MEDICAL UNIVERSITY - PLEVEN

Faculty of Health Care

Department Surgical Nursing Care

Dr. Georgi Georgiev

En bloc holmium laser prostate enucleation with early apical release

DISSERTATION PAPER

to acquire an educational and scientific degree "DOCTOR" in scientific specialty "Urology"

Supervisor:

Assoc. Dr. Boyan Atanasov, MD

Scientific jury:

Prof. Dr. Nikolay Kolev, MD

Prof. Dr. Dimitar Mladenov, MD

Assoc. Dr. Vladislav Dunev, MD

Assoc. Dr. Tosho Ganev, MD

Assoc. Dr. Nikolay Evtimov, MD

Pleven, 2022

The dissertation consists of 154 pages and is illustrated with 54 figures and 21 tables. The bibliographic list includes 204 literary sources.

The dissertation work has been approved and sent for defense by the extended departmental council of the Department of "Nursing Surgical Care" to the Medical Center of Pleven University of Medical Sciences.

The public defense of the dissertation work will be held on ....from .... hours in the hall "....... ....“of MU Pleven.

The defense materials are published on the website of the Medical University-Pleven (http://www.mu-pleven.bg/)

GLOSSARY OF USED ABBREVIATIONS

AUA - American Association of Urology

EAU – European Association of Urology (European Association of Urology)

HoLEP - Holmium Laser Prostate Enucleation

IPSS – International Prostate Symptom Score

Qmax – Maximum flow rate (maximum flow of urine), ml/s

TPV - Total prostate volume

BPH - Benign prostatic hyperplasia

OU – Residual urine

LUTS - Lower Urinary Tract Symptoms

TURP – Transurethral resection of the prostate

CONTENTS

1. Introduction 1

2 Purpose and objectives 3

3 Materials and methods 4
3.1 Object and place of the study 4
3.2 Sources of information 7
3.3 Statistical methods 8
3.4 Used equipment 9
3.5 Operative technique 9

4 Results 12
4.1 General characteristics of the therapeutic groups 12
4.2 Statistical analyzes 13

5 Discussion 40
5.1 General characteristics of the researched contingent 40
5.2 Postoperative symptoms and functional results 42
5.3 Early and late postoperative complications 43
5.3.1 Blood loss 44
5.3.2 Strictures 44
5.3.3 Bladder perforation 45
5.3.4 Stress incontinence 46
5.4 Total prostate volume and weight of enucleared tissue 46
5.5 Learning curve and change in statistics after technique improvement 47
5.5.1 Total prostate volume – TPV 48
5.5.2 Operating time 48
5.5.3 Enucleation time 49
5.5.4 Morcellation time 49
5.5.5 Weight of enucleated tissue 50
5.5.6 Enucleation and morcellation efficiency 51

6 Conclusions 52

7 Contributions 55

Literature 56

1. INTRODUCTION

Benign prostatic hyperplasia (BPH) is a disease that affects men in both adulthood and old age. With the current trends of population aging and increasing life expectancy, the issue of treating BPH will become increasingly relevant. The development of new technologies allows for the incorporation of modern equipment in operating rooms and the development of innovative methods.

The therapeutic approach to treating BPH can be varied and most often has a stepwise nature. Depending on the degree of complaints, valid treatment strategies are monitoring, lifestyle changes, phytotherapy, drug therapy, etc. In case of failure of conservative behavior or the presence of complications, surgical treatment is implemented.

Many factors are taken into consideration in the selection of operative treatment - the general condition of the patient, comorbidity, the size of the prostate gland, anatomical variations, anticoagulant use, age, patient/operator preference, etc. For several decades, transurethral resection of the prostate (TURP) has been the "gold standard" treatment for men with symptomatic BPH and a moderately enlarged prostate. Holmium enucleation of the prostate (HoLEP) provides a minimally invasive surgical approach for highly enlarged glands where the only alternative is open adenomectomy. HoLEP allows combining the minimal complication rates of endoscopic surgery with the effectiveness of open surgery without compromising postoperative results. For this reason, the method is gaining wider popularity in urological practice. The method itself continues to evolve as many clinics are developing their own approaches for further refinement.

Despite its many advantages, the misconception of a steep learning curve has prevented the method from becoming established in more hospital settings. In-depth anatomical knowledge is a key point for mastering the methodology.

Various technique modifications have been introduced to facilitate the training period and improve postoperative results. Most available studies are based on the classic three-lobe technique introduced by Gilling in the late 1990s. Since then, the method has gone through many modifications - two-lobe technique, en-bloc, "en-bloc no touch", "omega", with a horseshoe-shaped incision, etc. Clinical data regarding the advantages and disadvantages of these approaches is still emerging. In our study, we have chosen en-bloc enucleation with early apical release due to the promising advantages of the method - reduced frequency of stress incontinence, shortened operative time and learning curve, etc

2. PURPOSE AND OBJECTIVES

Objective: To introduce and improve a new operative method for the treatment of BPH that combines the minimal-invasiveness and reduced risks of complications of transurethral operations with the radicality and better long-term effect of open surgery.

Task 1:
To study and compare over time the effectiveness of the operative method (HoLEP) in terms of IPSS score and improved uroflowmetry.

Task 2:
To establish the risks of complications intraoperatively and postoperatively in the long term.

Task 3:
To compare the volume of enucleated tissue with the volume of the prostate gland determined by transrectal ultrasound.

Task 4:

To describe the learning curve and the change in statistics that come with surgical experience.

3. MATERIALS AND METHODS

3.1. Object and place of the study

A total of 253 men were included in the study, diagnosed and operated on in the urology department of "St. Marina" UMBAL - Pleven and Hill Clinic - Sofia for a period of 3 years (2017–2021). Patients were divided into 2 groups depending on the operative technique - TURP (103 patients) and HoLEP (150 patients). All patients in the HoLEP group were operated on by one urologist, with the first two cases were performed under the supervision of a mentor. Preoperatively, a thorough medical history, status, and signed informed consent for treatment were taken. The essence of the pathology and the advantages/disadvantages of each surgical treatment were explained in detail to the participants. The studied clinical contingent had an average age of 66.98±8.73 years in the range of 42-88 years. Of the sampled study participants, 150 (59.3%) underwent HoLEP and 103 (40.7%) TURP (Figure 1).

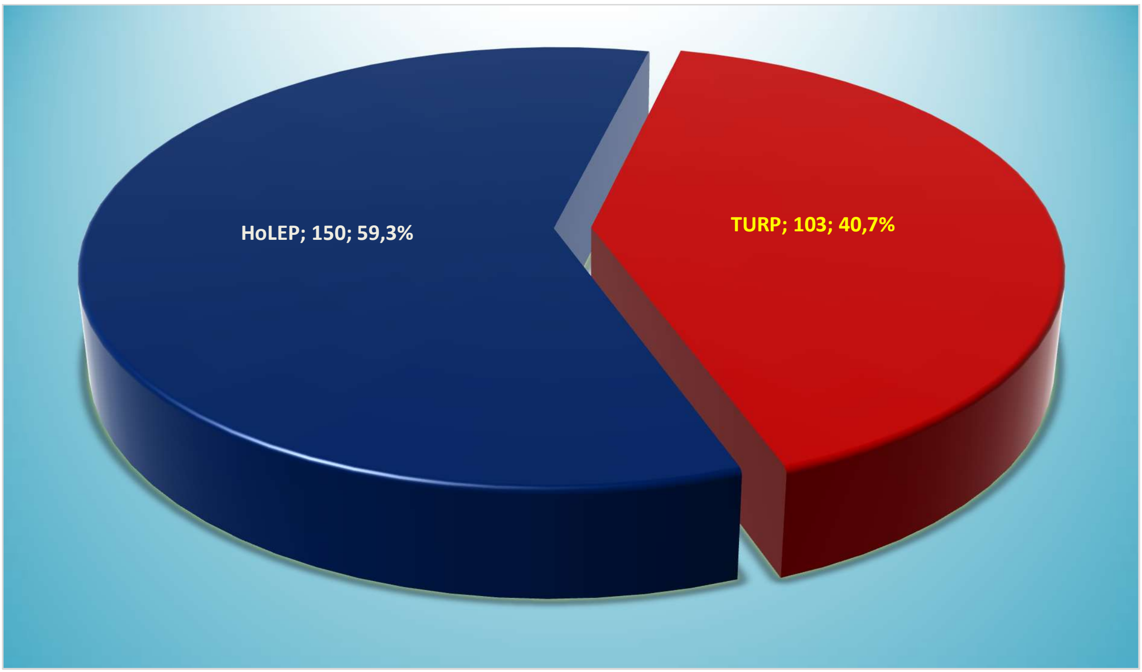

Fig. 1 Distribution of the studied contingent by surgical method.

The age group with the largest relative share (46%) in those operated on with HoLEP is 60–69 years, followed by 70–79 years with 30.7%, and with the smallest (2.7%) 40–49 years. Among those operated with TURP, the largest relative share (32.0%

each) is the age groups 60–69 and 70–79 years, followed by 50–59 years with 31.1%, and with the smallest (0%) – 40-49 years (figure 2).

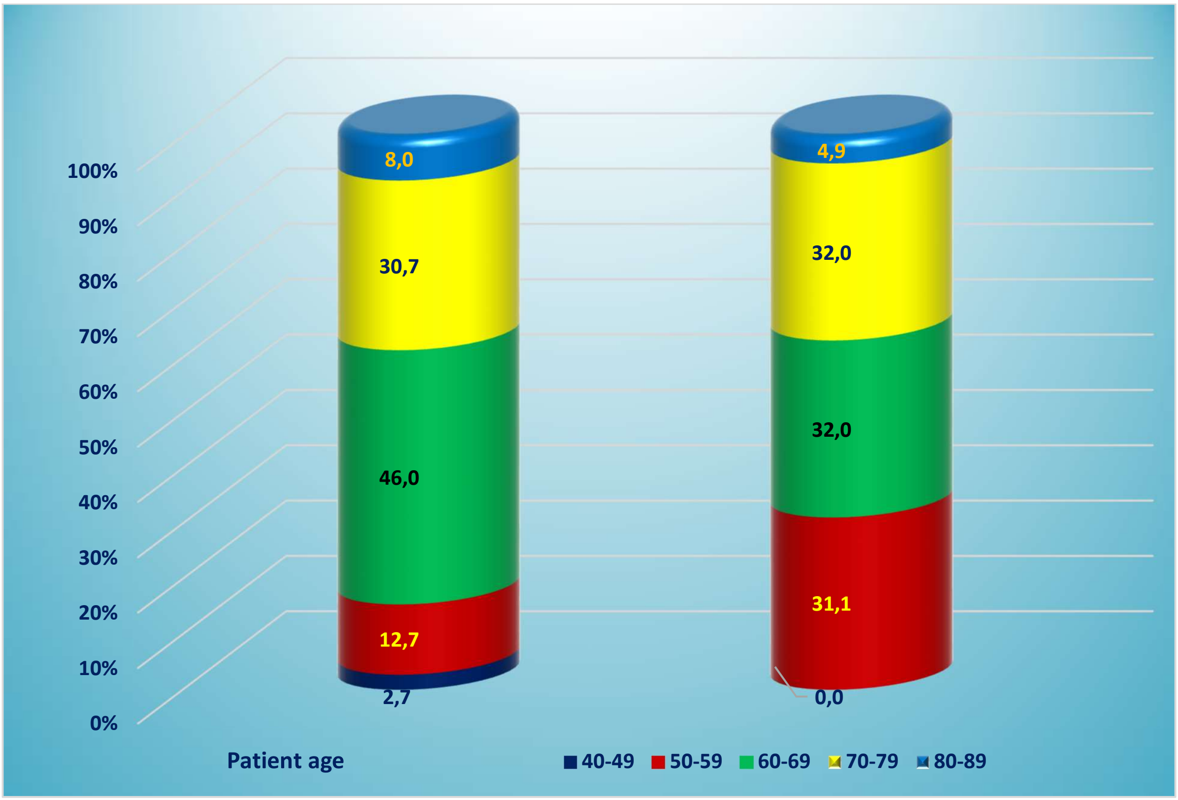

Fig. 2. Distribution of study participants by operative method and age groups

All patients were evaluated preoperatively according to the recommendations of the EAU guidelines - prostate-specific antigen (PSA), transrectal ultrasound, digital rectal examination, urinalysis, and the International Prostate Symptom Score (IPSS) as well and Qmax from pre-op uroflowmetry and hemoglobin values. The mean values of the preoperative parameters in both groups are presented in Table 1.

	TURP	HoLEP
Number of patients	103	150
Age (in years)	65.96	67.67
PSA (ng/ml)	2.63	3.54
Prostate volume (ml)	63.12	75.39
IPSS	22.54	21.84
Hemoglobin (g/l)	140	143
Qmax (ml/s)	9.46	8.31

Table 1. Average values of preoperative indicators

Perioperatively, the following were recorded: total operative time, resection/enucleation time, morcellation time (in the HoLEP group), weight of tissue removed, resection/enucleation efficiency, hospital stay in days, and catheterization time (Table 2).

Postoperative follow-up of patients is performed at the first, third and sixth month. Condition assessment is done based on IPSS and Qmax. Complications were reported in both groups - strictures, need for blood transfusion, revisions, perforations and presence of stress incontinence.

	ТУРП	HoLEP
Operative time	53.90	47.29
Resection time	45.93	-
Enucleation time	-	36.99
Morcellation time	-	4.38
Weight of removed tissue	31.45	57.22
Resection effectiveness	0.68	-
Enucleation effectiveness	-	1.52
Hospital stays(days)	4.17	1.04
Catheterisation time	5.08	1.38

Table 2. Average values of intra- and perioperative indicators.

3.2. Sources of information

To systematize patient data, we used the following sources of information:

- Patient history: data on age, preoperative PSA values , and preoperative and postoperative hemoglobin;
- Ultrasound evaluation of the volume of the prostate gland preoperatively;
- IPSS score preoperatively;
- Qmax from preoperative uroflowmetry;
- Operative protocol: data on the total operative time, resection/enucleation time, morcellation time (for the HoLEP group), the weight of the removed tissue. Resection efficiency (gram resected tissue per minute), enucleation efficiency (gram enucleated tissue per minute), and morcellation efficiency (gram morcellated tissue per minute) were calculated from the protocol data;

- Case history: data on the total hospital stay in days and the presence of perioperative complications;

- Ambulatory examination sheet for decatheterization: the total time for catheterization in days is reported;

- Outpatient sheet from the control examination at the first, third and sixth months

- IPSS assessment; Qmax and the presence of late complications.

3.3. Statistical methods

Data were entered and processed with the statistical packages IBM SPSS Statistics 25.0. and MedCalc Version 19.6.3., as well as Office Excel 2021. $p < 0.05$ was accepted as a level of significance at which the null hypothesis is rejected.

The following methods were applied:

1. Descriptive analysis – the frequency distribution of the considered signs is presented in tabular form.
2. Graphical analysis – for visualization of the obtained results.
3. Comparing relative shares.
4. Fisher's exact test - for testing hypotheses about the presence of dependence between categorical variables.
5. Non-parametric Kolmogorov-Smirnov test - to check the distribution for normality.
6. Student's t-test - for testing hypotheses about the difference between the arithmetic means of two independent samples.
7. Non-parametric Mann-Whitney test - for testing hypotheses of difference between two independent samples.
8. Student's T-test - for testing hypotheses of difference between two dependent samples.

9. Non-parametric Wilcoxon test - for testing hypotheses of difference between two dependent samples.

10. Correlation analysis – to test hypotheses about the existence of a linear relationship between quantitative variables

11. Regression analysis – to search and select a regression model describing the relationship between quantitative variables.

3.4. Used equipment

The equipment required to perform both operative techniques is presented in point 2.3.7.1. (TURP) and 2.3.7.3. (HoLEP) in the literature review. Since the subject of the current scientific work is En bloc holmium laser prostate enucleation, a detailed description of the specific equipment used during the operative intervention in the HoLEP group follows.

The energy source used is a 50 W holmium: YAG laser with a 600 µm fiber (Auriga XL). A power of 36 W is used during enucleation.

A 26Fr laser scope (Richard Wolf) and standard saline (NaCl 0.9%) were used for irrigation. The enucleated tissue was morcellated using a specialized PIRANHA system (Richard Wolf) introduced through a 0° nephroscope.

3.5. Operative technique

The patient is placed in the lithotomy position. Under general/spinal anesthesia, sterile processing of the genital area and sterile draping is performed. Operative intervention is as follows:

Step 1. Calibration of the urethra

Urethral calibration is performed using dilators or an Otis urethrotome. The goal is to minimize the possibility of developing postoperative strictures.

Step 2. Introduction of the resectoscope

Into the urethra, through an obturator, a resectoscope-26 Ch is introduced under constant irrigation, after which the laser fiber is introduced, having previously removed 3–5 mm of the distal insulation.

Step 3. Urethrocystoscopy and visualization of the anatomy (Figure 3)

An inspection of the urethra is performed for the presence of strictures, false passages, etc. The beginning of the urethral sphincter and its position relative to the verumontanum are marked. The size of the prostate gland, the degree of subvesical obstruction, and the presence or absence of a median lobe are noted. The position of the ostiums and their proximity to the prostate gland is evaluated cystoscopically. A careful examination of the bladder is performed.

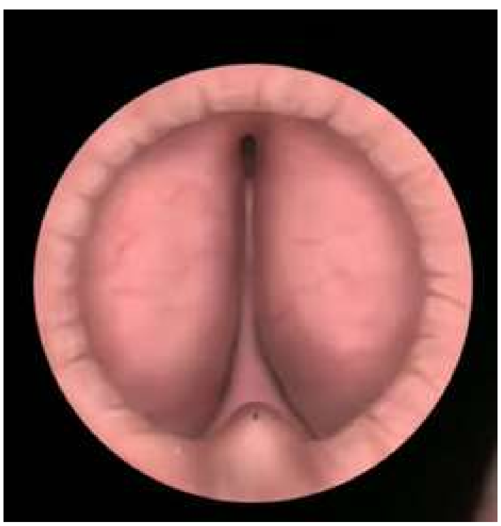

Fig. 3. Examination before surgery.

Step 4. Marking of the "white line" (figure 4)

By means of the laser fiber, the edge of the external urethral sphincter is marked. In addition to serving as a "border" to the dissection, this break in the mucosa prevents it from tearing during the procedure. In this way, the sphincter mucosa is not injured, reducing the risk of postoperative stress incontinence.

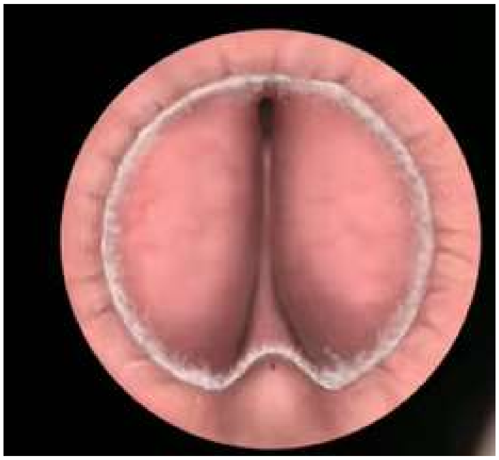

Fig.4. "White line" marking.

Step 5. Posterior apical dissection (Figure 5a, b)

By means of laser energy, the plane of dissection is deepened from the left or from the right of the verumontanum, after which dissection is proceeded from the contralateral side.

After reaching a satisfactory depth on both sides, the frenulum of the verumontanum is cut, thus joining the two planes.

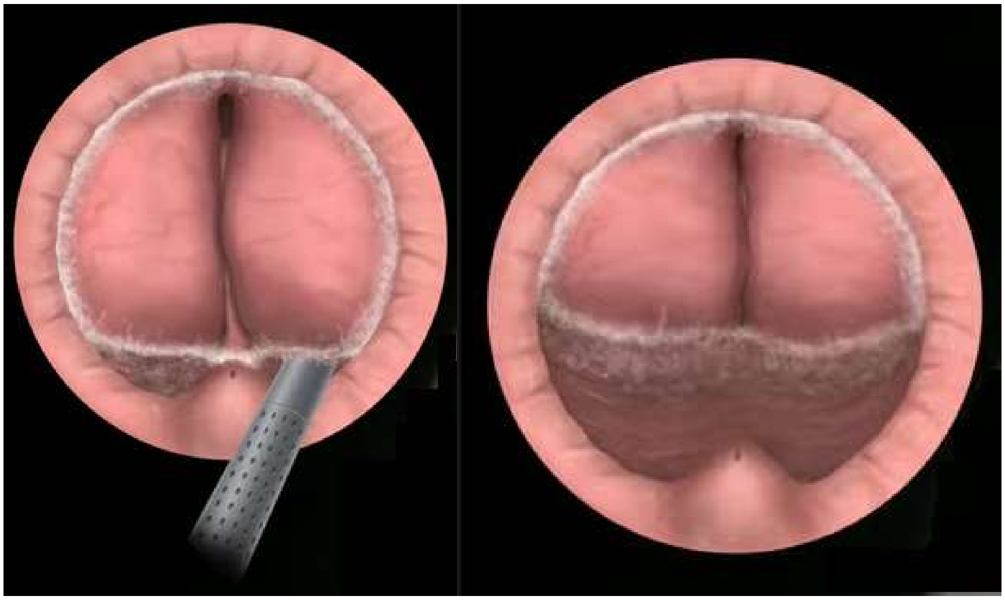

Fig. 5. Posterior apical dissection (a), (b).

Step 6. Anterior apical dissection (Figure 6a, b)

By means of an incision, the "white line" in the anterior part of the apex is deepened, until reaching an anatomical plane of dissection. Dissection is performed left and right, and the planes are joined after the tissue is cut at 12 o'clock.

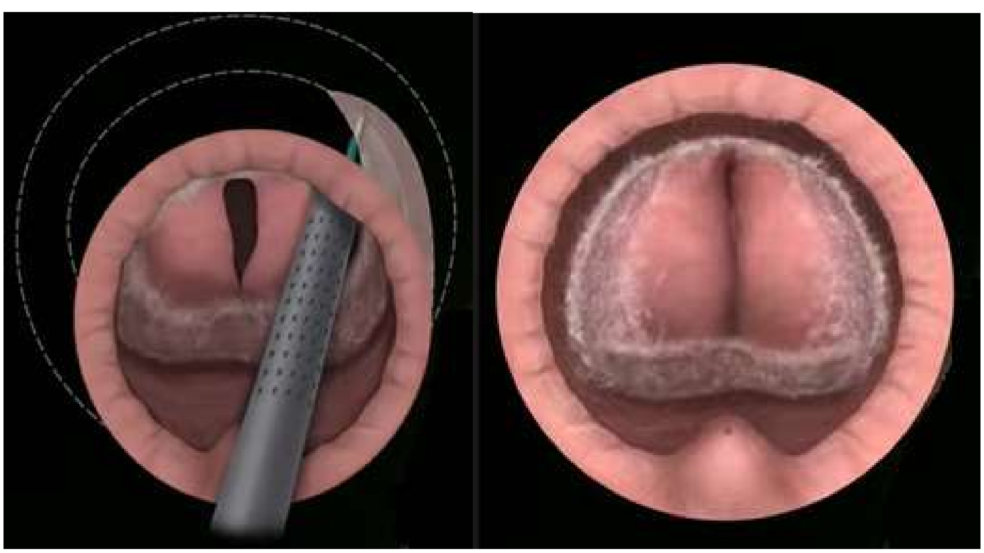

Fig. 6. Anterior apical dissection (a), (b).

Step 7. Progression of the dissection plan to the bullous cervix (Figure 7)

By adhering to the circular dissection plan, enucleation of the adenoma tissue is progressed. A pathognomonic sign of reaching the level of the bladder neck is the appearance of vertical fibers at 12 o'clock, which are interrupted. Dissection of the bladder neck is performed

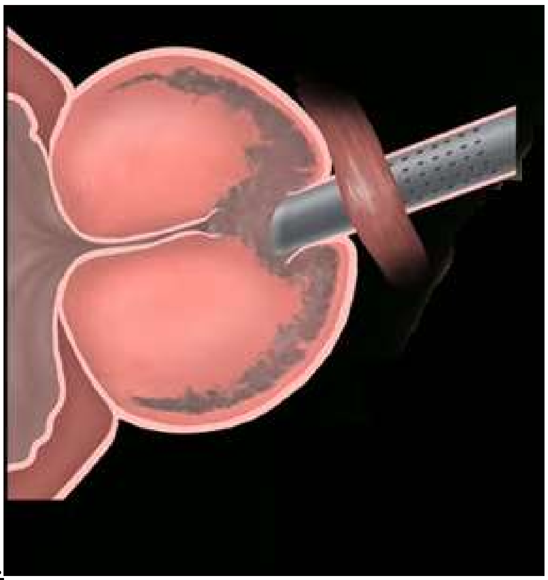
.

Fig. 7. Progression of the dissection plan.

Step 8. "Pushing" the prostate tissue into the lumen of the bladder (Figure 8)

The final incision before releasing the adenoma tissue is performed at 6 o'clock. The prostate is then mechanically pushed into the lumen of the bladder. An elaluation and, if necessary, coagulation of the prostate bed is performed.

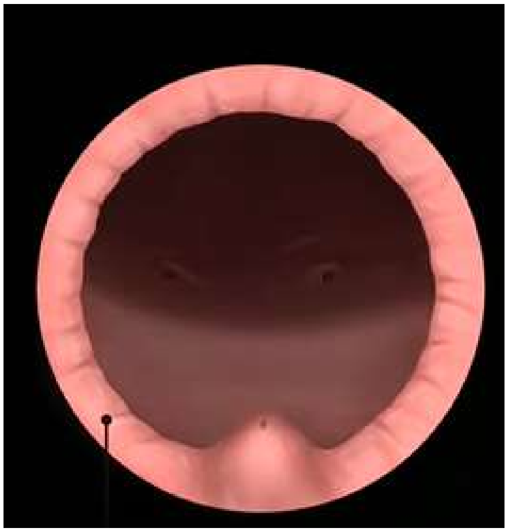

Fig. 8. Prostate after enucleation.

Step 9. Morcellation

The introduction of the morcellator is done through a nephroscope. A key point in the morcellation of the prostate tissue is to perform it with an adequately filled bladder and continuous visual control. This reduces the likelihood of bladder perforation.

The operation ends with placement of a three-way urethral catheter (20–22 Ch) with constant irrigation.

We believe that this technique, involving the dissection of the prostate tissue as a single material, has the following advantages over the two-lobe and three-lobe techniques: shortened operative time, optimal visualization of the operative field during operation, less bleeding, better irrigation thus improving the efficacy and safety of the method.The marking of the "white line" allows for early release of the sphincter from the apex, which prevents its overstretching and would reduce the likelihood of postoperative stress incontinence. Multiple authors have reported a high incidence of transient stress incontinence after laser enucleation regardless of energy source. There are many theories as to the origin of this incontinence despite sphincter preservation. During the classic three-lobe technique, the sphincter mucosa located at 12 o'clock is separated at the end of the operation, i.e. the sphincter is preserved but its mucous membrane is disturbed. In theory, the sphincter will be compromised until new epithelialization occurs. In addition, in the classic technique, with the incision at 12 o'clock, mechanical pressure is needed to reach the capsule, which leads to "splitting" of the mucosa.

Another possibility is that it may be due to stress-induced bladder overactivity, which may explain stress incontinence, which resolves over time. A hypoactive sphincter in patients with enlarged glands where the external sphincter has lost its tone, as well as longer catheterization time are also possible factors.

Another advantage of the method is the provision of a single dissection plan allowing efficient irrigation and a clean operative field during the entire procedure. During the three-lobe technique, it is difficult to coagulate the edges of the enucleated tissue. In addition, the passage of irrigation fluid to the bladder reduces its effectiveness. Currently, many additional techniques are being developed based on the en-block modification.

4. RESULTS

4.1. General characteristics of the therapeutic groups

Table 3 shows that:

● The average age of the patients operated on using HoLEP is 67.67±8.44 years, and the group with TURP – 65.96±9.08; the difference between the two groups is not significant;

● Regarding the results of the preoperative PSA and hemoglobin values, statistically significantly higher values are found in the patients of the HoLEP group;

● The fact that the two groups of patients are statistically equal according to the known confounding factor age means that the necessary prerequisite for a correct comparison according to the other indicators is met.

Indicator	HoLEP (n=150)				TURP (n=103)				P
	$\overline{X}$	SD	Min	Max	$\overline{X}$	SD	Min	Max	
Age	67,67	8,44	42,00	88,00	65,96	9,08	50,00	82,00	0,139
Pre-op PSA (ng/ml)	4,37	3,57	0,20	20,13	2,86	1,50	0,51	7,33	0,010
Pre-op Hemoglobin	148,04	15,37	109,00	186,00	142,93	7,44	130,00	155,00	<0,001

Table 3. Comparative analysis of the studied groups by age, preoperative PSA and hemoglobin

4.2. Statistical analyzes

It is clear from Table 4 and Figure 9 that both treatment groups achieved a statistically significant decrease in PSA one month after surgery.

The comparative analysis of the studied groups according to postoperative PSA and hemoglobin values (table 5) showed that:

● A statistically significant difference was observed only for hemoglobin;

● The higher mean value is of the HoLEP group.

Group	Pre-op PSA (ng/ml)				PSA at 1 month (ng/ml)				P
	$\overline{X}$	SD	Min	Max	$\overline{X}$	SD	Min	Max	
HoLEP (n=150)	4,37	3,57	0,20	20,13	1,37	1,17	0,11	5,60	<0,001
TURP (n=103)	2,86	1,50	0,51	7,33	1,24	0,67	0,29	3,22	<0,001

Table 4. Dynamics of the PSA indicator in the studied groups

Indicator	HoLEP (n=150)				TURP (n=103)				P
	$\overline{X}$	SD	Min	Max	$\overline{X}$	SD	Min	Max	
Post-op PSA (ng/ml)	1,37	1,17	0,11	5,60	1,24	0,67	0,29	3,22	0,272
Post-op Hemoglobin	142,85	17,16	80,00	185,00	133,87	12,65	85,00	152,00	<0,001

Table5. Comparative analysis of the studied groups according to postoperative PSA and hemoglobin values

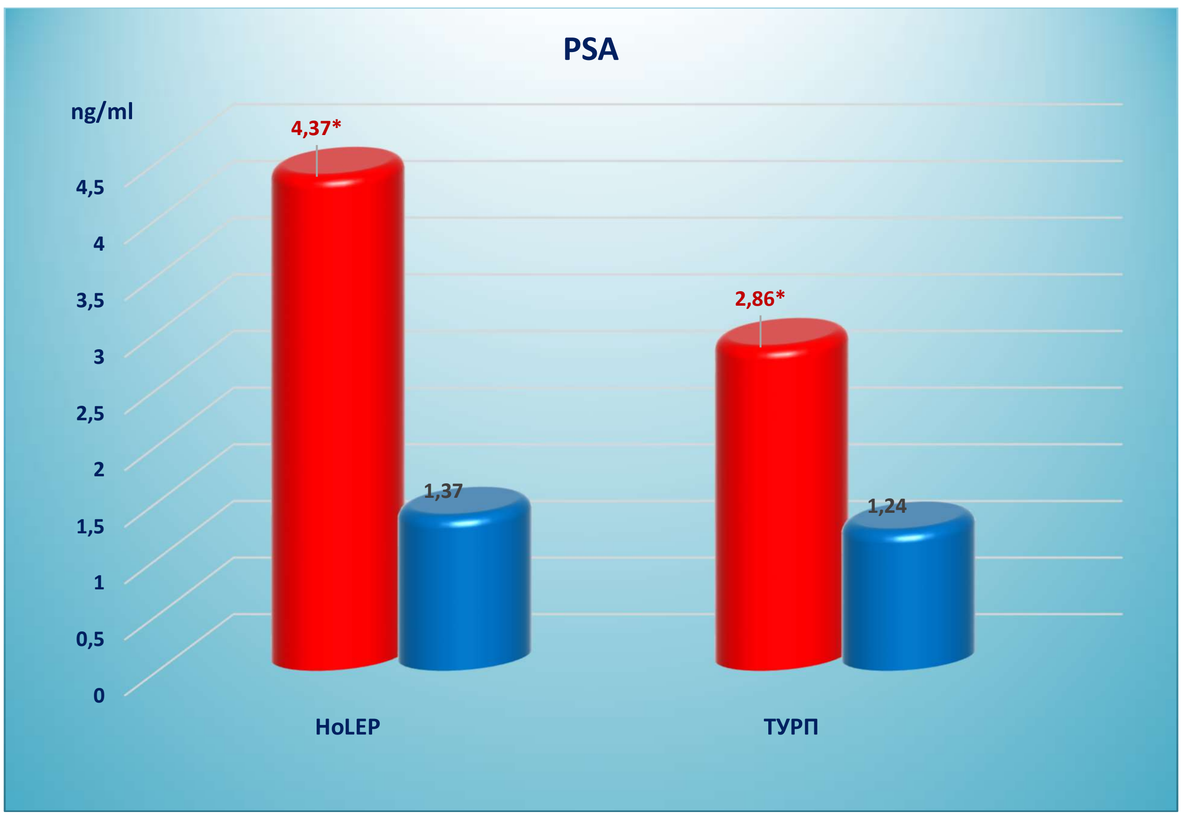

Fig. 9. Comparative analysis of the dynamics of the PSA indicator in the studied groups

The comparative analysis of the two studied groups regarding PSA is also of interest. A PSA above 4ng/ml is considered elevated. Table 6 shows that:

● The relative proportion of patients with an elevated preoperative PSA in the HoLEP operative method group was statistically significantly greater than that of the TURP group. Because PSA is a marker closely associated with TPV, it is an indirect marker for the higher prostate volume in the HoLEP group;

● After surgery, the difference between the two groups in terms of PSA was statistically insignificant. This means that, regardless of the larger sizes of the gland preoperatively, by means of HoLEP a result was achieved statistically equal to that after TURP.

Indicator	Percentage	HoLEP	ТУРП	P
Pre-op PSA				<0,001
Elevated	n	65	18	
	%	43,3	17,5	
Normal	n	85	85	
	%	56,7	82,5	
Post-op PSA				0,082
Elevated	n	5	0	
	%	3,3	0,0	
Normal	n	145	103	
	%	96,7	100,0	

Table 6. Comparative analysis of the two studied groups according to elevated and normal PSA

The conducted comparative analysis of the two studied groups in terms of IPSS (Table 7) found that:

● The difference between them preoperatively and one month after the operation is statistically insignificant;

● Postoperatively, at 3 and 6 months, the difference is already statistically reliable, and at both times the relative share of patients with mild symptoms is greater in the HoLEP group, while those with moderate symptoms are significantly more in the TURP group;

● This means that the results of the patients of the first group are statistically significantly better.

Indicator	Percentage	HoLEP	TURP	P
Pre-op IPSS				0,451
Mild (0-7)	n	3	0	
	%	2,0	0,0	
Moderate (8-19)	n	51	36	
	%	34,0	35,0	
Severe (20-35)	n	96	67	
	%	64,0	65,0	
IPSS at 1m				0,174
Mild (0-7)	n	106	64	
	%	70,7	62,1	
Moderate (8-19)	n	44	39	
	%	29,3	37,9	
IPSS at 3 m				0,001
Mild (0-7)	n	139	80	
	%	92,7	77,7	
Moderate (8-19)	n	11	21	
	%	7,3	20,4	
Severe (20-35)	n	0	2	
	%	0,0	1,9	
IPSS at 6 m				<0,001
Mild (0-7)	n	147	82	
	%	98,0	79,6	
Moderate (8-19)	n	3	21	
	%	2,0	20,4	

Table 7. Comparative analysis of the two studied groups according to the IPSS categories

The comparative analysis of the two studied groups in terms of subnormal and normal Max flow is also of interest. The results in table 8 show that:

- The relative share of patients with a substandard preoperative Max flow result in the HoLEP operative method group is statistically significantly greater than that of the TURP group. This means that the patients in the first group are in a more severe condition before the operation;
- Postoperatively, at all three measurement times, the difference between the two groups in subnormative and normal Max flow scores was statistically insignificant. This means that regardless of the more sever preoperative condition, HoLEP achieved results statistically equal to those of the TURP.

Показател	Percentage	HoLEP	TURP	P
Pre-op Max flow				0,016
Subnormal	n	115	72	
	%	84,6	71,3	
Normal	n	21	29	
	%	15,4	28,7	
Max flow at 1 m				0,148
Subnormal	n	4	0	
	%	2,7	0,0	
Normal	n	146	103	
	%	97,3	100,0	
Max flow at 3 m				0,162
Subnormal	n	1	4	
	%	0,7	3,9	
Normal	n	149	99	
	%	99,3	96,1	
Max flow at 6 m				1,000
Subnormal	n	1	0	

	%	0,7	0,0
Normal	n	149	103
	%	99,3	100,0

Table 8. Comparative analysis of the two studied groups according to subnormative and normal Max flow results

The conducted comparative analysis (Table 9 and Fig. 10) found that:

● Preoperatively, patients from both treatment groups had statistically equal values of the IPSS indicator;

● At the next three measurement times, significantly higher mean values were observed in the TURP group, i.e. the results achieved using HoLEP are significantly better.

Indicator	Operation	N	Mean	Median	SD	Min	Max	p
Pre-op IPSS	HoLEP	150	21,84	22,00	6,20	6,00	34,00	0,467
	TURP	103	22,54	22,00	5,69	14,00	32,00	
IPSS at 1m	HoLEP	150	6,12	5,00	3,43	1,00	18,00	0,021
	TURP	103	6,77	7,00	2,77	2,00	16,00	
IPSS at 3m	HoLEP	150	3,54	3,00	2,30	1,00	12,00	<0,001
	TURP	103	6,22	6,00	3,37	2,00	22,00	
IPSS at 6m	HoLEP	150	2,36	2,00	1,60	0,00	8,00	<0,001
	TURP	103	5,69	6,00	2,54	1,00	14,00	

Table 9. Comparative analysis of the investigated methods in terms of IPSS at the four measurement moments

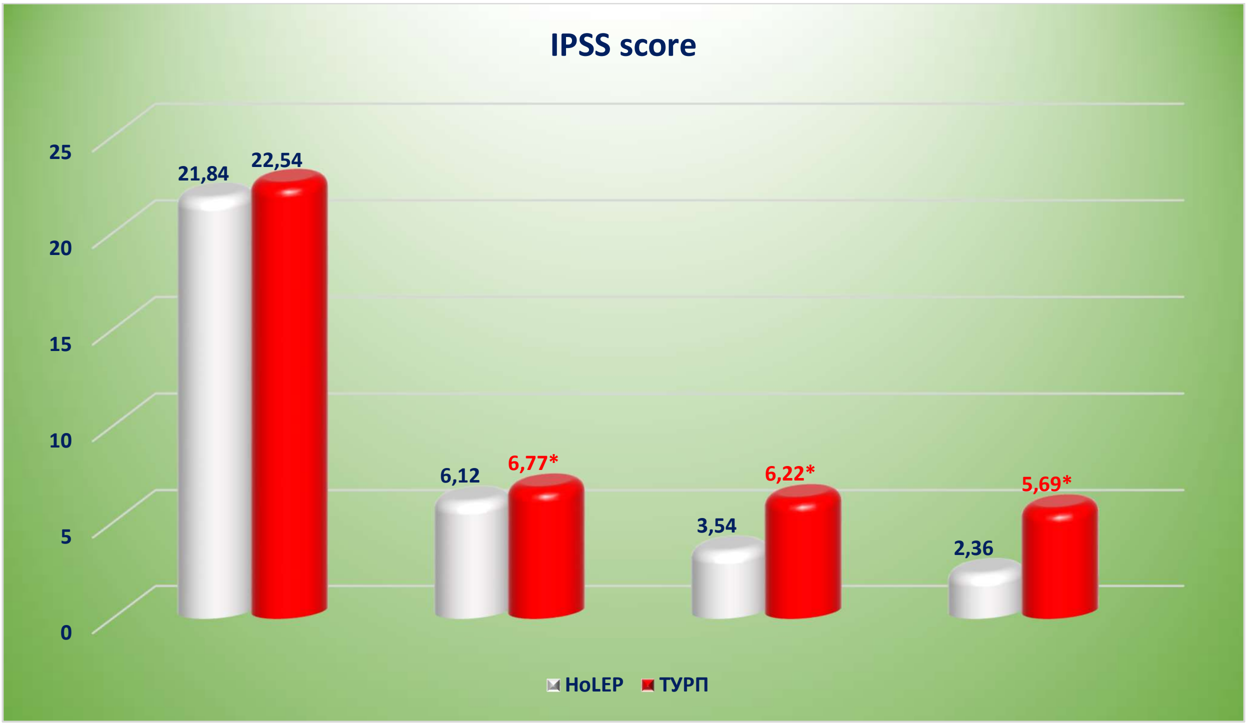

Fig10. Comparative analysis of the studied methods in terms of IPSS score in the four moments of measurement

According to the results of the comparative analysis of Max flow (table 10 and fig. 11):

● Preoperatively, patients from the TURP group are in a more advantageous position, having a statistically significantly higher average value of the indicator;

● At the next three measurement times, significantly higher mean values were observed in the HoLEP group, i.e. regardless of the more severe initial situation, the results achieved by this method become statistically significantly better.

Indicator	operation	N	Mean	Median	SD	Min	Max	p
Max flow pre-op	HoLEP	136	8,31	8,10	3,25	2,00	16,60	0,010
	ТУРП	101	9,46	9,50	3,55	3,30	15,80	
Max flow at 1m	HoLEP	150	21,08	19,85	5,50	10,70	38,80	0,005
	ТУРП	103	19,09	18,40	2,86	15,00	10	
Max flow at 3m	HoLEP	150	21,90	21,05	5,02	10,00	37,90	<0,001
	ТУРП	103	18,34	18,40	3,06	7,00	25,70	
Max flow at 6m	HoLEP	150	22,62	22,00	4,95	9,70	39,10	<0,001
	ТУРП	103	18,69	18,00	2,28	15,00	25,00	

Table 10. Comparative analysis of the investigated methods in terms of Max flow in the four moments of measurement

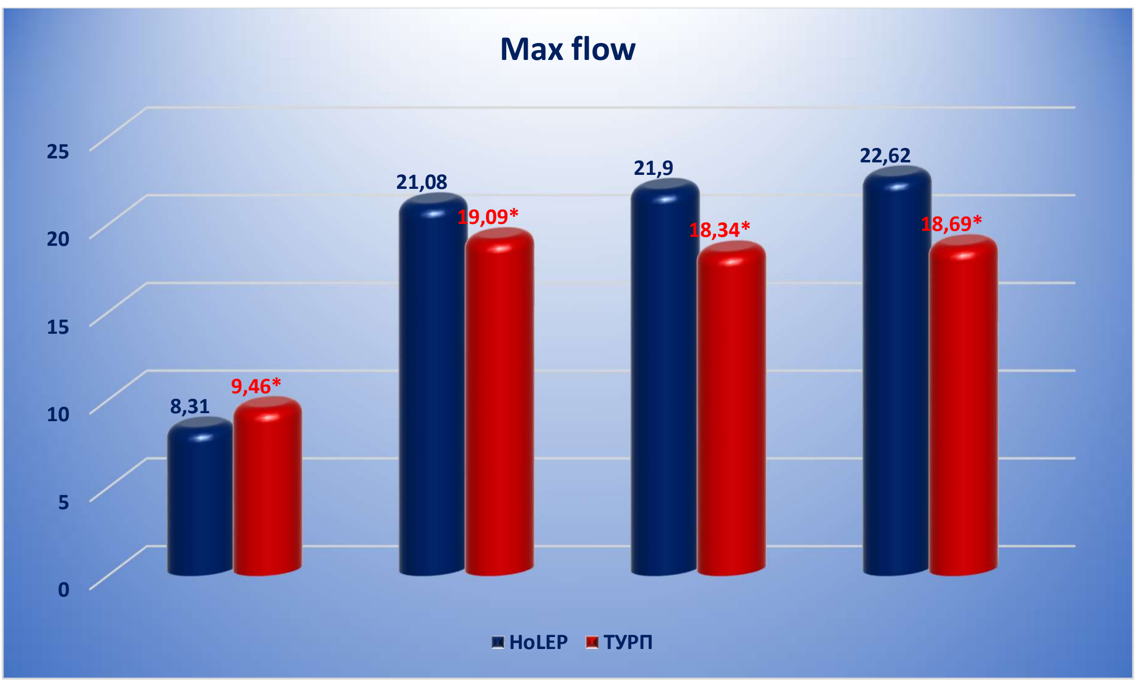

Fig. 11. Comparative analysis of the studied methods in terms of Max flow in the four moments of measurement

The conducted analysis of the dynamics of the average values of IPSS, HoLEP method (table 11 and fig. 12) found that at any moment of the follow-up there was a significant drop in the average value of the IPSS indicator.

Indicator (HoLEP)	N	Mean	Median	SD	Min	Max	p
Pre-op IPSS	150	21,84[a]	22,00	6,20	6,00	34,00	<0,001
IPSS at 1m	150	6,12[b]	5,00	3,43	1,00	18,00	
IPSS at 3m	150	3,54[c]	3,00	2,30	1,00	12,00	
IPSS at 6m	150	2,36[d]	2,00	1,60	0,00	8,00	

Table 11: Comparative analysis of the dynamics of average IPSS values, HoLEP method

** the same letters indicate the absence of a significant difference, and different letters indicate the presence of one (p <0.05)*

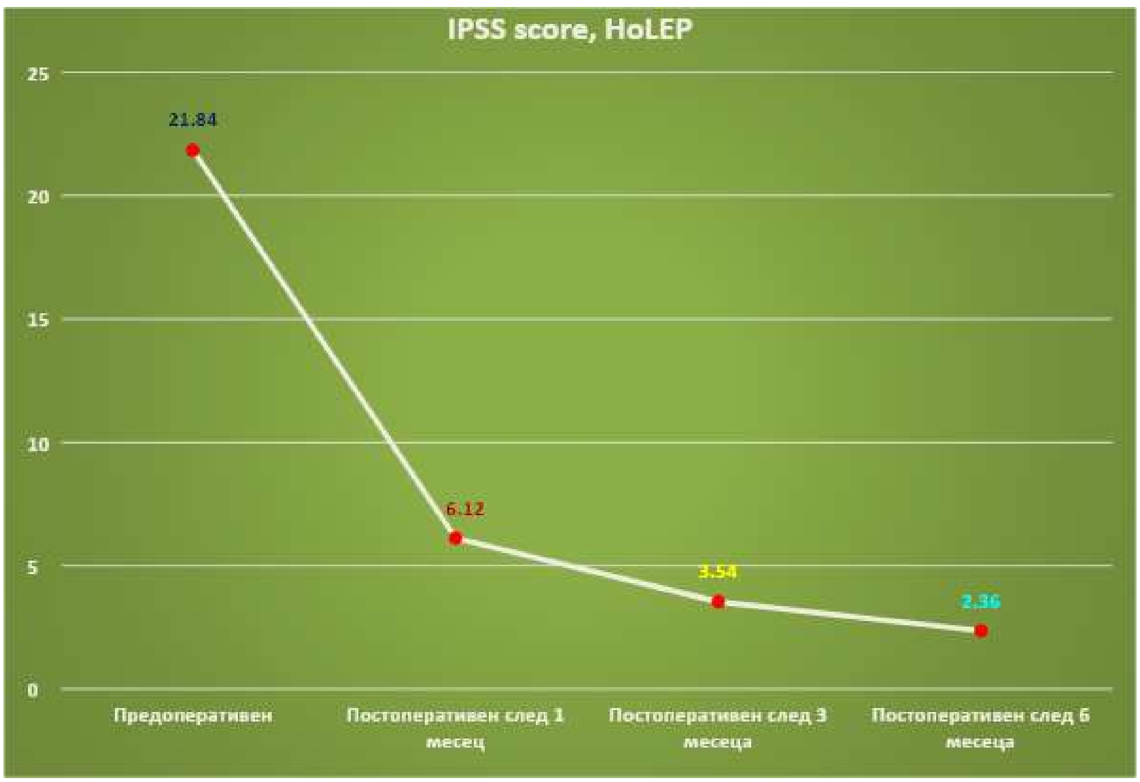

Fig. 12. Dynamics of average IPSS score values, HoLEP method

The dynamics of the average values of Max flow, TURP method

In fig. 13 it can be seen that:

• Max flow postoperatively after 1 month shows a significant increase compared to its preoperative average value;

• At the third month, there is a statistically significant decrease compared to the first, which continues into the sixth month, although the difference between the last two measurements is statistically insignificant.

Indicator (TURP)	N	Mean	Median	SD	Min	Max
Max flow pre-op	101	9,46[a]	9,50	3,55	3,30	15,80
Max flow at 1m	101	19,05[b]	18,40	2,87	15,00	25,10
Max flow at 3m	101	18,32[c]	18,40	3,09	7,00	25,70
Max flow at 6m	101	18,67[c]	18,00	2,29	15,00	25,00

Table 12. Dynamics of average Max flow values, TURP method

** the same letters indicate the absence of a significant difference, and different letters indicate the presence of one ($p<0.05$)*

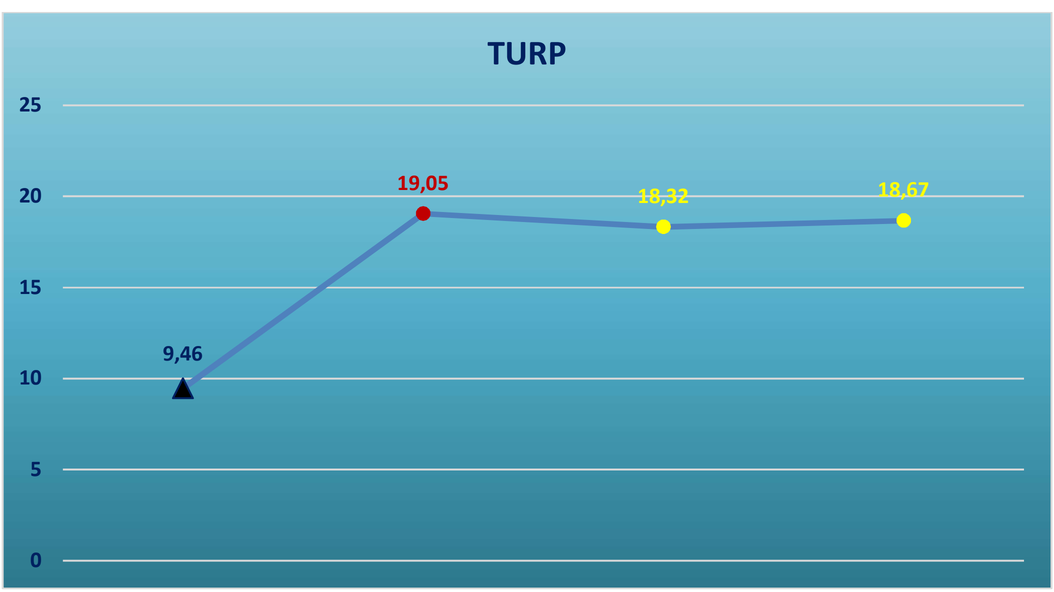

Fig. 13. Comparative analysis of the dynamics of the average values of Max flow, TURP method

From table 13 and fig. 14 it becomes clear that:

• The investigated operative methods differ significantly in terms of HS indicators/(d) hospital stay and catheterization time;

• Statistically significantly lower average values are observed in the group operated by means of the HoLEP method.

Indicator	Operation	N	Mean	Median	SD	Min	Max	p
Hospital stay(days)	HoLEP	150	1,04	1,00	0,26	1,00	3,00	<0,001
	TURP	103	4,17	4,00	0,77	3,00	5,00	
Catheterisation time (days)	HoLEP	150	1,31	1,00	0,79	1,00	5,00	<0,001
	TURP	103	5,08	5,00	1,50	3,00	7,00	

Table 13. Comparative analysis of the studied methods with regard to the indicators HS/(d) hospital stay and catheterization time in days

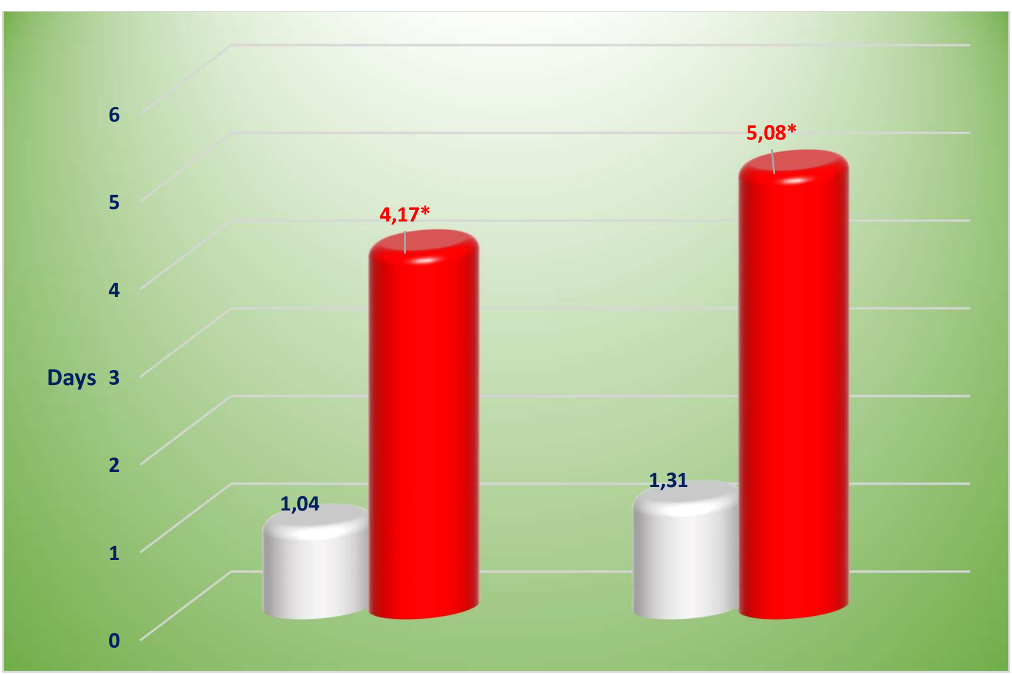

Fig. 14. Comparative analysis of the studied methods with regard to the indicators HS/(d) hospital stay and catheterization time in days

The comparative analysis of the complications of the two groups (Table 14) found that:

• The difference in the frequency of complications in both groups is statistically insignificant;

• Overall, the number of complications was low – the most common complication 'Stress Incontinence', for example, occurred in only 10 (4%) of patients in the sample, followed by 'Revision due to haematuria' in 8 (3.2%) ;

• About 90% of patients are without complications: in the HoLEP group their relative share is slightly higher.

Complication	Percentage	All	HoLEP	TURP	P
No	n	228	138	90	0,229
	%	90,1	92,0	87,4	
Stricture	n	6	3	3	0,644
	%	2,4	2,0	2,9	
Blood transfusion	n	5	2	3	0,367
	%	2,0	1,3	2,9	
Bladder perforation	n	1	1	0	0,396
	%	0,4	0,7	0	
Revision	n	8	3	5	0,197
	%	3,2	2,0	4,9	
Stress-incontinence	n	10	5	5	0,522
	%	4,0	3,3	4,9	

Table 14. Comparative analysis of the two studied groups according to complications

** percentages sum to over 100 because some patients had more than one complication*

The results of the table 15 and fig. 15 show that:

• The difference between the indicators of total prostate volume and weight of enucleated tissue in the HoLEP group is statistically reliable;

• The higher average value is on the first metric.

Indicator	N	Mean	Median	SD	Min	Max	p
TPV	150	75,39	70,00	33,48	30,00	280,00	<0,001
EnW	150	57,22	50,00	30,46	15,00	160,00	

Table 15. Comparative analysis of total prostate volume with weight of enucleated tissue in HoLEP group

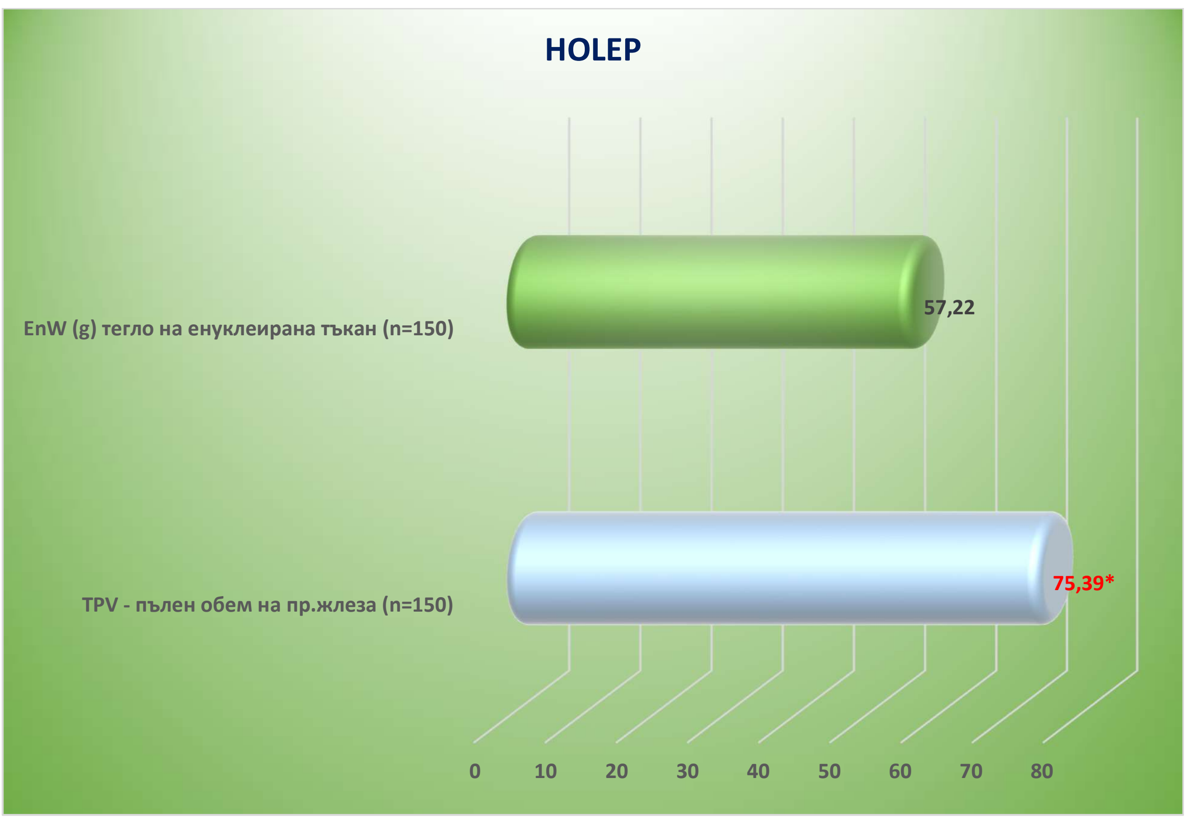

Fig. 15. Comparative analysis of total prostate volume with weight of enucleated tissue in HoLEP group

From table 16 and fig. 16 it becomes clear that:

• The difference between the indicators of total prostate volume and weight of resected tissue in the TURP group is significant;

• The higher average value is the HoLEP group.

When comparing the parameters TPV, weight of enucleated tissue and weight of resected tissue in the two operative methods (Table 17 and Fig. 17), it was found that statistically significantly higher average values were for the patients of the HoLEP group in terms of both TPV , as well as the weight of enucleated tissue relative to the weight of resected tissue.

Indicator	N	Mean	Median	SD	Min	Max	p
TPV	103	63,12	64,00	15,49	35,00	90,00	<0,001
RW (g)	103	31,45	31,00	9,93	15,00	55,00	

Table 16. Comparative analysis of total prostate volume with weight of resected tissue in TURP group

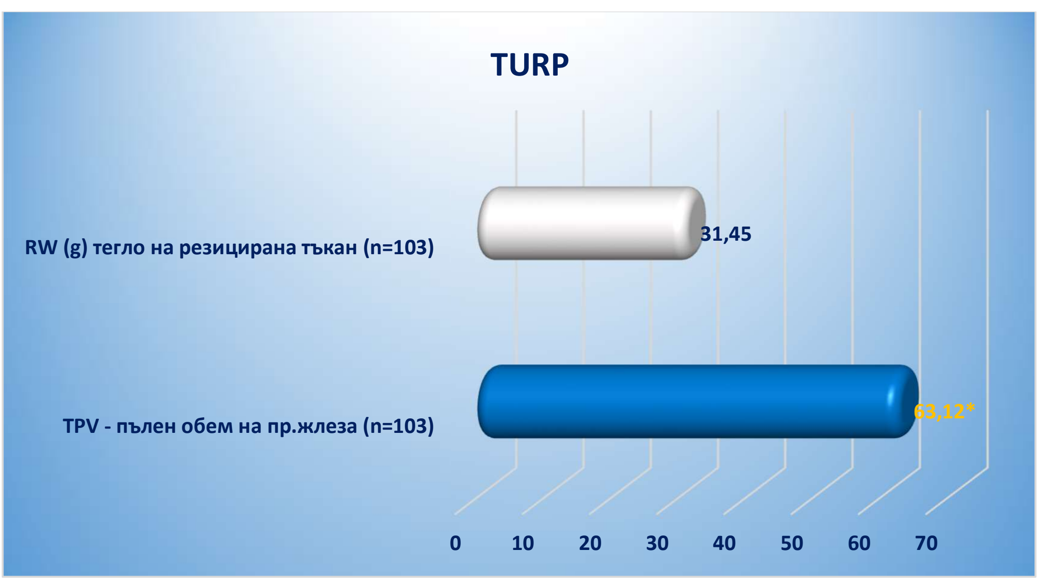

Fig. 16. Comparative analysis of total prostate volume with weight of resected tissue in TURP group

Indicator	Operation	N	Mean	Median	SD	Min	Max	p
TPV	HoLEP	149	74,02	70,00	29,05	30,00	180,00	0,017
	TURP	103	63,12	64,00	15,49	35,00	90,00	
EnW (g)	HoLEP	150	57,22	50,00	30,46	15,00	160,00	<0,001
RW (g)	TURP	103	31,45	31,00	9,93	15,00	55,00	

Table 17. Comparative analysis of TPV, weight of enucleated tissue and weight of resected tissue in the two operative methods

** The TPV value of 280 in the HoLEP group was not considered an outlier in the analysis*

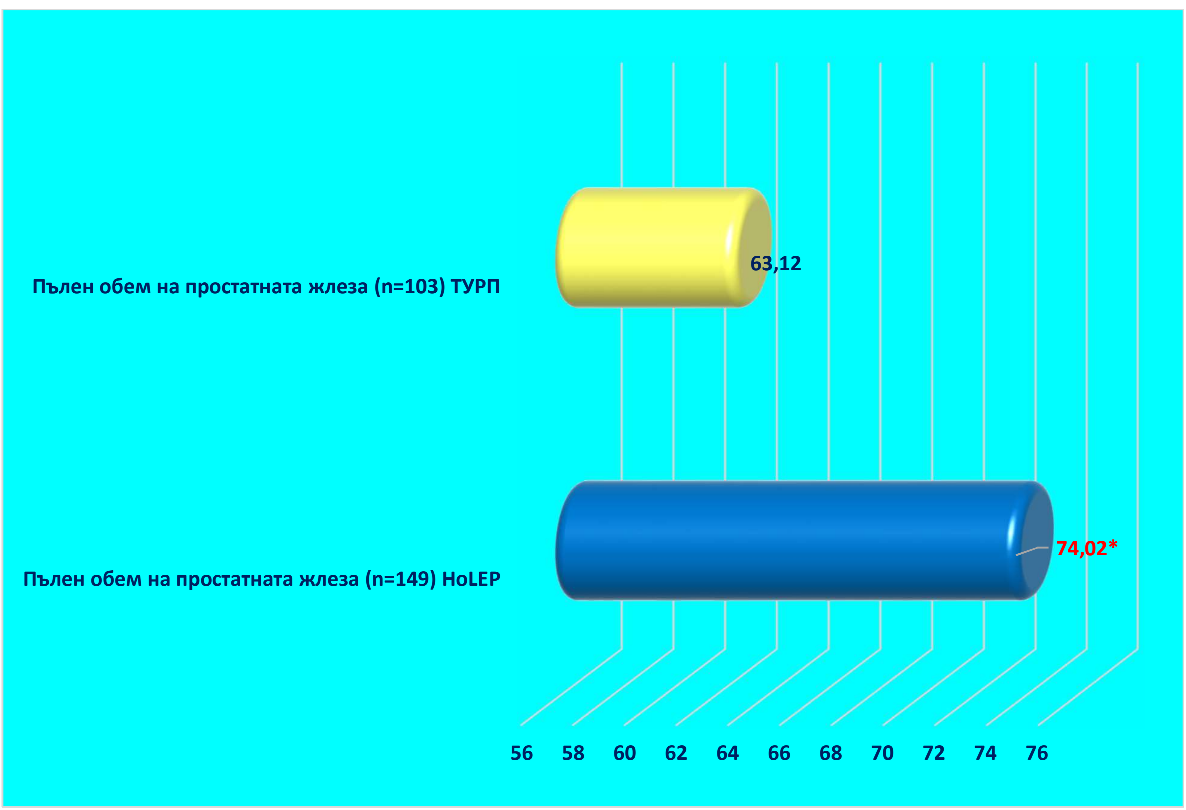

Fig. 17 Comparative analysis of TPV in the two operative methods

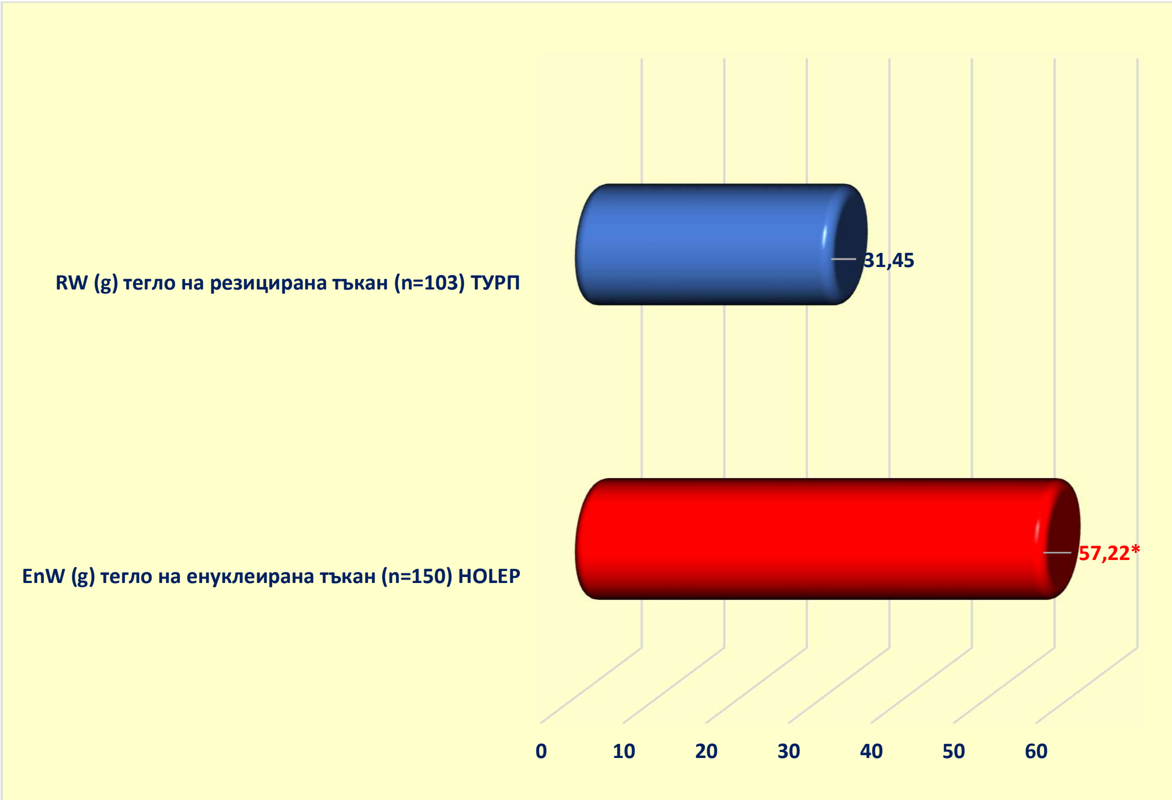

Fig. 18. Comparative analysis of weight of enucleated tissue and weight of resected tissue in the two operative methods

Dynamics of indicators related to improvement of the operational technique (HoLEP method)

Full volume of the prostate gland

The regression analysis conducted found that from the built-in statistics package IBM SPSS Statistics 25.0. eleven models the dependence of the total volume of the prostate gland on the time of refinement is best described by a polynomial equation of the second degree ($R2=0.199$, $p<0.001$):

$TPV = -0.0049t2 + 0.9638t + 38.075$

where t is the sequence number of the patients arranged in chronological order. The curve of the equation rises smoothly until the 97th patient, after which it also shows a smooth decline. The value of the coefficient of determination R2 shows that the variations of the studied indicator depend on about 20% of the time, and the rest (about 80%) - on other factors (Fig. 19).

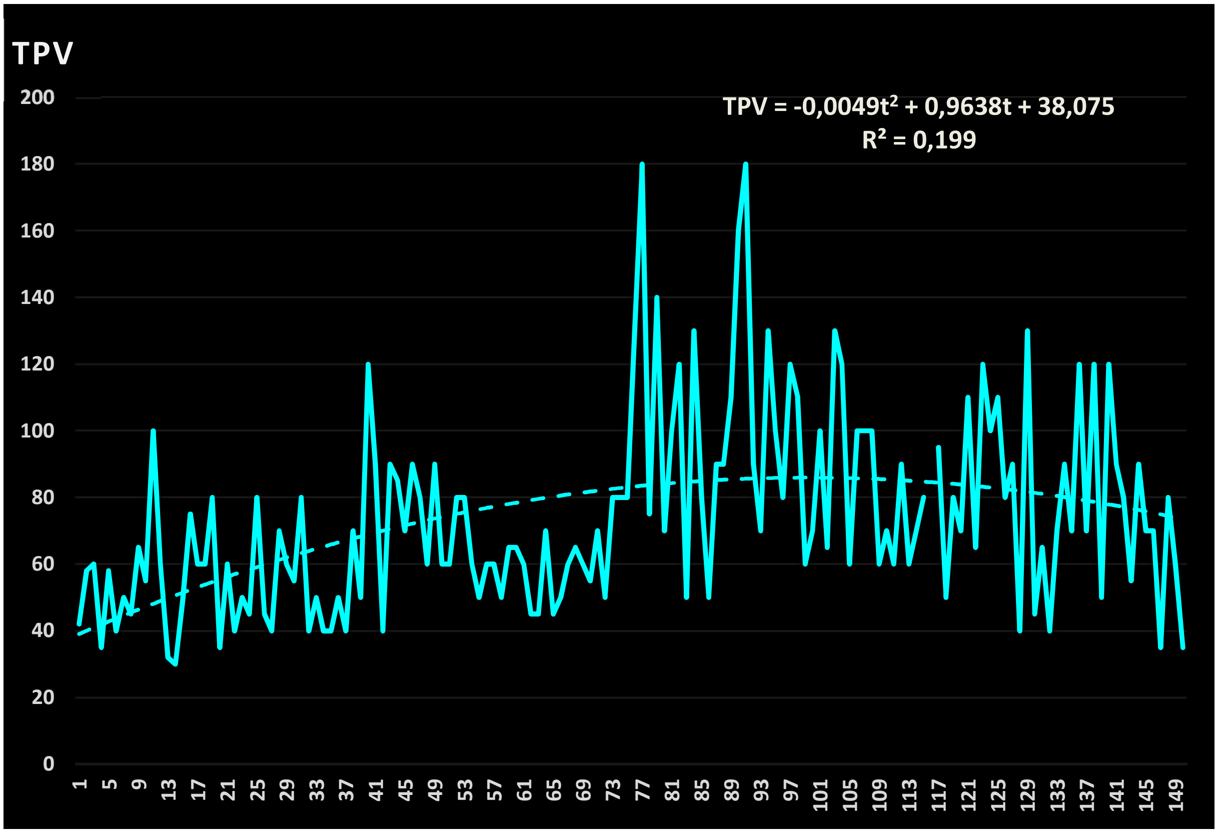

Fig. 19. Regression model of the changes of the total volume of the prostate in the process of improvement of the operative technique (HoLEP)

Operative time

The regression analysis conducted found that from the built-in statistics package IBM SPSS Statistics 25.0. eleven models the dependence of operational time on refinement time is best described by a polynomial equation of the second degree ($R2=0.145$, $p<0.001$):

$OpT = -0.0026t2 + 0.475t + 31.284$

where t is the sequence number of the patients arranged in chronological order. The curve of the equation rises smoothly until the 90th patient, after which it also shows a smooth decline. The value of the coefficient of determination R2 shows that the variations of the studied indicator depend on about 14% of the time, and the rest (about 86%) - on other factors (Fig. 20).

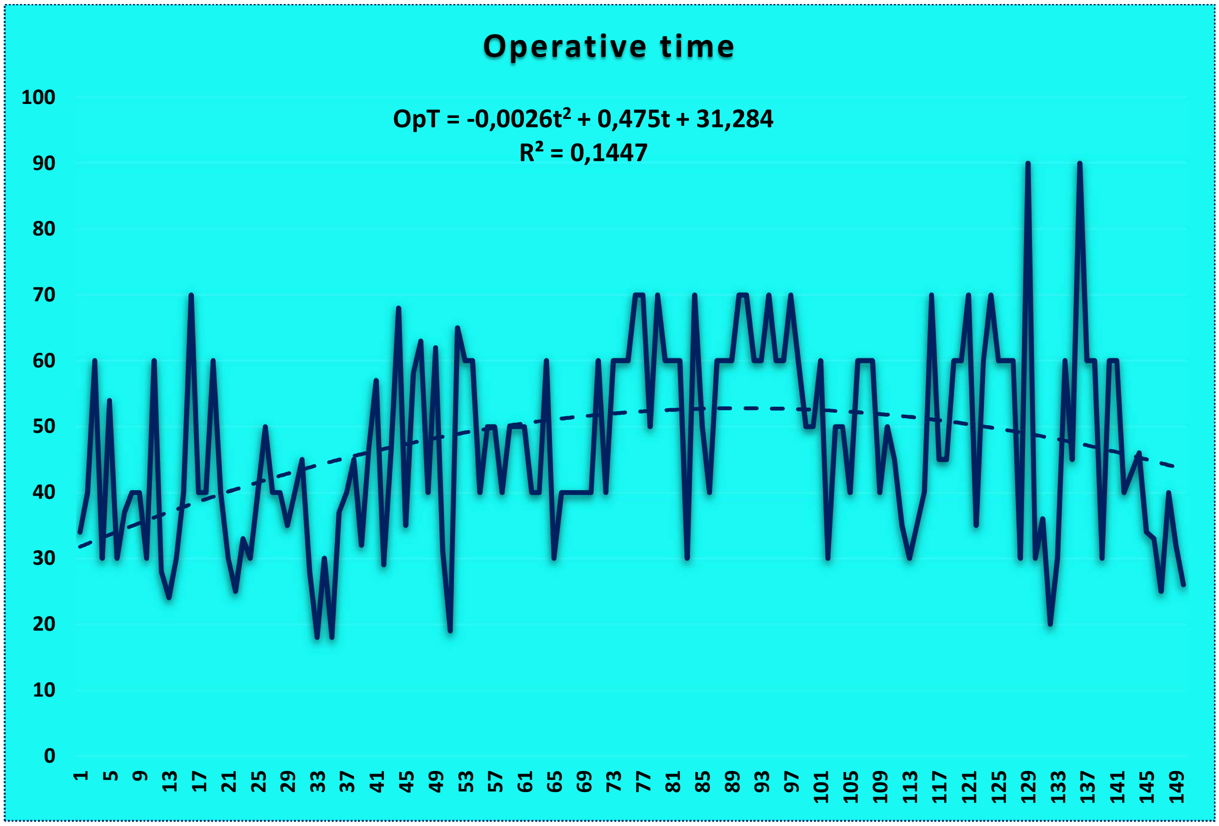

Fig. 20. Regression model of changes in operating time in the process of improving the operating technique (HoLEP)

Enucleation time

The regression analysis conducted found that from the built-in statistics package IBM SPSS Statistics 25.0. eleven models the dependence of enucleation time on refinement time is best described by a quadratic polynomial equation ($R2=0.174$, $p<0.001$):

$$EnT = -0.0024t2 + 0.4337t + 22.097$$

where t is the sequence number of the patients arranged in chronological order. The curve of the equation rises smoothly until the 93rd patient, after which it also shows a smooth decline. The value of the coefficient of determination R2 shows that the variations of the studied indicator depend on about 17% of the time, and the rest (about 83%) - on other factors (Fig. 21).

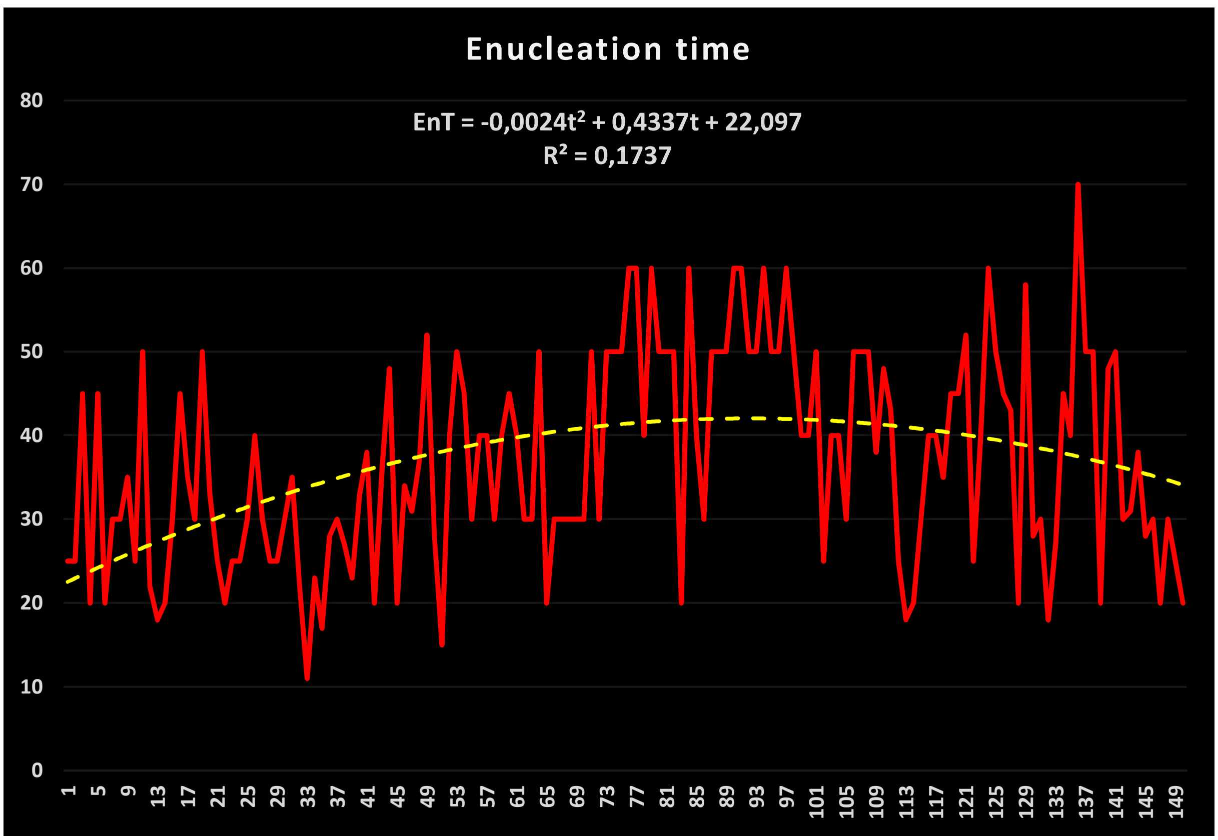

Fig. 21. Regression model of changes in enucleation time in the process of improving the operative technique (HoLEP)

Morcellation time

The regression analysis conducted found that from the built-in statistics package IBM SPSS Statistics 25.0. eleven models the dependence of morcellation time on refinement time is best described by a quadratic polynomial equation ($R2=0.137$, $p<0.001$):

$$MT = -0.0004t2 + 0.0764t + 1.5451$$

where t is the sequence number of the patients arranged in chronological order. The curve of the equation rises smoothly until the 100th patient, after which it also shows a smooth decline. The value of the coefficient of determination R2 shows that the variations of the studied indicator depend on about 14% of the time, and the rest (about 86%) - on other factors (Fig. 22).

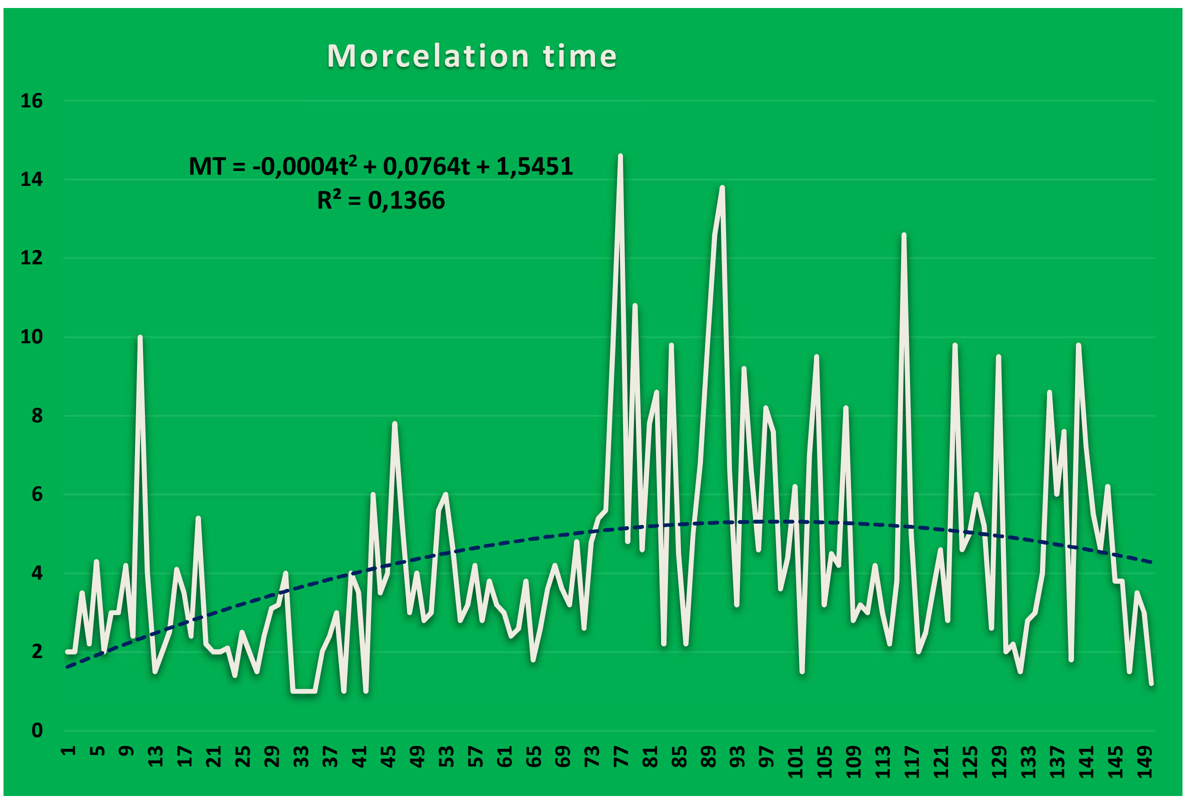

Fig. 22. Regression model of morcellation time changes in the process of improving the operative technique (HoLEP)

Weight of enucleated tissue

The regression analysis conducted found that from the built-in statistics package IBM SPSS Statistics 25.0. eleven models the dependence of enucleated tissue weight on refinement time is best described by a quadratic polynomial equation ($R2=0.218$, $p<0.001$):

$$EnW = -0.0052t2 + 1.0404t + 17.879$$

where t is the sequence number of the patients arranged in chronological order. The curve of the equation rises smoothly until the 103rd patient, after which it also shows a smooth decline. The value of the coefficient of determination R2 shows that the variations of the studied indicator depend on about 22% of the time, and the rest (about 78%) - on other factors (Fig. 23).

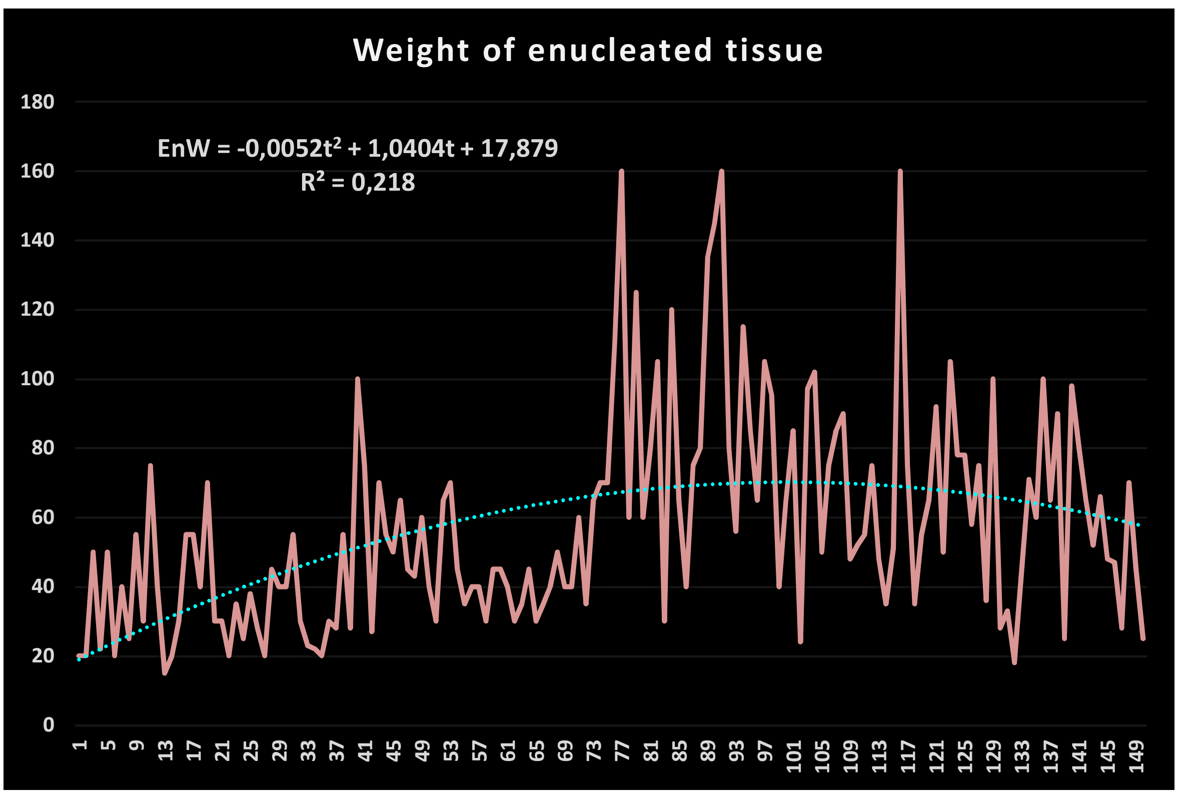

Fig. 23. Regression model of changes in the weight of enucleated tissue in the process of improving the operative technique (HoLEP)

Enucleation efficiency

The regression analysis conducted found that from the built-in statistics package IBM SPSS Statistics 25.0. eleven models the dependence of enucleation efficiency on refinement time is best described by an exponential equation (R2=0.135, p<0.001):

EnEff = 0.8188t0.1403

where t is the sequence number of the patients arranged in chronological order. The curve of the equation rises slightly steeper at the beginning and smoothly but permanently thereafter. The value of the coefficient of determination R2 shows that the variations of the studied indicator depend on about 13% of the time, and the rest (about 87%) - on other factors (Fig. 24).

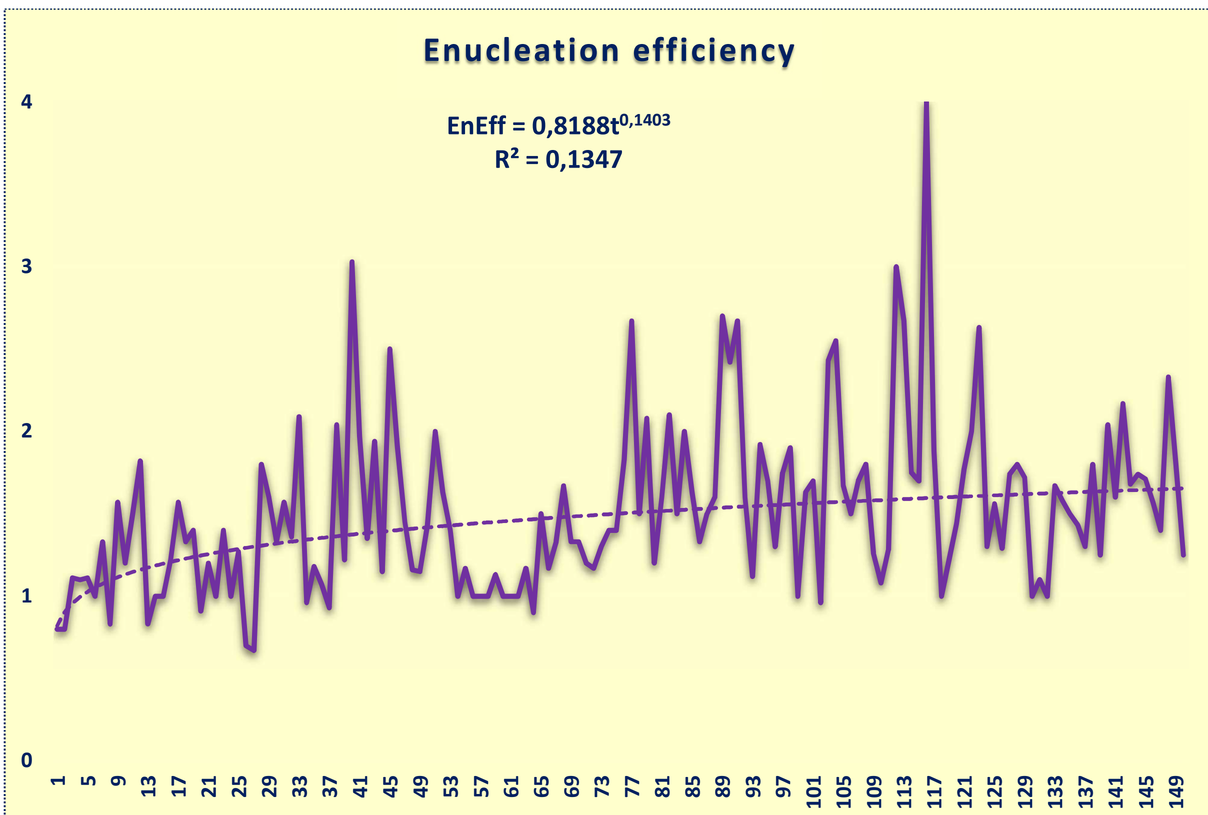

Fig. 24. Regression model of changes in enucleation efficiency in the process of improving the operative technique (HoLEP method)

Morcellation efficiency

The regression analysis conducted found that from the built-in statistics package IBM SPSS Statistics 25.0. eleven models the dependence of morcellation efficiency on refinement time is best described by an exponential equation (R2=0.020, p=0.018):

Meff = 11.116t0.0508

where t is the sequence number of the patients arranged in chronological order. The curve of the equation rises slightly steeper at the beginning and smoothly but permanently thereafter. The value of the coefficient of determination R2 shows that the variations of the studied indicator depend on only about 2% of the time, and the rest (about 98%) - on other factors (Fig. 25).

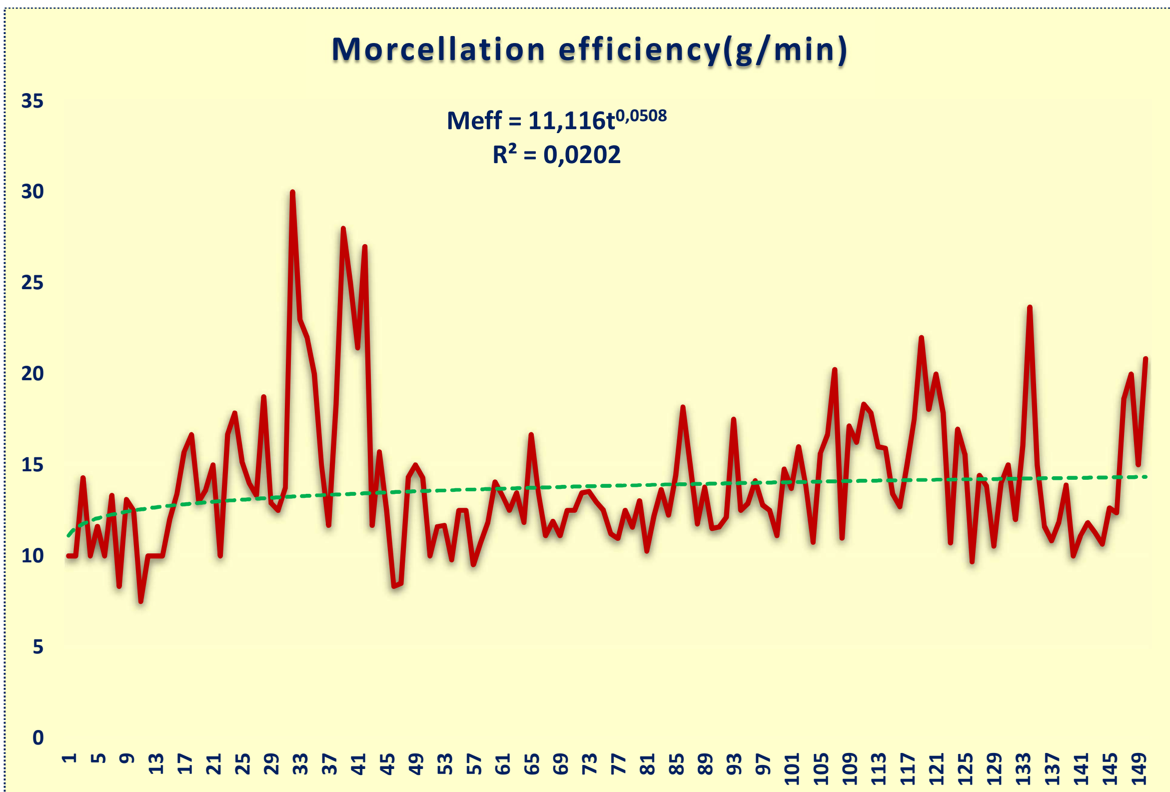

Fig. 25. Regression model of morcellation efficiency changes in the process of improving the operative technique (HoLEP method)

Summary of the established trends of the indicators suggesting a connection with the improvement of the operative technique (HoLEP method)

The statistical trends of five of the indicators - "TPV", "Operative time", "Enucleation time", "Morcellation time", "Weight of enucleated tissue" are described by a polynomial regression equation having the following characteristics:

- An increase in values was observed over time until the end of the first 2/3 of the follow-up time;
- During the last third of the period, a smooth decline is observed.

This suggests a strong correlation between them, but their interpretation with improvement in operative technique ends at the end of the first 2/3 of the chronological order, as it does not explain the decline thereafter.

The trend is different for the indicators related to efficiency ("Enucleation efficiency" and "Morcellation efficiency") - there the increase is smoother, but permanent, which suggests that they are related to the improvement of the operative technique.

In order to verify the reasoning made, a correlation analysis was conducted (Table 18), the results of which show that:

- There is a strong, directly proportional correlation between the top five indicators (all but the efficiency-related ones);
- Enucleation efficiency correlates unidirectionally and most strongly with enucleated tissue weight, TPV and morcellation time, and weakly with operative time and enucleation time;
- The effectiveness of morcellation correlates only with three of the investigated indicators, namely - in different directions and most strongly (but moderately as an absolute value) with the time for morcellation, and weakly with the operative time and the time for enucleation.

Indicator	Operative time	Enucleation time	Morcellation time	Weight of enucleated tissue	Enucleation efficiency	Morcellation efficiency
TPV	0,793***	0,765***	0,876***	0,944***	0,677***	-0,116
Operative time		0,949***	0,815***	0,820***	0,266**	-0,218**
Enucleation time			0,802***	0,817***	0,208*	-0,183*
Morcellation time				0,919***	0,602***	-0,438***
Weight of enucleated tissue					0,703***	-0,096
Enucleation efficiency						0,039

Table 18. Correlation analysis of the indicators related to improvement of the operational technique (HoLEP method)

** - p<0.05; ** - p<0.01; *** - p<0.001*

5. DISCUSSION OF RESULTS

5.1. General characteristics of the researched contingent

The average age of the participants was 66.98±8.73 years ranging from 42 to 88 years. The distribution in the HoLEP group is as follows - 60–69 (46%), 70–79 (30.7%), 50–59 (12.7%), 80–89% (8.0%) and 40–49 (2.5 %). For the TURP group, the distribution is as follows - 60–69 with 32.0%, 70–79 with 32.0%, 50–59 (31.1%) and 80–89% (4.9%). The incidence of BPH is closely correlated with age. McConnell and team demonstrated that the need for surgical treatment of BPH was directly proportional to age (from 0.1% to 9.5% in individuals aged 40–49 years and

70–79 years, respectively) (McConnell et al. 2003). This observation largely coincides with our data - 84.7% of the HoLEP group and 68.9% of the TURP group were over the age of 60. The paradoxically low relative percentage of men over the age of 80 in both groups may be due to different factors - the presence of numerous concomitant diseases that prevent surgical treatment, increasing the health culture of the population leading to medical interventions at the first manifestation of the disease, etc.

Regarding preoperative PSA, the mean values in the HoLEP group were significantly higher compared to the TURP group - 4.37 and 2.86 ng/ml, respectively. The range of these values is also wider in the first group - from 0.2 to 20 ng/ml compared to the second - from 0.5 to 7.33 ng/ml. These differences are due to the characteristics of PSA as a marker. It has a high sensitivity for prostate pathology, but relatively low specificity for specific prostate diseases. One of the factors that affect PSA levels in the blood is age. The relationship between the two factors is so well studied that the limits of "normal" PSA are adjusted to the age limit - 40–49 <2.5ng/ml, 50–59 <3.5ng/ml, 60-69 <4.5, over 70 years <6.5 (Saleh et al 2016). To simplify the results, we have chosen a cut-off value above 4ng/ml as elevated. Another factor influencing PSA values is the volume of the prostate gland. The combination of the two factors - increased age and higher TPV, both seen in the HoLEP group accounted for the higher PSA in this group.

During HoLEP, a complete anatomical enucleation of the transitional zone of the prostate gland is performed. For this reason, a 60 to 90 % drop in serum PSA is observed (Lambert et al. 2021). Elzayat and colleagues described a mean decrease in PSA from 5.8 ng/ml (0.11–26.7) to 2.1 ng/ml (0.10–10) in the sixth postoperative month (Elzayat EA, Elhilali MM 2006). In our study, a mean reduction of 68.6% was observed from the mean preoperative PSA in the HoLEP group, from 4.37ng/ml to 1.37ng/ml in the first postoperative month. Although the absolute mean value for the postoperative PSA in the TURP group was lower (1.24ng/ml), taking into account the mean value of the preoperative PSA, it is seen that the reduction in value was lower - 56.6%. This may be explained by the more complete removal of prostate tissue in the HoLEP group. The comparative analysis found that both treatment groups achieved a statistically significant decrease in PSA one month after surgery.

When comparing preoperative and postoperative serum hemoglobin values, a statistically significant difference was found between the two groups. Mean HoLEP hemoglobin values were 148.04ng/L preoperatively and 142.85ng/L postoperatively. This demonstrates an average decline of 5.19 units. The TURP guppy had preoperative hemoglobin of 142.93 ng/L and 133.87 ng/L postoperatively, i.e. an average decline of 9.06 units. Sun and colleagues demonstrated similar results in their comparative study between HoLEP and TURP based on 164 patients. The authors reported a mean drop of 7.88 units for HoLEP (139.43 baseline, 131.55 postoperative hemoglobin) and 14.08 units for TURP (140.49 baseline, 126.41 postoperative hemoglobin) (Sun et al 2014).

The hospital stay affects both the economic burden of the operative procedure and the comfort of the patients. One of the undeniable advantages of laser enucleation is a shorter hospital stay compared to other operative interventions - open adenomectomy, TURP, etc. According to our data, the average hospital stay for the HoLEP group was 1.04 days, with the shortest being 1 and the longest being 3 days. For the TURP group, the average length of stay was 4.17 days - between 3 and 5 days. Statistically significant ($p < 0.001$) lower mean values were observed in the HoLEP group. Multiple authors have published similar results regarding the mean length of hospitalization. Kuntz and colleagues conducted a comparative study between HoLEP and TURP in which they reported a significant difference in mean hospitalization time of 53.3h/2.22 days and 85.5h/3.56 days respectively (Kuntz et al., 2004). Tan and colleagues reported the following results: 0.95 days for HoLEP and 3.82 days for TURP (Tan et al 2007). Heidar and colleagues reported 1.29 days of mean length of stay for HoLEP and 2.05 for TURP (Heidar et al. 2020). The lack of need for a long hospital stay for enucleation is so well established that some urologists perform it as an outpatient procedure (Lee et al 2018).

Catheterization time is another indicator in the early postoperative period demonstrating the advantages of laser enucleation. As a rule, the extraction of the urethral catheter in both methods is performed after a permanent absence of postoperative hematuria. This is influenced by many factors - operative technique, size of the prostate, coagulation status of the patient, intake of anticoagulants, etc. According to our data, the mean catheterization time for the HoLEP group was 1.31 days and for the TURP group - 5.08 days. Statistically significant ($p < 0.001$) lower mean values were observed in the HoLEP group. Heidar described a mean HoLEP catheterization time of 24.35h (1.01 days) and 50.6h (2.1 days) (Tan et al 2007). Kuntz and colleagues conducted a comparative study between HoLEP and TURP in which they reported a significant difference in mean catheterization times of 27.6h/1.15 days and 43.4h/1.81 days respectively (Kuntz et al 2004).

The short hospital stay and catheterization time with HoLEP is due to several factors. The enucleation technique allows maximum anatomical "separation" of the prostate tissue, reducing the risk of bleeding. Laser equipment allows effective electrocoagulation and, accordingly, lower blood loss during surgery.

5.2. Postoperative symptoms and functional results

The use of the IPSS allows for the objective assessment of patients' symptoms. In addition to tracking the dynamics of the condition in each patient, it allows for comparing the effectiveness of different therapeutic methods. Depending on the severity of the symptoms, 3 groups are distinguished - mildly expressed (0-7t), moderately expressed (8-19t), and severely expressed (20-35t). The distribution of patients in the HoLEP group is as follows - mild 2%, moderate 34%, and severe symptoms 65%. In the TURP group, they are respectively 0%, 35%, and 65%. Follow-up of these patients is done at the first, third, and sixth months.

In the first postoperative month, the following dynamics were observed in the HoLEP group - 70.7% had mild symptoms and 29.3% had moderate symptoms.

None of the patients demonstrated an IPSS above 20, i.e. severe symptoms. The average IPSS is 6.12. In the TURP group, 62.1% and 37.9% had mild and moderate symptoms, respectively. The mean IPSS was 6.77. Based on these data, no statistically significant difference was found between the two groups. On the third postoperative month, the following statistically significant changes in indicators were observed. In the HoLEP group, patients with mild and moderate symptoms were 92.7% and 7.3%, respectively. None of the patients presented with severe symptoms. The average IPSS was 3.54. In the TURP group, the distribution was 77.7% mild, 20.4% moderate, and 1.9% severe symptoms. The average IPSS was 6.22. This trend is also maintained in the sixth postoperative month. In the HoLEP group, patients with mild and moderate symptoms were 98% and 2%, respectively. None of the patients presented with severe symptoms. The average IPSS was 2.36. In the TURP group, the distribution was 79.6% mild and 20.4% moderate symptoms. The average IPSS was 5.69.

These observations have also been reported by other authors. According to Huang and colleagues, no statistically significant differences were observed in the early postoperative period between the two methods (Huang et al. 2019). Other modern studies reach the same conclusions (Cornu et al. 2015, Zhang et al. 2019, Yin et al. 2013). As our data demonstrate, the effectiveness of HoLEP on prostatic symptoms improves over time. Gu et al. present a 6-year follow-up in which the mean IPSS was more favorable for the HoLEP group (8.79) than for the TURP (10.03) with $p < 0.001$. Ahyai and colleagues reported mean IPSS at the first, third, and sixth months of 4.3, 2.2, and 1.7 for HoLEP and 5.5, 3.7, and 3.9 for TURP (Ahyai et al 2007). Eltabey reported the following results: mean IPSS at first, third and sixth months of 4.1, 2.6, and 2.2 for HoLEP and 5.3, 3.8, and 3.7 for TURP. Gilling et al presented the following results in their 2012 study - mean IPSS at first, third and sixth months of 8.6, 6.0, and 4.6 for HoLEP and 5.8, 4.8, and 4.7 for TURP (Gilling et al 2012).

While IPSS allows a qualitative assessment of subjective complaints, Qmax (Max flow) is a urodynamic indicator demonstrating the functional status of the micturition phase. Max flow is the maximum speed that urine flow reaches during micturition. Above 15-20ml/s are considered normal values. In the context of our study, we have accepted values above 15 ml/s as normal and those below as subnormal. Because this is a study that reports results during spontaneous micturition, patients who are catheterized preoperatively cannot be evaluated - they are by definition substandard. 115 patients or 85.6% of the HoLEP group had Qmax below 15 ml/sec, while 21 patients (15.4%) had normal uroflowmetry. For the TURP group, 72 patients (71.3%) had subnormal Qmax and 29 patients (28.7%) had normal uroflowmetry. The relative proportion of patients with a substandard preoperative Max flow result in the HoLEP group was statistically significantly greater than that of the TURP group. The mean preoperative Qmax value was 8.31 in the HoLEP group and 9.49 for the TURP group. This means that patients from the first group have more severe symptoms.

At the first postoperative control (first month), the following results were found: only four patients from the HoLEP group and no patient from the TURP group had a subnormal uroflowmetry result. Statistically, significant improvement was observed in 97% of the first and 100% of the second group. The mean Qmax at enucleation increased from 8.31 to 21.08 ml/s, i.e. an improvement of 12.77 ml/s was observed. In the resection group, the mean Qmax increased from 9.49 to 19.09, i.e. an improvement of 9.6 ml/s. In the third month, a statistically significant difference was observed between the two groups - 21.9 ml/s for HoLEP and 18.34 ml/s for TURP. This trend is maintained in the sixth month when the difference between the average values of the two groups is 3.93 ml/s - average Qmax for HoLEP 22.63 ml/s and 18.69 ml/s for TURP.

These data largely coincide with those presented by other authors. Sun and colleagues described the following Qmax values at the first and twelfth months, 18.40 and 19.77 ml/s, respectively. Beltran and colleagues did follow-up in the first and sixth months - of 27.4 ml/s and 20.9 ml/s respectively (Beltran et al 2022). According to a meta-analysis published by Tan and colleagues, no statistically significant difference was found between the two methods in terms of Qmax (Tan et al. 2007), while according to other authors one was observed in favor of HoLEP (Cornu et al. 2015).

5.3. Early and late postoperative complications

The most common complications of endoscopic prostate surgery, regardless of the method, can be divided into perioperative and postoperative. The first group includes bladder perforation and hematuria leading to blood transfusion and/or revision. Postoperative complications include stress incontinence and urethral strictures. According to our data, 90.1% of the HoLEP and 84.4% of the TURP group had no complications during the hospital stay and the follow-up period.

5.3.1. Blood loss

From an operative point of view, blood loss is clinically relevant if it requires some conservative (drugs, blood transfusion) or operative intervention (revision). The difference in hemoglobin loss is the result of the different characteristics of the two operative methods. During enucleation, which is performed at the capsule level, blood vessels are interrupted once and coagulated instantaneously (Zhang et al 2015). During resection, the loop moves in several planes, resulting in repeated disruption of vessels, increasing the likelihood of bleeding, especially in larger glands. In addition, evacuation of the resected tissue leads to a dramatic intraluminal pressure difference, unlike morcellation, which does not show such a dramatic change (Chen et al 2013).

In our study, a total of two patients (1.3%) in the HoLEP group and three patients (2.9%) in the TURP group required blood transfusion postoperatively. A total of eight patients required revision postoperatively—three (2%) of the enucleation patients and five (4.9%) of the resection patients. The differences in these results were without statistical significance. Similar observations were published by Heidar and colleagues (Heidar et al 2020). In their study, based on 37,577 patients with TURP and 2869 patients with laser enucleation, blood transfusion was required in 682 patients (1.81%) of the first group and 38 patients of the second group (1.32), i.e. no statistical difference. Regarding the need for revision, the trend remains the same - 833 (2.2%) patients from the TURP group and 54 (1.9%) patients from the HoLEP group. Qian et al published a meta-analysis of 3 randomized and one retrospective study that found no statistically significant difference between the two methods in terms of transfusion and revisions (Qian et al 2017).

5.3.2. Strictures

Urethral strictures present with obstructive symptoms, residual urine, and dysuria. They are a common complication of all types of transurethral surgery. The frequency of postoperative strictures varies widely according to different authors. According to our data, three patients each in both groups had proven postoperative urethral stricture - 2% for the HoLEP and 2.9% for the TURP group. Woo et al published a meta-analysis comparing 408 patients with HoLEP and 353 with TURP. The two groups presented with a similar frequency of urethral strictures 6.5% versus 3.6% (Woo et al 2013). Krambeck et al. published a study of 1065 patients with HoLEP, finding the following outcomes at the first, sixth, and twelfth month and over 5 years - 9 (0.9%), 11 (1.3%), 4 (1.3%) and 0 patients, respectively. Elzayat and Elhilali performed a retrospective analysis of 225 patients with a mean prostate volume of 126 ml and a mean follow-up of 31 months. Urethral stricture was found in 3 patients (1.3%), meatus stenosis in 1 (0.4%) patient, and vesical neck sclerosis in 1 patient (0.4%). Elmansy et al published a retrospective analysis of 949 patients treated with HoLEP. Cystic sclerosis and urethral stricture were found in 0.8% and 1.6%, respectively, at a follow-up of 63 months (Elmansy et al 2011).

5.3.3. Bladder perforation

Bladder perforation during morcellation is one of the most feared complications for the surgeon during HoLEP. It is unique to the procedure due to the use of a morcellator to evacuate the enucleated tissue. Although cases of open repair of a vesical lesion have been described, most injuries involve only the vesical mucosa and are of no clinical significance (Seki et al. 2003). A large proportion of these superficial lesions likely remain unnoticed during surgery. In only one patient (0.7%) in our study a bladder lesion was registered - managed conservatively. The incidence of perforations varies widely among publications. In the majority of articles in which operations were performed by an experienced urologist, the incidence of perforations requiring reconstruction or those with sequelae was 0.1% (Enikeev et al 2018). Other authors have published statistics ranging from 2.1% (Shigemura et al) to 13% (Shah et al. 2008).

5.3.4. Stress incontinence

Surgical treatment of BPH accounts for about 10% of cases of stress incontinence in men (Arai et al 2009). The incidence of stress incontinence varies between 3%–9% after open adenomectomy and about 2% after TURP. Transient stress incontinence after HoLEP has been described in wide ranges - 4.9%–12.5% (Elmansy et al 2011; Krambeck et al 2010). According to Saitta et al., whose study included only grafts with early apical dissection identical to the one presented in our study, these values were 5.8%, 1.5%, and 0.7% at the first, third, and sixth months. According to our data, 5 patients from each group had a stress incontinence clinic within the follow-up period - 3.3% of the HoLEP group and 4.9% of the TURP group. It has been reported that 70% to 90% of patients regain continence spontaneously within three months (Kobayashi et al 2016).

According to our observations, the operative technique during enucleation is a key factor in the development of stress incontinence. During the classic three-lobe technique, the sphincter mucosa is detached at the end of the procedure, leaving only a portion of the mucosa at 12 o'clock. This preserves the "integrity" of the sphincter, but the deepithelialization is a prerequisite for transient incontinence. Another possible explanation is obstruction-induced bladder overactivity that resolves after the obstruction is removed. The en-bloc technique with early apical dissection was developed with this problem in mind. Early apical dissection allows early separation of the sphincter, thus avoiding its mechanical trauma and distension. In addition, this technique has a shorter operative time, further reducing the risk of traumatizing the sphincter apparatus.

5.4 Total prostate volume and weight of enucleated tissue

Multiple studies have demonstrated that HoLEP is a prostate size-independent treatment modality in patients with severe BPD (Assmus et al 2021). In comparison, TURP is the method of choice for glands with volumes between 30 and 80 ml. The current recommendations for clinical practice of the European Urological Society recommend performing an open adenomectomy for glands larger than 80 ml, in the absence of laser equipment to perform HoLEP. In our study, the average TPV (total volume of the prostate gland) for HoLEP was 74.02ml (30-180ml), and this value did not include a single patient with a prostate volume of 280ml, because would change the mean statistically implausibly. For the TURP group, the average volume was 63.12g (35-90g). This difference is statistically significant in favor of HoLEP. Besides the higher mean value in the enucleation group, the presence of patients with greatly enlarged glands is striking. In 30 patients from the HoLEP group, glands with volumes ≧100ml were measured. This is the main advantage of the method - it provides the opportunity to perform minimally invasive surgery without increasing the risk of complications and without compromising the functional postoperative result. Varma and colleagues described that the correlation between gland volume and density was equal to 1, i.e., 1 ml of volume is equivalent to 1 g of tissue (Varma M, Morgan JM 2010).

Effectiveness (grams per minute) of enucleation and morcellation are frequently reported outcomes in HoLEP publications, particularly as a comparative outcome to other surgical modalities for BPH. Wide ranges in enucleation and morcellation efficiency values have been reported, varying with gland size, operator experience, equipment used, etc. The dynamics of these values are used as an indirect marker for improvement in the operator's technique or as a marker for comparison between different operating techniques. One study examining HoLEP over an 8-year study period identified initial enucleation efficiency rates of 0.55 g/min, which improved to 1.32 g/min over the last 5 years of the study period (Dusing et al 2010). Morcellation efficiency has been reported in wide ranges - 1.73 g/min (0.1-7.7 g/min (Bae et al 2010) to 4.35 g/min (0.55-12.75 g/min) (Brunckhorst et al. 2015). According to our data the efficiency of enucleation is 1.52 g/min and of morcellation 14.09 g/min.

5.5 Learning curve and change in statistics after technique improvement

Despite the established results of HoLEP as a therapeutic approach, there is still a widespread perception that the procedure is technically difficult to perform. Even among experienced endourologists, prolonged operative time and difficulties in the course of work are observed (Cornu et al 2015; Kim et al 2013; Elzayat 2007). The learning curve is defined as "The time/number of procedures required for a surgeon to begin performing a procedure independently and with satisfactory results" (Subramonian et al 2004). After this initial period, the operator gains experience allowing for a reduction in operative time, a reduction in complication rates, and an improvement in functional outcomes. The learning curve depends on many factors - the skills of the surgeon, his anatomical knowledge, the nature of the procedure, the frequency of performing the procedure for a given period, the individuality of the patient, etc. (Valsamis et al 2018).

According to Tan and colleagues, between 20 and 30 procedures on a moderately enlarged gland (about 50ml) are required for to gain initial experience (Tan et al. 2003). Similar recommendations were published by El Hakim and Elhilali based on their 2002 study (El Hakim et Elhilali, 2002). In this study, enucleation was performed by a senior resident on 27 patients under the supervision of an experienced HoLEP surgeon. In the first 15 patients, the resident performed an average of 85% of the operation, with the supervising surgeon stepping in at any difficulty. The two most difficult technical steps are the initial apical dissection and the incision of the remaining antero-apical mucosal attachment of the lateral lobes. The last 12 patients were operated on entirely by the trainee physician without the intervention of the supervising surgeon. There was no difference in operative time or other operative variables between the first 15 and the next 12 patients, or a difference in postoperative outcomes or complications compared with patients treated by an experienced surgeon. The authors concluded that although HoLEP is technically more challenging than TURP, with close observation and feedback from an experienced surgeon, the trainee can gain confidence in the procedure after 10–15 cases.

Different studies describe the learning curve using different parameters. According to Brunckhorst et al., taking into account the efficacy of enucleation and morcellation, a plateau is reached around the sixtieth case (Brunckhorst et al. 2015). According to Placer, this result is achieved in about 50–70 cases, based on a cohort of 253 cases (Placer et al 2009). It should be noted that these cases were carried out without the presence of a mentor. El-Hakim et al. published the results of the first 27 cases of an inexperienced urologist performed under the supervision of an experienced surgeon. According to the authors, 20 cases are required for a complete initial adaptation to the method.

Patients in the HoLEP group were operated on by a single urologist with no experience in transurethral resection of the prostate gland. This contingent covers the initial experience of the surgeon, with the first 2 operations performed under the supervision of an experienced laser enucleation mentor. In our experience, between 20 and 30 cases are required to reach satisfactory confidence and achieve reliable postoperative results. To assess the learning curve, we will look at trends for prostate volume, operative time, enucleation time, morcellation time, enucleated tissue weight, enucleation efficiency, and morcellation efficiency.

5.5.1. Total prostate volume – TPV

Although one of the main advantages of HoLEP is the possibility of operating on greatly enlarged glands, the technical implementation of the procedure becomes difficult. As TPV increases, bleeding risk, total operative time, morcellation time, etc. increase. Different authors publish varying average TPV values when describing the learning curve. Bae and colleagues described a mean TPV of 51.6 ml (29–162 ml) for 161 patients (Bae et al 2010) with a trilobal technique. According to their observations, at least 50 cases are needed to achieve basic competence. Elzayat and Elhilali suggested the same number for an initial training period based on 118 patients with a mean TPV of 59.3ml (20–172ml) (Elzayat EA, Elhilali MM. 2006). According to El-Hakim, who described the shortest study period of 20 patients, the mean TPV was 54.8 ml (21–122). In our study, the mean TPV tended to increase until the 97th patient, after which it tended to gradually decrease. The average volume of the gland is 74.02 ml (30–180 ml), and when including the single patient with a TPV of 280 ml, this value increases to 75.39 ml. The data shows that our cohort has a similar TPV range to other publications, but the average is significantly higher. Prostate volume is an indirect marker of operator progression because can vary widely. As operator confidence increases, HoLEP can be performed on increasingly larger glands without increasing operative risks and without compromising functional postoperative outcomes.

5.5.2. Operating time

The operative time is influenced by two groups of factors - on the part of the patient (the volume of the gland, anatomical features, etc.) and on the part of the operator. As the experience of the surgeon increases, a reduction in operative time is observed. At the same time, as experience is gained, as we have already discussed, cases with larger TPVs are also taken on. Brunckhors described a mean operative time of 95.42 minutes (38–240) based on 253 patients with a mean TPV of 95.84 ml (Brunckhors et al 2015). El-Hakim described a mean operative time of 98 min (50–175) (El-Hakim A, Elhilali MM 2002) using the classical technique. Scoffone described an operative time of 63.9 min using the en-bloc technique (Scoffone, CM, Cracco, CM 2016). In our contingent, the average operating time is 47.29 minutes (18–90 minutes). The difference in these values is most likely due to the operative technique used in the other two studies, a three-lobe laser enucleation technique. According to studies comparing en bloc enucleation with the classical technique, a significantly shorter operative time was observed in the first group (Tuccio et al 2021). Analogous to prostate volume, the TPV curve traced chronologically demonstrated a smooth increase until the 90th patient, after which it also marked a smooth decline.

5.5.3. Enucleation time

The time for enucleation depends on the experience of the operator, the size of the prostate gland, the anatomical features of the gland, and the operative technique used. The mean operative time for the HoLEP group in our study was 36.99 min (11–70 min). The learning curve rises smoothly until the 93rd patient, after which it also shows a smooth decline. This largely coincides with the TPV and total operating time curve. According to our analysis, enucleation time correlated unidirectionally and most strongly with enucleated tissue weight ($p<0.01$) and TPV($p<0.01$). El-

Hakim described a mean enucleation time of 48 min (25–255) using a trilobed technique. The same technique was used by Bae and colleagues, describing a mean enucleation time of 61.3 min (10–180 min) (Bae et al 2010). Scoffone, using an en-bloc operative technique, described an enucleation time of 35 minutes (Scoffone, CM, Cracco, CM 2016). Rücker and colleagues described an enucleation time of 31.7 min with the same technique (Rücker et al 2021).

5.5.4. Morcellation time

Morcellation time is the second component of the total operative time. Like enucleation time, it is closely related to the experience of the operator, the weight of the gland, and the technique used. Using the en-bloc technique with early apical release, we observed a mean morcellation time of 4.38 min (1–14.6 min). The curve of the equation rises smoothly until the 100th patient, after which it also shows a smooth decline. El-Hakim described a mean morcellation time of 9 min (2–22 min) using a 3-lobe technique. The same technique was used by Bae and colleagues, describing a mean enucleation time of 12.3 min (2–60 min) (Bae et al 2010). According to our data, enucleation time values were statistically significantly ($p < 0.01$) associated with TPV, operative, and enucleation time. For this reason, most authors present the progression with respect to this parameter in the form of efficiency rather than total morcellation time.

5.5.5. Weight of enucleated tissue

The enucleated tissue weight is the absolute amount of tissue, measured in grams, that is enucleated at the end of the operation. It depends on the TPV and the operating technique. As we have already covered, HoLEP allows maximum radical separation of the prostatic tissue from the capsule. Accordingly, with an increase in TPV, the weight of the enucleated tissue increases. In our study, at a mean TPV of 74.02ml, the mean amount of enucleated tissue was 57.22g. The curve of the equation rises smoothly until the 103rd patient, after which it also shows a smooth decline. The weight of enucleated tissue allows us to calculate the most important indicators for tracking progress in the training period - efficiency of morcellation and enucleation.

5.5.6. Enucleation and morcellation efficiency

Enucleation/morcellation efficiency is defined as grams of tissue enucleated/morcellated per minute. It is also one of the main indicators reflecting the learning curve. It also allows reliable comparison of the effectiveness of different operative techniques. According to our data, the enucleation efficiency is 1.52 g/min (0.67–4.00), and the morcellation efficiency is 14.99 g/min (7.50–30.00). Enucleation efficiency correlated with enucleated tissue weight, TPV, and morcellation time, and weakly with operative time and enucleation time. Morcellation efficiency correlated with only three of the indicators, namely, multi-directionally and most strongly (but moderately in absolute value) with morcellation time, and weakly with operative time and enucleation time. The trend is for a smoother, but permanent, increase, which suggests that they are related to the improvement of the operative technique. Data published by other authors vary widely.

Bae and colleagues performed a three-lobe technique in 161 patients with a mean gland volume of 51.6 ml. According to their data, the average efficiency of enucleation is 0.32 g/min (0.02-1.25 g/min), and of morcellation 1.73 g/min (0.1-7.7 g/min). They describe reaching adequate enucleation efficiency around the 30th case and morcellation efficiency around the 20th case (Bae et al 2010).

Press and his team compared the classic three-lobe technique with en-bloc enucleation. Patients with similar TPVs were selected - in 49 patients a classic technique was performed, and in 46 en-bloc. Against the backdrop of a shorter operating time, the second technique is also characterized by higher efficiency. According to their results, the second grip was associated with a higher enucleation efficiency - 0.36 g/min and 0.49 g/min respectively at $p = .005$ (Press et al 2022).

Scoffone described en-bloc enucleation in 251 patients with a mean gland volume of 52.5 ml with a total operative time of 63.9 min. Mean enucleation time - 35 min and mean enucleation efficiency of 1.8g/min (0.29–5.5). These values approximate those presented in our patient cohort. The authors did not describe the effectiveness of morcellation (Scoffone, CM, Cracco, CM 2016).

Rücker et al compared en-bloc, bilobed, and trilobed operative methods. The three groups of patients had similar TPV - 77.4 ml, 80.2 ml, and 84.3 ml, respectively. The time for enucleation is significantly shorter with the third method - 31.7 min, 32 min, and 37.7 min, respectively. The enucleation efficiency follows the same trends - 1.82g/min, 1.76g/min, and 1.67g/min. Morcellation efficiency was reported as 7.5 g/min for en-bloc, 7.2 g/min for bilobed, and 7.1 g/min for trilobed technique (Rücker et al 2021).

6. CONCLUSIONS

For each of the assigned tasks, we can present the following conclusions based on the of the presented data:

General observations from the studied contingent:

• HoLEP is applicable to all patients, regardless of age group

• Preoperative PSA is closely associated with the size of the gland and the patient's age

• Postoperative drop in hemoglobin was significantly less in the HoLEP group

• Catheterization time and hospital stay were significantly shorter in the HoLEP group

Task 1. To study and compare over time the effectiveness of the operative method (HoLEP) in terms of IPSS score and improved indicators of uroflowmetry:

● HoLEP allows efficient and permanent reduction of prostate symptoms related to BPH;

● Regardless of the severity of the preoperative symptoms, a permanent improvement is observed in the postoperative period;

● HoLEP shows superiority over TURP in terms of postoperative IPSS, especially in long-term follow-up;

● Functional results after HoLEP are superior to those after TURP;

● After HoLEP, an immediate and sustained improvement in Qmax was observed at long-term follow-up;

● Postoperative results regarding IPSS and Qmax have a weak correlation with surgeon experience - ie. the effectiveness of the procedure is already present in the early phase of the learning curve;

● HoLEP is characterized by a shorter time for hospitalization, catheterization and a lower drop in serum hemoglobin values.

Task 2. To establish the risks of complications intraoperatively and postoperatively in the long term:

● 90% of patients are without complications, and in the HoLEP group their relative share is slightly higher;

● The difference in the frequency of complications between the two operative methods is statistically insignificant;

● The most common complication “stress incontinence”, for example, occurred in 3.3% of patients in the sample, followed by “revision due to hematuria” in 2%;

● En bloc enucleation with early apical dissection is characterized by a lower incidence of stress incontinence in comparison with other techniques.

Task 3. To compare the volume of enucleated tissue compared to the volume of the prostate gland determined by transrectal ultrasound:

● HoLEP is an operative method that has no restrictions on the size of the gland;
● During HoLEP, a greater percentage of tissue grows in comparison with the initial one - 77.3% compared to 49.82% in TURP;
● HoLEP is a more radical method compared to TURP, because it removes a larger amount of the adenoma.

Task 4. To describe the learning curve and the change in statistics after technique refinement:

● HoLEP is a procedure that does not require prior practical knowledge of other endoscopic operative techniques for the treatment of BPH;
● The presence of a mentor shortens the learning curve but does not change the postoperative results;
● As the experience of the operator increases, the average prostate volume of the operated contingent increases;
● The operative time increases in direct proportion to the increase in the volume of the prostate gland, until reaching about ⅔ of the learning curve, after which a plateau occurs;
● Similar to operative time, enucleation and morcellation times are directly dependent on the size of the gland, and to a lesser extent on the experience of the operator. This becomes especially apparent in the last ⅓ of the learning curve;
● The efficiency of enucleation and morcellation are the only factors that are related to the improvement of the operative technique.

7. CONTRIBUTIONS

1. For the first time in our literature, postoperative results related to en-bloc laser enucleation of the prostate gland with early apical release are presented;

2. We described in detail the technical implementation of the operative procedure in order to enrich the collective urological knowledge in our country;

3. Statistical data are presented that enrich the world literature regarding the results of innovative operative technique;

4. For the first time in Bulgarian urological practice, a thorough comparative analysis of all current endoscopic treatment methods is carried out.

REFERENCES

1. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, Van Kerrebroeck P, Victor A, Wein A. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Urology. 2003 Jan 1;61(1):37-49.

2. Ahyai SA, Gilling P, Kaplan SA, Kuntz RM, Madersbacher S, Montorsi F, Speakman MJ, Stief CG. Meta-analysis of functional outcomes and complications following transurethral procedures for lower urinary tract symptoms resulting from benign prostatic enlargement. European urology. 2010 Sep 1;58(3):384-97.

3. Ahyai SA, Lehrich K, Kuntz RM. Holmium laser enucleation versus transurethral resection of the prostate: 3-year follow-up results of a randomized clinical trial. European urology. 2007 Nov;52(5):1456-64.

4. Akinaga J, García-Sáinz JA, S. Pupo A. Updates in the function and regulation of α1-adrenoceptors. British journal of pharmacology. 2019 Jul;176(14):2343-57.

5. Al Khayal AM, Balaraj FK, Alferayan TA, Alrabeeah KA, Abumelha SM. Current surgical procedures for benign prostatic hyperplasia and impression of new surgical modalities. Urology Annals. 2021 Apr;13(2):95.

6. Alawad AA, Younis FH, Eltoum AM, Abdelgani SA. Serum prostate-specific antigen as a predictor of prostate volume in Sudanese patients with benign prostatic hyperplasia. Age (year). 2014;51(61):62-72.

7. Ali A, Du Feu A, Oliveira P, Choudhury A, Bristow RG, Baena E. Prostate zones and cancer: lost in transition? Nature Reviews Urology. 2022 Feb;19(2):101-15.

8. Andersson KE, Gratzke C. Pharmacology of α1-adrenoceptor antagonists in the lower urinary tract and central nervous system. Nature Clinical Practice Urology. 2007 Jul;4(7):368-78.

9. Arai Y, Kaiho Y, Takei M, Nonomura K, Baba S, Habuchi T, Matsuda T, Takahashi S, Igawa M, Nakagawa H. Burden of male stress urinary incontinence: a survey among urologists in Japan. International journal of urology. 2009 Nov;16(11):915-7.

10. Assmus MA, Large T, Lee MS, Agarwal DK, Rivera ME, Krambeck AE. Same-day discharge following holmium laser enucleation in patients assessed to have large gland prostates (≥ 175 cc). Journal of endourology. 2021 Sep 1;35(9):1386-92.

11. Ayala AG, Ro JY, Babaian R, Troncoso P, Grignon DJ. The prostatic capsule: does it exist? Its importance in the staging and treatment of prostatic carcinoma. Am J Surg Pathol. 1989 Jan;13(1):21-7.

12. Bach, T., et al. Aquablation of the prostate: single-center results of a non-selected, consecutive patient cohort. World J Urol, 2019. 37: 1369.

13. Bae J, Oh SJ, Paick JS. The learning curve for holmium laser enucleation of the prostate: a single-center experience. Korean journal of urology. 2010 Oct 1;51(10):688-93.

14. Bansal A, Sankhwar S, Kumar M, Jhanwar A, Purkait B, Aeron R, Goel S. Holmium Laser vs Monopolar Electrocautery Bladder Neck Incision for Prostates Less Than 30 Grams: A Prospective Randomized Trial. Urology. 2016 Jul 1; 93:158-63.

15. Barry MJ, Fowler Jr FJ, O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK, Cockett AT, Measurement Committee of the American Urological Association. The American Urological Association symptom index for benign prostatic hyperplasia. The Journal of urology. 1992 Nov 1;148(5):1549-57.

16. Belanger A, Candas B, Dupont A, Cusan L, Diamond P, Gomez JL, Labrie F. Changes in serum concentrations of conjugated and unconjugated steroids in 40-to 80-year-old men. The Journal of Clinical Endocrinology & Metabolism. 1994 Oct 1;79(4):1086-90.

17. Beltran, miguel, et al. lba01-05 surgical treatment of lower urinary tract symptoms due to benign prostatic enlargement by holmium laser enucleation of the prostate versus transurethral resection of the prostate and open adenomectomy. the journal of urology, 2022, 207.supplement 5: e1037.

18. Best SL, Nakada SY, editors. Minimally Invasive Urology: An Essential Clinical Guide to Endourology, Laparoscopy, LESS and Robotics. Springer Nature; 2019 Dec 3.

19. Bhavsar, Anil, and Sadhna Verma. "Anatomic imaging of the prostate." BioMed research international 2014 (2014).

20. Bilhim T, Pisco JM, Furtado A, Casal D, Pais D, Pinheiro LC, O'Neill JE. Prostatic arterial supply: demonstration by multirow detector angio CT and catheter angiography. European radiology. 2011 May;21(5):1119-26.

21. Bosch R, Abrams P, Cotterill N, Gotoh M, Nitti V, Novara G, Oh SJ, Turner B. Lower Urinary Tract Symptoms in Men (Male LUTS): Etiology, Patient Assessment and Predicting Outcome from Therapy. Male Lower Urinary Tract Symptoms (LUTS), An International Consultation on Male LUTS.

22. Bostwick D. The Pathology of Benign Prostatic Hyperplasia. Kirby P, McConnell J, Fitzpatrick J, editors. London Isis Medical Media 2002

23. Boyle P. New insights into the epidemiology and natural history of benign prostatic hyperplasia. Prog Clin Biol Res. 1994; 386:3-18.

24. Brunckhorst O, Ahmed K, Nehikhare O, Marra G, Challacombe B, Popert R. Evaluation of the learning curve for holmium laser enucleation of the prostate using multiple outcome measures. Urology. 2015 Oct 1;86(4):824-9.

25. Capitan C, Blazquez C, Martin MD, Hernandez V, de la Pena E, Llorente C. GreenLight HPS 120-W laser vaporization versus transurethral resection of the prostate for the treatment of lower urinary tract symptoms due to benign prostatic hyperplasia: a randomized clinical trial with 2-year follow-up. Eur Urol. 2011;60(4):734–9.

26. Chapple CR, Cardozo L, Nitti VW, Siddiqui E, Michel MC. Mirabegron in overactive bladder: a review of efficacy, safety, and tolerability. Neurourology and urodynamics. 2014 Jan;33(1):17-30.

27. Chapple CR, Nazir J, Hakimi Z, Bowditch S, Fatoye F, Guelfucci F, Khemiri A, Siddiqui E, Wagg A. Persistence and adherence with mirabegron versus antimuscarinic agents in patients with overactive bladder: a retrospective observational study in UK clinical practice. European urology. 2017 Sep 1;72(3):389-99.

28. Chapple CR, Yamanishi T, Chess-Williams R. Muscarinic receptor subtypes and management of the overactive bladder. Urology. 2002 Nov 1;60(5):82-8.

29. Chen S, Zhu L, Cai J, Zheng Z, Ge R, Wu M, Deng Z, Zhou H, Yang S, Wu W, Liao L. Plasmakinetic enucleation of the prostate compared with open prostatectomy for prostates larger than 100 grams: a randomized noninferiority controlled trial with long-term results at 6 years. European urology. 2014 Aug 1;66(2):284-91.

30. Chen YB, Chen Q, Wang Z, Peng YB, Ma LM, Zheng DC, Cai ZK, Li WJ, Ma LH. A prospective, randomized clinical trial comparing plasmakinetic resection of the prostate with holmium laser enucleation of the prostate based on a 2-year followup. The Journal of urology. 2013 Jan;189(1):217-22.

31. Chen Z, Miao L, Gao X, Wang G, Xu Y. Effect of obesity and hyperglycemia on benign prostatic hyperplasia in elderly patients with newly diagnosed type 2 diabetes. International journal of clinical and experimental medicine. 2015;8(7):11289.

32. Chin PT, Bolton DM, Jack G, Rashid P, Thavaseelan J, Yu RJ, Roehrborn CG, Woo HH. Prostatic urethral lift: two-year results after treatment for lower urinary tract symptoms secondary to benign prostatic hyperplasia. Urology. 2012 Jan 1;79(1):5-11.

33. Chiruvella M, Enganti B, Bendigeri MT, Ghouse SM, Ragoori D, Reddy P. Transurethral enucleation with bipolar energy (TUEB): AINU technique and short-term outcomes. Urology. 2018 Dec 1; 122:147-51.

34. Cho KJ, Kim HS, Koh JS, Han SB, Kim SH, Kim HW, Cho SY, Kim JC. Preoperative factors affecting postoperative early quality of life during the learning curve of holmium laser enucleation of the prostate. International neurourology journal. 2013 Jun;17(2):83.

35. Cho KJ, Koh JS, Choi JB, Kim JC. Factors associated with early recovery of stress urinary incontinence following holmium laser enucleation of the prostate in patients with benign prostatic enlargement. Int Neurourol J 2018; 22:200-5

36. Choo MS, Lee HE, Bae J, Cho SY, Oh SJ. Transurethral surgical anatomy of the arterial bleeder in the enucleated capsular plane of enlarged prostates during holmium laser enucleation of the prostate. International Neurourology Journal. 2014 Sep;18(3):138.

37. Chute CG, Panser LA, Girman CJ, Oesterling JE, Guess HA, Jacobsen SJ, Lieber MM. The prevalence of prostatism: a population-based survey of urinary symptoms. The Journal of urology. 1993 Jul 1;150(1):85-9.

38. Cilotti A, Danza G, Serio M. Clinical application of 5α-reductase inhibitors. Journal of endocrinological investigation. 2001 Mar;24(3):199-203.

39. Cornu JN, Ahyai S, Bachmann A, de la Rosette J, Gilling P, Gratzke C, McVary K, Novara G, Woo H, Madersbacher S. A systematic review and meta-analysis of functional outcomes and complications following transurethral procedures for lower urinary tract symptoms resulting from benign prostatic obstruction: an update. European urology. 2015 Jun 1;67(6):1066-96.

40. Coyne KS, Wein AJ, Tubaro A, Sexton CC, Thompson CL, Kopp ZS, Aiyer LP. The burden of lower urinary tract symptoms: evaluating the effect of LUTS on health-related quality of life, anxiety and depression: EpiLUTS. BJU international. 2009 Apr; 103:4-11.

41. Cynk M. Holmium laser enucleation of the prostate: a review of the clinical trial evidence. Therapeutic Advances in Urology. 2014 Apr;6(2):62-73.

42. Djavan B, Fong YK, Harik M, Milani S, Reissigl A, Chaudry A, Anagnostou T, Bagheri F, Waldert M, Kreuzer S, Fajkovic H. Longitudinal study of men with mild symptoms of bladder outlet obstruction treated with watchful waiting for four years. Urology. 2004 Dec 1;64(6):1144-8.

43. Dmochowski RR, Staskin DR, Duchin K, Paborji M, Tremblay TM. Clinical safety, tolerability and efficacy of combination tolterodine/pilocarpine in patients with overactive bladder. International Journal of Clinical Practice. 2014 Aug;68(8):986-94.

44. Drobnis EZ, Nangia AK. 5α-Reductase inhibitors (5ARIs) and male reproduction. Impacts of Medications on Male Fertility. 2017:59-61.

45. Dusing MW, Krambeck AE, Terry C, Matlaga BR, Miller NL, Humphreys MR, Gnessin E, Lingeman JE. Holmium laser enucleation of the prostate: efficiency gained by experience and operative technique. The Journal of urology. 2010 Aug;184(2):635-40.

46. Eglen RM. Muscarinic receptor subtype pharmacology and physiology. Progress in medicinal chemistry. 2005 Jan 1; 43:105-36.

47. El-Hakim A, Elhilali MM. Holmium laser enucleation of the prostate can be taught: the first learning experience. BJU international. 2002 Dec;90(9):863-9.

48. Elmansy HM, Kotb A, Elhilali MM. Holmium laser enucleation of the prostate: long-term durability of clinical outcomes and complication rates during 10 years of followup. J Urol 2011; 186:1972-1976

49. Elmansy HM, Kotb A, Elhilali MM. Is there a way to predict stress urinary incontinence after holmium laser enucleation of the prostate? J Urol. 2011; 186:1977–81.

50. Elshal AM, Soltan M, El-Tabey NA, Laymon M, Nabeeh A. Randomised trial of bipolar resection vs holmium laser enucleation vs Greenlight laser vapo-enucleation of the prostate for treatment of large benign prostate obstruction: 3-years outcomes. BJU international. 2020 Dec;126(6):731-8.

51. Eltabey MA, Sherif H, Hussein AA. Holmium laser enucleation versus transurethral resection of the prostate. Can J Urol 2010; 17:5447–5452.

52. Elzayat EA, Elhilali MM. Holmium laser enucleation of the prostate (HoLEP): the endourologic alternative to open prostatectomy. European urology. 2006 Jan 1;49(1):87-91.

53. Elzayat EA, Habib EI, Elhilali MM. Holmium laser enucleation of prostate for patients in urinary retention. Urology. 2005 Oct 1;66(4):789-93.

54. Elzayat EA, Habib EI, Elhilali MM. Holmium laser enucleation of the prostate: a size-independent new “gold standard”. Urology. 2005 Nov 1;66(5):108-13.

55. Endo F, Shiga Y, Minagawa S, Iwabuchi T, Fujisaki A, Yashi M, Hattori K, Muraishi O. Anteroposterior dissection HoLEP: a modification to prevent transient stress urinary incontinence. Urology. 2010 Dec 1;76(6):1451-5.

56. Enikeev D, Glybochko P, Rapoport L, Snurnitsyna O, Potoldykova N, Novoselova T, Laukhtina E, Taratkin M, Margulis V. Need for upper urinary tract stenting in cases of ureteral orifice injury during laser enucleation of the prostate. International Urology and Nephrology. 2018 Dec;50(12):2173-7.

57. Eredics K, Wachabauer D, Röthlin F, Madersbacher S, Schauer I. Reoperation rates and mortality after transurethral and open prostatectomy in a long-term nationwide analysis: have we improved over a decade? Urology. 2018 Aug; 118:152-7.
58. Foo KT. Solving the benign prostatic hyperplasia puzzle. Asian Journal of Urology. 2016 Jan;3(1):6.
59. Fraundorfer MR, Gilling PJ. Holmium: YAG laser enucleation of the prostate combined with mechanical morcellation: preliminary results. European urology. 1998;33(1):69-72.
60. Fraundorfer MR, Gilling PJ. Holmium: YAG laser enucleation of the prostate combined with mechanical morcellation: preliminary results. Eur Urol 1998; 33:69-72.
61. Fried NM, Murray KE. High-power thulium fiber laser ablation of urinary tissues at 1.94 μm. Journal of endourology. 2005 Jan 1;19(1):25-31.
62. Gacci M, Corona G, Salvi M, Vignozzi L, McVary KT, Kaplan SA, Roehrborn CG, Serni S, Mirone V, Carini M, Maggi M. A systematic review and meta-analysis on the use of phosphodiesterase 5 inhibitors alone or in combination with α-blockers for lower urinary tract symptoms due to benign prostatic hyperplasia. European urology. 2012 May 1;61(5):994-1003.
63. Gacci M, Ficarra V, Sebastianelli A, Corona G, Serni S, Shariat SF, Maggi M, Zattoni F, Carini M, Novara G. Impact of medical treatments for male lower urinary tract symptoms due to benign prostatic hyperplasia on ejaculatory function: a systematic review and meta-analysis. The journal of sexual medicine. 2014 Jun 1;11(6):1554-66.
64. Geldof AA. Models for cancer skeletal metastasis: a reappraisal of Batson's plexus. Anticancer research. 1997 May 1;17(3A):1535-9.
65. Gilling PJ, Aho TF, Frampton CM, King CJ, Fraundorfer MR. Holmium laser enucleation of the prostate: results at 6 years. European urology. 2008 Apr 1;53(4):744-9.
66. Gilling PJ, Barber N, Bidair M, Anderson P, Sutton M, Aho T, Kramolowsky E, Thomas A, Cowan B, Roehrborn C. Randomized controlled trial of aquablation versus transurethral resection of the prostate in benign prostatic hyperplasia: one-year outcomes. Urology. 2019 Mar 1; 125:169-73.
67. Gilling PJ, Wilson LC, King CJ, Westenberg AM, Frampton CM, Fraundorfer MR. Long-term results of a randomized trial comparing holmium laser enucleation of the prostate and transurethral resection of the prostate: results at 7 years. BJU international. 2012 Feb;109(3):408-11.
68. Giuliano F, Ückert S, Maggi M, Birder L, Kissel J, Viktrup L. The mechanism of action of phosphodiesterase type 5 inhibitors in the treatment of lower urinary tract symptoms related to benign prostatic hyperplasia. European urology. 2013 Mar 1;63(3):506-16.

69. Gong YG, He DL, Wang MZ, Li XD, Zhu GD, Zheng ZH, Du YF, Chang LS, Nan XY. Holmium laser enucleation of the prostate: a modified enucleation technique and initial results. The Journal of urology. 2012 Apr;187(4):1336-40.

70. Gratzke C, Schlenker B, Seitz M, Karl A, Hermanek P, Lack N, Stief CG, Reich O. Complications and early postoperative outcome after open prostatectomy in patients with benign prostatic enlargement: results of a prospective multicenter study. The Journal of urology. 2007 Apr 1;177(4):1419-22.

71. Greene LF. Transurethral prostatic resection. Greene LF, Segura JW. Transurethral surgery. WB Saunders: Philadelphia, PA; 1979: p 108.

72. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA. Costa F; American Heart Association; National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005Sep. 12;112(17):2735–52.

73. Gu M, Chen YB, Liu C, Wan X, Cai ZK, Chen Q, Wang Z. Comparison of holmium laser enucleation and plasmakinetic resection of prostate: a randomized trial with 72-month follow-up. Journal of Endourology. 2018 Feb 1;32(2):139-43.

74. Hammarsten J, Lindqvist K, Sunzel H. Urethral strictures following transurethral resection of the prostate. The role of the catheter. British journal of urology. 1989 Apr;63(4):397-400.

75. Hardy LA, Wilson CR, Irby PB, Fried NM. Thulium fiber laser lithotripsy in an in vitro ureter model. Journal of Biomedical Optics. 2014 Dec;19(12):128001.

76. Heidar NA, Labban M, Misrai V, Mailhac A, Tamim H, El-Hajj A. Laser enucleation of the prostate versus transurethral resection of the prostate: perioperative outcomes from the ACS NSQIP database. World Journal of Urology. 2020 Nov;38(11):2891-7.

77. Hellwege JN, Stallings S, Torstenson ES, Carroll R, Borthwick KM, Brilliant MH, Crosslin D, Gordon A, Hripcsak G, Jarvik GP, Linneman JG. Heritability and genome-wide association study of benign prostatic hyperplasia (BPH) in the eMERGE network. Scientific reports. 2019 Apr 15;9(1):1-0.

78. Hiramatsu I, Tsujimura A, Soejima M, Yoshiyama A, Nagashima Y, Ishikawa K, Uesaka Y, Nozaki T, Ogishima T, Shirai M, Mitsuhashi I. Tadalafil is sufficiently effective for severe chronic prostatitis/chronic pelvic pain syndrome in patients with benign prostatic hyperplasia. International Journal of Urology. 2020 Jan;27(1):53-7.

79. Hofmann R, Frohme C. Transurethrale Resektion (TURP) und transurethrale Inzision (TUIP) der Prostata. InEndoskopische Urologie 2018 (pp. 61-113). Springer, Berlin, Heidelberg.

80. Holder KG, Galvan B, Knight AS, Ha F, Collins R, Weaver PE, Brandi L, de Riese WT. Possible clinical implications of prostate capsule thickness and glandular epithelial cell density in benign prostate hyperplasia. Investigative and Clinical Urology. 2021 Jul;62(4):423.

81. Holtgrewe HL. Transurethral prostatectomy. Urol Clin North Am. 1995 May;22(2):357-68.94. Hawtrey CE, Williams RD. Historical evolution of transurethral resection at the University of Iowa: Alcock and Flocks. J Urol. 2008;180(1):55–61.

82. Huang SW, Tsai CY, Tseng CS, Shih MC, Yeh YC, Chien KL, Pu YS, Tu YK. Comparative efficacy and safety of new surgical treatments for benign prostatic hyperplasia: systematic review and network meta-analysis. bmj. 2019 Nov 14;367.

83. Jones P, Alzweri L, Rai BP, Somani BK, Bates C, Aboumarzouk OM. Holmium laser enucleation versus simple prostatectomy for treating large prostates: results of a systematic review and meta-analysis. Arab journal of urology. 2016 Mar 1;14(1):50-8.

84. Kaplan SA, Lee JY, Meehan AG, Kusek JW, MTOPS Research Group. Long-term treatment with finasteride improves clinical progression of benign prostatic hyperplasia in men with an enlarged versus a smaller prostate: data from the MTOPS trial. The Journal of urology. 2011 Apr 1;185(4):1369-73.

85. Kim EH, Larson JA, Andriole GL. Management of benign prostatic hyperplasia. Annu Rev Med. 2016 Jan 14;67(1):137-51.

86. Kim M, Piao S, Lee HE, Kim SH, Oh SJ. Efficacy and safety of holmium laser enucleation of the prostate for extremely large prostatic adenoma in patients with benign prostatic hyperplasia. Korean J Urol 2015; 56:218-26.

87. Kobayashi S, Yano M, Nakayama T, Kitahara S. Predictive risk factors of postoperative urinary incontinence following holmium laser enucleation of the prostate during the initial learning period. Int Braz J Urol. 2016; 42:740–6.

88. Koraitim MM. The male urethral sphincter complex revisited: an anatomical concept and its physiological correlate. The Journal of urology. 2008 May;179(5):1683-9.

89. Krambeck AE, Handa SE, Lingeman JE. Experience with more than 1,000 holmium laser prostate enucleations for benign prostatic hyperplasia. J Urol 2010; 183:1105-9.

90. Kravchick S, Bunkin I, Peled R, Yulish E, Ben-Dor D, Kravchenko Y, Cytron S. Patients with elevated serum PSA and indwelling catheter after acute urinary retention: prospective study of 63 patients with 7-year follow-up. Journal of endourology. 2007 Oct 1;21(10):1203-6.

91. Kuntz RM, Ahyai S, Lehrich K, Fayad AM. Transurethral holmium laser enucleation of the prostate versus transurethral electrocautery resection of the prostate: a randomized prospective trial in 200 patients. The Journal of urology. 2004 Sep;172(3):1012-6.
92. Kuntz RM, Lehrich K, Ahyai S. Does perioperative outcome of transurethral holmium laser enucleation of the prostate depend on prostate size? J Endourol. 2004;18(2):183–188.
93. Kuntz RM, Lehrich K, Ahyai SA. Holmium laser enucleation of the prostate versus open prostatectomy for prostates greater than 100 grams: 5-year follow-up results of a randomised clinical trial. European urology. 2008 Jan 1;53(1):160-8.
94. Kuntz RM, Lehrich K. Transurethral holmium laser enucleation versus transvesical open enucleation for prostate adenoma greater than 100 gm.: a randomized prospective trial of 120 patients. The Journal of urology. 2002 Oct;168(4 Part 1):1465-9.
95. Kuntz RM. Current role of lasers in the treatment of benign prostatic hyperplasia (BPH). Eur Urol. 2006;49(6):961–969.
96. La Rosette D, Lim TL. The ICS-'BPH'Study: uroflowmetry, lower urinary tract symptoms and bladder outlet obstruction. British journal of urology. 1998 Nov;82(5):619-23.54. Oelke M, Kirschner-Hermanns R, Thiruchelvam N, Heesakkers J. Can we identify men who will have complications from benign prostatic obstruction (BPO)?: ICI-RS 2011. Neurourology and urodynamics. 2012 Mar;31(3):322-6.
97. Lambert E, Goossens M, Palagonia E, Vollemaere J, Mazzone E, Dell'Oglio P, Pauwels E, De Groote R, D'Hondt F, Mottrie A, De Naeyer G. Changes in serum PSA after endoscopic enucleation of theprostate are predictive for the future diagnosis of prostate cancer. World Journal of Urology. 2021 Jul;39(7):2621-6.
98. Lee SM, Gordon K, McMillan R, Crystal F, Acher P. Day-case holmium laser enucleation of the prostate: feasibility, safety and predictive factors. The Annals of The Royal College of Surgeons of England. 2018 Jul;100(6):475-9.
99. Lenzi A. Epidemiology, diagnosis and treatment of male hypogonadotrophic hypogonadism. J Endocrinol Invest. 2009; 32:934-8.
100. Li M, Qiu J, Hou Q, Wang D, Huang W, Hu C, Li K, Gao X. Endoscopic enucleation versus open prostatectomy for treating large benign prostatic hyperplasia: a meta-analysis of randomized controlled trials. PloS one. 2015 Mar 31;10(3): e0121265.
101. Liao CH, Kuo HC. How to choose first-line treatment for men with predominant storage lower urinary tract symptoms: a prospective randomised comparative study. International Journal of Clinical Practice. 2015 Jan;69(1):124-30.

102. Lim KB. Epidemiology of clinical benign prostatic hyperplasia. Asian journal of urology. 2017 Jul 1;4(3):148-51.

103. Lokeshwar SD, Harper BT, Webb E, et al. Epidemiology and treatment modalities for the management of benign prostatic hyperplasia. Transl Androl Urol. 2019;8(5):529-539.

104. Lourenco T, Armstrong N, N'dow J, Nabi G, Deverill M, Pickard R, Vale L, MacLennan G, Fraser C, McClinton S, Wong S. Systematic review and economic modelling of effectiveness and cost utility of surgical treatments for men with benign prostatic enlargement. Health Technol Assess. 2008 Nov 1;12(35):1-46.

105. Lourenco T, Shaw M, Fraser C, MacLennan G, N'Dow J, Pickard R. The clinical effectiveness of transurethral incision of the prostate: a systematic review of randomised controlled trials. World journal of urology. 2010 Feb;28(1):23-32.

106. MacRae C, Gilling P. How I do it: aquablation of the prostate using the AQUABEAM system. Can J Urol. 2016 Dec 1;23(6):8590-3.

107. Madersbacher S, Marberger M. Is transurethral resection of the prostate still justified? British journal of urology (Print). 1999;83(3):227-37.

108. Madsen PO, Iversen P. A point system for selecting operative candidates. InBenign prostatic hypertrophy Springer, New York, NY.1983 p. 763-765).

109. Mahadevan V. Anatomy of the lower urinary tract. Surgery (Oxford). 2016 Jul 1;34(7):318-25.

110. Malek RS. Contemporary management of the benign obstructive prostate: an overview. Mayo Clin Proc. 1998;73(6):589.

111. Mamoulakis C, Schulze M, Skolarikos A, Alivizatos G, Scarpa RM, Rassweiler JJ, De La Rosette JJ, Scoffone CM. Midterm results from an international multicentre randomised controlled trial comparing bipolar with monopolar transurethral resection of the prostate. European urology. 2013 Apr 1;63(4):667-76.

112. Manjunatha R, Pundarikaksha HP, Madhusudhana HR, Amarkumar J, Hanumantharaju BK. A randomized, comparative, open-label study of efficacy and tolerability of alfuzosin, tamsulosin and silodosin in benign prostatic hyperplasia. Indian journal of pharmacology. 2016 Mar;48(2):134.

113. Matlaga, B. R., & Lingeman, J. E. Ch. Glenn's urologic surgeryPhiladelphia, PA: Wolters Kluwer Lippincott Williams & Wilkins Health 2010. 166–175p

114. Mayer EK, Kroeze SG, Chopra S, Bottle A, Patel A. Examining the 'gold standard': a comparative critical analysis of three consecutive decades of monopolar transurethral resection of the prostate (TURP) outcomes. BJU international. 2012 Dec;110(11):1595-601.

115. Mc Namara K, Alzubaidi H, Jackson JK. Cardiovascular disease as a leading cause of death: how are pharmacists getting involved? Integrated pharmacy research & practice. 2019; 8:1.

116. McConnell JD, Roehrborn CG, Bautista OM, Andriole Jr GL, Dixon CM, Kusek JW, Lepor H, McVary KT, Nyberg Jr LM, Clarke HS, Crawford ED. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. New England Journal of Medicine. 2003 Dec 18;349(25):2387-98.

117. McNicholas TA, Woo HH, Chin PT, Bolton D, Arjona MF, Sievert KD, Schoenthaler M, Wetterauer U, Vrijhof EJ, Gange S, Montorsi F. Minimally invasive prostatic urethral lift: surgical technique and multinational experience. European urology. 2013 Aug 1;64(2):292-9.

118. McVary KT, Roehrborn CG, Avins AL, Barry MJ, Bruskewitz RC, Donnell RF, Foster HE, Gonzalez CM, Kaplan SA, Penson DF, Ulchaker JC. Update on AUA guideline on the management of benign prostatic hyperplasia. The Journal of urology. 2011 May;185(5):1793-803.

119. Michel MC, Gravas S. Safety and tolerability of β3-adrenoceptor agonists in the treatment of overactive bladder syndrome–insight from transcriptosome and experimental studies. Expert opinion on drug safety. 2016 May 3;15(5):647-57.

120. Miernik A, Schoeb DS. "Three horse shoe-like incision" holmium laser enucleation of the prostate: first experience with a novel en bloc technique for anatomic transurethral prostatectomy. World J Urol 2019; 37:523-8

121. Montorsi F, Naspro R, Salonia A, Suardi N, Briganti A, Zanoni M, Valenti S, Vavassori I, Rigatti P. Holmium laser enucleation versus transurethral resection of the prostate: results from a 2-center, prospective, randomized trial in patients with obstructive benign prostatic hyperplasia. The Journal of urology. 2004 Nov;172(5):1926-9.

122. Moody Ja, Lingeman Je. Holmium Laser Enucleation For Prostate Adenoma Greater Than 100 Gm.: Comparison To Open Prostatectomy. The Journal Of Urology. 2001 Feb;165(2):459-62.

123. Nam JK, Kim HW, Lee DH, Han JY, Lee JZ, Park SW. Risk factors for transient urinary incontinence after holmium laser enucleation of the prostate. The world journal of men's health. 2015 Aug 1;33(2):88-94.

124. Naspro R, Suardi N, Salonia A, Scattoni V, Guazzoni G, Colombo R, Cestari A, Briganti A, Mazzoccoli B, Rigatti P, Montorsi F. Holmium laser enucleation of the prostate versus open prostatectomy for prostates> 70 g: 24-month follow-up. European urology. 2006 Sep 1;50(3):563-8.

125. Netto Jr NR, de Lima ML, Netto MR, D'Ancona CA. Evaluation of patients with bladder outlet obstruction and mild international prostate symptom score followed up by watchful waiting. Urology. 1999 Feb 1;53(2):314-6.
126. Nicholson TM, Ricke WA. Androgens and estrogens in benign prostatic hyperplasia: past, present and future. Differentiation. 2011 Nov 1;82(4-5):184-99.
127. Nitti VW, Rosenberg S, Mitcheson DH, He W, Fakhoury A, Martin NE. Urodynamics and safety of the β3-adrenoceptor agonist mirabegron in males with lower urinary tract symptoms and bladder outlet obstruction. The Journal of urology. 2013 Oct;190(4):1320-7.
128. Nomura H, Kawashima H, Masaki S, Hosono TY, Matsumura K, Tamada S, Tanaka T, Nakatani T. Effect of selective estrogen receptor modulators on cell proliferation and estrogen receptor activities in normal human prostate stromal and epithelial cells. Prostate Cancer and Prostatic Diseases. 2009 Dec;12(4):375-81.
129. Oelke M, Bachmann A, Descazeaud A, Emberton M, Gravas S, Michel MC, N'dow J, Nordling J, Jean J. EAU guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. European urology. 2013 Jul 1;64(1):118-40.
130. Oh SJ, Shitara T. Enucleation of the prostate: An anatomical perspective. Andrologia. 2020 Sep;52(8): e13744.
131. Parsons JK, Bergstrom J, Barrett-Connor E. Lipids, lipoproteins and the risk of benign prostatic hyperplasia in community-dwelling men. BJU international. 2008 Feb;101(3):313-8.
132. Parsons JK, Carter HB, Partin AW, Windham BG, Metter EJ, Ferrucci L, Landis P, Platz EA. Metabolic factors associated with benign prostatic hyperplasia. The Journal of Clinical Endocrinology & Metabolism. 2006 Jul 1;91(7):2562-8.
133. Parsons JK, Im R. Alcohol consumption is associated with a decreased risk of benign prostatic hyperplasia. The Journal of urology. 2009 Oct;182(4):1463-8.
134. Parsons JK. Modifiable risk factors for benign prostatic hyperplasia and lower urinary tract symptoms: new approaches to old problems. The Journal of urology. 2007 Aug 1;178(2):395-401.
135. Partin AW, Page WF, Lee BR, Sanda MG, Miller RN, Walsh PC. Concordance rates for benign prostatic disease among twins suggest hereditary influence. Urology. 1994;44(5):646-50.
136. Perera M, Roberts MJ, Doi SA, Bolton D. Prostatic urethral lift improves urinary symptoms and flow while preserving sexual function for men with benign prostatic hyperplasia: a systematic review and meta-analysis. European urology. 2015 Apr 1;67(4):704-13.

137. Placer J, Gelabert-Mas A, Vallmanya F, Manresa JM, Menéndez V, Cortadellas R, Arango O. Holmium laser enucleation of prostate: outcome and complications of self-taught learning curve. Urology. 2009 May 1;73(5):1042-8.
138. Press B, Ghiraldi E, Kim DD, Nair H, Johnson K, Kellner D. “En-Bloc” Enucleation With Early Apical Release Compared to Standard Holmium Laser Enucleation of the Prostate: A Retrospective Pilot Study During the Initial Learning Curve of a Single Surgeon. Urology. 2022 Jan 19.
139. Qian X, Liu H, Xu D, Xu L, Huang F, He W, Qi J, Zhu Y, Xu D. Functional outcomes and complications following B-TURP versus HoLEP for the treatment of benign prostatic hyperplasia: a review of the literature and Meta-analysis. The Aging Male. 2017 Jul 3;20(3):184-91.
140. Reich O, Gratzke C, Bachmann A, Seitz M, Schlenker B, Hermanek P, Lack N, Stief CG, Urology Section of the Bavarian Working Group for Quality Assurance†. Morbidity, mortality and early outcome of transurethral resection of the prostate: a prospective multicenter evaluation of 10,654 patients. The Journal of urology. 2008 Jul;180(1):246-9.
141. Reynard JM. Does anticholinergic medication have a role for men with lower urinary tract symptoms/benign prostatic hyperplasia either alone or in combination with other agents? Current opinion in urology. 2004 Jan 1;14(1):13-6.
142. Rieken M, Ebinger Mundorff N, Bonkat G, Wyler S, Bachmann A. Complications of laser prostatectomy: a review of recent data. World journal of urology. 2010 Feb;28(1):53-62.
143. Rivera ME, Lingeman JE, Krambeck AE. Holmium laser enucleation of the prostate. Journal of Endourology. 2018 May 1;32(S1) :S-7.
144. Roehrborn CG, Barkin J, Siami P, Tubaro A, Wilson TH, Morrill BB, Gagnier RP. Clinical outcomes after combined therapy with dutasteride plus tamsulosin or either monotherapy in men with benign prostatic hyperplasia (BPH) by baseline characteristics: 4-year results from the randomized, double-blind Combination of Avodart and Tamsulosin (CombAT) trial. BJU international. 2011 Mar;107(6):946-54.
145. Roehrborn CG, Boyle P, Nickel JC, Hoefner K, Andriole G. Efficacy and safety of a dual inhibitor of 5-alpha-reductase types 1 and 2 (dutasteride) in men with benign prostatic hyperplasia. Urology. 2002 Sep 1;60(3):434-41.
146. Roehrborn CG, McConnell JO, Bonilla J, Rosenblatt S, Hudson PB, Malek GH, Schellhammer PF, Bruskewitz R, Matsumoto AM, Harrison LH, Fuselier HA. Serum prostate specific antigen is a strong predictor of future prostate growth in men with benign prostatic hyperplasia. The Journal of urology. 2000 Jan;163(1):13-20.

147. Roehrborn CG, Siami P, Barkin J, Damião R, Major-Walker K, Nandy I, Morrill BB, Gagnier RP, Montorsi F, CombAT Study Group. The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4-year results from the CombAT study. European urology. 2010 Jan 1;57(1):123-31.

148. Roehrborn CG. Three months' treatment with the α1-blocker alfuzosin does not affect total or transition zone volume of the prostate. Prostate cancer and prostatic diseases. 2006 Jun;9(2):121-5.

149. Rohrmann S, De Marzo AM, Smit E, Giovannucci E, Platz EA. Serum C-reactive protein concentration and lower urinary tract symptoms in older men in the Third National Health and Nutrition Examination Survey (NHANES III). Prostate 2005;62(1):27–33.

150. Roos NP, Ramsey EW. A population-based study of prostatectomy: outcomes associated with differing surgical approaches. The Journal of urology. 1987 Jun 1;137(6):1184-8.

151. Roos NP, Wennberg JE, Malenka DJ, Fisher ES, McPherson K, Andersen TF, Cohen MM, Ramsey E. Mortality and reoperation after open and transurethral resection of the prostate for benign prostatic hyperplasia. New England Journal of Medicine. 1989 Apr 27;320(17):1120-4.

152. Rücker F, Lehrich K, Böhme A, Zacharias M, Ahyai SA, Hansen J. A call for HoLEP: en-bloc vs. two-lobe vs. three-lobe. World Journal of Urology. 2021 Jul;39(7):2337-45.

153. Ryang SH, Ly TH, Tran AV, Oh SJ, Cho SY. Bipolar enucleation of the prostate—step by step. Andrologia. 2020 Sep;52(8): e13631.

154. Saitta G, Becerra JE, Del Álamo JF, González LL, Elbers JR, Suardi N, Gómez-Sancha F. 'En Bloc'HoLEP with early apical release in men with benign prostatic hyperplasia. World journal of urology. 2019 Nov;37(11):2451-8.

155. Sakakibara R, Yamamoto T, Uchiyama T, Liu Z, Ito T, Yamazaki M, Awa Y, Yamanishi T, Hattori T. Is lumbar spondylosis a cause of urinary retention in elderly women? J Neurol. 2005 Aug;252(8):953-7. EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam 2022. ISBN 978-94-92671-16-5.

156. Saleh AM, FOOLADI MM, PETRO-NUSTAS WA, DWEIK G, ABUADAS MH. Early Detection and Screening for Prostate Cancer. Mintage Journal of Pharmaceutical and Medical Sciences. 2016:1-5.

157. Salonia A, Suardi N, Naspro R, Mazzoccoli B, Zanni G, Gallina A, Bua L, Scattoni V, Rigatti P, Montorsi F. Holmium laser enucleation versus open prostatectomy for benign prostatic hyperplasia: an inpatient cost analysis. Urology. 2006 Aug 1;68(2):302-6.

158. Samir M, Tawfick A, a Mahmoud M, Elawady H, Abuelnaga M, Shabayek M, Tawfeek AM. Two-year follow-up in bipolar transurethral enucleation and resection of the prostate in comparison with bipolar transurethral resection of the prostate in treatment of large prostates. Randomized controlled trial. Urology. 2019 Nov 1; 133:192-8.
159. Sarma AV, Wei JT. Benign prostatic hyperplasia and lower urinary tract symptoms. N Engl J Med 2012;367(3):248–57.
160. Sattar AA, Noël JC, Vanderhaeghen JJ, Schulman CC, Wespes E. Prostate capsule: computerized morphometric analysis of its components. Urology. 1995 Aug 1;46(2):178-81.
161. Schlomm T, Heinzer H, Steuber T, Salomon G, Engel O, Michl U, Haese A, Graefen M, Huland H. Full functional-length urethral sphincter preservation during radical prostatectomy. European urology. 2011 Aug 1;60(2):320-9.
162. Scoffone, CM, Cracco, CM. The en-bloc no-touch holmium laser enucleation of the prostate (HoLEP) technique. World J Urol 2016; 34: 1175–1181.
163. Seki N, Mochida O, Kinukawa N, Sagiyama K, Naito S. Holmium laser enucleation for prostatic adenoma: analysis of learning curve over the course of 70 consecutive cases. The Journal of urology. 2003 Nov;170(5):1847-50.
164. Sellers DJ, Chess-Williams R. Muscarinic agonists and antagonists: effects on the urinary bladder. Muscarinic Receptors. 2012:375-400.
165. Semple JE. Surgical capsule of the benign enlargement of the prostate. Its development and action. Br Med J. 1963; 1:1640–1643.
166. Shah HN, Mahajan AP, Hegde SS, Bansal MB. Peri-operative complications of holmium laser enucleation of the prostate: experience in the first 280 patients, and a review of literature. BJU international. 2007 Jul;100(1):94-101.
167. Shah, HN, et al. Influence of prostate size on the outcome of holmium laser enucleation of the prostate. BJU Int. 2008; 101:1536–1541.
168. Shaikhibrahim Z, Lindstrot A, Ellinger J, Rogenhofer S, Buettner R, Perner S, Wernert N. The peripheral zone of the prostate is more prone to tumor development than the transitionalzone: is the ETS family the key? Molecular medicine reports. 2012 Feb 1;5(2):313-6.
169. Shigemura K, Tanaka K, Yamamichi F, Chiba K, Fujisawa M. Comparison of predictive factors for postoperative incontinence of Holmium laser enucleation of the prostate by the surgeons' experience during learning curve. Int Neurourol J. 2016; 20:59–68.
170. Shigemura K, Yamamichi F, Kitagawa K, Yamashita M, Oka Y, Tanaka H, Fujisawa M. Does surgeon experience affect operative time, adverse events and continence outcomes in

holmium laser enucleation of the prostate? A review of more than 1,000 cases. The Journal of Urology. 2017 Sep;198(3):663-70.

171. Sinanoglu O, Ekici S, Tatar MN, Turan G, Keles A, Erdem Z. Postoperative outcomes of plasmakinetic transurethral resection of the prostate compared to monopolar transurethral resection of the prostate in patients with comorbidities. Urology. 2012 Aug 1;80(2):402-7.

172. Singh DV, Mete UK, Mandal AK, Singh SK. A comparative randomized prospective study to evaluate efficacy and safety of combination of tamsulosin and tadalafil vs. tamsulosin or tadalafil alone in patients with lower urinary tract symptoms due to benign prostatic hyperplasia. The journal of sexual medicine. 2014 Jan 1;11(1):187-96.

173. Skolarikos A, Papachristou C, Athanasiadis G, Chalikopoulos D, Deliveliotis C, Alivizatos G. Eighteen-month results of a randomized prospective study comparing transurethral photoselective vaporization with transvesical open enucleation for prostatic adenomas greater than 80 cc. Journal of endourology. 2008 Oct 1;22(10):2333-40.

174. Sögütdelen E, Haberal HB, Guliyev F, Akdogan B. Urethral stricture is an unpleasant complication after prostate surgery: a critical review of current literature. Journal of Urological Surgery. 2016 Mar 1;3(1):1.

175. Stravodimos KG, Petrolekas A, Kapetanakis T, Vourekas S, Koritsiadis G, Adamakis I, Mitropoulos D, Constantinides C. TRUS versus transabdominal ultrasound as a predictor of enucleated adenoma weight in patients with BPH. International urology and nephrology. 2009 Dec;41(4):767-71

176. Subramonian K, Muir G. The 'learning curve'in surgery: what is it, how do we measure it and can we influence it?. BJU international. 2004 Jun;93(9):1173-4.

177. Sun N, Fu Y, Tian T, Gao J, Wang Y, Wang S, An W. Holmium laser enucleation of the prostate versus transurethral resection of the prostate: a randomized clinical trial. International urology and nephrology. 2014 Jul;46(7):1277-82.

178. Tan A, Liao C, Mo Z, Cao Y. Meta-analysis of holmium laser enucleation versus transurethral resection of the prostate for symptomatic prostatic obstruction. Journal of British Surgery. 2007 Oct;94(10):1201-8.

179. Tan AH, Gilling PJ, Kennett KM, Frampton C, Westenberg AM, Fraundorfer MR. A randomized trial comparing holmium laser enucleation of the prostate with transurethral resection of the prostate for the treatment of bladder outlet obstruction secondary to benign prostatic hyperplasia in large glands (40 to 200 grams). The Journal of urology. 2003 Oct;170(4 Part 1):1270-4.

180. Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, Lieber MM, Cespedes RD, Atkins JN, Lippman SM, Carlin SM. The influence of finasteride on the development of prostate cancer. New England journal of medicine. 2003 Jul 17;349(3):215-24.

181. Tubaro A, Batista JE, Nitti VW, Herschorn S, Chapple CR, Blauwet MB, Siddiqui E, Huang M, Oelke M. Efficacy and safety of daily mirabegron 50 mg in male patients with overactive bladder: a critical analysis of five phase III studies. Therapeutic advances in urology. 2017 Jun;9(6):137-54.

182. Tuccio A, Grosso AA, Sessa F, Salvi M, Tellini R, Cocci A, Viola L, Verrienti P, Di Camillo M, Di Maida F, Mari A. En-bloc holmium laser enucleation of the prostate with early apical release: are we ready for a new paradigm?. Journal of Endourology. 2021 Nov 1;35(11):1675-83.

183. Turner-Warwick R. A urodynamic review of bladder outlet obstruction in the male and its clinical implications. Urol Clin North Am. 1979;6(1):171–192.

184. Valsamis EM, Chouari T, O'Dowd-Booth C, Rogers B, Ricketts D. Learning curves in surgery: variables, analysis and applications. Postgraduate medical journal. 2018 Sep 1;94(1115):525-30.

185. van Dijk MM, de la Rosette JJ, Michel MC. Effects of α1-adrenoceptor antagonists on male sexual function. Drugs. 2006 Feb;66(3):287-301.

186. Vargas HA, Akin O, Franiel T, Goldman DA, Udo K, Touijer KA, Reuter VE, Hricak H. Normal central zone of the prostate and central zone involvement by prostate cancer: clinical and MR imaging implications. Radiology. 2012 Mar;262(3):894.

187. Varma M, Morgan JM. The weight of the prostate gland is an excellent surrogate for gland volume. Histopathology. 2010 Jul;57(1):55-8.

188. Vavassori, I, Valenti, S, Naspro, R, et al. Three-year outcome following holmium laser enucleation of the prostate combined with mechanical morcellation in 330 consecutive patients. Eur Urol 2008; 53: 599–604.

189. Vela-Navarrete R, Alcaraz A, Rodríguez-Antolín A, Minana Lopez B, Fernández-Gómez JM, Angulo JC, Castro Diaz D, Romero-Otero J, Brenes FJ, Carballido J, Molero García JM. Efficacy and safety of a hexanic extract of Serenoa repens (Permixon®) for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia (LUTS/BPH): systematic review and meta-analysis of randomised controlled trials and observational studies. BJU international. 2018 Dec;122(6):1049-65.

190. Vignozzi L, Gacci M, Cellai I, Morelli A, Maneschi E, Comeglio P, Santi R, Filippi S, Sebastianelli A, Nesi G, Serni S. PDE5 inhibitors blunt inflammation in human BPH: a potential mechanism of action for PDE5 inhibitors in LUTS. The Prostate. 2013 Sep;73(13):1391-402.

191. Vignozzi L, Rastrelli G, Corona G, Gacci M, Forti G, Maggi M. Benign prostatic hyperplasia: a new metabolic disease?. Journal of endocrinological investigation. 2014 Apr;37(4):313-22.

192. Vuichoud C, Loughlin KR. Benign prostatic hyperplasia: epidemiology, economics and evaluation. Can J Urol. 2015 Oct 1;22(Suppl 1):1-6.

193. Wallner, C., Dabhoiwala, N. F., DeRuiter, M. C., & Lamers, W. H. (2009). The anatomical components of urinary continence. European urology, 55(4), 932-944.

194. Walz J, Epstein JI, Ganzer R, Graefen M, Guazzoni G, Kaouk J, Menon M, Mottrie A, Myers RP, Patel V, Tewari A. A critical analysis of the current knowledge of surgical anatomy of the prostate related to optimisation of cancer control and preservation of continence and erection in candidates for radical prostatectomy: an update. European urology. 2016 Aug 1;70(2):301-11.

195. Wang Z, Xiao X, Ge R, Li J, Johnson CW, Rassoulian C, Olumi AF. Metformin inhibits the proliferation of benign prostatic epithelial cells. PloS one. 2017 Mar 2;12(3): e0173335.

196. Welk B, McArthur E, Fraser LA, Hayward J, Dixon S, Hwang YJ, Ordon M. The risk of fall and fracture with the initiation of a prostate-selective α antagonist: a population based cohort study. BMJ. 2015 Oct 26;351.

197. Westhofen T, Weinhold P, Kolb M, Stief CG, Magistro G. Evaluation of holmium laser enucleation of the prostate learning curves with and without a structured training programme. Current Urology. 2020;14(4):191-9.

198. Williams AM, Simon I, Landis PK, Moser C, CHRISTENS-BARRY WI, Carter HB, Metter EJ, Partin AW. Prostatic growth rate determined from MRI data: age-related longitudinal changes. Journal of andrology. 1999 Jul 8;20(4):474-80.

199. Wilson LC, Gilling PJ, Williams A, Kennett KM, Frampton CM, Westenberg AM, Fraundorfer MR. A randomised trial comparing holmium laser enucleation versus transurethral resection in the treatment of prostates larger than 40 grams: results at 2 years. european urology. 2006 Sep 1;50(3):569-73.

200. Woo H, Thangasamy I, Chalasani V. Photoselective vaporization with the green light laser vs transurethral resection of the prostate for treating benign prostate hyperplasia: a systematic review and meta-analysis. BJU international. 2013 Apr;111(4): E137-.

201. Zhang K, Sun D, Zhang H, Cao Q, Fu Q. Plasmakinetic vapor enucleation of the prostate with button electrode versus plasmakinetic resection of the prostate for benign prostatic enlargement> 90 ml: perioperative and 3-month follow-up results of a prospective, randomized clinical trial. Urologia Internationalis. 2015;95(3):260-4.
202. Zhang Y, Yuan P, Ma D, Gao X, Wei C, Liu Z, Li R, Wang S, Liu J, Liu X. Efficacy and safety of enucleation vs. resection of prostate for treatment of benign prostatic hyperplasia: a meta-analysis of randomized controlled trials. Prostate Cancer Prostatic Dis. 2019 Dec;22(4):493-508.
203. Zhao Z, Zeng G, Zhong W, Mai Z, Zeng S, Tao X. A prospective, randomised trial comparing plasmakinetic enucleation to standard transurethral resection of the prostate for symptomatic benign prostatic hyperplasia: three-year follow-up results. European urology. 2010 Nov 1;58(5):752-8.
204. Zheng SB, Liu CX, Xu YW. Application of intracavitary retrograde dissection in transurethral vaporization resection of the prostate. Di 1 jun yi da xue xue bao= Academic Journal of the First Medical College of PLA. 2005 Jun 1;25(6):734-5.

Publications and scientific annaousments related to the topic of the dissertation

1. Георги Георгиев, Горан Деримачковски, Борислав Божков; Първи български опит с 50 случая на Ен-блок холмиум лазер простатна енуклеация с ранно апикално освобождаване; 2020; сп.Мединфо; бр.10, стр.72-73

2. Fernando Gomez Sancha , Georgi Georgiev, Vanesa Cuadros; Common trend: move to enucleation-Is there a case for GreenLight enucleation? Development and description of the technique; World J Urol. 2015; 33(4): 539-547

3. Георги Георгиев, Боян Атанасов; Първи български опит със сто и петдесет случая на ен-блок холмиум лазер простатна енуклеация с ранно апикално освобождаване; сп.Клинична урология Фондация Урология и Андрология; том 1, бр.2/2021; стр.5-10