of 98.5 mL (IQR: 83.0-130.0 mL), and a median follow-up of 18 months seems to go in this direction, with no reoperation. Obviously, more studies are needed to confirm this finding.

Some limitations are present in our study, the first being the retrospective nature and the participation of 20 centers. An additional issue to be taken into consideration is the absence of enucleation procedures. Nevertheless, the follow-up period is one of the longest in the literature. In our experience, the re-treatment rate of 1.4% and the 2.6% rate of bladder neck contracture requiring endoscopic revision after a median of

23 months postoperatively are in line with results from other greenlight and TURP series. Prostate volume  $\geq$  100 mL, preoperative urethral stricture, and the early-onset complications correlate with the re-treatment risk. Greenlight PVP has good functional long/mid-term results. The presence of preoperative urethral stricture and the occurrence of early complications correlate with the risk of late re-treatment. In patients with prostate  $\geq$  100 mL, the enucleation technique may be superior to vaporization in terms of lower long-term risk of re-intervention for a LUTS relapse.

## DECLARATIONS

### Authors' contributions

Conception and design: Campobasso D, Cindolo L

Data acquisition: Greco F, De Nunzio C, Destefanis P, Varvello F, Reale G, Cai T, Malossini G, Oriti R, Tuccio A, Ruggera L, Laganà A, Dadone C, De Rienzo G, Pucci L, Montefiore F, Rabito S, Germani S

Data analysis and interpretation: Campobasso D, Marchioni M, Cindolo L

Drafting the manuscript: Campobasso D, Cindolo L

Critical revision of the manuscript for scientific and factual content: Greco F, De Nunzio C, Ferrari G

Statistical analysis: Marchioni M

Supervision: Destefanis P, Fasolis G, Voce S, Cai T, Ruggera L, Tubaro A, Dadone C, Gontero P, Carrino M, Miano R, Schips L, Frattini A

### Availability of data and materials

Not applicable.

### Financial support and sponsorship

None.

### Conflict of interest

Destefanis P, Ruggera L, Dadone C, Ferrari G and Cindolo L do surgical tutorship for American Medical System and received honoraria for their tutorship.

### Ethical approval and consent to participate

Written informed consent was obtained from all patients.

### Consent for publication

Not applicable.

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