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ФГАОУ ВО ПЕРВЫЙ МОСКОВСКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ ИМЕНИ И.М. СЕЧЕНОВА МИНИСТЕРСТВА ЗДРАВООХРАНЕНИЯ РОССИЙСКОЙ ФЕДЕРАЦИИ (СЕЧЕНОВСКИЙ УНИВЕРСИТЕТ)

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117485 RUSSIAN FEDERATION, MOSCOW,
OBRUCHEVA STR., 30/1, P. 2
TEL. (FAX): +7(495) 334-43-88
E-MAIL: UROLOGY@BIONIKA-MEDIA.RU

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ООО "БИОНИКА МЕДИА"

CONTENTS

M.I. Kogan[1], V.L. Medvedev[2,3], Yu.L. Naboka[4], S.N. Ivanov[1], G.A. Palaguta[2,3], M.V. Arkhipenko[3]

MICROBIAL SPECTRUM OF URINE BEFORE AND AFTER TRANSURETHRAL PROCEDURES ON THE PROSTATE IN PATIENTS WITH POSTOPERATIVE URINARY TRACT INFECTIONS

[1]Department of Urology and Human Reproductive Health with the course of pediatric urology and andrology, FGBOU VO Rostov State Medical University of the Ministry of Health of the Russian Federation, Rostov-on-Don, Russia;
[2]FGBOU VO Kuban State Medical University of the Ministry of Health of the Russian Federation, Krasnodar, Russia;
[3]Scientific and Research Institute of the Regional Clinical Hospital №1 named after prof. S.V. Ochapovsky, Krasnodar, Russia;
[4]Department of Microbiology and Virology No.1, FGBOU VO Rostov State Medical University of the Ministry of Health of the Russian Federation, Rostov-on-Don, Russia

Corresponding author: S.N. Ivanov – Ph.D. student at the FGBOU VO Rostov State Medical University of the Ministry of Health of the Russian Federation, Rostov-on-Don, Russia; e-mail: ivanovsergey19@gmail.com

Aim. To evaluate the microbial spectrum of urine before and after transurethral resection of prostate (TURP) in patients with postoperative infectious complications.

Materials and methods. A single-center retrospective observational study between 2016 and 2023 was carried out. Patients who developed urinary tract infections (UTIs) after mono- or bipolar TURP during the hospitalization were included. Bacteriological examination of urine obtained before procedure and after the manifestation of UTI was done in accordance with the Guidelines. In the presence of suprapubic or urethral catheter, the drainage was previously replaced with further microbiological study. The level of significant bacteriuria was ⩾ 103 CFU/ml, with a level of significant leukocyturia ⩾ 10 per field of view. Statistical analysis was carried out using IBM SPSS Statistics 23.0.

Results. Bacteriuria was not detected in 77.9% of cases of UTIs after TURP. At the same time, according to the preoperative examination in 76.2% of these patients, there was no bacteriuria ⩾ 103 CFU/ml. In 17 of 122 men (13.9%) without bacteriuria at baseline, microorganisms were isolated after the development of UTIs. A decrease in bacteriuria level was noted in only 19 of 29 patients (65.5%) who had a positive urine culture before TURP. Only in 4 out of 10 cases of persistent bacteriuria the same microorganism was isolated, while in the remaining 6 cases the initial spectrum was replaced by another bacteria.

Conclusion. Our data indicate a low detection rate of microorganisms in urine of patients with UTIs after TURP using a standard bacteriological study. The data indicate that the standard antibiotic prophylaxis regimen and ongoing anti-infective measures are partly effective in reducing a narrow range of aerobic microorganisms detected preoperatively using standard media, which, however, does not exclude the development of an infectious process.

K e y w o r d s: *bacteriuria; infectious complications; transurethral procedure on the prostate, urinary tract infections*

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Introduction. Infectious complications of transurethral procedures for benign prostatic hyperplasia (BPH) represent a negative component of their safety profile [1]. The main cause for the development of infectious complications aside from altered reactivity of the macroorganism, which can be a result of medical manipulations and surgical aggression, is a change in the microbiota in general and the urinary system in particular [2, 3]. The assessment of the microbial factor of urine and urinary tract in the implementation of preventive measures with an assessment of the antibacterial resistance of microorganisms is of relevance. Understanding the changes of the microbial spectrum in physiologic conditions and under pathology is the most important component of an effective strategy for managing the risks of infectious complications, but the current standards of bacteriological examination of urine do not provide reliable and comprehensive information about the microbiota.

Aim. To evaluate the microbial spectrum of urine before and after transurethral surgery for BPH in patients with postoperative infectious complications.

Materials and methods. A single-center retrospective observational study was carried out from January 2016 to February 2023. Inclusion criteria were a presence of indications for surgical treatment of BPH, prostate volume of 30–80 cc, no history of sexually transmitted diseases and urinary tract infections at the time and at least 1 month before hospitalization, no history of antibacterial therapy at least 1 month prior to surgery, no prostate cancer, informed consent to participate in the study. The study included patients who underwent mono- or bipolar transurethral resection of the prostate (TURP) and who developed urinary tract and genital infections during hospitalization. Patients who were confirmed to have prostate cancer according to postoperative histological examination were excluded. If there were no

significant bacteriuria (⩾10^3 CFU/ml), patients received antibacterial prophylaxis with a single administration of second- or third-generation cephalosporins, inhibitor-protected aminopenicillins, or aminoglycosides for 1 hour prior to intervention. In case of significant bacteriuria at baseline, antimicrobial therapy was started 48 hours before surgery and the efficiency of the therapy was confirmed by repeated bacteriological examination of urine prior to intervention.

The antibacterial prophylaxis was stopped no later than 24 hours postoperatively. All patients with an elevated total PSA level (>4 ng/ml), as well as abnormalities at digital rectal examination or magnetic resonance imaging, underwent prostate biopsy at least 2 months before transurethral prostate surgery. Urine collection before surgery and in case of development of infectious complications, as well as bacteriological examination of urine, were performed in accordance with the Clinical Guidelines of the Russian Federation [4]. In the absence of urinary drainage, midstream urine was collected in a sterile Sterile Uricol container. In patients with cystostomy tube or a urethral catheter, the drainage was first replaced with subsequent urine collection. The results of the bacteriological study were confirmed by mass spectrometry using MALDI Biotyper 3.0 (Bruker Daltonics, USA). The significant bacteriuria was defined as ⩾10^3 CFU/ml and significant leukocyturia as ⩾10 per field. Statistical analysis was performed using statistical processing and visualization environment of IBM SPSS Statistics ver. 23.0.

Results

1) Sample characteristics

The study included 122 patients who developed postoperative infectious complications during hospitalization. The median age was 68 (63; 72) years. 21 (17.2%) men had cystostomy tube at baseline, while 101 (82.8%) patients had no drainage (p<0.05). Only in 3 (2.5%) cases, signs of infection developed earlier than 48 hours after intervention, while in the remaining 119 (97.5%) patients, the infectious process manifested later than the second postoperative day (p<0.05). Clinical manifestations included fever, symptoms of urinary tract infection, ascending pyelonephritis, as well as genital infection, the presence of ⩾10 leukocytes per field in urine.

2) Preoperative spectrum of microorganisms detected in urine of patients with postoperative infectious complications

Bacteriological examination of urine using standard media allowed to detect microorganisms at baseline only in 27 patients (22.1% of cases). Thus, 33 isolates and 95 negative results of urine culture were obtained. The spectrum of isolated microorganisms and CFU levels are presented in table 1. E. faecalis and representatives of Enterobacterales, including *E. coli* and *K. pneumoniae* were most often isolated from urine.

3) Microbial spectrum of urine in patients with infectious complications in the postoperative period

In vast majority of patients with postoperative infectious complications there was no bacteriuria ⩾10^3 CFU/ml at baseline (76.2%). Only 29 (23.8%) men had bacteriuria ⩾10^3 CFU/ml. The spectrum of urine microorganisms is presented in *table 2*. E. faecalis and Enterobacterales representatives (*E. coli, K. pneumoniae, P. rettgeri*) predominated in urine.

4) Comparison of pre- and postoperative bacteriuria in patients with infectious complications of transurethral prostate surgery

The results of the perioperative bacteriological study of urine in 122 patients with postoperative infectious complications are presented in *Fig. 1*. The absence of bacteriuria was noted in 19 (65.5%) of 29 patients who had a positive urine culture at baseline. Among 93patients without bacteriuria before the intervention, no microorganisms were isolated from urine in 76 (81.7%) cases. However, in 17 (18.3%) men, various taxa of microorganisms were detected.

Ten (8.2%) of 122 patients had bacteriuria both before and after the intervention. The results of this part of the study are presented in *table 3*.

A comparative analysis of the pre- and postoperative bacterial spectrum in patients with infectious complications demonstrates negative urine culture in 76.2% of cases before and in 77.9% cases after the intervention (*Fig. 2*). Of the 122 patients, 19 (15.6%) had significant bacteriuria

Table 1

Spectrum of microbial species (⩾ 10^3 CFU/ml)

Microorganisms	N	Rate, %	CFU/ml
Enterococcus faecalis	8	24.3	10^4–10^5
Escherichia coli	8	24.3	10^3–10^5
Klebsiella pneumoniae	3	9.1	10^4–10^5
Pseudomonas aeruginosa	2	6.1	10^3–10^5
Enterococcus faecium	2	6.1	10^4–10^5
Streptococcus agalactiae	2	6.1	10^3
Klebsiella oxytoca	1	3.0	10^5
Morganella morganii	1	3.0	10^5
Providencia rettgeri	1	3.0	10^5
Staphylococcus haemolyticus	1	3.0	10^5
Acinetobacter junii	1	3.0	10^5
Candida glabrata	1	3.0	10^5
Corynebacterium striatum	1	3.0	10^5
Serratia marcescens	1	3.0	10^5
Total number of species	33	100	

Table 2

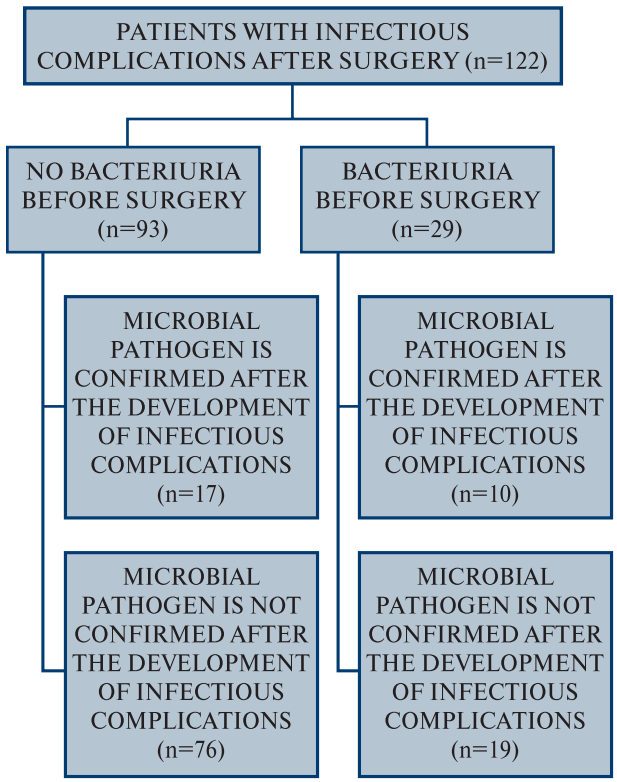
Spectrum of microorganisms isolated from urine preoperatively

Microorganisms	N	Rate, %	CFU/ml
Enterococcus faecalis	11	32.3	10^5
Klebsiella pneumoniae	5	14.7	10^5
Providencia rettgeri	3	9.0	10^5
Escherichia coli	2	5.9	10^3–10^5
Staphylococcus aureus	2	5.9	10^5
Pseudomonas aeruginosa	2	5.9	10^5
Stenotrophomonas maltophilia	2	5.9	10^3–10^5
Morganella morganii	2	5.9	10^4
Proteus mirabilis	1	2.9	10^4
Enterobacter cloacae ssp. cloacae	1	2.9	10^5
Serratia marcescens	1	2.9	10^5
Enterococcus faecium	1	2.9	10^5
Candida albicans	1	2.9	10^5
Total (122)	34	100	

only at baseline, which is 65.5% of the total number of men with initial bacteriuria (29 patients). In 17 (13.9%) of 122 patients with no bacteriuria at baseline, the microbial agent was isolated postoperatively, while in 76 (62.3%) of 122 patients, urine culture was negative both before and after intervention. Only in 4 of 10 patients with bacteriuria before and after surgery, the same microorganism was isolated, while in the remaining 6 cases, there was a change in the microbial spectrum. The combined graph (*Fig. 3*) of the preoperative bacteriuria spectrum and the postoperative microbial spectrum demonstrates the possibilities and key disadvantages of using standard media in bacteriological examination of urine. Thus, the existing standard allows assessing the aerobic cluster of microorganisms in concentrations of at least 10^3 CFU/ml, while the dynamics of the anaerobic cluster, as well as the composition and changes in the microbial flora with concentrations below 10^3 CFU/ml, remain completely missed.

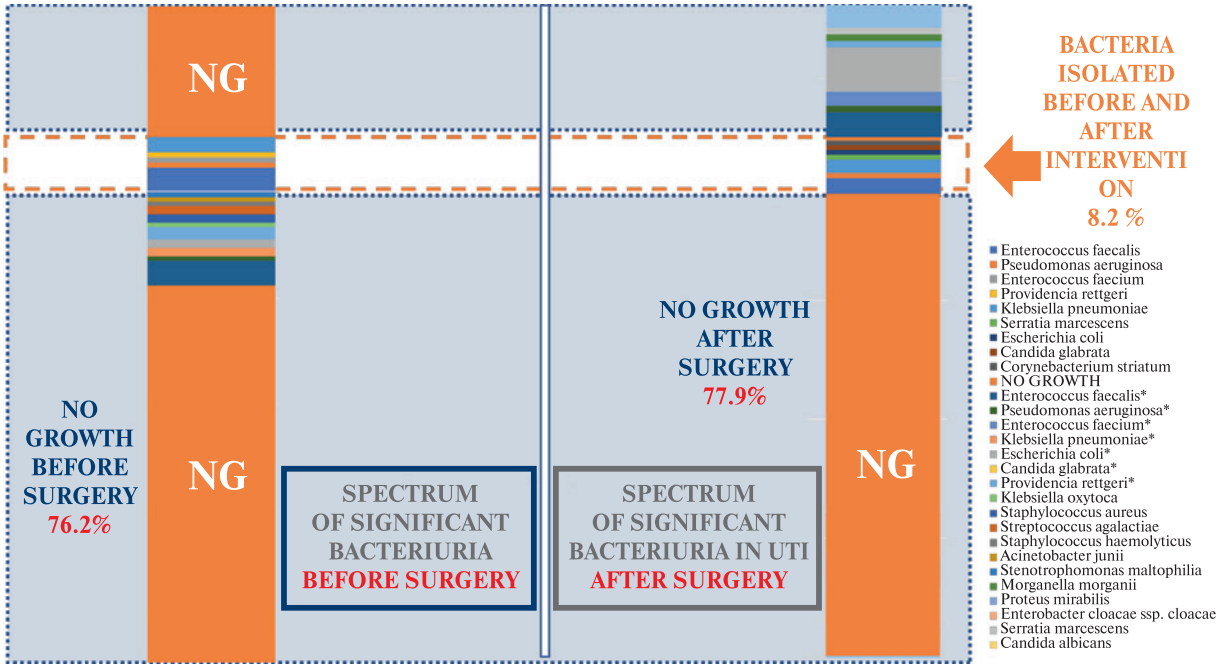
Discussion. Approaches to assessing the infectious factor in patients undergoing surgical treatment for BPH are not unified and therefore often do not provide a full understanding of the initial bacterial status of urine. Moreover, the assessment of preoperative leukocyturia is considered a criterion for excluding/presence of an infectious process. An analysis of data from more than 825 patients from 138 centers around the world (Europe, Africa, Asia, South America) demonstrated that the frequency of routine bacteriological testing of urine before transurethral prostate procedures is 59.2% [2]. There is no doubt that the growing burden of resistance to antibiotics and variability in microbial spectrum dictates the need for a more thorough assessment of the risks of developing infectious complications for effective treatment [5, 6].

Data from a number of studies indicate that preoperative bacteriuria may be an independent risk factor for the development of postoperative infectious complications [7]. According to reports, the frequency of significant bacteriuria before surgical treatment varies from 27.0 to 44.7% [8–13]. In most studies *E. coli* was



*IO – infectious complications.

Fig. 1. Detection rate of microorganisms in urine before and after intervention in patients who experienced infectious complications



*NG – no growth; BU – bacteriuria; UTI – urinary tract infections

Fig. 2. Column charts of detection of bacteriuria before and after surgery

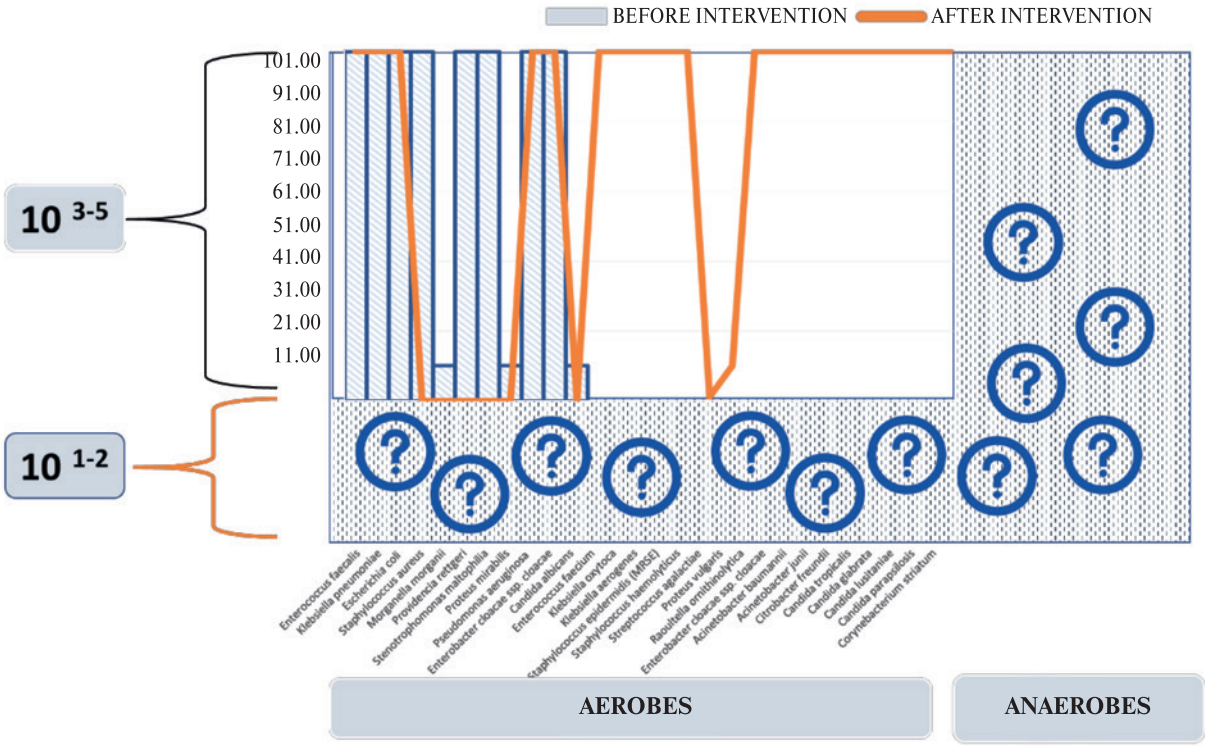


Fig. 3. Combined graph of the spectrum of bacteriuria before and after intervention

the predominant pathogens, isolated in 10.0–20.0% of cases [10–14], and E. faecalis was found in 8.2–40.0% of cases [10, 14]. Among other microorganisms, *S. aureus, K. pneumoniae, P. aeruginosa*, as well as *S. epidermidis, P. mirabilis, Citrobacter* spp., *K. oxytoca, A. baumannii, Providencia spp., S. marcencens, S. viridans* are isolated from urine with varying frequencies [10–14]. These data are consistent with the microbial spectrum of urine in our study. However, it should be noted that there are no published data on the preoperative bacterial spectrum of urine among patients who developed infectious complications after transurethral procedures. These are the data presented in our study.

The bacterial spectrum of pathogens in patients who experience infectious complications after transurethral prostate surgery has been described by many authors. According to a survey of 400 patients, the urine microbiota included Coagulase-Negative *Staphylococci* (CNS), *Enterococcus* spp., *E. coli, S. aureus, Proteus* spp., *Klebsiella* spp., *Pseudomonas* spp., *Streptococcus* spp., *Enterobacter* spp., *Serratia marcescens* [15, 16]. In a later study of postoperative infectious complications of transurethral prostate surgery, carried out in 2016, M. Kikuchi et al. provide data on the dominance of E. faecalis and *E. coli* ($\geqslant 10^4$ CFU/ml) in urine of 190 patients with infectious complications, while *E. cloacae, A. baumannii, MRSA, S. haemolyticus, S. caprae, Corynebacterium* spp., *S. epidermidis, S. hominis, P. aeruginosa, E. aerogenes* were isolated in lower concentrations [10].

The microbial spectrum of urine, verified in patients with infectious complications, demonstrates that only 57.7% of isolates belong to the group of dominant uropathogens, while the rest of the spectrum (42.3%) is represented by minor taxa. Our data on the sequential

Table 3

Microbial spectrum of bacteriuria in 10 patients before and after transurethral prostate surgery

Before the operation			After the operation		
Microorganisms	N	CFU/ml	Microorganisms	N	CFU/ml
Enterococcus faecalis	1	10^5	*Enterococcus faecalis*	1	10^5
Enterococcus faecalis	1	10^5	*Escherichia coli*	1	10^5
Enterococcus faecalis	1	10^5	*Candida glabrata*	1	10^5
Pseudomonas aeruginosa	1	10^5			
Pseudomonas aeruginosa	1	10^5	*Pseudomonas aeruginosa*	1	10^5
Enterococcus faecium	1	10^5	*Escherichia coli*	1	10^5
Providencia rettgeri	1	10^5	*Corynebacterium striatum*	1	10^5
Klebsiella pneumoniae	2	10^5	*Klebsiella pneumoniae*	2	10^5
Serratia marcescens	1	10^5	*Enterococcus faecalis*	1	10^5
			Escherichia coli	1	10^5

assessment of the microbial spectrum of urine before and after transurethral procedure in patients with infectious complications, obtained using a standard bacteriological study, allow to present a perioperative bacterial status in a narrow range available for assessment using a standard set of nutrient media. On the other hand, areas that remain outside the standard assessment of the microbial composition of urine are key potential areas for studying the full dynamics of the bacterial status of urine.

Conclusion. Our results indicate an extremely low detection of bacterial agents in urine of patients with BPH who experienced infectious complications of transurethral procedures in cases of using standard bacteriological testing. In addition, the assessment of significant bacteriuria before surgery gives approximately the same ratio of negative and positive results of urine culture. Only a small proportion of men experience persistent bacteriuria, and the same microorganism is detected in less than half of them. Thus, the standard antibiotic prophylaxis and the preventive measures are partly effective in reducing a narrow spectrum of aerobic microorganisms detected before surgery using standard nutrient media, which, however, does not exclude the development of infectious complications. The microbial spectrum in lower concentrations, which remains outside the scope of the standard bacteriological analysis, as well as its anaerobic component, are potential areas of interest for studying intermicrobial interactions.

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Author information:

Kogan M.I. – Honored Scientist of Russian Federation, Ph.D., MD, professor, Head of the Department of Urology and Human Reproductive Health with the course of pediatric urology and andrology, FGBOU VO Rostov State Medical University of the Ministry of Health of the Russian Federation, Rostov-on-Don, Russia; e-mail: kogan_dept@mail.ru. ORCID iD 0000-0002-1710-0169

Medvedev V.L. – Honored Scientist of Russian Federation, Ph.D., MD, professor, Deputy Chief on Urology of GBUZ Scientific and Research Institute of Regional Clinical Hospital №1 named after prof. S.V. Ochapovsky, Chief Urologist of the Ministry of Health of Kuban Region, Head of the Uronephrologic Center of Regional Clinical Hospital №1 named after prof. S.V. Ochapovsky, Krasnodar, Russia; email: medvedev_vl@mail.ru. ORCID iD 0000-0001-8335-2578

Naboka Yu.L. – Ph.D., MD, professor, Head of the Department of Microbiology and Virology No.1, FGBOU VO Rostov State Medical University of the Ministry of Health of the Russian Federation, Rostov-on-Don, Russia; e-mail: nula33@mail.ru. ORCID iD 0000-0002-0937-4573

Ivanov S.N. – Ph.D. student at the FGBOU VO Rostov State Medical University of the Ministry of Health of the Russian Federation, Rostov-on-Don, Russia, ORCID iD 0000-0002-9772-937X; e-mail: ivanovsergey19@gmail.com. ORCID iD 0000-0002-9772-937X

Palaguta G.A. – assistant at the Department of Urology, Kuban State Medical University; urologist at the Urologic Department No 1, Scientific and Research Institute of the Regional Clinical Hospital №1 named after prof. S.V. Ochapovsky, Krasnodar, Russia; e-mail: palaguta83@gmail.com. https://orcid.org/0000-0002-3462-8766

Arkhipenko M.V. – Head of the bacteriological laboratory of Scientific and Research Institute of the Regional Clinical Hospital №1 named after prof. S.V. Ochapovsky, Krasnodar, Russia; e-mail: arxipenko.m@mail.ru. ORCID iD 0009-0005-0859-0804

O.B. Loran[1,3], Guspanov R.I.[2,4], S.V. Kotov[2,4], A.V. Seregin[1,3], A.D. Morozov[3], D.A. Bogdanov[2,4]

RECONSTRUCTIVE PROCEDURES IN WOMEN WITH IRRADIATION INJURIES OF URINARY TRACT: CHANGE OF A PARADIGM

[1]Russian Medical Academy of Continuous Professional Education (RMACPE), Department of Urology and Surgical Andrology, Moscow, Russia [2]FGAOU VO Pirogov Russian National Research University, Moscow, Russia
[3]S.P. Botkin's State Clinical Hospital, Moscow, Russia 4GBUZ MMKC "Kommunarka", Moscow, Russia

Corresponding author: R.I. Guspanov – Ph.D., associate professor at the Department of Urology and Andrology of Pirogov Russian National Research Medical University, Moscow, Russia; e-mail: renat@guspanov.ru

Introduction. Radiation therapy is one of the main methods of treating pelvic malignant tumors, which provides good oncological results. Specific features of the pelvic anatomy may result in various radiation injuries of adjacent organs, which are complicated by genitourinary fistulas, post-radiation fibrosis with the formation of hydronephrosis, microcyst, reducing the quality of life.
Aim. To describe the relevance and importance of the correct choice of surgical treatment in patients with post-radiation urinary tract injuries.
Materials and methods. The group of irradiation injuries of the urinary tract included 60 patients aged 39–65 years. 19 (31.7%) women with various post-radiation ureteral injurie, who underwent reconstructive surgery using isolated bowel segments, were included in the study group.
Results. Substitution of the ureter by intestinal segment in patients with extensive post-radiation ureteral strictures provides good functional results. During follow-up computed tomography, an absence of urinary tract obstruction was confirmed in 16 (84.2%) patients, while in 3 (15.8%) cases an obstruction was diagnosed, followed by nephrectomy due to loss of function in 1 woman (5.3%). When assessing renal function using the dynamic nuclear scintigraphy, improvement in function was revealed in 14 (73.7%) patients, stabilization in 2 (10.5%), deterioration in 3 (15.8%). Histological examination revealed that inflammatory infiltration and the absence of a clear margins of the stricture area were more pronounced in patients who had had internal ureteral stent prior to reconstruction. A number of clinical cases demonstrating the treatment tactics of this group of patients is presented in the article.
Conclusion. Based on the extensive experience of two centers and long follow-up, we suggest scientifically proven approach to surgical treatment of radiation injuries of the urinary tract, the implementation of which will significantly improve medical and social rehabilitation.

K e y w o r d s: radiation therapy, complications, ureteral stricture, substitution by the bowel segment

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Introduction. Currently, pelvic cancers account for up to 35% of newly diagnosed malignant neoplasms in men (prostate gland, bladder, colon) and 18% in women (bladder, cervix and body of the uterus, colon) [1].

Radiation therapy (RT) is the main method of treating pelvic tumors, which provides good oncological results. It is generally recognized that the therapeutic effect of ionizing radiation is due to double-strand breaks in the DNA of tumor cells, which occurs as a result of ionization of surrounding water molecules and the release of free radicals, as well as due to the direct ionization of DNA molecules. The current RT methods allow the use of high doses of radiation, while the surrounding organs and tissues are also exposed to significant exposure. Peculiarities of the pelvic anatomy can explain various radiation injuries to nearby organs, including the bladder, ureters, rectum, which are complicated by urogenital fistulas, post-radiation fibrosis with the formation of hydronephrosis and microcyst. All of these specific complications significantly reduce the quality of life of patients.

Ureteral strictures are a relatively rare complication that occurs after surgery or RT of pelvic tumors with the incidence after 5, 10, 15, 20 and 25 years of 1.0%, 1.2%, 2.2%, 2.5% and 3.3%, respectively [2].

In most cases, ureteral strictures caused by RT are diagnosed late. Their manifestations vary from asymptomatic hydronephrosis to loss of renal function and the development of life-threatening urosepsis [3]. Strictures that develop most often after RT for cervical cancer (CC) usually occur 4–6 cm proximal to the ureteral orifice, near the area that is most exposed to ionizing radiation [4].

Aim. To highlight the relevance and importance of the correct choice of surgical intervention for patients with radiation-induced urinary tract injuries.

Materials and methods. The group of radiation injuries of the urinary tract included 60 patients aged 39–65 years. The distribution of patients by the total radiation dose and the time of development of post-radiation complications, as well as by the method of primary drainage of the upper urinary tract is presented in *tables 1–3*. Taking into account the minimal post-radiation changes in the pelvic tissue, preserved bladder capacity and short ureteral stricture, 41 (68.3%) patients underwent the Boari procedure and ureterovesical anastomosis. Other

Table 1

Distribution of patients by radiation dose

	Total absorbed dose (Gy)					
	До 60	60–100	100–140	Более 140	No data	
Number of patients	6 (10%)	24 (40%)	12 (20%)	9 (15%)	9 (15%)	60 (100%)

Table 2

Distribution of patients by time of development of complications

Time of development of complications	Number of patients	%
Within 1 year	31	51.7
From 1 to 5 years	20	33.3
From 5 to 10 years	5	8.3
After 10 years	4	6.7
Total	60	100

19 (31.7%) patients with various post-radiation injuries of the ureters underwent reconstruction using bowel segments. These patients were included in the study group. The types of intestinal reconstructions are shown in *table 4*.

During the surgical intervention, histological and immunohistochemical (IHC) studies of the distal end of the ureter in the stricture area were performed to assess the true radiation damage. After deparaffinization and dehydration of the sections, IHC testing was performed according to the standard protocol in automatic mode in the BenchMark XT Ventana immunohistostainer (Biovitrum, Russia) to identify diagnostic markers of the regenerative process.

As primary antibodies in all reactions, mouse monoclonal antibodies to contractile proteins (Smooth Muscle Actin, Vimentin) and inflammation markers (CD45R, CD58, CD138, CD20, CD3) from Leica Biosystems Newcastle Ltd, United Kingdom were used. The intensity of staining was assessed according to the manufacturers' recommendations and using a color detection scale: -, no expression, +, weak expression; ++, moderate expression; +++, pronounced expression (high-intensity immunoperoxidase staining).

One month after interventions, nephrostomy drainage/internal stent was removed, and antegrade pyelography was performed to assess the urine passage. After 12 months, computed tomography (CT) with intravenous contrast and dynamic scintigraphy were done to assess renal function.

Results. Impaired urine passage with the development of hydronephrosis was detected in 3 (15.8%) patients. Subsequently, one patient underwent nephrectomy for terminal hydronephrosis and loss of renal function. During follow-up dynamic scintigraphy, slight improvement in renal function was observed in 14 patients ($p<0.05$). In 6 (31.6%) cases, renal function was complete normalized (*table 5*).

Fig. 1 shows a fragment of the ureter with a sharply narrowed lumen, covered with atrophic transitional epithelium. In the wall there is a proliferation of dense fibrous tissue. The wall has pronounced sclerotic changes and foci of chronic infiltration. Before reconstruction, a nephrostomy tibe was put.

Table 3

Type of upper urinary tract drainage

Type of derivation	Number of patients	%
Nephrostomy tube	41	68.3
Ureteral stent	19	31.7

Table 4

Distribution of patients by type of surgical procedure

Side of the intervention	Number of patients	Type of reconstruction	Number of patients (%)
Left ureteral substitution by bowel segment	7	Total ureteroplasty	2 (10.5)
		Substitution of the two lower thirds of the ureter	5 (26.3)
Right ureteral substitution by bowel segment	9	Total substitution of the ureter	3 (15.8)
		Substitution of the two lower thirds of the ureter	6 (31.6)
Bilateral ureteral substitution by bowel segment	3	S-shaped flap	3 (15.8)

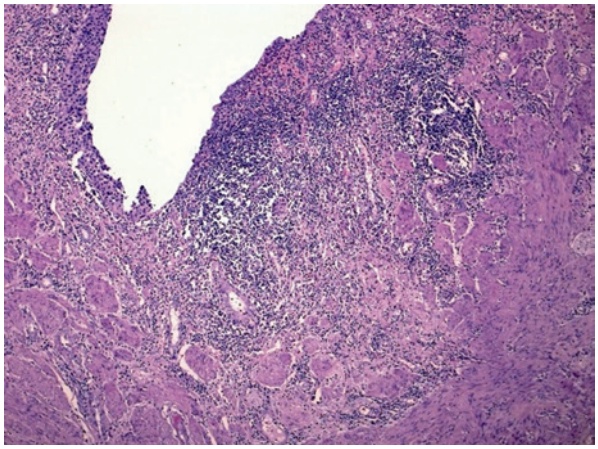


Fig. 1. Histological examination of a ureter after putting of nephrostomy tube. Staining by hematoxylin and eosin, magnification x56

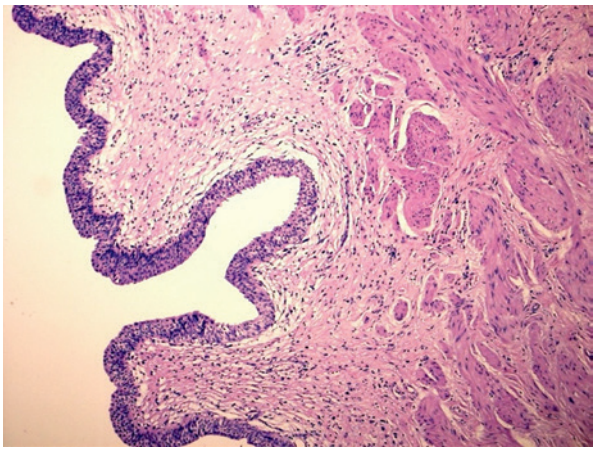


Fig. 2. Histological examination of a ureter fragment after putting of ureteral stent. Staining by hematoxylin and eosin, magnification x56

Fig. 2 shows fragments of the ureter with predominantly fibrous tissue, in the center of which there is an irregularly shaped narrow duct lined with urothelium. The muscular membrane is atrophied with fibrosis; in some areas there is salt deposition. This patient had previously had an internal stent.

Fig. 3 presents the results of IHC, which showed that inflammatory infiltration and the absence of a clear boundary of the stricture zone are more pronounced in patients with an internal ureteral stent. This was not observed in those who had nephrostomy tubes. It was also noted that the early postoperative period in 5 (26.3%) patients was complicated by the development of acute non-obstructive pyelonephritis requiring antibacterial therapy (grade II complication according to the Clavien-Dindo). No other complications were identified in the immediate postoperative period.

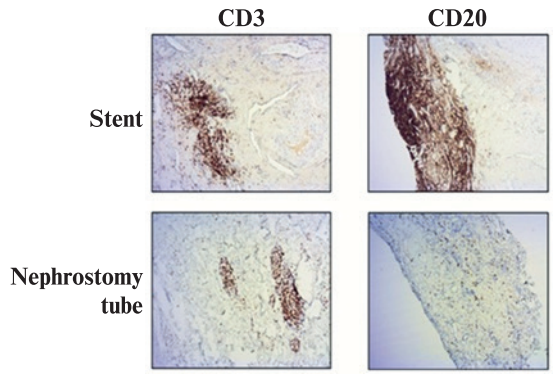


Fig. 3. Immunohistochemical examination of a ureter fragment

Clinical cases

Clinical case No. 1. Patient M., 46 years old. Combined treatment for cervical cancer was performed in 2004. Further, reconstructive surgeries on the urinary tract were done. She had microcyst, ureterostomy on the left and nephrostomy on the right. Considering the reduced bladder capacity and the preserved urethral sphincters, a decision was made to perform cystectomy with a formation of a Studer orthotopic bladder (*Fig. 4*).

A control follow-up did not reveal any urodynamic disorders, and the bladder capacity was sufficient (*Fig. 5*).

Clinical case No. 2. Patient P., 56 years old. A diagnosis is cervical cancer pT2NoMo. Combined treatment (extended hysterectomy + radiation therapy SOD 75 Gy + chemotherapy) was performed in January of 2017. She had microcyst and obliteration of the lower thirds of both ureters with bilateral nephrostomy from 04.2017.

Taking into account the presence of long obliteration in combination with microcyst, in order to restore the urine passage, a decision was made to perform reconstruction using intestinal segment. Bowel substitution of the ureters and bladder with an L-shaped segment of the ileum was performed. CT after 1 year is shown on *Fig. 6.* In the long-term period after 4 years, no urodynamic disorders were detected.

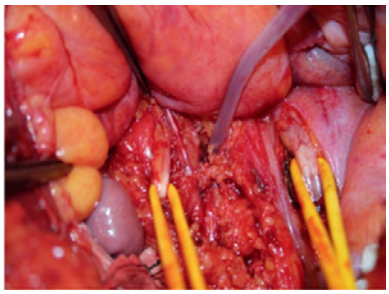
Clinical observation No. 3. The following clinical example demonstrates the erroneous treatment tactics for a patient with severe radiation damage to the urinary tract, who underwent unsuccessful attempts to reconstruct the right ureter using standard procedures.

Patient O., 49 years old. In 2021, combined treatment for cervical cancer was carried out. Initially, extended hysterectomy and pelvic lymphadenectomy was done,

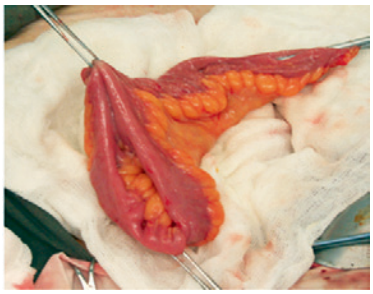
Table 5

Evaluation of renal function and urine passage during follow-up studies

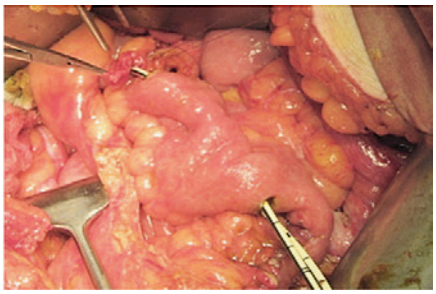
	Improvement (%)	Stabilization (%)	Deterioration (%)	*p*-value
CT	16 (84.2)	–	3 (15.8)	$p<0.05$
Dynamic scintigraphy	14 (73.7)	2 (10.5)	3 (15.8)	$p<0.05$



a – cystectomy, dissection of ureters



b – ileum segment, formation of orthotopic neobladder



c – intestinal reservoir

Fig. 4. Intraoperative view. Stages of the procedure performed in patient M

followed by combined radiation therapy (external RT 50 Gy + brachytherapy 15 Gy). Subsequently, right-side hydronephrosis and post-radiation stricture of the lower third of the right ureter were diagnosed. A nephrostomy tube was placed.

On 05/24/2022, a laparoscopic ureterovesical anastomosis on the right was performed. On 06/14/2022, the internal ureteral stent was removed. After that, urine passage was not restored; antegrade pyeloureterography revealed a recurrence of the right ureteral stricture (*Fig. 7*).

On 10/04/2022, a repeat intervention was performed, namely lower midline laparotomy, adhesiolysis, and Boari flap technique on the right. Intraoperatively, a filiform ureter of a whitish color was seen (*Fig. 8*).

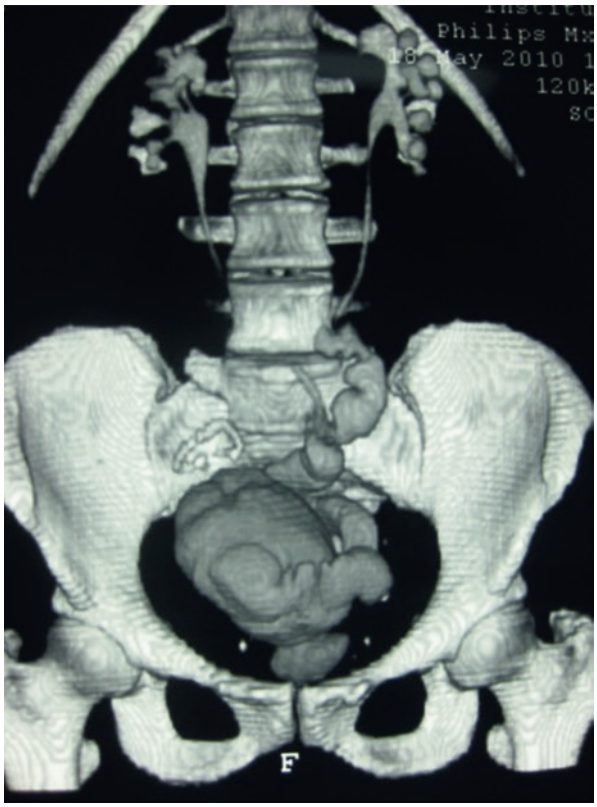


Fig. 5. Follow-up CT

Due to prolonged hyperthermia in the postoperative period, CT of the abdominal cavity and pelvic organs with intravenous contrast was performed, according to which signs of a failure of bladder flap with leakage of a contrast agent into the retroperitoneal space were detected (*Fig. 9*).

To ensure adequate drainage of the upper urinary tract and to prevent urine extravasation, external ureteral stents were placed, which made it possible to close the bladder flap defect (*Fig. 10*).

01/13/2023, according to the results of MRI of the abdominal organs and urinary system with intravenous contrast, there was no urine leak. A pronounced adhesive process was noted in the abdominal cavity.

External ureteral stents and a urethral catheter were removed in stages, but the patient showed a progressive decrease in bladder capacity to 50 ml and deterioration of hydronephrosis. During the follow-up, microcyst and bilateral hydronephrosis were diagnosed, which required bilateral nephrostomy. On March 6, 2023, a ureterovesical anastomosis was performed with an ileal segment. External

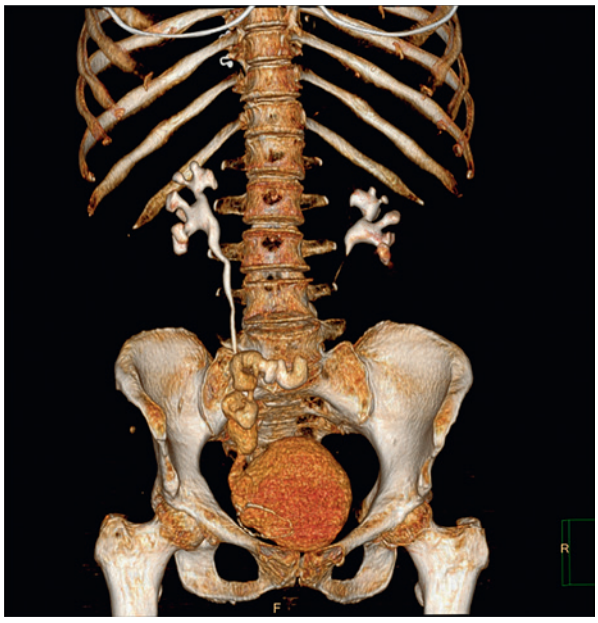


Fig. 6. CT after 1 year. No impairments of urine passage were detected

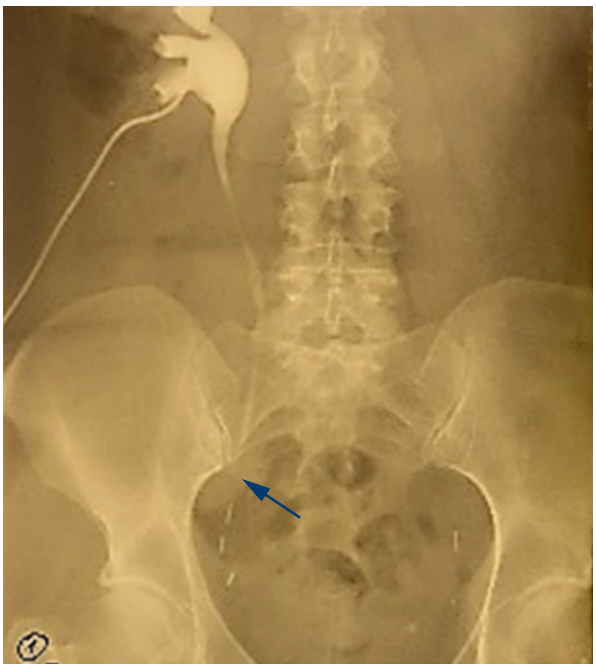


Fig. 7. Antegrade pyelography. Recurrent ureteral stricture (indicated by the arrow)

ureteral stents and a urethral catheter were removed in stages. After removal of the urethral catheter, the patient continued to urinate in small portions and had pain during voiding. Cystoscopy revealed excessive granulation tissue in the area of the anastomosis of the bladder with an artificial intestinal reservoir. A transurethral resection was performed on April 19, 2023, which allowed to achieve adequate communication of the artificial urinary reservoir with the bladder. Conservative therapy and two courses of hyperbaric oxygen therapy increased the capacity of the artificial urinary reservoir to 250 ml.

During follow-up, no impairment of upper urinary tract urodynamics were observed (*Fig. 11*). In our opinion, the reason for the failure of previous reconstruction the ureter using bladder flap was the underestimated progression of post-radiation fibrosis of the pelvic tissue and recurrent urinary infection resistant to most antibiotics.

Discussion. Currently, radiation therapy, both as monotherapy and in combination with surgical treatment, is performed for the majority of patients with gynecologic tumors. In particular, according to L.I. Krikunova (2004), radiation therapy is used in more than 90% of patients with cervical cancer [5]. The incidence of urological complications of radiation therapy for cervical cancer ranges from 0.6 to 46.3% [6–10].

Long or total radiation damage to the urinary tract is a complex problem in reconstructive urology, considering irreversible changes in tissues due to ionizing radiation that have lost their plastic properties (D.V. Kan, 1986) [11, 19]. The use of "standard" techniques, such as ureterovesical anastomosis or Boari operation, for long ureteral strictures rarely leads to success, as evidenced by our histological and immunohistochemical studies of biopsy specimens of irradiated tissues. In this regard, most authors refuse attempts to restore the urinary tract by performing substitution reconstruction, giving preference to various methods of supra-vesical urine

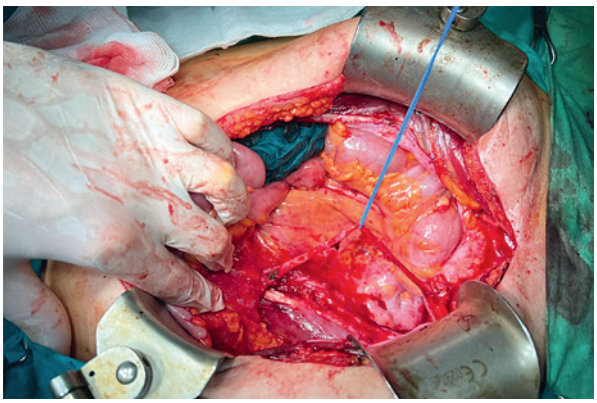


Fig. 8. Intraoperative view of Boari procedure. Vessel loop is placed around the isolated narrow ureter

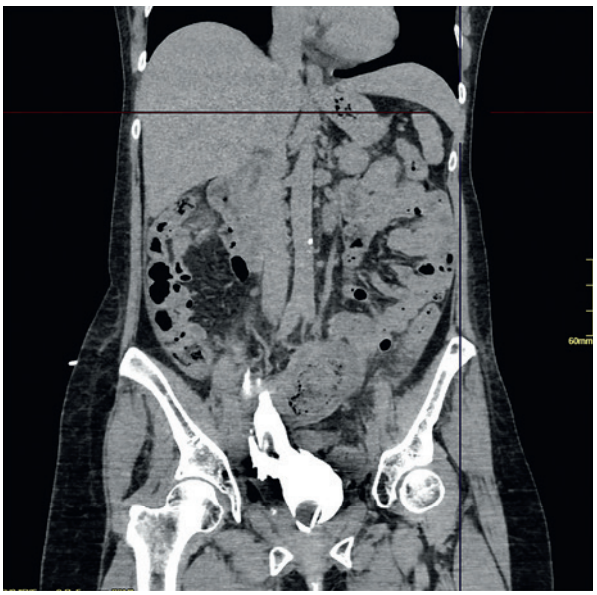


Fig. 9. Contrast-enhanced CT. Bladder defect with urine extravasation into the retroperitoneal space

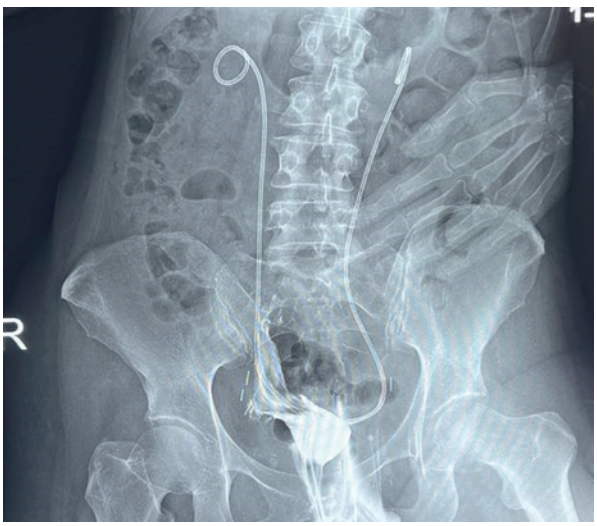


Fig. 10. Plain urography. Ureteral stents are put

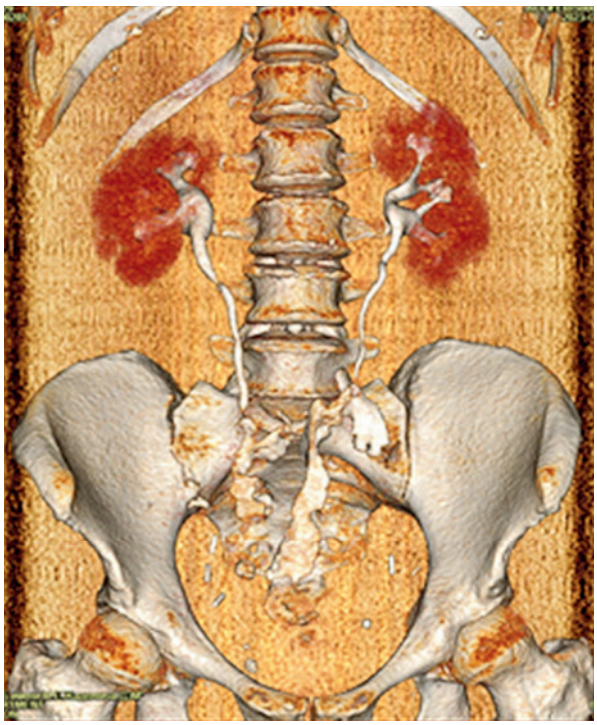


Fig. 11. Follow-up CT – unimpaired urine passage from the upper urinary tract

diversion, such as ureterostomy [12], nephrostomy [8], transverse colon conduit [13-16] or Bricker conduit [17, 18]. Before reconstructive procedures, in the absence of cancer recurrence, preference should be given to putting nephrostomy tubes and avoid the ureteral stents, which aggravate the inflammatory process in the ureters. The choice in favor of percutaneous nephrostomy, in our opinion, ensures adequate urine outflow and favors the preservation of renal tissue, and also causes some improvement in renal function in all patients during follow-up dynamic scintigraphy. This is confirmed by the results of the IHC study.

Reconstruction of the urinary tract after radiation therapy requires to find the optimal material for substitution and proper reconstructive technique. Proper diagnostics, determination of treatment tactics and improvement of the quality of life of patients who have undergone reconstructive surgery for radiation injuries of the urinary tract remain urgent problems of modern urology.

Conclusion. Based on the extensive experience of two centers and long-term postoperative follow-up, we have proved an efficiency of our approaches to surgical treatment of socially significant radiation-induced injuries of the ureter, the implementation of which will significantly improve medical and social rehabilitation for this category of patients. Our data can serve as a basis for the development of guidelines and protocols for the management of patients with radiation injuries of the urinary tract.

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Author information:

Loran O.B. –Academician of RAS, Ph.D., MD, professor, Chief of Department of Urology and Surgical Andrology, Russian Medical Academy of Continuous Professional Education, Moscow, Russia; e-mail: olegloran@gmail.com. ORCID: 0000-0002-7531-1511

Guspanov R.I. – Ph.D., associate professor at the Department of Urology and Andrology of Pirogov Russian National Research Medical University, Moscow, Russia; e-mail: uroguspanov@yandex.ru. ORCID: 0000-0002-2944-2668

Kotov S.V. – Ph.D., MD, professor, Head of the Department of Urology and Andrology of Pirogov Russian National Research Medical University, Moscow, Russia, urokotov@mail.ru. ORCID: 0000-0003-3764-6131

Seregin A.V. – Ph.D., MD, professor, Head of the Urologic Department No41 of S.P. Botkin city clinical hospital, Moscow, Russia; e-mail: av_seregin@mail.ru. ORCID: 0000-0002-5842-7344

Morozov A.D. – Ph.D., urologist of the Urologic Department No41 of S.P. Botkin city clinical hospital, Moscow, Russia

Bogdanov D.A. – Ph.D. student at the Department of Urology and Andrology of Pirogov Russian National Research Medical University, Moscow, Russia. ORCID: 0000-0001-6847-5684

M.M. Iritsyan[1,2], R.I. Guspanov[1,2], S.A. Pulbere[1,2], A.A. Klimenko[1], R.U. Mammaev[1], R.A. Rakhmatov[1], E.M. Alekberov[1], A.A. Mantsov[1], S.V. Kotov[1,2]

COMPARATIVE ANALYSIS OF THE RESULTS OF TREATMENT OF PATIENTS WITH RECURRENT URETHRAL STRICTURE USING PLATELET-RICH PLASMA

[1]Department of Urology and Andrology, Russian National Research Medical University. N.I. Pirogov, Moscow, Russia;
[2]GKB No. 1 named after N.I. Pirogov, Moscow, Russia

Corresponding author: S.V. Kotov – Ph.D., MD, professor, Head of the Department of Urology and Andrology of Pirogov Russian National Research Medical University, Moscow, Russia, e-mail: urokotov@mail.ru

Introduction. The treatment tactics of patients with recurrent urethral stricture requires an integrated approach. An increase in the treatment efficiency is possible not only through improvements in surgical technique, but also by influencing the pathogenetic mechanisms of the formation of urethral stricture and stimulating regeneration.

Aim. To evaluate the efficiency of reconstructive procedures using platelet-rich plasma in patients with recurrent urethral stricture.

Materials and methods. A comparative analysis of the results of surgical treatment of patients with recurrent urethral stricture with and without the use of platelet-rich plasma, who were treated at the University Clinic of Urology of Russian National Research Medical University named after N.I. Pirogov, was carried out. A total of 60 patients were included in the study. They were divided into the control (n=30) and the main group (n=30). There were no differences in length, median age, and localization of urethral stricture. The median maximum urinary flow rate preoperatively was 4.7 ml/s (1.7–11). According to etiological factors, there were 45 iatrogenic (75%), 7 traumatic (11.7%), 2 infectious strictures (3.3%) and 6 patients with hypospadias (10%).

Results. In the main group, end-to-end anastomotic urethroplasty was performed in 17, augmentation urethroplasty in 9, multi-stage urethroplasty/perineal urethrostomy in 4 cases. In the control group, end-to-end anastomotic urethroplasty was done in 24, augmentation urethroplasty in 4, multi-stage urethroplasty in 2 patients.

Efficiency in the main group was 93.3%. In 2 cases, recurrence of the stricture was seen. In the control group, the efficiency was 76.7%. There were 7 recurrences. The median period of catheterization was 14 and 7 days in the control and experimental groups, respectively. The frequency of infectious complications (urethritis, epididymitis, infected wound) was 6 times lower in the main group.

Median Qmax in the control group during follow-up was (min-max) 19.85 ml/sec (9–23.8), compared to 24 ml/sec (10–40) in the main group.

Conclusion. A combination of urethroplasty with a use of platelet-rich plasma improves the treatment outcomes of patients with recurrent urethral stricture. Reducing the length of bladder catheterization due to the stimulation of regeneration and the organization of the extracellular matrix allows to reduce the frequency of recurrence by 3 times. A decrease in the frequency of infectious complications also improves the results of surgical treatment, reduces the risk of recurrence and improves the quality of life of patients.

K e y w o r d s: urethral stricture, buccal graft, urethroplasty

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Introduction. Surgical treatment of urethral stricture requires a comprehensive approach. Endoscopic procedures have low efficiency. Urethroplasty has better results than minimally invasive methods, but in case of recurrent urethral strictures outcomes are significantly lower [1–5]. The main mechanism of urethral stricture formation is spongiofibrosis caused by excessive collagen synthesis and changes in the composition of the extracellular matrix [6]. In order to prolong the relapse-free period, surgical treatment is combined with methods that affect the pathogenesis of the development of urethral stricture or affect the regeneration process.

A new direction in the treatment of urethral stricture is the use of drugs to stimulate regeneration processes and neoangiogenesis, which prevents the formation of scar tissue after surgical intervention. One of these directions is the use of platelet-rich plasma (PRP) [1].

Aim. To evaluate the efficiency of reconstructive procedures using PRP in patients with recurrent urethral stricture.

Materials and methods. The study includes a comparative analysis of the treatment of 60 patients, who were divided into the main and control groups.

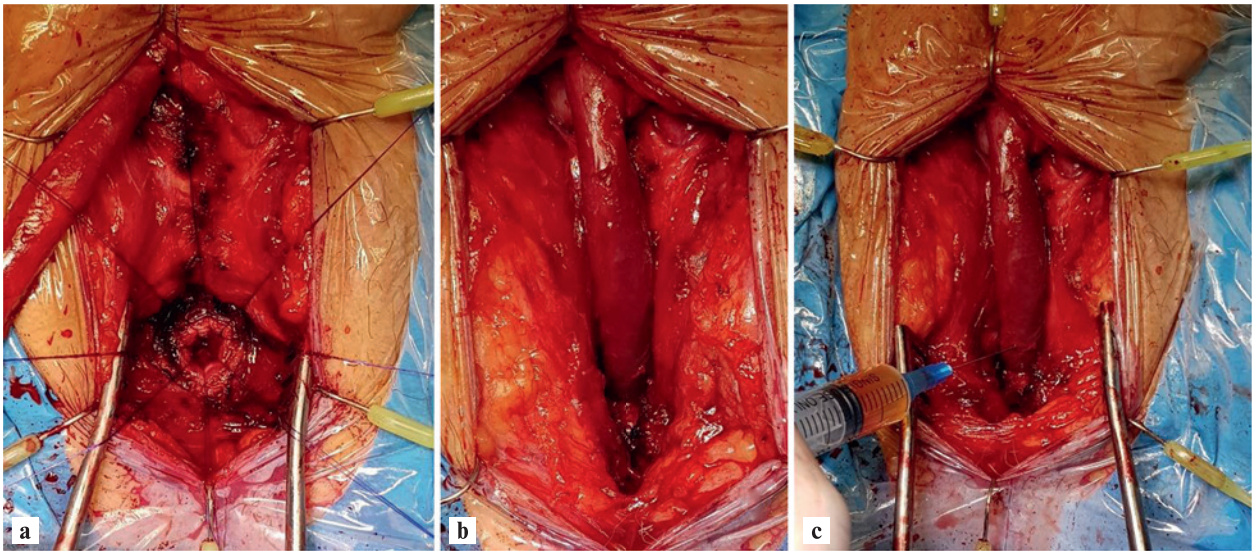

Fig. 1. Intraoperative view, stages of the procedure
a – interrupted sutures on the proximal end of the urethra; b – final view of the end-to-end anastomosis; c – injection of PRP into the corpus spongiosum [1]

The inclusion criterion for the study was the presence of recurrent urethral stricture in men who were planned to undergo urethral reconstruction.

Exclusion criteria:
– unsigned informed consent;
– the presence of untreated malignant neoplasms of any localization;
– severe concomitant diseases;
– severe anemia.

The main group included 30 patients. In the main group, patients underwent to the injection of PRP into the corpus spongiosum during surgical treatment (*Fig. 1*). In 17 (56.7%) patients, 2 to 3 DVIU or urethral dilation were previously done. In addition, five patients (16.7%) had previously undergone end-to-end urethroplasty, 4 (13.3%) correction of urethral plate after the first stage of urethroplasty, and 4 (13.3%) single-stage urethroplasty using the buccal mucosa.

The control group included 30 patients, who underwent the injection of saline into the corpus spongiosum intraoperatively. 24 (80%) patients had history of 2-3 DVIU or urethral dilation. Four patients (13.3%) had previously undergone end-to-end anastomotic urethroplasty, and 2 (6.7%) correction of urethral plate after the first stage of urethroplasty [1].

The characteristics of the patients of both groups are presented in *table 1*.

All patients underwent pericatheter urethrography on the 7th day (*Fig. 2*) after end-to-end urethroplasty, and on the 10th day after augmentation and multi-stage urethroplasty. In the absence of contrast extravasation, urethral catheter removal was accompanied by micturition cystourethrography, uroflowmetry, and assessment of post-void residual [1].

Statistical analysis was performed on an individual computer using Microsoft Excel spreadsheets and the

Table 1

Characteristics of patients in the main and control groups

Parameter	Me (min–max); (median) or mean±SD	
	Main group	Control group
Age, years	64 (27–77)	68.5 (37–78)
IPSS, score	17.5±6.7	19.7±3.3
IIEF-5, score	11.2±7.3	11.4±7.1
Baseline Qmax, ml/sec	5.6±(4–8.4)	4.6 (1.1–7.6)
PVR	100 мл (0–180 мл)	150 мл (0–500 мл)
QoL, score	4.4±0.8	5.1±0.8
Etiology (%)	Iatrogenic – 23 (76.7) Trauma – 3 (10) Hypospadias – 4 (13.3)	Iatrogenic – 22 (73.3) Trauma – 4 (13.3) Infection – 2 (6.7) Hypospadias – 2 (6.7)
Localization (%)	Bulbar – 26 (86.7) Penile – 3 (10) Panurethral – 1 (3.3)	Bulbar – 24 (80.0) Penile – 4 (13.3) Panurethral – 2 (6.7)
Cystostomy (%)	5 (16.7) patients	6 (20.0) patients

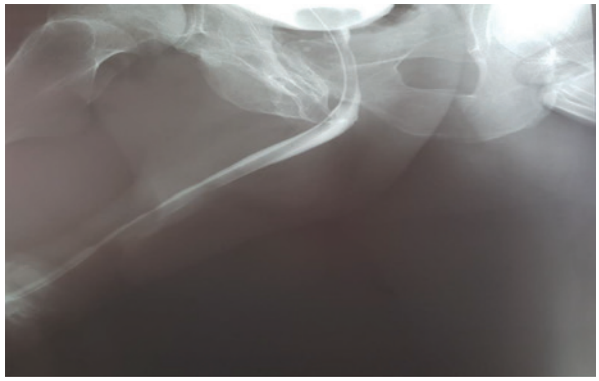

Fig. 2. Patient K. Pericatheter urethrography on the 7th day after the intervention [1]

Prism 6 for Windows v 6.04 software package (GraphPad Software, Inc). All history, clinical, laboratory, and instrumental data were entered into a Microsoft Excel database developed by the author and processed using the variation statistics. For each quantitative parameter, the mean value (*M*), standard deviation (*δ*), error of the mean (*m*), median (*Me*), 95% confidence interval were evaluated, while for qualitative data, frequency (%) was determined.

Results. The criterion of efficiency was the absence of the need for urethral dilation during one year of follow-up, a decrease in the maximum urine flow rate (Qmax) to less than 15 ml/s, the absence of voiding symptoms. The main criterion was the absence of the need for repeated surgical treatment or other manipulations (urethrocystoscopy using flexible cystoscope and urethral calibration were not considered) [1].

The efficiency in the main group was 93.3%. There were two relapses. In the control group, the efficiency was 76.7% (seven relapses) [1].

Also, in both groups, an analysis of the efficiency was carried out depending on the method of surgical treatment (*table 2*).

The average quality of life (QoL) score before surgery was significantly worse in the main group ($p<0.05$), which may be associated with the previous treatment. In the main group, more patients had previously had urethroplasty (*table 3*) [1].

The average preoperative Qmax value in both groups did not differ significantly ($p>0.05$). When comparing Qmax after urethroplasty, a significant difference was obtained at the 12th month ($p<0.05$) (*table 3*) [1].

The average duration of bladder drainage in the main group was 8.8±2.9 days, which was significantly less than in the control group (14.3±4.4 days; Student's coefficient, $p<0.001$). According to the statistical analysis, in the main group, relapses were associated with the duration of bladder catheterization ($r=0.597$; $p<0.01$). This fact confirms our hypothesis, that regenerative potential of PRP allows for earlier removal of the urethral catheter, reducing the incidence of infectious complications by 20% and thereby reducing the incidence of recurrence of urethral stricture [1].

Discussion. There is sufficient data on the efficiency of PRP in various fields of medicine, beginning from aesthetics to traumatology and maxillofacial surgery and reconstruction of complex purulent wounds [1, 7-9]. Many factors of platelets have various effects, some of which are still unknown. Well-studied are 7 factors that can stimulate cellular proliferation and angiogenesis [1, 10, 11]. Also, PRP stimulates the formation of endothelium, provides hemostasis, reduces pain, has an anti-inflammatory effect, reduces the risk of infectious complications and prevents postoperative complications [12]. In reconstructive urethral procedures, there are a small number of studies on the use of PRP. There are no studies at all dedicated to the treatment of recurrent urethral strictures in order to not only improve the outcomes, but also reduce the risk of relapse. E.G. Karpushchenko

Table 2

Treatment efficiency in the main and control groups, according to the type of procedure for recurrent urethral stricture

Type of procedure	Main group		Control group	
	Efficiency, number/ total number (%)	Recurrences,	Efficiency, number/ total number (%)	Recurrences,
End-to-end urethroplasty	17/17 (100)	–	19/24 (79.2)	5 (20.8)
Augmentation urethroplasty	7/9 (77.8)	2 (22.2)	2/4 (50)	2 (50)
Multistage urethroplasty/ perineostomy	4/4 (100)	–	2/2 (100)	–

Table 3

Comparative analysis of IPSS, QoL, Qmax scores in the main and control groups

	At baseline		6 months		12 months	
	Main group	Control group	Main group	Control group	Main group	Control group
IPSS	19.68 ±3.3	17.53±6.69	4.33±2.56	8.73±5.1	2.9±2.0	7.1±4.6
QoL	5.1±0.7	4.4±0.8	2.4±1.1	3.2±1.1	2.3±1.0	3.0±1.1
Qmax	7.5±1.3	5.69±1.7	21.7±7.9	18.5±3.9	23.6±8.7	18.3±4.7

assessed the efficiency of substitution urethroplasty with a buccal graft depending on the use of PRP. The author obtained a 2-fold decrease in the recurrence rate [13].

Scarcia et al. used gel-like PRP in the form of a plate during urethroplasty using a buccal graft. Such procedure was performed in 10 patients. After 20 months of follow-up, no recurrence was noted [14].

Our results proved the efficiency of PRP (93.3% vs. 76.7% in main and control groups, respectively) [1].

In the main group, the efficiency of end-to-end urethroplasty was 100%, and there was no relapse. When using PRP during augmentation urethroplasty, the efficiency was 77.8%. Multi-stage urethroplasty using PRP showed high efficiency (100%). It should also be noted that the efficiency was higher for urethroplasty, when complete excision of scar tissue was done, since PRP has a stimulating effect on the healing process, but does not affect the pre-existing scar tissue and does not lyse it [1, 15].

The efficiency of end-to-end urethroplasty in the control group was 79.2%. There were 5 cases of relapse. The efficiency augmentation urethroplasty in the control group was lower than in the main group (50%). Multi-stage urethroplasty showed a high efficiency, which was comparable to the main group (100%).

The positive effect of PRP on regeneration and a decrease in the inflammatory response allows to lower risk of postoperative complications, which can also lead to a relapse.

Eryilmaz et al. used PRP for the treatment of penile shaft hypospadias in children and noted a decrease in rate of postoperative complications. When using PRP, fistulas occurred in 10%, relapse in 5% and infectious complications in 5% of patients, compared to 25%, 20% and 35% in the control group, respectively [16].

Effective use of PRP in the treatment of recurrent urethral strictures improves treatment outcomes and reduces the recurrence rate. This result is facilitated by the stimulating effect on the processes of regeneration and angiogenesis, which accelerates tissue healing. In our work, we also found a reduction in the time of bladder catheterization, thereby reliably reducing the frequency of both stricture relapse and infectious complications, which also led to recurrence [1].

Conclusions. A combined approach to treatment (optimal surgical procedure + stimulation of regeneration by injection of PRP into the corpus spongiosum) allows to improve outcomes in patients with recurrent urethral stricture. In addition, this improves the physical condition of patients, increases emotional and mental health, and consequently positively affect quality of life.

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Author information:

Iritsyan M.M. – Ph.D., assistant at the Ph.D. student at the Department of Urology and Andrology of Pirogov Russian National Research Medical University, Moscow, Russia, e-mail: misha-res@yandex.ru

Guspanov R.I. – Ph.D., associate professor at the Department of Urology and Andrology of Pirogov Russian National Research Medical University, urologist at the Department of Urology of N.I. Pirogov City Clinical Hospital №1, Moscow, Russia; e-mail: uroguspanov@yandex.ru

Pulbere S. A. – Ph.D., MD, Professor of the Department of Urology and Andrology of Pirogov Russian National Research

Medical University, urologist at the Department of Urology of N.I. Pirogov City Clinical Hospital №1, Moscow, Russia, e-mail: pulpiv@mail.ru

Klimenko A.A. – Ph.D. student at the Department of Urology and Andrology of Pirogov Russian National Research Medical University, Moscow, Russia, e-mail: dr.klimenkoaa@yandex.ru

Rakhmatov R. A. – Resident of the Department of Urology and Andrology, Russian National Research Medical University. N.I. Pirogov, Moscow, e-mail: rrahmatov7777@mail.ru

Alekberov E.M. – Ph.D. student at the Department of Urology and Andrology of Pirogov Russian National Research Medical University, Moscow, Russia, e-mail: alekberov.e.m@yandex.ru

Mantsov A.A. – Ph.D. student at the Department of Urology and Andrology of Pirogov Russian National Research Medical University, Moscow, Russia, e-mail: mantsow2016@yandex.ru

Kotov S.V. – Ph.D., MD, Head of the Department of Urology and Andrology of Pirogov Russian National Research Medical University, Moscow, Russia; e-mail: urokotov@mail.ru

E.S. Sirota[1,2], I.A. Kuznetsov[2], P.V. Glybochko[1], D.V. Butnaru[1], Yu.G. Alyaev[1], D.N. Fiev[1], A.V. Proskura[1], A.R. Adzhiev[1], A.A. Zholdubaev[1]

INTERPRETATION OF THE PROGNOSIS OF EARLY RESULTS OF NEPHRON-SPARING SURGERY WITH CONSIDERATION OF SURGICAL LEARNING CURVE USING CLINICAL DECISION SUPPORT SYSTEMS

[1]Institute of Urology and Reproductive Health, FGAOU VO I.M. Sechenov First Moscow State Medical University, Moscow, Russia; [2]FGBUN Center for Information Technologies in Design, Russian Academy of Sciences, Odintsovo, Russia

Corresponding author: E.S. Syrota – Ph.D., MD, urologist, oncologist, Chief of the Center of Neural Network Technologies of Institute of Urology and Reproductive Health, FGAOU VO I.M. Sechenov First Moscow State Medical University, Moscow, Russia; e-mail: essirota@mail.ru

Aim. To assess the possibility of interpreting machine learning models to predict the early results of laparoscopic nephron-sparing surgery (NSS) in kidney tumors with consideration of surgical learning curve.
Materials and methods. The results of 320 consecutive laparoscopic NSS in patients with localized kidney tumors, performed by 4 surgeons, were analyzed. The construction of a machine learning model taking into account surgical learning curve was carried out based on the extreme gradient boosting (eXtreme Gradient Boosting). To identify significant factors and interpret the prognostic ability of the model, the SHapley Additive exPlanations method was used with a calculation of the Shapley value. Three groups of factors were chosen as an array of input data. The first group included demographic and clinical characteristics of patients, such as age, gender, Charlson comorbidity index, body mass index, preoperative glomerular filtration rate (GFR). In the second group, there were morphometric indicators of the kidney tumor, including RENAL. Nephrometry Score, PADUA (Preoperative Aspects and Dimensions Used for an Anatomical), C-index (Centrality index score), absolute tumor volume, localization of the tumor in relation to the kidney surface. In addition, factors associated with surgical learning curve, such as case number and perioperative results last 10 procedures, were analyzed. The target variables were duration of the procedure, warm ischemia time, and postoperative GFR after 24 hours.
Results. The SHAP method allows a visual interpretation of a machine learning algorithm based on the extreme gradient boosting for individual prediction of early perioperative outcomes of laparoscopic NSS in patients with renal tumors. For the calculated new features "complexity", "slope angle" and others using the SHAP method, the high significance in building predictive models for target variables was confirmed, and an interpretation of the influence of specific features on the target variable in the constructed machine learning models was also given.
Conclusion. The SHAP method showed good practical results that coincide with the observations of specialists. The use of such solutions will allow in the future to introduce machine learning models to form clinical decision support systems.

K e y w o r d s: *renal cell cancer, laparoscopy, learning curve, 3D technologies, prediction, machine learning, artificial intelligence.*

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Introduction. Renal cell cancer (RCC) takes a leading position in the world and in Russia in terms of the growth rate of newly diagnosed cases among malignant tumors of the urinary system [1, 2]. More than 50% of patients have a localized RCC at diagnosis [3].

Nephron-sparing surgery (NSS) is the main option for the treatment of patients with stage T1-2 RCC [4–6].

The priority approaches for NSS are minimally invasive laparoscopic and/or robot-assisted procedures.

The main goal of performing NSS in patients with RCC is to achieve acceptable functional and oncological outcomes, which, in turn, directly depend on perioperative factors (duration of procedure, volume of blood loss, warm ischemia time [WIT], complications).

All outcomes of the NSS are influenced by many factors that are directly related to the general condition of the patient, nephrometry scores, as well as the level of surgical skills («learning curve») for performing a complex surgical procedure [7]. The ability to predict perioperative results of the NSS taking into account all groups of factors will allow surgeons to determine the tactics in a personalized manner.

To take these factors into account, it is necessary to use artificial intelligence technologies using various machine learning algorithms. Modern capabilities of intelligent analysis allow to consider a variety of data with prediction of surgical results. Existing approaches to building clinical decision support systems are based on the «black box» principle [8].

The machine learning algorithms do not allow any interpretation of the obtained predictive decisions, which affects the confidence coefficient in modern systems. Explanation and interpretation of the decisions made allow for a deeper understanding of cause-and-effect relationships and changes in approaches to surgical intervention. In this regard, in the scientific practice for interpretation of complex predictive processes by artificial intelligence algorithms, the concept of additive explanation of Shapley Additive Explanation Values (SHAP) is used [9].

In the available literature, there are studies devoted to the interpretation of predictions or other conclusions for creating of predictive intelligent systems for early outcomes of laparoscopic NSS in patients with RCC.

Aim. To study the possibility of using standard machine learning models to predict the first results of laparoscopic NSS in patients with RCC, taking into account the «learning curve» of the surgeon.

Materials and methods. A total of 320 patients with localized RCC who undergone to laparoscopic NSS at the Institute of Urology and Human Reproductive Health of Sechenov University for the period from January 2014 to June 2019 were included in the study.

The analysis did not include patients with a single kidney, renal anomalies, multiple tumors, as well as retroperitoneoscopic interventions.

NSS were performed by 4 surgeons with experience in performing at least 40 cases from a laparoscopic approach using instruments and video endoscopic equipment from Karl Storz and Eskulap. The standard technique was used. The main demographic, clinical and perioperative data of the patients are presented in *table 1.*

In addition to standard examination methods, all patients preoperatively underwent 3D modeling and virtual operations using the Amira 3D modeling program by VSG version 5.4.5 (ASTND.44644 license) according to the previously described method [10].

Using nephrometry scores (RENAL, PADUA and C-index), a new feature characterizing the complexity of the procedure was formed for each case. The complexity of the intervention was assessed on a scale from 1 to 3, where 3 is the highest complexity. To calculate the complexity, each nephrometry score was divided in a certain way into three parts, which were assigned a complexity (*table 2*).

Based on the identified complexity of the surgical intervention, new features were calculated in several sections: average values for the surgeon and average values for the surgeon depending on the complexity. These features were calculated for the duration of the procedure, WTI and GFR 24 h after the intervention.

An example of a new feature is:

- Average time by complexity (by surgeon), the calculated average duration of the procedure for each surgeon in the context of the complexity.

Additionally, the value of «Slope angle» and «Error deviation» (standard error value) were calculated based on the regression line of the predicted perioperative parameters. The new calculated indicators allow to assess the current skill level of the surgeon, which can significantly affect the quality of predicting perioperative parameters, where the evaluation of the models was performed on the F-measure scale [11].

Predictive models for the selected target variables (duration of the procedure, WTI and GFR after 24 hours) were built using the eXtreme Gradient Boosting algorithm. The key drawback of such machine learning models is the lack of interpretability, when the predictive model acts as a «black box» and it is impossible to understand how exactly this or that feature affects the final result. However, recently, the SHapley Additive exPlanations (SHAP) method for calculating the Shapley value has become very popular for identifying significant

Table 1

Demographic, clinical and perioperative data of patients

Parameters	*n=320*
Age, years (SD)	54.40 (11.37)
Male (%)	191 (59.7)
Female (%)	129 (40.3)
Body mass index, kg/m2 (SD)	28.55 (3.85)
Absolute volume of tumor, mm3 (SD)	26.72 (43.72)
Charlson comorbidity index score (SD)	1.46 (1.29)
R.E.N.A.L. score (SD)	6.38 (1.75)
PADUA score (SD)	7.92 (1.51)
Blood loss, ml (SD)	227.94 (280.22)
Baseline GFR, ml/min	83.56 (16.49)
GFR after 24 hours, ml/min	73.62 (17.50)
Warm ischemia time, min (SD)	13.28 (7.82)
Duration of procedure, min (SD)	150.36 (50.18)
Postoperative complications according to the Clavien-Dindo score (%)	36 (11.2)
Stage 1	22 (6.9)
Stage 2	6 (1.9)
Stages 3a-b	6 (1.9)
MIC (positive margin, ischemia, and complications) (%)	243 (75.9)
Positive surgical margin (%)	4 (1.2)
Degree of surgery complexity (%)	
Complexity 1	152 (47.5)
Complexity 2	124 (38.8)
Complexity 3	44 (13.8)

Table 2

Distribution by degree of complexity depending on the nephrometry scores (RENAL, PADUA, C-index)

	Complexity 1	Complexity 2	Complexity 3
RENAL (score)	4–6	7–9	>10
PADUA (score)	6–7	8–9	>10
C-index	>3	2–3	1–2

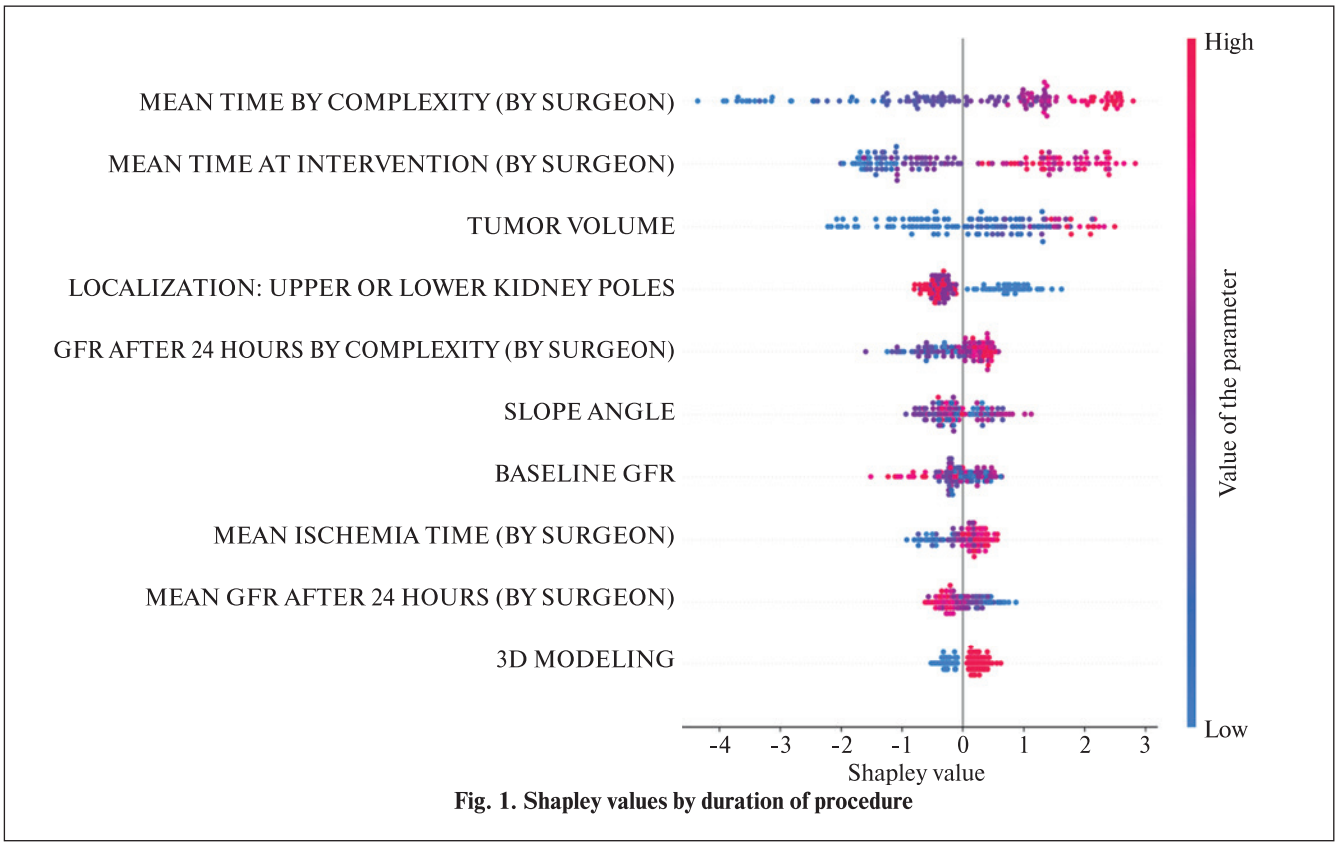

Fig. 1. Shapley values by duration of procedure

factors and interpreting the work of the predictive model. This method allows to evaluate how the trained model will behave with the addition of a parameter and how it will behave without adding this parameter.

Results. For each of the target variables (duration of procedure, WIT, and GFR after 24 hours), the following classes were defined:

- Duration of procedure: «⩽120 min» (1), «>120 min» (2);
- WIT: «⩽15 min» (1), «>15 min» (2);
- GFR after 24 hours: «⩽45 ml/min» (1), «>45 ml/min» (2).

The corresponding prediction models were built based on the extreme gradient boosting algorithm, and then the Shapley value was calculated using the SHAP method, on the basis of which the graphs of the importance of the parameters were built (see *Figs. 1–3*), which can be interpreted as follows:

- the values to the left of the central vertical line are the class with label (1), and to the right are the class with label (2);
- the thickness of the line is directly proportional to the number of observation points;
- the redder the dots, the greater the significance of the feature at this point.

For the target variable «duration of procedure», a graph was constructed (see Fig. 1) and the significance values of the independent variables were calculated:

- Mean time by complexity (by surgeon) - 1.49;
- Mean time at intervention (by surgeon) - 1.33;
- Tumor volume - 0.99;
- Localization: upper or lower kidney poles - 0.51;
- Mean GFR after 24 hours by complexity (by surgeon) - 0.38;
- Slope angle - 0.36;
- Baseline GFR - 0.29;
- Mean ischemia time (by surgeon) - 0.28;
- Mean GFR after 24 hours (by surgeon) - 0.26;
- 3D modeling - 0.25.

On the graph (see Fig. 1), where the value has the greatest impact on the prognosis, we can highlight the most significant parameters and their Shapley values, which make the greatest contribution to predicting the target class:

- «Mean time by complexity (by surgeon)", with an increase in the value, the probability of the class ">120 min" increases;
- «Mean time at intervention (by surgeon)", with an increase in the value, the probability of the class ">120 min" increases;
- «Localization: upper or lower segment», in case of a tumor of the upper pole, the probability of the class ">120 min" increases;
- «Mean GFR after 24 hours by complexity (by surgeon)", with an increase in the value, the probability of the class ">120 min" increases;
- «Mean ischemia time (by surgeon)", with an increase in the value, the probability of the class ">120 min" increases.

For the target variable «warm ischemia time», a graph was constructed (see Fig. 2) and the significance values of the independent variables were calculated:

- Mean ischemia by complexity (by surgeon) - 1.94;
- Tumor volume - 1.06;
- C-index - 0.57;
- Mean ischemia time (by surgeon) - 0.41;
- Slope angle - 0.39;
- Mean GFR after 24 hours (by surgeon) - 0.37;
- Error deviation - 0.35;
- Baseline GFR - 0.31;
- Mean GFR after 24 hours by complexity (by surgeon) - 0.29;

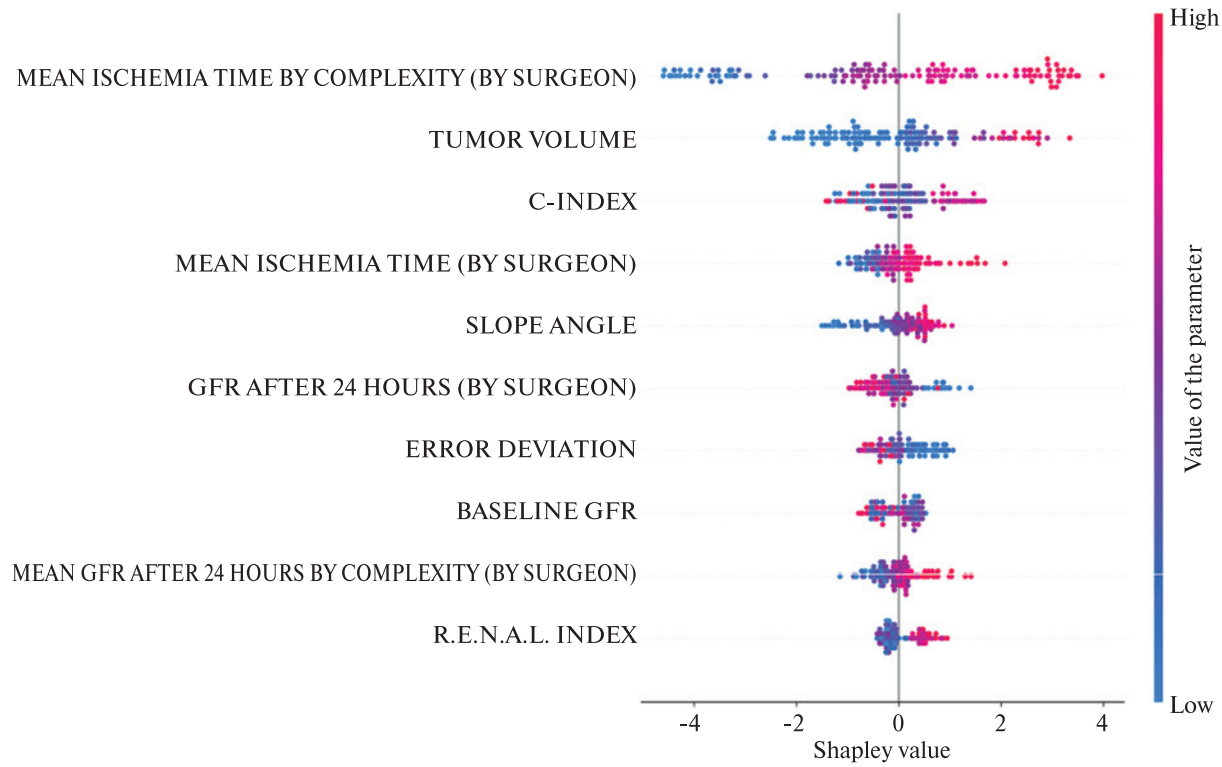

Fig. 2. Shapley values by warm ischemia time

• R.E.N.A.L. index - 0.29.

On the graph (*Fig. 2*) among the most significant parameters, where the value has the greatest impact on the prognosis, we can highlight:

• "Mean ischemia time by complexity (by surgeon)", with an increase in the value, the probability of the class ">15 min" increases;
• "Tumor volume", with a decrease in the value, the probability of the class "⩽15 min" increases;
• "Mean ischemia value (by surgeon)", with an increase in the value, the probability of the class ">15 min" increases;
• "Slope angle", with a decrease in the value, the probability of the class "⩽15 min" increases;
• "Error deviation", with a decrease in the value, the probability of the class ">15 min" increases;
• "Mean GFR after 24 hours by complexity (by surgeon)", with an increase in the value, the probability of the class ">15 min" increases;
• "R.E.N.A.L. index", with an increase in the value, the probability of the class ">15 min" increases.

For the target variable "GFR after 24 hours" a graph was constructed (see *Fig. 3*)

and the significance values of the independent variables were calculated:

• Baseline GFR - 1.64;
• Slope angle - 0.62;
• Volume of blood loss by complexity (by surgeon) - 0.51;
• R.E.N.A.L. index - 0.51;
• Mean time at intervention (by surgeon) - 0.35;
• Volume of blood loss (by surgeon) - 0.31;
• Mean GFR after 24 hours by complexity (by surgeon) - 0.29;
• C-index - 0.27;
• Tumor volume - 0.25;
• Localization: left or right - 0.23.

On the graph (*Fig. 3*), among the most significant parameters, where the value has the greatest impact on the prognosis, we can highlight:

• "Baseline GFR", as the value decreases, the probability of the class "⩽45 ml/min" increases;
• "Slope angle", as the value increases, the probability of the class "⩽45 ml/min" increases;
• "Volume of blood loss by complexity (by surgeon)", as the value decreases, the probability of the class "⩽45 ml/min" increases;
• "RENAL index", as the value increases, the probability of the class "⩽45 ml/min" increases;
• "Mean time at intervention (by surgeon)", as the value increases, the probability of the class "⩽45 ml/min" increases;
• "Volume of blood loss", as the value decreases, the probability of the class "⩽45 ml/min" increases;
• "Mean GFR after 24 hours by complexity (by surgeon)", as the value decreases, the probability of the class "⩽45 ml/min" increases;
• "C-index", as the value decreases, the probability of the class "⩽45 ml/min" increases;
• "Tumor volume", as the value decreases, the probability of the class "⩽45 ml/min" increases;
• "Localization: left or right", if there is a tumor in the left kidney, the probability of the class "⩽ 45 ml/min" increases.

Discussion. In the modern world, laparoscopic surgery is the main surgical option for patients with RCC [12]. This fact can be explained by the fact that laparoscopic procedures allow achieving better functional and oncological outcomes with a low mortality rate compared to radical interventions [13].

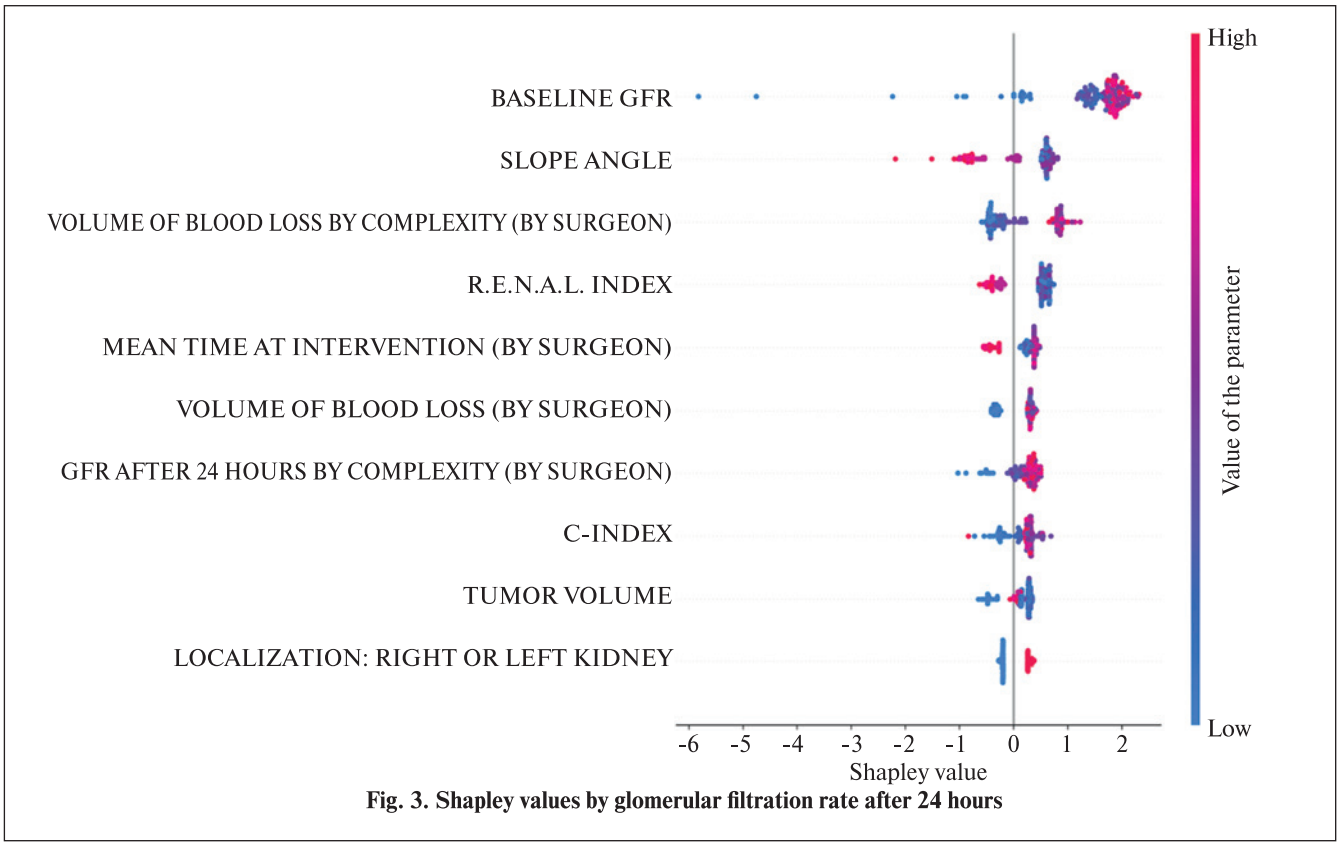

Fig. 3. Shapley values by glomerular filtration rate after 24 hours

The number of surgical procedures required to achieve the proper level of laparoscopic skills varies depending on the surgical approach.

The concept of «learning curve» is determined by the number of procedures that a surgeon must perform to reach the point where his skills no longer affect the results of an intervention [10]. Of the three surgical approaches, laparoscopic surgery has the longest «learning curve» [15, 16].

Our work is based on the results of our previous study, which was dedicated to assessment of achieving MIC score (margin, ischemia, and complications) [17].

In our study on the development of prognostic models, we used the eXtreme Gradient Boosting machine learning algorithm. The prediction accuracy by the F-measure metric achieved satisfactory quality of the models for all three indicators: 0.77 for duration of surgery, 0.62 for WIT, and 0.69 for GFR after 24 h.

One of the objectives of this study is to provide a visual interpretation for each observation using SHAP plots [18].

SHAP decision plots allow to demonstrate how each factor influences the final prediction of the perioperative outcome. Moving from the bottom to up, SHAP of each element was added to the base value of the XGBoost model, showing how each parameter affects the overall prediction, including positive and negative effects.

In relation to our work, when evaluating the SHAP plot (see *Fig. 1*), the duration of NSS>120 min was significantly affected by the average NSS time by complexity (by surgeon), the operator's NSS «learning curve», tumor volume and localization in relation to the kidney surface (anterior, posterior). In this case, the least influence on achieving the time of the NSS>120 min was noted by the use of 3D modeling of the tumor for all patients in the group.

The minimal influence of 3D modeling on the duration of the procedure is most likely due to the fact that observations without 3D modeling were not included in our work, which once again confirms the results of a study previously carried out in our clinic [10].

The duration of the procedure depends not only on the «learning curve» and nephrometry score, but also the coordinated work of a surgical team. It is quite difficult to take into account the contribution of each of the participants in the procedure. Minimally invasive NSS is an interaction between the members of the surgical team due to not only the coordinated work of the «hands», but also the dependence on the visualization of surgical movements on the screen. Visual coordination is a very important element of the laparoscopic approach, and often the surgeon has to stop the procedure to adjust the horizontal image provided by the assistant [19].

In addition, our study did not take into account the presence of "toxic" paranephric fat. According to a number of publications, the presence of "toxic" paranephric fat can affect the duration of NSS [20].

Analyzing the SHAP graph (see *Fig. 2*) with prediction of WTI > 15 min, a strong impact of the following factors was established: average WTI by complexity (by surgeon), tumor volume, C-index, «learning curve» for NSS. However, the R.E.N.A.L. score did not significantly affect WTI.

When choosing the threshold value for the WTI prediction of 15 min, we based on the average values in the studied sample of 13.28 ± 7.82 min. The WTI during the implementation of NSS is a significant indicator for achieving acceptable long-term functional results [21].

The prognostic data we obtained are completely consistent with numerous studies of recent years [22, 23]. Thus, in the work of Hu et al. it was found that the C-index significantly correlates with the WIT compared to the R.E.N.A.L. and PADUA scores [24]. However, according to a meta-analysis of 50 studies performed by Veccia et al., the R.E.N.A.L. and PADUA scores allow to predict WIT (p=0.006 and p<0.001, respectively). Despite their results, the authors note that nephrometric indices (C-index, RAIV, Renal And Ischemia Volume, CSA, Contact Surface Area) require mathematical calculations, therefore they are not widely used. Thus, there is no evidences for their prognostic significance [25]. The main reason for the complexity of mathematical calculations of C-index, RAIV and CSA is the use of 2D data from multispiral CT and/or MRI. In our work, we used 3D modeling to determine the C-index and did not note any complexity in its analysis.

The assessment of the SHAP graph (see *Fig. 3*) in the prediction of GFR after 24 h > 45 ml/min revealed the greatest influence of the preoperative GFR level, the volume of blood loss by complexity (by surgeon), and the R.E.N.A.L. score.

Prediction of GFR level, in our opinion, is an early generally available surrogate indicator of the functional results of NSS. However, the optimal prediction of the functional viability of the renal parenchyma consists of taking into account three groups of factors: the volume of parenchyma removed, the number of devascularized nephrons and the number of incompletely restored nephrons after ischemia [26]. A complete assessment of the above components is currently impossible.

It should also be noted that a decrease in GFR after 24 h⩾ 33% may indicate acute kidney injury after NSS, and the duration of the GFR decline is directly related to long-term functional results [27]. Thus, the prediction of GFR after 24 hours allows for a personalized assessment of kidney function at the stage of NSS planning, taking into account the surgeon's "learning curve" and the patient's data.

When analyzing the factors influencing GFR after 24 hours > 45 ml/min, the baseline GFR, which many researchers mention as the "quality factor," was ranked first [28].

The next most significant factor influencing on GFR after 24 hours was the volume of blood loss due to the complexity of the procedure, associated with "learning curve." The presence of this factor can be explained by the fact that a decrease in blood volume directly affects the functioning of the nephrons of a healthy kidney and, to a greater extent, the kidney that underwent NSS, due to the pathophysiological mechanisms that are activated after the restoration of blood flow [29].

Conclusion. The strengths of our study are the interpretation of the mechanisms of machine learning algorithms and eliminating the «black box» principle. Our machine learning predictive models consider three main groups of factors influencing perioperative outcomes of NSS.

The ability to explain the results of predictive models using SHAP is based on the interpretation of each clinical observation, and then personalized patient characteristics are averaged to obtain a homogeneous visualization of the SHAP graph.

Our study has some limitations. Initially, retrospective cases were included and external validation was not performed to assess the performance of developed models. It is also necessary to note the limited presentation of the predicted indicators of the perioperative outcomes of NSS.

For the parameters "volume of blood loss" and "the rate of perioperative complications", the predictive models showed poor quality, and therefore we did not include them, when interpreted the results using SHAP.

In the future, it is necessary to consider the possibility of developing a clinical decision support system for predicting long-term oncological and functional outcomes of NSS in patients with RCC.

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Author information:

Syrota E.S. – Ph.D., MD, urologist, oncologist, Chief of the Center of Neural Network Technologies of Institute of Urology and Reproductive Health, FGAOU VO I.M. Sechenov First Moscow State Medical University, Moscow, Russia; e-mail: sirota_e_s@staff.sechenov.ru

Kuznetsov I.A. – Ph.D. in technical sciences, associate professor, Head of the Laboratory of FGBU Center for Information Technologies in Design of the Russian Academy of Sciences (CITP), Odintsovo, Moscow Region, Russia; e-mail: info@ditc.ras.ru

Glybochko P.V. – academician of RSA, professor, Ph.D., MD, rector, FGAOU VO I.M. Sechenov First Moscow State Medical University, Moscow, Russia; e-mail: glybochko_p_v@staff.sechenov.ru

Butnaru D.V. – M.D., urologist, associate professor, Chief Physician of the University Clinical Hospital No. 1 FGAOU VO I.M. Sechenov First Moscow State Medical University Sechenov University), Moscow, Russia; e-mail: butnaru_dv@mail.ru

Alyaev Yu.G. – corresponding member of RAS, Ph.D., MD, professor at the Institute of Urology and Reproductive Health, FGAOU VO I.M. Sechenov First Moscow State Medical University, Moscow, Russia; e-mail: ugalyaev@mail.ru

Fiev D.N. – Ph.D., MD, urologist, chief researcher of the Institute of Urology and Reproductive Health, FGAOU VO I.M. Sechenov First Moscow State Medical University, Moscow, Russia; e-mail: fiev_d_n@staff.sechenov.ru

Proskura A.V. – Ph.D., urologist, oncologist, assistant of the Institute for Urology and Human Reproductive Health of I.M. SechenovFirst Moscow State Medical University, Moscow, Russia; e-mail: proskura_a_v_1@staff.sechenov.ru

Adzhiev A.R. – 2-year resident, Institute of Urology and Reproductive Health, FGAOU VO I.M. Sechenov First Moscow State Medical University, Moscow, Russia; e-mail: adzhiev-1998@bk.ru

Zholdubaev A.A. – urologist, Ph.D. student at the Institute of Urology and Reproductive Health, FGAOU VO I.M. Sechenov First Moscow State Medical University, Moscow, Russia; e-mail: gradmonaco@yandex.ru

Lee Y.A., Dymov A.M., Ali S.H., Chislov P.A., Mikhailov V.Y., Lobanov M.V., Akopyan G.N., Chinenov D.V., Gazimiyev M.A., Vinarov A.Z.

ARE «OPTIMAL» MODES OF LASER LITHOTRIPSY OPTIMAL?

Institute for Urology and Reproductive Health, Sechenov University, Moscow, Russia

Corresponding author: A.M. Dymov – PhD, professor of the Institute for urology and reproductive health of Federal State Autonomous Educational Institution of Higher Education I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University), Moscow, Russia; e-mail: alimdv@mail.ru

Objective: to evaluate the effectiveness of the recommended modes of laser lithotripsy in clinical practice by analyzing the necessity of changing laser radiation parameters during percutaneous nephrolithotripsy (PCNL), ureterolithotripsy (URS) and retrograde intrarenal surgery (RIRS).
Materials and methods: a prospective non-randomized clinical study was conducted from October 2023 to December 2023. Patients who underwent surgical procedures for urinary stones using a Thulium fiber laser at the Clinic of Urology of Sechenov University were included. Data on localization, size and radiological density of the stones, initial parameters of laser radiation, presence or absence of mode change were recorded. Statistical data was processed using IBM SPSS Statistics software, version 26.0.0.0.0.
Results: 90 patients were included in the study. Laser radiation mode change was recorded in 38% of cases when performing RIRS, in 25% – during PCNL, and in 24% – during URS. A significantly higher total energy consumption at comparable volumes and radiological density of the stones was registered in the group of mode change at RIRS. In the URS group the results suggest that the laser radiation mode change depends on the volume and density of urinary stones.
Discussion: the need for intraoperative change of laser radiation modes in 31% of all observations may indicate that the existing optimal modes for stone destruction in clinical practice may be suboptimal. New studies of the structure and mechanical properties of urinary stones, assessment of their porosity, hardness, size and properties of crystals, as well as the use of Artificial Intelligence for automatic set up of laser radiation parameters for higher efficiency of lithotripsy.
Conclusion: In addition to linear size and radiologic density urinary stones have a whole complex of morphometric and physicochemical characteristics, so the laser lithotripsy parameters preset should be viewed only as a guideline, while effective settings are to be selected intraoperatively considering urologist's knowledge of laser radiation physical properties.

K e y w o r d s: urinary stones, laser lithotripsy, RIRS, URS, PCNL

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Introduction. Currently, laser lithotripsy is one of the most common options for the destruction of urinary stones, and for retrograde intrarenal surgery (RIRS) it is the only possible one [1]. The key indicator of the efficiency of stone removal is the absence of residual fragments, which defined as stone-free status. Residual fragments can pass spontaneously at sizes less than 4 mm in 42%, remain and grow in 32% or require repeat intervention in 36% of cases [2]. The stone-free rate (SFR) accurately characterizes the efficiency of fragment removal, but does not take into account the duration of the procedure. In turn, the time of intervention, in our opinion, is an integral coefficient of the efficiency, since it indirectly reflects the presence of intraoperative complications, and the speed of lithotripsy, and the comfort of the surgeon, and in the case of RIRS it directly correlates with the risk of infectious complications [3]. Most current laser devices have preset laser modes for various lithotripsy techniques (fragmentation, dusting, popcorning), based mainly on studies in vitro [4, 5].

Aim. To evaluate the efficiency of the recommended laser lithotripsy settings in routine clinical practice by analyzing the need to change the parameters during percutaneous nephrolithotomy (PCNL), ureteroscopy (URS) and RIRS.

Materials and methods. A prospective non-randomized study was carried out from October to December 2023.

The study included patients who underwent surgical interventions for urolithiasis in the Urology Clinic of Sechenov University, including PCNL, URS and RIRS. Laser lithotripsy was performed using the thulium fiber laser (TFL) FiberLase U2 and U3 (IRE-Polus, Fryazino, Russia). All procedures were performed by experienced surgeons (over 150 endourological cases).

The initial parameters of laser lithotripsy were selected based on previously conducted experimental and clinical studies [4–10]. The following modes were most frequently used: for URS 0.5 J, 30 Hz (dusting) and 1 J, 10 Hz (fragmentation), for RIRS 0.5 J, 30 Hz (dusting) and 0.1 J, 20 Hz (popcorning), for PCNL 0.8 J, 30 Hz

Table 1

Changes in laser settings for lithotripsy

Type of procedure	Increase in energy pulse	Decrease in energy pulse	Increase in frequency	Decrease in frequency	Change in mode
RIRS	14	0	3	0	17
PCNL	2	2	1	0	5
URS	4	1	1	0	6

(dusting) and 1.5 J, 20 Hz (fragmentation). Data on the initial parameters of laser energy, a change in the mode, the number and quality of changes in laser settings were recorded. The following clinical data were also analyzed: stone localization, size and density according to the Hounsfield scale (HU) on computed tomography (CT).

Statistical analysis was performed using IBM SPSS Statistics software, version 27.0.1. The normality of the distribution of the assessed parameters was tested using the Shapiro-Wilk criterion. Comparative analysis of data in the study groups was performed using the nonparametric Mann-Whitney U-test. Differences were considered significant if p was <0.05.

Results. The study included 90 patients, including 45 in the group of RIRS, 25 in the group of URS and 20 in the group of PCNL.

A change in laser settings was required in 31% of cases (*n*=28), with the most frequent change observed during RIRS (*n*=17; 38%). At the same time, a comparable number of settings changes were recorded during URS (*n*=6; 24%) and PCNL (*n*=5; 25%).

A change in the lithotripsy settings in the vast majority of patients consisted of an increase in the laser power, with an increase in the pulse energy in 20 (71%) of 28 cases and pulse frequency in 5 (18%) cases.

In 3 cases, during lithotripsy, the laser power was reduced by decreasing the pulse energy (*table 1*). All patients were divided into subgroups depending on the need to change the initial laser settings when performing RIRS, URS, and PCNL (*table 2*).

In RIRS group, significant differences between the subgroups with and without changes in lithotripsy modes in terms of stone volume and density, as well as the duration of the procedure taking into account the stone volume were not found. However, with similar duration of procedure, in 38% of cases there was a need to increase the laser power, which is confirmed by a significantly higher total energy in the subgroup with change of settings.

In URS group, where laser settings were changed, a larger stone volume and density were noted. The differences between the subgroups in the duration of procedures and the total energy did not reach statistical significance.

In PCNL group, stone volume, density, procedure time, and total energy were homogeneous regardless of changes in the laser radiation settings. The differences in the efficiency, assessed by the SFR, were insignificant. The absence of residual fragments during a repeat CT examination was found in 89% of cases in PCNL and RIRS groups and in 92% in URS group.

Discussion. The need for intraoperative change of laser settings in 31% of cases may indicate that highly effective in vitro modes for stone destruction may be suboptimal in routine clinical practice. It can be associated with both intraoperative features (anatomic features of the urinary tract, quality of irrigation, etc.) and structural properties of urinary stones. Standard laser modes for lithotripsy were determined as a result of a series of experimental [4] and clinical studies [5–10]. The most effective modes for fragmentation are 1 J, 10 Hz, and for dusting 0.6 J, 30 Hz. Later, the results of clinical studies were published [5–12], in which high SFR rates were achieved, but no attention was paid to the surgeon's desire to change the settings for laser lithotripsy.

Today, thulium fiber laser has preset parameters for various lithotripsy techniques. IRE-Polus Company offers the following modes for kidney stones: 0.3 J, 26 Hz in dusting mode, 0.4 J, 38 Hz for popcorning, and 0.9 J, 22 Hz for fragmentation. When performing URS, the corresponding values are 0.9 J, 8 Hz for fragmentation and 0.3 J, 10 Hz for dusting. It is worth emphasizing that

Table 2

Characteristics of groups (Me [Q1; Q3])

Type of procedure		Stone volume, mm^3	Density, HU	Length of procedure, min	Total energy, kJ
RIRS	Change of settings (*n*=17)	763 [187; 1128]	1300 [1110; 1445]	60 [50; 70]	15.3 [8.6; 19.5]
	No changes (*n*=45)	570 [116; 975]	1200 [1000; 1400]	50 [40; 65]	6.4 [2.5; 13.2]
	p	>0.05	>0.05	>0.05	<0.05*
URS	Change of settings (*n*=6)	480 [324; 537]	1460 [1401; 1498]	40 [33; 48]	3.3 [2.8; 5.7]
	No changes (*n*=19)	168 [120; 210]	812 [650; 1100]	40 [30; 60]	3.3 [0.3; 5.1]
	p	<0.05*	<0.05*	>0.05	>0.05
PCNL	Change of settings (*n*=5)	2688 [1158; 6424]	1040 [1000; 1050]	85 [60; 100]	7.4 [2.9; 14.8]
	No changes (*n*=20)	2720 (1001-4550)	1254 [944; 1400]	60 [43; 68]	8.6 [1.9; 11.1]
		>0.05	>0.05	>0.05	>0.05

*– significant differences.

today there is no consensus on the optimal settings for laser lithotripsy, and expert recommendations do not always coincide [13]. A. Mishra et al. [14] suggest using the 0.8 J, 12 Hz mode for calcium oxalate monohydrate stones based on their treatment outcome, increase in SFR and decrease in the risk of thermal damage to the renal pelvis and calyces [14]. P. Jones et al. [15] recommended to start lithotripsy with a 0.4 J, 6 Hz, as in holmium lithotripsy, with a further increase in pulse energy and frequency depending on the intraoperative features. D.V. Enikeev et al. studied a 0.5 J, 30 Hz mode for fragmentation and 0.15 J, 100 Hz for dusting with a possible increase in frequency to 200 Hz [16]. P. Kronenberg et al. [17] suggest performing PCNL at 1.5 J, 15–30 Hz for fragmentation and 0.6–0.3 J, 50–100 Hz for dusting [17]. D. Shah et al. [18] suggested that laser settings for mini-PCNL should vary depending on the stone density on CT, with higher frequencies for dense stones. For stones with a density of less than 1000 HU, 0.2 J, 125–150 Hz mode should be used, from 1000 HU to 1400 HU a mode of 0.2 J, 150–200 Hz, and for stones with the highest (>1400 HU), 0.2 J, 200 Hz settings are suggested. It should also be remembered that the criterion for the efficiency for urolithiasis is not the speed of destruction of stones, but its safety. The desire to achieve high efficiency of lithotripsy by increasing its speed is based on a significant decrease in the safety, since "low-energy" laser pulses at high frequency result in a high total energy transmitted to the surrounding tissues.

In addition to linear dimensions and density, urinary stones have a whole range of morphometric and physicochemical characteristics, the diversity of which makes it impossible to determine a single, equally effective settings for laser lithotripsy in all cases. Therefore, the preset parameters of laser lithotripsy are only a recommendation, and effective settings are selected intraoperatively. Attempts at visual intraoperative assessment [19] and automated determination of stone composition (computer vision) [20, 21] remain difficult to apply in clinical practice.

Conclusion. New studies of the structure and mechanical properties of urinary stones, assessment of their porosity, hardness, size and properties of crystals, as well as the use of artificial intelligence technology for automatic selection of laser settings will improve the efficiency and safety of lithotripsy.

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Authors' information:

Dymov A.M. – PhD, professor of the Institute for urology and reproductive health of Federal State Autonomous Educational Institution of Higher Education I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University), Moscow, Russia; e-mail: alimdv@mail.ru ORCID: 0000-0001-6513-9888

Lee Y.A. – clinical resident of Federal State Autonomous Educational Institution of Higher Education I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University), Moscow, Russia; e-mail: julee1806@gmail.com

Ali S.H. – associate professor of the Institute for urology and reproductive health of Federal State Autonomous Educational Institution of Higher Education I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University), Moscow, Russia; e-mail: ali_s_kh@staff.sechenov.ru

Lee Y.A. – clinical resident of Federal State Autonomous Educational Institution of Higher Education I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University), Moscow, Russia; e-mail: pavel_chislov@mail.ru

Lobanov M.V. – urologist, Urology Clinic of Federal State Autonomous Educational Institution of Higher Education I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University), Moscow, Russia; e-mail: lobanov_m_v@staff.sechenov.ru

Akopyan G.N. – phd, professor of the Institute for urology and reproductive health of Federal State Autonomous Educational Institution of Higher Education I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University), Moscow, Russia; e-mail: akopyan_g_n@staff.sechenov.ru

Chinenov D.V. – associate professor of the Institute for urology and reproductive health of Federal State Autonomous Educational Institution of Higher Education I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University), Moscow, Russia; e-mail: chinenov_d_v@staff.sechenov.ru

Gazimiev M.A. – phd, professor of the Institute for urology and reproductive health of Federal State Autonomous Educational Institution of Higher Education I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University), Moscow, Russia; e-mail: gazimiev_m_a@staff.sechenov.ru

Mikhailov V.Y. – phd, senior researcher of the Institute for urology and reproductive health of Federal State Autonomous Educational Institution of Higher Education I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University), Moscow, Russia; e-mail: mikhaylov_v_yu@staff.sechenov.ru

Vinarov A.Z. – phd, professor of the Institute for urology and reproductive health of Federal State Autonomous Educational Institution of Higher Education I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University), Moscow, Russia; e-mail: avinarov@mail.ru

S.V. Kotov [1,2], N.D. Korochkin [1,2], A.V. Vasilyiev[2], M.M. Iritsyan [1,2]

RECURRENT VARICOCELE: CAUSES AND TREATMENT

[1] N.I. Pirogov Russian National Research Medical University of the Ministry of Health of the Russian Federation, Moscow, Russian Federation; [2] N.I. Pirogov First City hospital, Moscow, Russian Federation

Corresponding author: N.D. Korochkin – postgraduate of the Department of Urology and Andrology of Medical Faculty of N.I. Pirogov Russian National Research Medical University, urologist of First City hospital named after N.I. Pirogov, Moscow, Russian Federation; e-mail: nikoro4kin@yandex.ru

Introduction. Among the different options for varicocele surgery, microsurgical varicocelectomy demonstrates the best results, but a relapse is subsequently detected in 1–3% of cases. It was previously believed that the cause of recurrence lies in the presence of various sources of venous outflow from the testicle, but recent studies show that the collaterals of the gonadal vein are the main reason of recurrence.
Purpose of the study: to determine the leading cause of recurrence, to evaluate the effectiveness and optimal surgical tactics depending on the method of primary treatment.
Materials and methods. Surgical treatment of 74 patients with recurrent varicocele was performed for 5 years. Depending on the method of primary treatment, two groups were formed: 1 – relapse after non-microsurgical varicocelectomy (n=37), 2 – relapse after microsurgical varicocelectomy (n=37). Patients of the first group underwent microsurgical subinguinal varicocelectomy. Patients of the second group underwent endovascular surgery or redo microsurgical varicocelectomy.
Results. 1 group. Scrotal pain syndrome was relieved in 90% of cases (n=18). Among patients with complaints of infertility (n=8), natural pregnancy occurred in 57,1% (n=4). An improvement in sperm parameters was found among 18 (75%) patients with pathospermia. The US-recurrence rate was 5.4% (n=2), clinical manifestation revealed in 1 case (2,7%). Intraoperatively, preserved branches of the gonadal vein were detected in all cases.
2 group. Scrotal pain syndrome was relieved in 95,8% of cases (n=23). Among patients with complaints of infertility (n=11), natural pregnancy occurred in 27,3% (n=3). An improvement in sperm parameters was found among 14 (73,7%) patients with pathospermia. The US recurrence rate after repeated microsurgery was 13% (n=3), after endovascular intervention – 38.5% (n=5). Clinical manifestation and indications for reoperation were identified in one patient who underwent endovascular embolization. Other cases of the second recurrence were subclinical, no indications for surgical treatment were identified. Renospermatic reflux was determined in all cases of phlebographic recurrence confirmation. No patients with ileospermatic reflux, as well as May-Turner syndrome, were identified. In 8 cases of phlebography, there was no technical possibility to perform embolization; in 3 patients, recurrence was not confirmed. Always the intact gonadal vein branches were identified mainly in the immediate vicinity of the testicular artery, in case of repeated microsurgical operation. There were no cases of testicular atrophy or postoperative hydrocele in any of the groups.
Conclusion. Missing collaterals from the gonadal vein basin play a key role in the genesis of varicocele recurrence. When choosing a surgical treatment option for patients with recurrent varicocele, it is necessary to take into account the method of primary treatment. The main factor to minimize the recurrence risk is the obligatory using of microsurgical techniques and a thorough revision of the spermatic cord components during the primary operation.

K e y w o r d s: varicocele, microsurgical varicocelectomy, Marmar operation, male infertility

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Introduction. Many surgical treatment options for varicocele have been proposed, most of which are of purely historical significance due to the high rate of recurrence and complications. Microsurgical varicocelectomy can be considered the first-line treatment, but recurrence is detected in 1–3% of cases [1]. There is a point of view that the cause of recurrence is a variety of sources of venous outflow from the testicle, but recent studies show that only gonadal vein collaterals are of importance [2–5].

Aim. To determine the main cause of varicocele recurrence, as well as the efficiency and optimal surgical tactics depending on the method of primary treatment.

Materials and methods. In the University Clinic of Urology of the Pirogov Russian National Research Medical University, based on the Urology Department of the Pirogov City Clinical Hospital No. 1, a total 74 patients with recurrent varicocele were undergone to treatment from 2017 to 2022. Depending on the primary intervention, they were included into two groups.

The group 1 included 37 patients who underwent various types of non-microsurgical varicocelectomy (*table 1*) and had clinical and ultrasound evidences of varicocele recurrence (dilated veins of the spermatic cord with a change in their diameter in orthostasis and retrograde blood flow at rest and/or during the Valsalva maneuver).

The age of the patients ranged from 18 to 42 years; the median age was 28 years. Left-side varicocele was

determined in 33 (89.2%), bilateral varicocele was found in 4 (10.8%) patients. According to the WHO classification, varicocele of Grade I was found in 2 (5.4%), II in 22 (59.5%), III in 13 (35.1%) cases [2]. During ultrasound examination, the average vein diameter of the pampiniform plexus in supine position was 2.9±0.2 mm, in orthostasis 3.6±0.2 mm, the average velocity of retrograde blood flow at rest was 8.9±1.3 cm/s. In all cases a positive Valsalva test was detected with an average velocity of retrograde blood flow of 27.0±4.2 cm/s; the volume of the ipsilateral testicle averaged 13.3±0.9 cc. Pain syndrome was presented in 20 (55.6%) patients. Infertile marriage was detected in 7 (18.9%) cases. Pathospermia was determined in 24 (66.7%) patients. The median total sperm count in patients with oligozoospermia (n=6) was 24.1 million [6.7; 31.2], the median concentration was 9.0 million/ml [3; 10.5], the median proportion of progressively motile sperm in those with asthenozoospermia (n=17) was 17% [11; 26]; the median proportion of sperm with normal morphology among patients with teratozoospermia (n=19) was 2% [1; 3].

The group 2 (n=37) included patients with clinical and ultrasound evidence of varicocele recurrence after microsurgical varicocelectomy.

The age of patients in the group 2 ranged from 18 to 43 years; the median age was 27 years. Most of patients had left-side varicocele (n=35; 94.6%), while 2 patients (5.4%) who had previously undergone bilateral intervention, had a relapse on the right. According to the WHO classification, grade I varicocele was determined in 3 (8.1%), grade II in 18 (48.7%), and grade III in 16 (43.2%) patients.

During ultrasound examination, the average vein diameter of the pampiniform plexus in supine position was 3.3±0.8 mm, in orthostasis 3.9±0.8 mm, the average velocity of retrograde blood flow at rest was 13.6±3.3 cm/s. In all cases a positive Valsalva test was revealed with a retrograde blood flow velocity of 31.7±6.9 cm/s; the volume of the ipsilateral testicle averaged 14.2±1.1 cc. Pain syndrome was presented in 27 patients (73.0%). Infertile marriage was detected in 12 (32.4%) men. Pathospermia was detected in 23 (62.2%) patients. The median total sperm count in patients with oligozoospermia (n=10) was 18.0 million [10.2; 31.7], the median concentration was 10.0 million/ml [2.9; 13.5], the median proportion of progressively motile sperm in patients with asthenozoospermia (n=12) was 20% [15; 26], and the median proportion of sperm with normal morphology among those with teratozoospermia (n=15) was 1% [1; 3].

During 6–12 months after the intervention, a follow-up examination was performed, including taking history, a physical examination, ultrasound examination and ejaculate analysis.

The end points of the study were the pregnancy rate, the frequency of pain relief, changes in ejaculate, ultrasound features, and the rate of varicocele recurrence. In case of exclusively ultrasound signs of varicocele recurrence the term «ultrasound recurrence» was used. If the patient had indications for repeated intervention in addition to the ultrasound features, this condition was designated by the term «clinical recurrence».

The study was prospective. In case of recurrent varicocele after non-microsurgical interventions, patients underwent microsurgical subinguinal varicocelectomy as the most effective and safe treatment option. In patients with recurrent varicocele after microsurgical varicocelectomy, patients underwent retrograde phlebography, depending on the results of which a decision was made on the method of treatment, including embolization, repeated microsurgical varicocelectomy or dynamic follow-up, if there was no phlebographic features of recurrence. In addition, in 14 men, repeated microsurgical varicocelectomy was performed without previous endovascular intervention due to the patient's refusal.

Statistical analysis was done on a personal computer using Microsoft Excel, 2016, and IBM SPSS Statistics, 26. All obtained medical history, clinical, laboratory, and imaging data were entered into a Microsoft Excel database developed by the author and processed using descriptive statistics. Quantitative indicators were tested for the normal distribution using the Shapiro–Wilk test. Quantitative indicators that had a normal distribution were described using means (M) and standard deviations (SD), the boundaries of the 95% confidence interval (95% CI). In the absence of a normal distribution, quantitative data were described using the median (Me), lower and upper quartiles (Q1–Q3). Categorical data were described using absolute values and percentages. With a normal distribution of quantitative indicators for two independent samples, Student's t-test was used. Comparison of quantitative indicators that do not follow a normal distribution was performed using the Mann–Whitney U test.

Results. The method of choice of surgical treatment for patients in Group 1 was microsurgical subinguinal varicocelectomy. In all cases, intact branches of the internal testicular vein were identified and ligated. The median number of ligated veins was 7.5 [5; 9.5]. The average duration of surgery was 1 hour 15 minutes (from 40 minutes to 2 hours).

Scrotal pain syndrome persisted in two cases (10% of patients complaining of pain), and no signs of recurrence were found. Four (57.1%) of seven men with infertility

Table 1

Distribution of patients in group 1 depending on the type of primary procedure

Type of primary procedure	n	
	Abs.	%
Ivanissevich technique	23	62,2
Palomo procedure	2	5,4
Laparoscopic varicocelectomy	9	24,3
Embolization	3	8,1

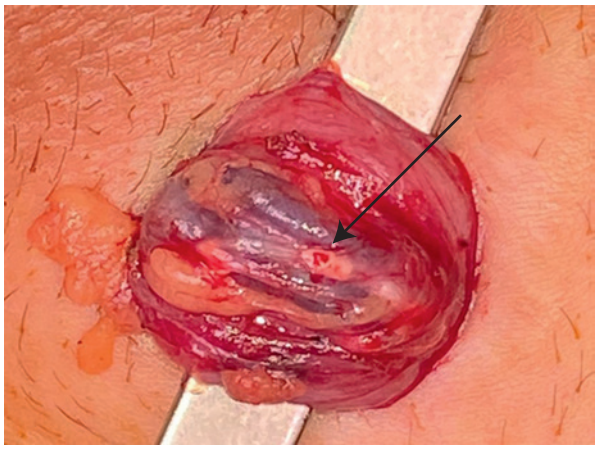

Figure. Residual veins of the pampiniform plexus. The arrow shows the stump of the vein ligated during the primary procedure

achieved natural conception. Among patients with pathospermia, improvement in ejaculate parameters was found in 18 (75%) cases. The median increase in the total sperm count in those with oligozoospermia was 36.7 [9.5; 41.4] million (p<0.05), the median increase in concentration was 7.5 [3.8; 10.5] million/ml (p<0.05). The proportion of progressively motile spermatozoa among patients with asthenozoospermia increased by 12% [7; 20] (p<0.05). The proportion of spermatozoa with normal morphology in patients with teratozoospermia increased by 1.0% [0.5; 1.0] (p<0.05). Ultrasound examination revealed a decrease in the average diameter of the veins of the pampiniform plexus in supine position to 2.2±0.5 mm (p<0.05), in orthostasis to 2.6±0.6 mm (p<0.05), an increase in the volume of the ipsilateral testicle to 15.1±2.7 cc (p<0.05).

There were no cases of postoperative hydrocele or testicular atrophy. The frequency of second ultrasound relapse was 5.4% (n=2) (*table 2*). In both cases, the primary procedure was the Ivanissevich technique. Indications for repeated surgical intervention were identified in one (2.7%) of them. He underwent embolization of the left testicular vein with an achievement of a clinical effect. However, ultrasound examination recorded retrograde blood flow and dilated veins of the pampiniform plexus. Despite the ultrasound recurrence, there were no indications for surgical treatment. Patients in the group 2 underwent microsurgical subinguinal varicocelectomy (n=14) or retrograde phlebography of the gonadal and iliac veins (n=23). Embolization was performed in 12 cases. In 8 (34.8%) patients, there was no technical possibility of embolization due to the structural features of the testicular vein; these men underwent repeated microsurgical varicocelectomy. In all cases of phlebographic verification of relapse (n=20), reflux from renal vein was detected. There were no patients with iliac reflux or May-Thurner syndrome. In 3 (13%) cases, relapse was not confirmed by phlebography; patients were excluded from the study. The average duration of the endovascular intervention was 50 min (from 25 min to 1 h 30 min). In all cases, patients were discharged the next day after the procedure.

As in the group 1, in all patients (n=22) during microsurgical varicocelectomy, the remaining branches of the internal testicular vein were identified and ligated (see the figure). The median number of ligated veins was 8 [4; 10]. The average time of repeated microsurgical varicocelectomy was 1 h 20 min (from 45 min to 2 h 20 min). Patients were treated in a short-stay hospital and discharged for outpatient treatment on the same day.

One patient had scrotal pain (4.2% of those complaining of pain). Three (27.3%) patients out of 11 with infertility achieved natural conception. Improvement of ejaculate parameters was noted in 14 (73.7%) men with pathospermia. The median increase in the total sperm count in patients with oligozoospermia was 25.6 [14.6; 34.3] million (p<0.05), the median elevation of concentration was 5.5 [4.3; 7.6] million/ml. The median increase in the proportion of progressively motile sperm among those with asthenozoospermia was 15% [4; 18] (p<0.05). The median increase in the proportion of sperm with normal morphology in patients with initial teratozoospermia was 1.0% [0.0; 1.0] (p<0.05). Ultrasound examination revealed a decrease in the average diameter of the veins of the pampiniform plexus in supine position to 2.4±0.7 (p<0.05), in orthostasis to 2.7±0.7 mm (p<0.05), an increase in the volume of the testicle to 15.8±3.1 cc (p<0.05).

No cases of testicular atrophy or postoperative hydrocele were found. In 8 patients in the group 2, ultrasound signs of relapse persisted (dilation of the veins of the pampiniform plexus by more than 3 mm in combination with retrograde blood flow for more than 2 s) (see *table 2*), including 4 patients after embolization of gonadal vein. Two men underwent diagnostic phlebography followed by repeated microsurgical varicocelectomy. One patient underwent embolization and then microsurgical varicocelectomy. It should be noted that, despite the ultrasound evidence for varicocele recurrence, all these patients achieved a clinical effect and there were no indications for repeated treatment.

Discussion. The main collector of venous blood from the testicle is the internal gonadal vein, which can be represented by various anatomical variants. It was demonstrated in the studies of Bahren and Murray and served as the basis for respective classifications [7, 8]. In

Table 2

Varicocele recurrence rate

Group	Method of retreatment	n	Rate of second recurrence based on ultrasound, %	Rate of second clinical recurrence, %
1	Microsurgical varicocelectomy	37	5.3 (n=2)	2.7 (n=1)
2	Embolization	13	38.5 (n=5)	7.7 (n=1)
	Microsurgical varicocelectomy	23	13.0 (n=3)	0

addition, the testicle has a developed system of venous collaterals, including the vein of the vas deferens, the cremasteric vein, the external genital vein, transscrotal collaterals and gubernaculum veins [9].

A key issue in understanding the true genesis of recurrence is the possibility of reflux through the veins of the vas deferens and the cremaster muscle [10]. In our study, 23 patients with retrograde blood flow detected by ultrasound examination underwent retrograde phlebography of the testicular and iliac veins, and in all 20 cases where relapse was verified, reflux into the pampiniform plexus occurred exclusively through the gonadal vein.

In turn, there were no patients with reflux from the iliac vein system, which doubts on the possibility of significant reflux through the veins of the vas deferens and the cremaster muscle.

Similar results were obtained in a number of phlebographic studies performed at the end of the 20th century [2–4]. Having studied the anatomy of the venous plexus in patients with and without varicocele, Wishany argues that venous outflow occurs primarily through the gonadal vein, as well as the external genital vein, while the cremasteric collaterals and the veins of the vas deferens are of secondary importance [2].

In 1999, Franco et al. [3] published the results of phlebography of 73 patients with varicocele, 19 of whom had a relapse. The authors concluded that the gonadal vein plays a leading role in the recurrence, while the remaining venous collaterals dilate due to hemodynamic overload as a result of reflux in the main vessel. Thus, the question was raised about the necessity of routine ligation of these veins [4]. Fifteen years later, in a study of 33 patients with recurrent varicocele after laparoscopic and microsurgical procedures, the same conclusions were made [5].

Among domestic articles, the thesis of A.S. Sidnev «Laparoscopic treatment of recurrent varicocele in children» was devoted to this problem. The authors compared endovascular and laparoscopic treatment options. There was no reflux from iliac vein in any case, «which confirms the exceptional role of renal-testicular venous reflux in the development of varicocele».

The obtained results, as well as published data, allow to conclude that the cause of varicocele recurrence are collaterals of the testicular vein. On the other hand, there is an opinion about the role of gubernacular veins. Goldstein's study showed that delivery of the testicle into the wound and ligation of the gubernaculum veins reduces the recurrence rate to 0.6% [11]. However, when directly comparing microsurgical varicocelectomy with and without testicular delivery, no significant differences were found in either the results or the recurrence rate [12].

It is also worth noting that recurrence of varicocele may be associated with systemic disorders, such as undifferentiated connective tissue disease [13, 14]. An association of recurrence with May-Thurner syndrome, which is associated with compression of the left common iliac vein between the right common iliac artery and the spine, is also possible [15, 16].

Recurrence after Ivanissevich and Palomo procedures, laparoscopic and endovascular interventions is associated with the presence of additional branches of the testicular vein at the retroperitoneal and inguinal levels. These branches can anastomose with either the main gonadal vein, renal vein or inferior vena cava. Cross-communicating veins between the right and left testicular veins have also been described [17]. For these reasons, microsurgical subinguinal varicocelectomy can be considered the method of choice in case of recurrence after non-microsurgical interventions.

The fundamental issue in our study was recurrence after microsurgical varicocelectomy. On the one hand, the recurrence rate is minimal compared to other treatment options, on the other hand, this method does not guarantee a completely absence of recurrence. According to a systematic review, a rate of recurrences reaches 3.57% [18].

In our study, the overall rate of second ultrasound recurrence after microsurgical varicocelectomy was 8.3% (5.3% vs. 13.0% in Group 1 and Group 2, respectively). It is noteworthy that the rate of recurrence was higher in Group 2. Retrograde embolization in this group demonstrated the worst result, which consisted of 38.5% of second recurrences, and in a third of the cases it was not performed due to anatomical features. On the other hand, the rate of clinical recurrence did not differ between the groups.

According to a systematic review [19], the rate of second recurrence after open, laparoscopic and endovascular procedures was 3.8%, 17.6% and 3.3%, respectively. When comparing open techniques, the rate of recurrence for microsurgical varicocelectomy was significantly lower (0.6%) than for non- microsurgical (19%). Microsurgical varicocelectomy demonstrates good long-term results, including an increase in sperm concentration and natural pregnancy rate, which depend, among other, on the method of primary treatment [20, 21]. In our study, significant improvement of ejaculate parameters was achieved in 73–75% of patients with initial pathospermia, including an increase in the total number of spermatozoa (group 1 by 36.7 million, group 2 by 25.6), sperm concentration (by 7.5 and 5.5 million/ml, respectively), the proportion of progressively motile forms (by 12 and 15%, respectively), and the proportion of morphologically normal forms (by 1% in both groups). In a systematic review comparing different treatment methods for patients with recurrent varicocele, improvement in sperm parameters was achieved in 77.5% of cases with surgical treatment (open/laparoscopic/microsurgical) and in 62.5% with endovascular procedures [19]. In our study, no significant differences in the improvement of sperm parameters were found between the embolization and microsurgical varicocelectomy. On the other hand, the improvement in sperm parameters was comparable to the results of varicocelectomy for primary varicocele [22]. In the meta-analysis, the average improvement in the proportion of progressively motile forms was 9.69% (95% CI: 4.86–14.52), while the sperm concentration increased by 12.3 million/ml (95% CI: 9.45–15.19).

In the group 1, the pregnancy rate was significantly higher (57.1 vs. 27.3% in the group 2). Among primary procedures, microsurgical varicocelectomy demonstrates the highest pregnancy rate of 41.9% [22]. In the meta-analysis performed by Marmar et al. [23], pregnancy after surgical treatment developed in 33% of cases. A systematic review [19] showed that after treatment of recurrent varicocele, the pregnancy rate was higher with surgical (44.3%) than with endovascular (17.9%)

procedures. The pain relief rate in our study was 90% in the group 1 and 95.8% in the group 2. According to the literature [24, 25], varicocelectomy leads to pain relief in 88% of cases. However, there is a lack of randomized studies evaluating the efficiency of varicocelectomy for orchalgia [20].

Recurrence after Marmar procedure is also caused by branches of the gonadal vein, so the use of microsurgical techniques and careful revision of all elements of the spermatic cord remain extremely important factors. In particular, unligated veins around branches of the testicular artery are most often detected during reoperation. An important aspect is the correct performance of ultrasonography of the scrotum, which allows avoiding overdiagnosis of recurrence [26]. During reoperation, the surgeon has to dissect abnormal tissues, and in some cases, it is difficult to identify the structures of the spermatic cord, which is associated with an increased risk of complications due to injury to the testicular artery and lymphatic vessels. The endovascular approach allows to overcome these difficulties, but is inferior to the microsurgical technique in terms of postoperative results, recurrence rate, and is not always technically feasible [27]. The failure rate of phlebography after varicocelectomy is 15–22% [28, 29]. The main reasons for technical failure in phlebography are anatomical variations, as well as vasospasm during an attempt to catheterize the vessel [29]. As a consequence, the choice of method will depend on many factors, including the experience of the surgeon, the technical equipment of the clinic, and the patient's desire.

Conclusion. Missed collaterals from the gonadal vein play a key role in the varicocele recurrence. The choice of surgical treatment option for patients with recurrence should be determined by the primary treatment method. In case of recurrence after non-microsurgical varicocelectomy options, microsurgical surgery via inguinal or subinguinal approach is preferable. In case of recurrence after microsurgical surgery, various treatment options and their combinations can be used. The fundamental factors for minimizing the risk of recurrence are the mandatory use of microsurgical technique and careful revision of the spermatic cord components during the primary procedure.

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Information about authors:

Kotov S.V. – Dr.Sc., Head of the Department of Urology and Andrology, N.I. Pirogov Russian National Research Medical University, Head of the University Urology Clinic of N.I. Pirogov RNRMU, Moscow, Russia; e-mail: urokotov@mail.ru. ORCID iD 0000-0003-3764-6131

Korochkin N.D. – postgraduate of the Department of Urology and Andrology of Medical Faculty of N.I. Pirogov Russian National Research Medical University, urologist of First City hospital named after N.I. Pirogov, Moscow, Russia; e-mail: nikoro4kin@yandex.ru. ORCID iD 0000-0002-9075-2948

Vasilyiev A.V. – head of the Department of X-ray surgical methods of diagnosis and treatment №2 of First City hospital named after N.I. Pirogov, Moscow, Russia; e-mail: drvasilevav@mail.ru. ORCID iD 0000-0002-3881-6107

Iritsyan M.M. – PhD, assistant of the Department of Urology and Andrology of Medical Faculty of N.I. Pirogov Russian National Research Medical University, urologist of First City hospital named after N.I. Pirogov, Moscow, Russia; e-mail: misha-res@yandex.ru. ORCID iD 0000-0002-6271-0556

Kh.S. Ibishev[1], T.O. Lapteva[2], S.S. Todorov[1], I.D. Goncharov[1], A. Alkhashash[1], V.K. Mamedov[1]

PATHOMORPHOLOGICAL CRITERIA FOR THE DIFFERENTIAL DIAGNOSIS OF LEUKOPLAKIA AND CHRONIC RECURRENT PAPILLOMAVIRUS CYSTITIS

[1]Federal State Budgetary Educational Institution of Higher Education «Rostov State Medical University» of the Ministry of Health of Russia, Rostov-on-Don, Russia [2]State Autonomous Institution of the Rostov Region «Regional Consultative and Diagnostic Center» of the Ministry of Health of Russia, Rostov-on-Don, Russia

Corresponding author: Kh.S. Ibishev – M.D., Dr. Sc. (Med), Full Prof.; Prof. Dept. of Urology, Pediatric Urology & Reproductive Health, Rostov State Medical University, Rostov-on-Don, Russian Federation, e-mail: ibishev22@mail.ru

Introduction: According to the literature of recent years, there has been an increased interest in non-oncological diseases of the bladder, between which differential diagnostics have to be carried out in order to determine a plan for the diagnosis and treatment of patients with these nosologies. There are often certain difficulties in the differential diagnosis of some forms of viral cystitis and leukoplakia
Objective: to determine pathomorphological criteria for the differential diagnosis of leukoplakia and chronic recurrent papillomavirus cystitis.
Materials and methods: The prospective study included 85 sexually active patients aged 20–45 years, who were divided into two groups depending on the etiological factor. Patients of group I (n=70) – with chronic recurrent cystitis (CRC) of papillomavirus (PV) etiology, group II (n=15) – with leukoplakia. All patients were examined in accordance with the recommendations of the European Association of Urology (EAU) and the Russian Society of Urology (ROU); an additional endoscopic examination of the bladder (cystoscopy) was performed, followed by a morphological examination of the bladder biopsy.
Results: A morphological examination of biopsy tissue in all patients of group I revealed koilocytic transformation of the urothelium combined with non-keratinizing metaplasia of the urothelium, and in patients of group II, in all cases, keratinizing metaplasia of the urothelium with hyperkeratosis was detected.
Conclusion: Morphological examination is the gold standard in differential leukoplakia and chronic recurrent papillomavirus cystitis

K e y w o r d s: leukoplakia; chronic recurrent cystitis; papillomavirus infection

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Introduction. According to the recent publications, there is an increased interest in non-oncological diseases of the bladder, where it is necessary to carry out differential diagnostics in order to determine the diagnostic and treatment strategy [1, 2]. Some difficulties are often encountered in the differential diagnosis of some forms of viral cystitis and leukoplakia [1, 3, 4].

In viral cystitis, the most characteristic proliferative features in the bladder wall, identical to leukoplakia, are recorded in chronic recurrent cystitis of papillomavirus etiology [4, 5].

Human papillomavirus (HPV) in the bladder causes cytological changes in the multilayered layer of the urothelium, which are manifested by metaplasia with koilocytic atypia. In this case, a number of important functions of the bladder are disrupted, including barrier, immune, hormonal and others [6, 7]. As a rule, koilocytic changes of the urothelium is characterized by the absence of the keratinization. In addition, a long-term persistent infectious and inflammatory process of papillomavirus etiology can be a basis for the development of proliferative forms of HPV, including genital warts, inverted papilloma and bladder neoplasia, which in some cases, namely leukoplakia, can be precancerous lesions [5, 8, 9].

Bladder leukoplakia is characterized by proliferation and squamous cell metaplasia of the urothelium with keratinization. Its pathogenesis is associated with the involvement of infectious and inflammatory factors [4, 10].

In most cases, both diseases have a similar clinical and laboratory manifestations, including pain, increased frequency, urgency and hematuria [4, 11]. It is possible to differentiate papillomavirus cystitis only by characteristic endoscopic and morphological features [12].

Aim. To determine pathomorphological criteria for the differential diagnosis of leukoplakia and chronic recurrent cystitis associated with HPV.

Materials and methods. Ethical statement. The study was designed and carried out in accordance with the provisions of the Helsinki Declaration (revised in Fortaleza, Brazil, October 2013) and approved by the Local Independent Ethics Committee of the Rostov State Medical University of the Ministry of Health of the Russian Federation based on the review of the design and the implementation plan (protocol No. 16/17 dated October 5, 2017).

The study was carried out as part of the dissertation work «Optimization of differential diagnostics and choice of first-line therapy for chronic recurrent cystitis in women» and did not have sponsorship support.

Patients. The prospective study included 85 sexually active patients aged 20–45 years who had previously had

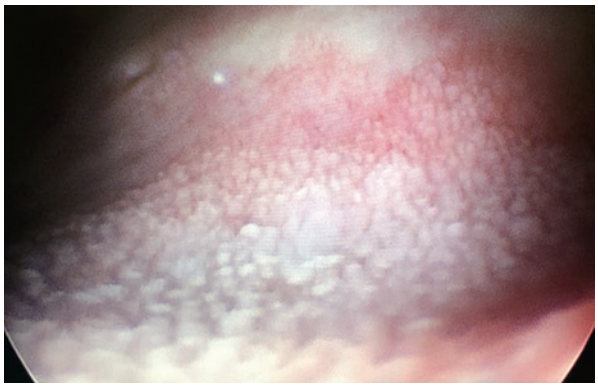

Fig. 1. Cystoscopy. Exophytic lesions of the urinary bladder

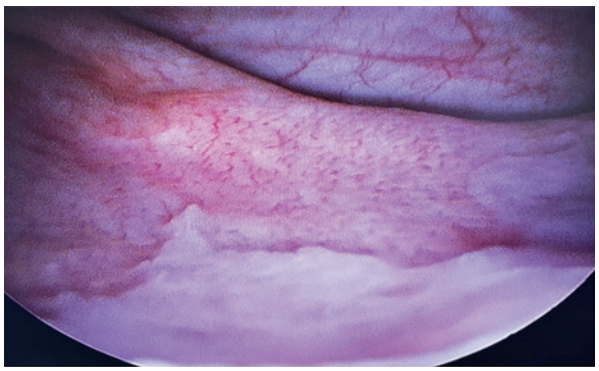

Fig. 2. Cystoscopy. Leukoplakia of the urinary bladder

recurrent lower urinary tract infection, particularly of HPV etiology during a phase of exacerbation. Inclusion criteria: age over 18 years, clinically and laboratory confirmed diagnosis of chronic recurrent cystitis of HPV etiology, and signed consent to participate in the study. Exclusion criteria: age over 45 years, cystitis caused by other non-infectious causes (interstitial, radiation, chemical, foreign-bodies, drug-induced); proven neurogenic dysfunction of the lower urinary tract; sexually transmitted diseases; infectious and inflammatory diseases of the upper urinary tract; infectious and inflammatory diseases of the female reproductive system; bladder stones; bladder outlet obstruction; concomitant cardiovascular, neurological, endocrine, systemic diseases; hormonal disorders of female reproductive system; prior or current history of oncological diseases; congenital anomalies of the urinary tract and female reproductive system; immunodeficiency states of various origins; pregnancy/lactation, menopause and the postmenopause; contraindications to general anesthesia.

Initial examination of patients included history taking and bacteriological examination of the morning midstream urine to exclude the bacterial cystitis. Bladder damage by HPV was confirmed by polymerase chain reaction (PCR) test of the morning midstream urine, urethral and vaginal swabs, and cytological examination of 24-hours urine. The final distribution of groups was performed after cystoscopy. In group I (n=70), a chronic recurrent cystitis of HPV etiology was diagnosed, while in group II, 15 patients with leukoplakia were included.

Bladder biopsy. During the remission phase of the cystitis, all patients underwent standard cystoscopy after premedication under general anesthesia. "Cold" biopsies were taken from the altered areas. The obtained morphological material was fixed in a solution of neutral 10% buffered formalin «HistoSafe®» (OOO «ErgoProduction», St. Petersburg, Russia) with a 24-hour exposure. Histological processing (dehydration-degreasing, enlightenment, paraffinization) was performed using standard technology in a tissue processor. Sections from paraffin blocks of 3-5 μm thick were obtained using a Leica RM 2265 rotary microtome (Leica Microsystems GmbH, Wetzlar, Germany), stained with Hematoxylin-eosin [H&E] (BlikMedicalProduction, Russian Federation). Microscopy of the slides was done using a direct light microscope Leica DM2000 (Leica Microsystems GmbH, Wetzlar, Germany) in resolutions x100, x200, x400. Photofixation of pathomorphological changes was performed with a digital camera Leica DFC295 3 Mpx (Leica Microsystems GmbH, Wetzlar, Germany). During microscopic study, the urothelium, signs of tissue inflammation, features of the cellular infiltrates and pathological transformation of tissues were evaluated.

Results. During cystoscopy in patients of group I, a presence of exophytic, polypoid whitish, whitish-gray lesions localized in most cases in the bladder trigone was found during cystoscopy (*Fig. 1*).

Unlike leukoplakia, whitish lesions in chronic recurrent cystitis, associated with HPV, are characterized by multiple separately located, merging pathological structures like snow. This is called «a positive symptom of snow or snowstorm», which was seen in the group I in 96 (100%) patients. At the same time, abnormalities in the bladder trigone were noted in 76 (79.2%) cases, in the bladder trigone in combination with the lateral wall of the bladder in 25 (26.0%), and abnormalities in whole bladder in 1 (1.0%) patient. After contact with a cystoscope, polypoid formations are easily separated from the bladder wall and do not cause bleeding.

In patients of group II, a single lesion (patch) with a «positive carpet symptom» rising above the urothelium was found. Localization of leukoplakia in most cases [n=10; 66.7%] was noted in the bladder trigone, while in 5 (33.3%) patients there was an additional lesion at the lateral wall (*Fig. 2*).

In morphological analysis, there was chronic inflammation in all patients in group I with signs of HPV lesions in the mucous membrane with hyperplasia, squamous cell subtotal or total metaplasia. In most cases it manifested as lymphocytic infiltration with an admixture of plasma cells, in addition to impairment of the vascular architectonics and mucosal edema. All patients had total koilocytic transformation of the urothelium. In most cases, koilocytes were randomly located in the epithelium and were characterized by abnormal, sharply enlarged, dark, irregularly shaped nuclei with a folded borders and a perinuclear zone or a halo of enlightenment. In addition, most altered urothelial cells in HPV showed pronounced dystrophic changes in the nuclei, including hyperchromatism, hypertrophy, karyorrhexis, and karyopyknosis (*Fig. 3*).

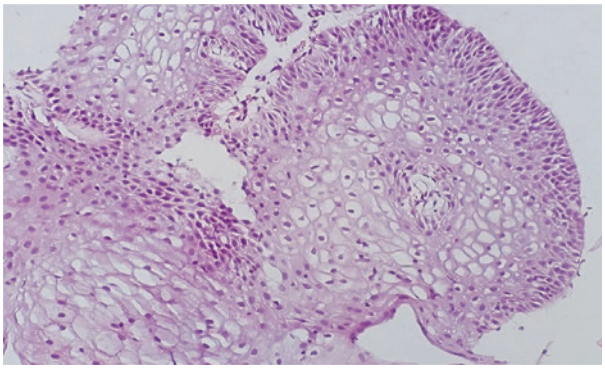

Fig. 3. Morphological study. Pathological reorganization of urothelial cells: papillomatous hyperplasia with signs of HPV infection (koilocytosis, dyskaryosis). [H&E, magnification x200]

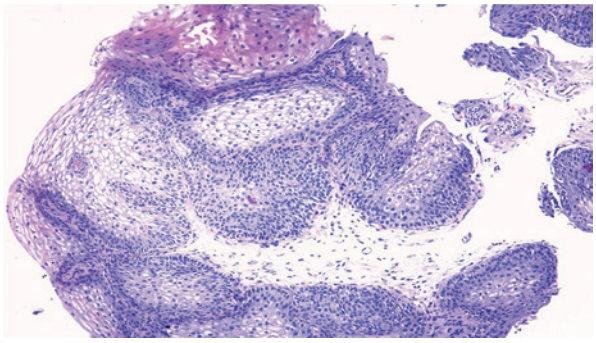

Fig. 4. Morphological study. Pathological reorganization of urothelial cells: squamous cell metaplasia with keratinization, hyperkeratosis [H&E, magnification x100]

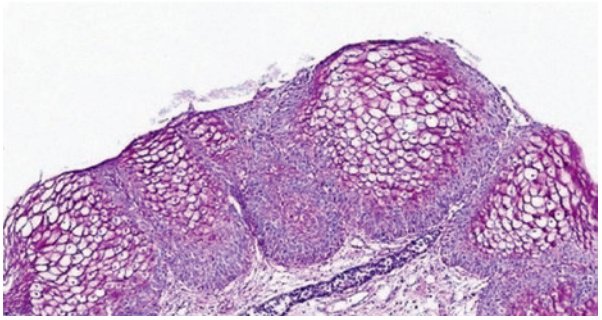

Fig. 5. Morphological study. Pathological reorganization of urothelial cells: squamous cell metaplasia with eosinophilic staining of flat hyperkeratotic (glycogenized) flat epithelium [H&E, magnification x100]

In all patients in group II, the pathomorphological picture was characterized by the presence of squamous cell metaplasia with a pronounced keratinization of the urothelium, combined with hyperkeratosis (*Fig. 4*).

In addition, 13 (86.7%) patients had metaplasia with diffuse hyperkeratosis (*Fig. 5*).

Discussion. According to the literature, leukoplakia is a cause of 7-8% of hospitalizations of women with non-oncologic bladder lesions, which suggests that it may not be as rare as other studies have shown [3]. Most urologists consider non-oncologic bladder diseases with a typical lesion of the bladder trigone as leukoplakia. In addition, leukoplakia is a «waste basket» for all underdiagnosed bladder conditions [4]. The leading method of differential diagnosis of bladder proliferative diseases is cystoscopy with a biopsy and morphological examination [13, 14]. The main morphological sign of leukoplakia is the presence of squamous cell keratinizing metaplasia of the urothelium. Non-keratinizing squamous cell metaplasia is often observed without clinical manifestations. It is localized in the bladder trigone (especially in women) and is rich in glycogen. This is considered a variant of normal histology without an increased risk of neoplastic progression and predisposing factors. However, in the presence of a long-term infectious and inflammatory process, neurogenic dysfunction of the lower urinary tract associated with chronic urinary retention, dysfunction of local immunity, dysbiosis of the urinary tract, squamous cell metaplasia can transform into keratinizing [4]. Cystoscopically keratinizing metaplasia (leukoplakia) is designated by many authors as any whitish exophytic lesions in the bladder trigone. In our study, we proposed diagnostic approaches to the differential diagnosis of leukoplakia and chronic recurrent cystitis, associated with HPV. The main diagnostic methods that allow identifying and describing squamous cell metaplasia are cystoscopy, biopsy and morphological examination [12].

Conclusion. The morphological method is the gold standard in the differential diagnosis of leukoplakia and papillomavirus cystitis. In leukoplakia, there is keratinizing squamous cell metaplasia, which is combined with hyperkeratosis. Conversely, in chronic recurrent cystitis, associated with HPV, non-keratinizing metaplasia is found in combination with koilocytic changes.

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Authors’ information:

Ibishev Kh.S. – M.D., Dr. Sc. (Med), Full Prof.; Prof. Dept. of Urology, Pediatric Urology & Reproductive Health, Rostov State Medical University, Rostov-on-Don, Russia; e-mail: Ibishev22@mail.ru. ORCID iD 0000-0002- 2954-842X

Lapteva T.O. – M.D., Pathologist, Pathology Division, Rostov Research Institute of Oncology, Rostov-on-Don, Russia; e-mail: Lto-96@yandex.ru. ORCID iD 0000-0002-6544-6113

Todorov S.S. – Dr. Sc. (Med.), Associate Professor of the Department of Operative Surgery, Clinical Anatomy and Pathological Anatomy, head of the morphological department of the clinic, pathologist of the highest category, Rostov State Medical University, Rostov-on-Don, Russia, e-mail: sertodorov@gmail.com. ORCID: 0000-0001-8476-5606

Goncharov I.D. – resident of the Department of Urology and Human Reproductive Health (with a course of pediatric urology-andrology) Rostov State Medical University of the Ministry of Health of Russia, Rostov-on-Don, Russia; e-mail: ilagoncarov11250@gmail.com. ORCID iD 0009-0005-0770-7230

Alkhashash A.M.S. – postgraduate student of the Department of Urology and Human Reproductive Health (with a course of pediatric urology-andrology) Rostov State Medical University of the Ministry of Health of Russia, Rostov-on-Don, Russia; e-mail: Ahmadalhashash95@gmail.com. ORCID iD 0009-0002-8983-3107

Mamedov V.K. – M.O. Urologist, Postgraduate student, Dept. of Urology and Human Reproductive Health (with Podiatrie Urology and Andrology Course), Rostov State Magical University, Rostov-on-Don, Russia; e-mail: mamedov1007@yandex.ru. ORCID ID 0000-0001-5508-4510

Ch.D. Dibiraliev, Ch.N. Abdulaev, S.P. Danilov, A.M. Dymov, R.B. Sukhanov, E.A. Bezrukov

ANALYSIS OF PERI- AND POSTOPERATIVE RESULTS OF LASER ENUCLEATION OF THE PROSTATE USING VARIOUS TECHNIQUES

Institute for Urology and Reproductive Health, I.M. Sechenov First Moscow State Medical University, Moscow, Russia

Corresponding author: Ch.D. Dibiraluev – urologist, Ph.D. student, Institute for Urology and Reproductive Health, FGAOU VO I.M. Sechenov First Moscow State Medical University, Moscow, Russia; e-mail: chinghiz.dibiraliev@yandex.ru

Introduction. Several techniques are used for laser enucleation of benign prostate hyperplasia, including two- and three-lobe enucleation, enucleation of all lobes in a single block (en-bloc), and enucleation of all nodes in a single block without longitudinal incisions (total en-bloc).
Aim. A prospective and retrospective analysis of the results of two-lobe, en-bloc, and total en-bloc using thulium fiber laser enucleation of the prostate (ThuFLEP) techniques was performed.
Methods. The study included a retrospective and prospective comparative analysis of the peri- and post-operative results of ThuFLEP using several techniques. Patients with benign prostatic hyperplasia causing bladder outlet obstruction (IPSS>20, Qmax<15) were undergone to ThuFLEP from January 2015 to May 2022. All patients were examined prior to and 1, 3, and 6 months after the procedure. In the pre- and postoperative period, the age of the patients, prostate volume, level of prostate-specific antigen, functional parameters (IPSS, post-void residual, Qmax, and QoL), the stress urinary incontinence were evaluated. In addition, the following intraoperative parameters were assessed: duration of the procedure, enucleation rate, morcellation rate, and mass of enucleated tissue.
Results. We found 450 patients who underwent thulium fiber laser enucleation of prostate hyperplasia (ThuFLEP). Three laser enucleation techniques were used, including two-lobe (n=148; group A), en-bloc (n=150; group B), and total en-bloc without longitudinal incision (n=152; group C). The mean prostate volume was comparable between groups. The mean operation time for the total en-bloc technique (group C) was less compared to the other two techniques (58.9±30.1 vs. 68.8±30.6 for group A and 67.4±30.1 min for group B, respectively; p<0.005). The mean enucleation rate in group C was higher compared to groups A and B (2.3±0.78 vs. 1.9±0.74 and 1.9±0.69 g/min, respectively; p<0.005). The mean morcellation rate in all three groups was comparable (2.8±1.7, 3.0±1.1, and 2.9±2.1 g/min; p>0.05). After 6 months, there were no differences in functional results, according to the IPSS, PVR, Qmax, and QoL.
Conclusion. The two-lobe, en-bloc, and total en-bloc techniques were comparable in functional results and the complication rate. Total en-bloc enucleation showed the higher enucleation efficiency.

K e y w o r d s: laser enucleation, prostate hyperplasia, en-bloc, total en-bloc, two-lobe technique

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Introduction. Currently, surgical treatment remains the most effective for patients with benign prostatic hyperplasia (BPH). The "gold" standard are transurethral procedures, such as transurethral resection (TUR) and laser enucleation of the prostate [1, 2]. According to the European Association of Urologists (EAU) and Russian guidelines, transurethral laser enucleation is recommended for patients with a prostate volume of more than 30 cc. This procedure is the method of choice and is considered preferable for patients taking anticoagulants or antiplatelet agents without the possibility of their discontinuation [3-5]. Several techniques for performing laser enucleation have been developed, all of them involve identification of the proper layer between the surgical capsule and adenomatous tissue, followed by retrograde enucleation within this plane [6, 7]. The first technique included prostate incisions at 5, 7, and 12 o'clock. If a middle lobe present, it is initially enucleated, followed by the lateral lobes [8–10]. The next step in the development of laser enucleation techniques was the development of a two-lobe technique, which began from the incisions of bladder neck at 5 or 7 o'clock. According to this technique, the middle lobe was enucleated together with one of the lateral lobes, and then the second lateral lobe was dissected separately [7, 11, 12]. A.E. Krambeck and A.S. Baazeem were the first to propose a two-lobe technique for enucleation of the prostate (*Fig. 1*). This technique begins with an incision from bladder neck at 6 o'clock in the absence of the middle lobe (in case of the middle lobe, the incision was made at 7 o'clock) in the direction of the verumontanum until the circular fibers of the surgical capsule are visualized. Next, one of the lateral lobes is excised together with the middle lobe. The incision continues counterclockwise towards the bladder neck to 2–3 o'clock. Then an incision is made at 12 o'clock from the bladder neck towards the verumontanum. Further, the incisions at 6 and 12 o'clock are connected, thus enucleating the left lobe and pushing it into the bladder. The same is done for enucleation of the right lobe [11, 12].

In 2015, C.M. Scofone et al. [14] proposed the en-bloc technique for laser enucleation (*Fig. 2*) to simplify the

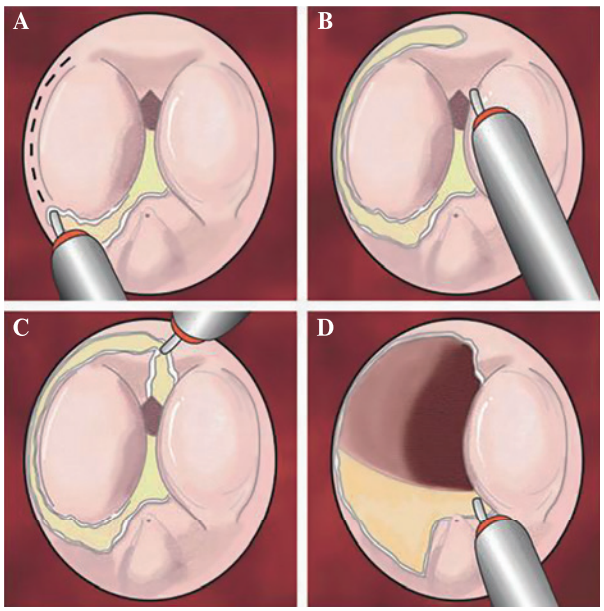

Fig. 1. Scheme of the two-lobe laser enucleation technique
A – tissue dissection at the verumontanum on the right and dissection of the layer between the adenomatous tissue and the surgical capsule; B – enucleation of the right lobe; C – tissue dissection at 12 o'clock; D – enucleation of the left lobe [13]

learning process and improve treatment outcomes. This technique was an evolutionary step, during which a single longitudinal incision is made and the prostate lobes are enucleated in a single horseshoe-shaped manner. This technique proved to be superior in terms of identifying and visualizing the surgical capsule, the proper layer for enucleation, and early apical release, which allows for better sphincter preservation.

With the accumulation of experience in performing en-bloc laser enucleation, surgeons began to modify it, since the incision of adenomatous tissue often led to bleeding and disorientation, which ultimately increased the operating time. A modified total en-bloc laser enucleation technique without a longitudinal incision was first described in 2019 by F. Gomez-Sancha (*Fig. 3*) [7].

Aim. To compare the results of thulium fiber laser enucleation of the prostate using different techniques.

Materials and methods. This study is retro- and prospective in nature and was carried out between January 2015 and May 2022. Patients with a history of prostate surgery, prostate cancer, urethral strictures, or bladder stones were excluded. For ThuFLEP, UROLAZ laser device from NTO IRE-Polus (Russia) with a wavelength of 1940 nm and laser fibers of 600 and 550 μm was used. All stages of the procedure were performed at a laser power of 60 W. Thulium enucleation of the prostate was done using a 26 Ch resectoscope from Karl Storz (Germany) or Richard Wolf (Germany), which provide continuous irrigation, and have a working element with a channel for the laser fiber. All procedures were performed by three surgeons with extensive experience in transurethral laser enucleations of the prostate. 450 patients were divided into three groups (A, B and C) according to the enucleation techniques. In group A, traditional two-lobes technique was done, in group B a classical technique of enucleation in a single block with longitudinal incision (en-bloc) was used, and in group C total enucleation in a single block without additional longitudinal incisions (total en-bloc) was performed. These techniques were used sequentially during the following period: two-lobes from January 2015 to October 2018, traditional en-bloc technique from October 2018 to November 2021 and total en-boc technique from November 2021 to May 2022.

Laser enucleation of the prostate using the two-lobe technique was done according to the scheme described by A.E. Krambeck and A.S. Baazeem. When performing laser enucleation using the en-bloc technique, we adhered to the basic principles described in the works of C. M. Scoffone.

A detailed description of the en-bloc technique performed by our surgeons is presented below.

Initially, it is important to identify the fold of the external sphincter (Nesbit's sign), which determines the border between adenomatous tissue and the urethral sphincter. The procedure begins with tissue dissection to the left and right of the verumontanum. This area is most

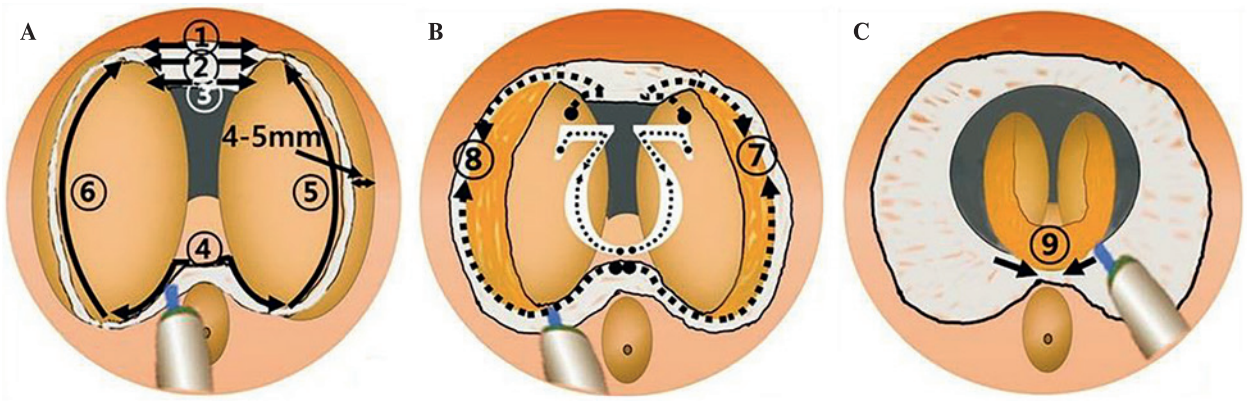

Fig. 2. Scheme of the en-bloc laser enucleation technique
A – tissue dissection to the right and left of the verumontanum, continuation of the incisions along the circumference on both sides; B – the process of enucleation of adenomatous tissue in a single block with dissection at 12 o'clock; C – the enucleated tissue is pushed into the bladder in a single block [15]

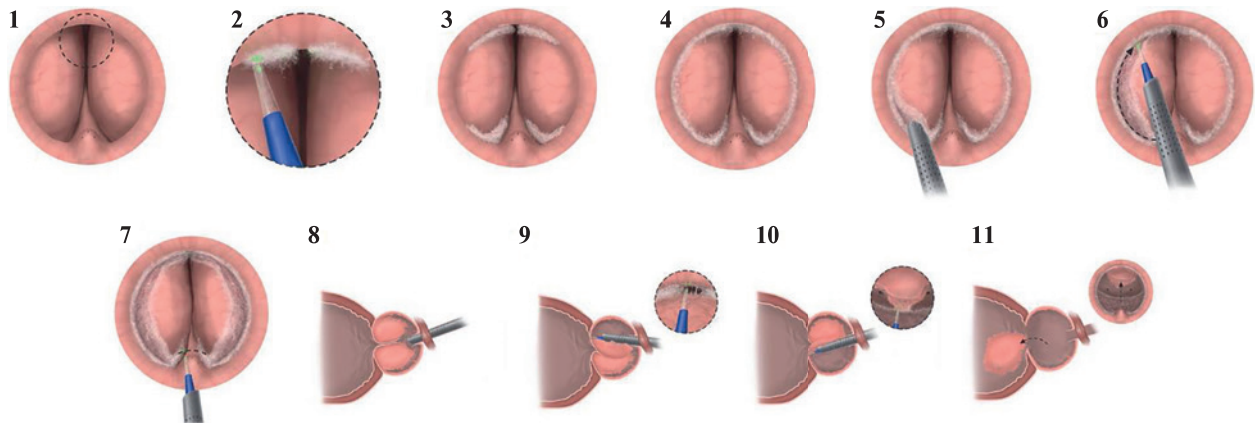

Fig. 3. Scheme of total en-bloc laser enucleation technique

1 – visualization of the external sphincter fold (Nesbitt sign); 2 – tissue dissection in the area of the external sphincter fold; 3 – tissue dissection to the right and left of the verumontanum; 4 – continuation of incisions on both sides along the circumference up to 12 o'clock; 5 – enucleation of the right and left lobes along the lateral surfaces; 6 – transverse incision at 6 o'clock; 8 – enucleation of the right and left lobes along the lateral surfaces; 9 – enucleation of adenomatous tissue along the upper semicircle; 10 – enucleation of adenomatous tissue along the lower semicircle; 11 – enucleated adenomatous tissue is pushed into the bladder [7]

convenient for determining the proper layer between the lobes and the surgical capsule. The incision continues from the verumontanum to 3 o'clock on the left and 9 o'clock on the right lobe, respectively. Then one can proceed to a circular incision at the level of the prostate apex at the proximal edge of the external sphincter. This maneuver leads to separation of the apex of the prostate from the sphincter, which minimizes a risk of sphincter injury. Subsequent enucleation of adenomatous tissue is performed within this layer. Enucleation of one of the lateral lobes is done in a circle with the surgical capsule as a reference point. The same is completed on the opposite side. In this case, a plane is formed along the surgical capsule in the direction from the verumontanum to the bladder with the displacement of all adenomatous tissue forward in a single block almost to the bladder neck. Next, prostatic lobes are dissected at 6 o'clock in the direction from the bladder neck to the verumontanum, visually focusing on the surgical capsule. Then, the adenomatous tissue is cut off from the bladder neck along its circumference [10, 14, 16].

When performing the enucleation using the total en-bloc technique, we followed the basic principles described by F. Gómez Sancha, making minor changes to the sequence of stages.

A description of the technique of enucleation without additional longitudinal incisions (total en-bloc), performed by our surgeons, is presented below.

The total en-bloc technique has been described relatively recently. Like the standard en-bloc technique, it begins with early apical release, i.e. with determining the strip of the external sphincter and a circular incision at the level of the apex at the proximal edge of the sphincter. Then, tissue is also dissected to the left and right of the verumontanum, where the plane between the adenomatous tissue and the surgical capsule is easily determined due to the protrusion in this place and the minimal amount of tissue regardless of the prostate size. Next, the incision is retrogradely expanded circumferentially towards the left lobe, thus continuing it at the verumontanum along the existing plane between the left lobe and the surgical capsule. Further, enucleation of the left lobe is continued, rising circumferentially from 5 to 3 o'clock, then to 12 o'clock behind the external sphincter until reaching the bladder neck. After that, one can return to the original incision at the verumontanum and continue the incision, reaching the apical part of the right lobe, and enucleation of the right and middle lobes is performed in the same way as described for the opposite side, connecting circumferentially with the already enucleated left lobe at 12 o'clock. Thus, we obtain an almost completely enucleated tissue in a single block, fixed along the lower semicircle from 10 to 2 o'clock. It is important to correctly incise the remaining fixing mucous membrane without damaging the external sphincter. Then, the enucleated tissue is pushed into the bladder for subsequent morcellation [7, 17].

After completing the enucleation stage, if the hemostasis was unsatisfactory, additional coagulation of the bleeding vessels was performed with electrical loop.

Removal of the enucleated tissue from the bladder in all three techniques was performed using a Piranha mechanical morcellator (Richard Wolf, Germany).

At the end of the procedure, a 18F three-way Rusch catheter was put for continuous irrigation of the bladder with saline in order to avoid bladder tamponade. Continuous irrigation was stopped in most cases on the 1st day after surgery, provided that there was no bleeding. The urethral catheter was removed in most patients on the 2nd day. The patients were followed up for 6 months.

The following parameters were assessed after 1, 3 and 6 months: prostate-specific antigen (PSA) level, the International Prostate Symptom Score (IPSS) and quality of life (QoL) scores, maximum (Qmax) and average (Qave) urine flow rates. The primary endpoint of the study was the efficiency (enucleation time, morcellation time and duration of procedure) of each of the techniques. The secondary endpoint was the incidence

of complications, particularly the rate of postoperative stress urinary incontinence.

For statistical analysis IBM SPSS Statistics 23.0 was used. Patient data are presented as mean ± standard deviation. To compare mean values, analysis of variance (ANOVA) was performed. Post hoc analysis was done using the Mann–Whitney U-test. The $\chi 2$ criterion was used to determine the significance of differences between frequencies. A p-value of 0.05 was chosen as the threshold for statistical significance.

Results. A total of 450 patients who underwent ThuFLEP were analyzed. Three techniques of laser enucleation were used, including two-lobe (n=148), en-bloc (n=150) and total en-bloc (n=152). The mean preoperative prostate volume was comparable (75.21; 76.12 and 75.82 cc in groups A, B and C, respectively, p>0.05) with the minimum and maximum volume of 34 and 205 cc, respectively. The mean age of patients was 64, 65 and 66 years (p>0.05). The mean baseline IPSS score, Qmax, Qave and QoL did not differ between groups. The average duration of the procedure when performing the total en-bloc technique was shorter compared to two-lobe and the en-bloc techniques (58.9±30.1 versus 68.8±30.6 and 67.4±30.1 min, respectively, p<0.05). The average weight of the enucleated tissue (dry residue) was equivalent (56.41±30.65, 57.09±31.87 and 56.87±32.45 g, respectively; p>0.05). Postoperatively, the prostate volume was also comparable in three groups (14.12±6.87, 15.14±7.78 and 14.21±7.56 cc, respectively; p>0.05). For a more reliable assessment of the differences in enucleation and morcellation times, it was decided to divide patients into three subgroups depending on the prostate volume: <80 cc, 80–150 cc, and >150 cc. The enucleation rate became higher with increasing prostate volume. For the two-lobe technique, it increased from 1.59 to 2.01 g/min; for the en-boc technique from 1.81 to 2.3 g/min and for the total en-bloc technique from 1.95 to 2.81 g/min.

The average enucleation rate when using the total en-bloc technique was higher compared to other two techniques (2.71±0.78 versus 1.9±0.74 and 2.02±0.69 g/min; p<0.05). The average morcellation speed was similar for all three techniques (2.8±1.7, 2.9±1.1, and 2.8±2.1 g/min; p>0.05). All three techniques were quite effective; no significant differences were found between groups. After 1 and 3 months, significant differences were seen between the groups in rate of stress urinary incontinence and QoL. After 6 months of follow-up, no differences were found in functional results (IPSS, PVR, Qmax, QoL). In addition, no significant differences were documented in PSA levels. The number of postoperative complications did not differ significantly. Stress urinary incontinence in the early postoperative period after removal of the urethral catheter was recorded in 38 (25.6%) patients in group A, in 29 (19.3%) patients in group B and in 27 (18%) patients in group C. After 3 months, stress urinary incontinence was found in 21 (13.9%) patients in group A, in 19 (12.4%) patients in group B and in 9 (5.4%) patients in group C. In the late postoperative period after 6-month follow-up, mild stress urinary incontinence (1 pad within 24 hours) was presented in 14 (9.3%), 6 (4%) and 4 (2.6%) cases, respectively (p=0.505). Formation of blood clots that resulted in urethral catheter obstruction, but did not require repeated endoscopic intervention and hemostasis, occurred in 67 (44.6%), 43 (28.6%) and 42 (28%) men in group A, B and C, respectively (p=0.291). Complications such as TUR syndrome, bladder wall trauma and blood loss requiring blood transfusion were not observed in any of groups.

Discussion. Retrograde dissection of the prostate lobes from the apical part to the bladder neck helps to better identify the proper plane and prevents damage to the bladder neck. With this technique, one need to determine the proper plane between the lobes and the surgical capsule only once, and not three times (at 5, 7 and 12 o'clock), which in turn reduces the risk of erroneous choosing of the enucleation plane. When continuing the procedure, one can focus on the existing plane throughout the enucleation, trying not to go beyond it, which eliminates the risk of incomplete removal of adenomatous tissue or perforation of the surgical capsule.

With the use of laser energy for the surgical treatment of lower urinary tract symptoms associated with BPH, new surgical treatment methods have been introduced. Currently, several laser devices with different sources of laser energy are available [18]. Surgical methods ranging from vaporization to resection and enucleation were developed.

In 1986, Y. Huraoka et al. [19] firstly described a technique for endoscopic enucleation of the prostate. This technique was technically imperfect, which prevented its widespread introduction. It involved using a loop to resect the lobes and was time-consuming.

In 1996, P.J. Gilling was the first to describe holmium laser resection of the prostate (HoLRP). The adenomatous tissue was resected with a laser in small pieces in the same way as with a loop during TURP [20].

With the advent of the tissue morcellator, laser enucleation of the prostate became widespread and gradually began to replace TUR. The development of enucleation of the entire prostate lobes in the existing layer between the surgical capsule and adenomatous tissue allowed for a significant reduction in surgical time compared to HoLRP. The laser fiber and the resectoscope tip in this technique act like a surgeon's finger during simple prostatectomy [21].

Laser enucleation of the prostate is currently the most evolutionarily developed and technically effective method of surgical treatment of BPH, which is essentially an endoscopic replication of simple prostatectomy [22].

Previous studies confirm the usefulness of modification and improvement of surgical techniques of laser enucleation, including the en-bloc technique. All previously developed techniques require one or more incisions in the adenomatous tissue. The prostate most often has three lobes, and quite often the problem is to find proper anatomical layer between the lateral and middle lobes, which requires a separate incision. This leads to unnecessary blood loss and loss of anatomical orientation. Considering these factors, a new technique of total en-bloc enucleation without additional incisions was developed, which allows enucleation in a single block without longitudinal incisions.

In our study, the clinical outcomes of three different techniques of laser enucleation of the prostate were compared, including two-lobe, classical en-bloc and relatively recently developed total en-bloc. No significant differences in functional outcomes (IPSS, residual urine volume, Qmax and QoL) were found. However, the total en-bloc technique was associated with significantly lower operating time and higher enucleation efficiency compared to the other two techniques.

Study limitations. The first important limitation is the retrospective and non-randomized design. The second limitation is that different time periods were analyzed, including skill acquisition and advanced training, which may influence on results. The third limitation was the short follow-up period (6 months), precluding assessment of possible late complications, such as urethral strictures, bladder neck stenosis, or recurrence of BPH.

Conclusion. All laser enucleation techniques are effective and safe for treating patients with BPH. Peri- and postoperative results, as well as the number of complications, were equivalent in all groups. However, when performing laser enucleation using the total en-bloc technique, the duration of the procedure, particularly the enucleation stage, was significantly lower compared to two other techniques. Laser enucleation of the prostate using the total en-bloc technique is a safe procedure that allows for easier recognition of the surgical capsule and preservation of the external sphincter mucosa, which ensures a low incidence of postoperative stress incontinence.

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Author information:

Dibiraliev Ch.D. – urologist, Ph.D. student, Institute for Urology and Reproductive Health, FGAOU VO I.M. Sechenov First Moscow State Medical University, Moscow, Russia; e-mail: chinghiz.dibiraliev@yandex.ru

Abdulaev Ch.N. – resident, Ph.D. student, Institute for Urology and Reproductive Health, FGAOU VO I.M. Sechenov First Moscow State Medical University, Moscow, Russia; e-mail: abdulaev.ch@yandex.ru

Danilov S.P. – Ph.D., urologist, Institute for Urology and Reproductive Health, FGAOU VO I.M. Sechenov First Moscow State Medical University, Moscow, Russia; e-mail: spdanilov@gmail.com

Sukhanov R.B. – Ph.D., assistant, Institute for Urology and Reproductive Health, FGAOU VO I.M. Sechenov First Moscow State Medical University, Moscow, Russia; e-mail: rb_suhanov@mail.ru

Dymov A.M. – Ph.D., Institute for Urology and Reproductive Health, FGAOU VO I.M. Sechenov First Moscow State Medical University, Moscow, Russia; e-mail: alimdv@mail.ru

Bezrukov E.A. – Ph.D., MD, professor of the Institute for Urology and Reproductive Health, FGAOU VO I.M. Sechenov First Moscow State Medical University, Moscow, Russia; e-mail: eabezrukov@rambler.ru

LITERATURE REVIEWS

I.V. Kuzmin

BIOREGULATORY THERAPY FOR OVERACTIVE BLADDER

FGBOU VO Pavlov First Saint Petersburg State Medical University of the Ministry of Health of Russia, Saint-Petersburg, Russia

Corresponding author: I.V. Kuzmin – Ph.D., MD, professor of the Department of Urology of FGBOU VO Pavlov First Saint Petersburg State Medical University of the Ministry of Health of Russia, Saint-Petersburg, Russia; e-mail: kuzminigor@mail.ru

This review is devoted to the pathogenetic basis and clinical results of the use of a new domestic innovative drug Vesusten, which is based on polypeptides made of animal bladder tissue, for the treatment of patients with overactive bladder. Data are given regarding the epidemiology, pathogenesis factors and current treatment methods. The mechanisms of peptide regulation of physiological processes in humans are also described. The basic principles of the use of bioregulatory peptides for therapeutic purposes. The results of preclinical and clinical studies of the drug Vesusten are discussed in detail.

Key words: *overactive bladder, detrusor overactivity, bioregulatory therapy, regulatory peptides, Vesusten*

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Urination disorders caused by overactive bladder (OAB) are one of the most common reasons for seeking outpatient urological care [1, 2]. Patients with OAB have increased frequency and urgency, which often cause urgent urinary incontinence. The generally accepted definition of OAB by the International Continence Society emphasizes the absence of infectious or any other bladder disorders [3]. The prevalence of OAB is high and reaches 15–25% among adults [1, 4, 5]. The significance of OAB is determined not only by its high prevalence, but also by the negative impact on the quality of life, which in many cases represents both a medical and a social problem. Many aspects of the pathogenesis of OAB have not yet been fully elucidated, but its multifactorial nature is undoubtful. Neurological diseases, bladder outlet obstruction, bladder wall ischemia and urothelial dysfunction are considered to be the main causes of OAB development [6]. The pathogenetic factors of non-neurogenic OAB are closely interconnected. Thus, bladder outlet obstruction causes hemodynamic disturbances in the bladder, which in turn may result in urothelial dysfunction [7, 8]. Bladder wall ischemia is especially pronounced in the case of a combination of systemic atherosclerosis and bladder outlet obstruction, which is often observed in older men [9, 10]. A relationship has been found between the degree of blood flow disturbance in the bladder and the severity of OAB symptoms: the more severe the ischemia, the greater the severity of dysuria [11, 12]. In recent years, numerous evidences have been obtained proving a connection between OAB and the inflammatory process in the bladder wall [13]. Patients with OAB have higher levels of inflammation biomarkers in the urine, including cytokines and chemokines, compared to healthy individuals, which correlates with the severity of dysuria [14, 15]. Moreover, it has been shown that the inflammatory component is more pronounced in patients with lower efficiency of anticholinergic therapy for OAB [16, 17]. With inflammation, the release of neurotransmitters interacting with afferent neurons elevates, which increases bladder sensitivity. First of all, this applies to adenosine triphosphate, since the purinergic signaling system plays a key role in ensuring the sensory function of the urothelium, but also to acetylcholine, neurokinin A and prostaglandins [18]. Aseptic inflammation can develop in case of disruption of the barrier function of the urothelium and penetration of various substances from urine into the bladder mucosa [19]. Thus, in the pathogenesis of OAB, along with neurological deficit, bladder outlet obstruction and ischemia, an important role belongs to inflammation in the bladder wall, which can be the cause of sensory impairment of the urothelium. This circumstance has not only theoretical but also important clinical significance.

General principles of treatment of overactive bladder

The treatment tactics for patients with OAB depends on its cause, the presence of concomitant diseases and their therapy, the efficiency and tolerability of previously administered treatment, as well as the presence of contraindications to certain types of drugs [20]. It is recommended to begin treatment with a combination of conservative (behavioral) and drug therapy. Pharmacotherapy plays a leading role in patients with OAB. For the treatment of OAB, M-anticholinergics and β3-adrenomimetics are used [21–23]. Drugs with an anticholinergic effect have been used in the treatment

of OAB for almost half a century. The first report on the clinical use of oxybutynin dates back to 1976 [24]. Over the past time, extensive experience in the use of M-anticholinergics has been accumulated, proving their efficiency in patients with OAB. At the same time, a number of limitations have been identified. M-anticholinergics may be accompanied by side effects due to their antimuscarinic activity, including dry mouth, constipation, nausea, blurring vision, urinary retention. For elderly patients and those with neurological disorders, the ability of most M-anticholinergics to cross the blood-brain barrier is especially significant, which can cause side effects from the central nervous system, such as drowsiness, confusion, emotional lability, and cognitive impairment [25]. Drugs of this group increases the overall anticholinergic load, which is important to consider in case of simultaneous use of other medications with a similar effect. In addition, in some diseases and pathological conditions, M-anticholinergics are contraindicated, included closed-angle glaucoma, myasthenia, gastrointestinal obstruction and others. In some cases, anticholinergic therapy for OAB is ineffective. The incidence of the disease refractory to antimuscarinic drugs remains a subject of debate, which is largely due to the lack of criteria and a standardized definition [26]. A number of researchers showed that incidence of refractory OAB is nearly 20% [27, 28]. If M-anticholinergics are effective, many patients experience a relapse fairly quickly after stopping therapy [29, 30, 31]. According to Y.S. Lee et al. (2011), OAB symptoms recurred within 3 months after completion of therapy in 62% of patients [30].

A.R. Morris et al. (2008) indicated that a stable and long-lasting effect after a successful course of M-anticholinergics is achieved only in 20% of women with OAB [31]. In case of insufficient efficacy and poor tolerability of pharmacotherapy, as well as the presence of contraindications, the next line of treatment, namely invasive therapy, is indicated. Attempts are being made to increase the capabilities of traditional pharmacotherapy without moving to invasive methods. Over the past few years, the results of a number of clinical studies have been published that examined various pharmacological strategies for the treatment of refractory OAB, from increasing the dose of anticholinergic drugs, combining two M-anticholinergics, to using a β3-adrenergic agonist and a phosphodiesterase type 5 inhibitor as monotherapy or in combination with an M-anticholinergic [32–34]. The treatment results were varied from relatively successful to complete lack of effect, but in general the problem of therapy for refractory OAB has not been solved. The reasons for the insufficient efficiency of treatment and the early development of OAB recurrence after stopping M-anticholinergics are apparently related to the fact that they do not affect the pathogenesis, being essentially symptomatic therapy.

Inflammation and ischemia of the bladder wall are considered to be the leading factors of cholinergic resistance in patients with OAB [17, 35]. Ischemia causes increased activity of vanilloid and purinergic afferent receptors in the urothelium, which leads to an increase in its sensitivity and the development of OAB symptoms [36]. G.A. Digesu et al. (2013) performed a morphological study of bladder biopsies from 110 women with refractory OAB and found chronic inflammation in 94 cases [17]. From a pathogenetic point of view, it is apparently justified to prescribe anti-inflammatory drugs to patients with refractory OAB. Studies of their efficiency in patients with OAB were carried out in the early 1980s, and quite encouraging results were obtained in some cases [37, 38]. However, these studies did not continue, which is due to several reasons. Firstly, at that time, increased attention was attracted by M-anticholinergics, which had just begun to be actively used. Secondly, there was no concept of "cholinergic-resistant OAB", while in this category of patients, anti-inflammatory therapy could show its advantages. And finally, inflammation was not considered as a factor in the pathogenesis of OAB. Thus, the search for an effective drug strategy for patients with OAB, especially refractory to anticholinergics, as well as for those with poor tolerance or contraindications to standard therapy, remains very relevant. In this regard, the use of bioregulatory therapy seems very promising.

Peptide regulation of physiological processes

The concept of peptide regulation of physiological processes was proposed by the outstanding Russian physiologist and biochemist, Academician of the Russian Academy of Sciences I.P. Ashmarin (1925-2007). It is based on the idea of peptides as carriers and transmitters of information that ensure intercellular interaction [39]. According to the teachings of I. P. Ashmarin, regulatory peptides have two important properties. Polyfunctionality means that each type of molecule has its own unique characteristics, and at the same time they are able to induce the synthesis of other peptides that also have unique properties. Thus, the same peptide can directly or indirectly affect different physiological processes. Regulatory peptides, initiating the release of new portions of peptide regulators, start a process called the "peptide cascade" [39]. The presence of a peptide cascade, which is the second main characteristic of peptide regulation, allows the required number of regulatory molecules to be formed in a short time [40]. Regulatory peptides, along with cytokines, are the important intercellular mediators, which main functions are regulation of cell functional activity, maintenance of homeostasis of cell populations and adequate response to various stimuli [41]. Molecular studies have shown that polypeptide complexes have “active loci” consisting of 2–4 amino acids that directly exert a regulatory effect [42]. For a long time, the question remained unclear, how do regulatory peptides provide their function at the molecular level. Do they penetrate the cytoplasmic and nuclear membranes, or do these molecules interact with membrane receptors and activate intracellular signaling pathway? Studies have shown that peptides are able to penetrate the cell nucleus and interact with DNA [43]. It has been established that there are nucleopores in the membrane of nuclei, formed by special proteins, which are called nucleoporins. The diameter of nucleopores is about 50 nm, and low-molecular substances with a molecular weight of less than 3,5 kDa can penetrate through them. Regulatory peptides or their active regions are quite suitable for these characteristics [44]. Oligopeptides penetrate through the cell membrane into the nucleus. Then the “active loci” of these peptides bind to the promoter zones of DNA and activate the transcription of genes responsible for the synthesis of proteins, including regulatory ones [43,

45]. Thus, oligopeptides, into which larger molecules disintegrate during proteolysis, regulate gene expression and affect cell proliferation, differentiation and apoptosis in various tissues [46, 47].

General principles of bioregulatory therapy

Based on the teachings of I.P. Ashmarin, the concept of bioregulatory therapy was proposed, which is the use of regulatory peptides for therapeutic purposes. The most important step towards its implementation in clinical practice was the development in the 1970s by Russian scientists V.Kh. Khavinson and V.G. Morozov of a method for extracting low-molecular peptides, namely cytomedins, from animal tissues [48].

Taking into account the inherent properties of regulatory peptides, cytomedins were classified to this class of biologically active molecules. Along with "cytomedins", terms "bioregulatory peptides" or "peptide bioregulators" are often used. This emphasizes their ability to participate in the regulation of biological processes. It was suggested and subsequently confirmed that cytomedins in each organ constitute a special peptide pool, and its composition is the same in different species of mammals [49]. Thus, cytomedins have properties inherent to the entire class of regulatory peptides, namely tissue specificity and organ specificity in the absence of species specificity. In other words, bioregulatory peptides obtained from the same mammalian organ will have similar biological activity, but it will differ from that of peptides isolated from other organs of a representative of the same species. Another important property of cytomedins was also discovered, which is to influence not only on the organ from which they were isolated, but also the entire body [40]. The first organ from which cytomedins were obtained was the thymus gland. Then, regulatory peptides were isolated from many other organs and tissues, and a significant number of them found wide application in various fields of medicine [51]. In urology, the most widespread are drugs created on the basis of prostatic peptides. Owing pharmacological properties (anti-inflammatory and immunotropic effects, the ability to improve hemodynamics and rheological properties of blood, direct myotropic effect), these drugs take an important place in the treatment of prostatic diseases [51–54]. Taking into account the organ specificity of regulatory peptides, a drug based on peptides isolated from the bladder was developed for the treatment of bladder diseases.

Vesustene is a peptide drug from bladder tissue

In 2022, the peptide drug Vesustene was registered as a medicinal product (registration number: LP-008223 dated 02.06.2022). It is a complex of regulatory peptides with a molecular weight of no more than 10 kDa, isolated from the bladder of cattle (bulls). The registration of Vesustene was preceded by more than 10 years of studies that proved its safety and high efficacy in the treatment of patients with OAB.

Preclinical studies

At the preclinical stage, the safety of the drug in experimental animals was assessed. In 2012, data were obtained according to which Vesusten does not increase the incidence of spontaneous tumor development, that is, the absence of oncogenic potential in the drug was proven [55]. Two years later, in 2014, the tests were completed, proving the absence of acute and chronic toxicity [56–58], local irritant [59] and immunotoxic effects [60], allergenicity [61] and mutagenicity [62] of Vesusten. Three years later, in 2017, the results of a study using the DNA comet assay were obtained, confirming the absence of carcinogenic activity in Vesusten [63]. This test is very sensitive and allows for the detection of DNA damage in individual cells. In the same year, the absence of reproductive toxicity in Vesusten was proven [64]. Experimental studies were carried out, confirming the presence of the fundamental property of cytomedins in Vesusten, which is organ specificity [65]. Fragments of various tissues were cultured in the presence of Vesusten. A reliable increase in the growth zone of the bladder wall explants of young and old rats (890 explants in total) was found, which proves that the drug has an organ-specific effect on bladder tissue. At the same time, adding preparations of other organs and tissues (cartilage, blood vessels, testicles, ovaries, liver, brain, kidneys) in similar concentrations did not have the same effect. In 2017, the results of a study of the effect of Vesusten on the contractile activity of the detrusor were obtained. An experimental model of obstructive detrusor hyperactivity due to partial bladder outlet obstruction was created. The experiments were carried out on small laboratory animals. Bladder outlet obstruction was modeled by ligating the urethra for a period of 6 weeks, leaving only a thin catheter. On the 4th week, treatment with Vesusten was started. The drug was administered i.m. once a day for 10 days, and the results were assessed 10 days after the end of therapy. The control group consisted of animals with bladder outlet obstruction that did not receive treatment. Cystometry was performed on the animals of the main and control groups. The results indicated that Vesusten has a normalizing effect on the contractile activity of the detrusor. A decrease in the severity of detrusor hyperactivity was noted. In animals with induced detrusor hyperactivity, the elevated detrusor pressure decreased by 12.7%, 33.4%, and 43.8% when using dosages of Vesusten of 8, 16, and 32 μg/ml, respectively. In further experiments, a concentration of 32 μg/ml was taken as a therapeutically effective dose, which corresponds to 5 mg for the human dosage. At the end of the treatment, the weight and volume of the urinary bladder, as well as the amount of postvoid residual, did not differ significantly from those of intact animals and were significantly less than in the control group [66].

Thus, the high safety profile of Vesusten, its organ-specificity for the urinary bladder and its ability to normalize the contractile activity of the detrusor were confirmed at the preclinical stage. The greatest effect of the drug was obtained at a dosage of 32 μg/ml, which corresponds to a human dosage of 5 mg.

Clinical studies

The favorable results obtained at the preclinical stage served as the basis for carrying out clinical trials. The safety and efficacy of Vesusten were studied in phases I–III studies, which were carried out in accordance with GCP standards. A total of 290 patients were included, of which 32 were healthy volunteers and 258 were patients with OAB.

A phase I study demonstrated a favorable safety profile and good tolerability of increasing doses of Vesusten with

single and subsequent multiple administrations to healthy volunteers.

No serious adverse events (AEs) were observed during the study. A total of 28 AEs were registered, all of which were mild. The most common was pain at the injection site (24 cases, 85.7% of all AEs), which were recorded in 10 (31.2%) volunteers. The remaining 4 (14.3%) AEs were abnormal laboratory test results and, according to the investigators, were not related to the studied drug. There was no case of treatment discontinuation or to prescribing additional treatment due to AEs [67]. A multicenter, placebo-controlled, randomized phase II study carried out in 2019, which involved 108 patients with OAB, assessed the efficacy and safety of different doses of Vesusten. Patients were divided into 3 groups of 36 people each. Patients in groups 1 and 2 were prescribed Vesusten 2 and 3 times a week, respectively, 5 mg i.m. for a course of 10 injections. Patients in group 3 were prescribed placebo 5 mg i.m., 10 injections two ($n = 18$) and three times a week ($n = 18$). The study demonstrated a favorable safety profile of Vesusten. The incidence of AEs in the treatment groups did not exceed that in the placebo group. In patients of the groups 1 and 2 who received Vesusten, a significant decrease in the severity of OAB symptoms (increased frequency, urgency, and urgent urinary incontinence) and an improvement in the quality of life were noted. At the same time, a slightly higher efficacy of Vesusten was revealed when the drug was prescribed 3 times a week [68].

The results of the phase II study served as the basis for carrying out a phase III clinical trial [69], involving 150 patients of both sexes aged 18 to 70 years with a diagnosis of OAB lasting at least 3 months. They should have at least 3 imperative episodes of urgency over the past 3 days, and at least 7 urinations on average per day. All patients were randomized into two groups of 75 people. Patients of the main group were prescribed Vesusten, while in the control group patients received placebo. The studied drug and placebo were administered i.m. at 5 mg 3 times a week for a course of 10 injections. The results demonstrated the clinical efficacy of Vesusten in patients with OAB. A significant decrease in the severity of OAB symptoms and an improvement in the quality of life were noted compared to placebo. Thus, in the main group, a significant decrease in the severity of urgency, assessed by the TUFS (Total Urgency and Frequency Score) score, was observed compared to the placebo group. The average decrease in the TUFS score in the Vesusten group was 1.97 times greater than in the placebo group. The proportion of patients in the Vesusten group with significant improvement, which was defined as a decrease in the TUFS score by more than 20% compared to the baseline level, was 54.05% immediately after therapy and 66.67% 21 days later, i.e. an increase in the effect was noted. These values significantly differed from the corresponding values in the placebo group. Significant differences between the main and control groups were also noted in the number of patients who had a decrease in the number of episodes of urgent urinary incontinence per day by 50% or more.

In the main group, a proportion of such patients 21 days after the end of therapy was 65.33%. The average decrease in the number of episodes of urinary incontinence in the Vesusten group was higher compared to the placebo group by more than 2 times. A significant decrease in the degree of anxiety due to OAB symptoms in the Vesusten group was also noted according to the OAB-q questionnaire.

Vesusten was well tolerated, and the incidence of AEs did not differ from that in the placebo group. The most common AEs were abnormal laboratory test results. However, according to the researchers, their relationship with the studied drug was questionable or absent. In rare cases, pain at the injection site was noted. There was no treatment discontinuation due to AEs. Thus, the results of the study showed that Vesusten reduces the severity of OAB symptoms, and the drug has a favorable safety profile. The efficacy of Vesusten significantly exceeds placebo, while the incidence of AEs did not differ from that in the control group [69].

An important advantage of Vesusten is that its therapeutic effect is not limited to the period of administration, but persists for a long time after end of therapy. This phenomenon is due to the unique property of regulatory peptides, which is a presence of a peptide cascade. A relatively short course of treatment can lead to a significantly longer therapeutic effect. Medicinal products based on regulatory peptides have another important feature, namely the impossibility of drug overdose, since after reaching a certain concentration of regulatory peptides, their pharmacological effect does not longer increase [70]. The effect of cytomedines, and Vesusten is no exception, is based on the ability to normalize the functions of tissues and organs. In other words, the therapeutic effect will be exerted only in the case of some pathological deviations, whereas in normal conditions, drug will not work. Vesusten, as was shown at the preclinical stage, reduced the increased contractility of the detrusor, but did not have a similar effect in case of normal contractility. This is the most important feature of regulatory peptides, which distinguishes them from drugs of other groups. The results of clinical trials, as well as the post-registration data, served as the basis for the Expert Council on Urodynamics and Neurourology of the Section of Neurourology of the Russian Society of Urologists to recommend Vesusten for use in routine clinical practice both as a starting therapy for OAB and in cases of limitations or insufficient efficiency of traditional pharmacotherapy for OAB [71]. The possibility of prescribing Vesusten in combination with symptomatic drugs for the treatment of OAB was also noted. The experts spoke in favor of including the drug based on bladder polypeptides Vesusten in clinical guidelines for the treatment of urinary incontinence and urination disorders.

Conclusion

The introduction of the domestic innovative drug Vesusten in the armamentarium of urologists significantly expands the possibilities of treating patients with OAB. It can be argued that the drug has a pathogenetic effect, and its use in clinical practice is based on the positive results of experimental and clinical studies.

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Author information:

Kuzmin I.V. – Ph.D., MD, professor of the Department of Urology of FGBOU VO Pavlov First Saint Petersburg State Medical University of the Ministry of Health of Russia, Saint Petersburg, Russia; e-mail: kuzminigor@mail.ru. ORCID: https://orcid.org/0000-0002-7724-7832; eLibrary SPIN: 2684-4070; SCOPUS: 56878681300

SYSTEMATIC REVIEW

V.A. Malkhasyan[1,2], A.G. Martov[3,4], N.K. Gadzhiev[5], S.O. Sukhikh[2], B.L. Grigoryan[1], D. Yu. Pushkar[1,2]

COMPLICATIONS OF FLEXIBLE URETERORENOSCOPY: A SYSTEMATIC REVIEW

[1]Russian University of Medicine, Moscow, Russia; [2]Botkin City Clinical Hospital, Moscow, Russia; [3]A.I.Burnazyan Federal Medical Biophysical Center of the FMBA of Russia, Moscow, Russia; [4]M.V. Lomonosov Medical Research and Educational Center Moscow State University, Moscow, Russia; [5]N.I.Pirogov High Medical Technologies Clinic, Saint Petersburg State University, Saint Petersburg, Russia

Corresponding author: V.A. Malkhasyan – M.D., Dr.Med.Sci.; Professor of the Department of Urology, Russian University of Medicine; Head of Urology Department №67, Botkin City Clinical Hospital, Moscow, Russia; e-mail: vigenmalkhasyan@gmail.com

Retrograde intrarenal surgery (RIRS) is a type of endoscopic intervention on the kidneys performed using a semi-rigid or flexible fiber optic endoscope. RIRS is recommended by national clinical guidelines for stone management sized up to 20 mm. However, like any other surgical intervention, RIRS is associated with the risk of complications. Complications affect the patient's quality of life, and cause additional costs determined by prolonged hospital stay and subsequent treatment. This systematic review is devoted to the complications of RIRS, methods of their prevention and treatment, which should make possible to increase the effectiveness and safety of care for patients with urolithiasis.

K e y w o r d s: retrograde intrarenal surgery, flexible ureterorenoscopy, fURS, complications

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Introduction. Urolithiasis is one of the most common urologic diseases, the peak of which occurs in the third and fourth decades of life [1]. Treatment strategy varies from observation to surgical removal of the stone. The types of surgical intervention depend on the stone number, size, density and location. Over the past decades, "open" surgery has been almost completely replaced by minimally invasive endoscopic procedures. Percutaneous nephrolithotomy has become the most widely used treatment option for upper urinary tract stones larger than 2 cm. This method has high efficacy, but is associated with the risk of developing serious complications, such as bleeding, infections and damage to adjacent organs. In this regard, in recent years, flexible ureteroscopy has been actively introduced into clinical practice as a less traumatic and safe option. Technical advances in the endoscopic instruments, the emergence of digital and disposable endoscopes, and the miniaturization of instruments contribute to the constant expansion of indications for retrograde intrarenal surgery (RIRS) [2]. However, despite the presumed safety, according to many studies, RIRS is also associated with a number of complications, the incidence of which can reach 8% [3–5]. In our systematic review, we analyzed the published data, formulating recommendations to help predict, prevent, and effectively overcome complications of flexible ureteroscopy. We carried out a systematic search of publications from 2007 to September 2022 (over the past 15 years) dedicated to complications of RIRS in PubMed, Google Scholar, and Scopus. This review was conducted according to the PRISMA checklist (*Fig. 1*). The search strategy included free-text using the following key words: ureterorenoscopy, retrograde intrarenal surgery, flexible ureteroscopy, lithotripsy, intraoperative complication, postoperative complication, fURS, RIRS, mortality.

When forming the search query, studies devoted to the pediatric patient population and those published in languages other than English were excluded.

Two researchers carried out the search independently. Eligible studies were read in full-text. Their reference lists were also reviewed for possible additional publications. After full-text screening, duplicates were excluded. Any disagreements regarding the inclusion or exclusion of preselected studies for the systematic review or any other disagreements during the review process were resolved by discussion or involving a third author.

The initial search identified 278 articles. After removing duplicates, the following types of publications were further excluded: commentaries to articles, conference abstracts, articles without abstracts, description of clinical cases. The remaining 47 publications included 21 clinical trials, 16 literature reviews, and 10 meta-analyses. After reviewing the abstracts, 37 publications were selected for further analysis. Of priority interest were studies performed on a large number of patients (n> 50), containing the Clavien–Dindo classification of complications or having a detailed description of complications that can be easily assessed using this classification. Publications devoted to methods of eliminating complications were also of interest.

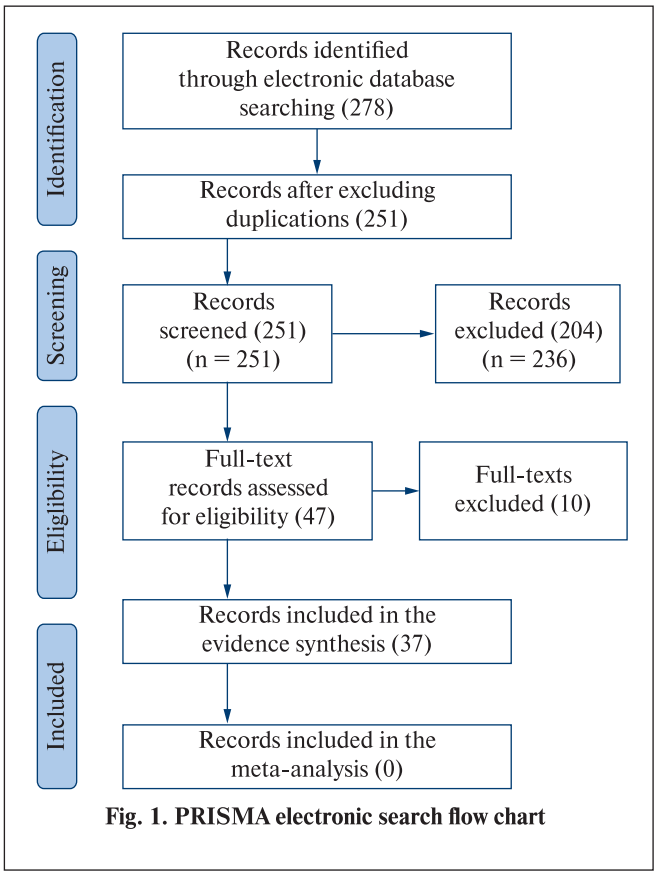

Fig. 1. PRISMA electronic search flow chart

Clavien–Dindo classification of complications. The standardized Clavien–Dindo classification of surgical complications is used as a simple and widely used tool for assessing and recording surgical complications. In most literature sources, this classification is used to describe and compare complications of specific surgical procedures [6].

The Clavien–Dindo classification, modified for assessing complications of ureteroscopy and RIRS, was first used by Mandal et al. in 2012 [7]. The result of this study was the addition of complications that were not mentioned by previous researchers in retrospective analyses. They included hematuria, transient increase in serum creatinine levels, and fever. All of the above phenomena resolved spontaneously without pharmacological treatment or additional surgical interventions. Currently, the modified Clavien-Dindo classification allows for a more subtle assessment of the treatment outcomes and demonstrates a more complete description of the postoperative course.

In the modified Clavien-Dindo classification, five degrees of complications are distinguished, which can be divided into three groups: infectious, traumatic, and hemorrhagic (see table). Using this scale for assessing adverse events in a retrospective study, E. Ogreden et al. in 2016 analyzed 811 patients. As a result, the first quantitative distribution of complications of semirigid ureteroscopy was developed [8]. Complications of RIRS can be classified as infectious, hemorrhagic, and traumatic.

Table

Modified Clavien-Dindo classification of complications of flexible URS and the results of a retrospective study by E. Ogreden et al. with the percentage of adverse events

Grade	Complication	*n* (%)
I	Fever	83 (10.2)
	Transient increase in creatinine	3 (0.37)
	Transient hematuria	110 (13.6)
	Persistent hematuria	46 (5.7)
	Total complications	242 (29.8)
II	Blood transfusion	2 (0.24)
	Urinoma requiring urinary tract drainage with a stent	56 (6.9)
	Total complications	58 (7.1)
IIIa	Urinoma requiring urinary tract drainage with a stent	18.2 (2.2)
	Bladder hemotamponade	11 (1.4)
	Ureteral mucosal injury	41 (5.0)
	Total complications	70 (8.6)
IIIв	Ureteral stent migration	16 (1.9)
	Stone migration	30 (3.7)
	Ureteral perforation	37 (4.6)
	Ureteral avulsion	7 (0.86)
	Ureteral stricture	0 (0)
	Total complications	90 (11)
IVa	Myocardial infarction	0 (0)
	CKD	0 (0)
	Total complications	0 (0)
IVв	Urosepsis	10 (1.2)
	Multiple organ failure	0 (0)
	Total complications	10 (1.2)
V	Death	0 (0)
Total number		470 (5.9)

Infectious complications. For flexible URS, they include hyperthermia, acute pyelonephritis, systemic inflammatory response syndrome (SIRS) and sepsis. The latter is a dangerous complication that can lead to the death. In a survey of 11 endourologists with extensive experience in performing flexible URS, carried out by L. Cindol et al., 4 cases of urosepsis with a lethal outcome were identified [9].

According to various publications, a rate of infectious complications is about 7.7–8.4%. SIRS can develop in 1.7–4.4% of cases, while the incidence of urosepsis is within 0.7–1.3% [4, 10–12]. According to F. Berardinelli et al., the overall rate of infectious complications, including hyperthermia (4.4%), SIRS (1.7%) and sepsis (0.7%), can reach 7.7% even despite preoperative antibiotic prophylaxis [9]. In a retrospective study, S. Fan et al. analyzed 227 patients who underwent flexible URS [10]. The authors showed that in the absence of residual fragments ("stone free") in 81.9% of patients, the incidence of infectious complications was 8.4%. The most common postoperative complication that does not require reoperation is fever, which can have various origin. On average, fever occurs in 9% of patients with negative urine culture even if preoperative antibiotic prophylaxis is used [8, 13–16]. The main risk factors for infectious complications, according to the literature data:

- female gender,
- diabetes mellitus,
- duration of the procedure over 60 min,
- stone size over 2 cm,
- infectious stones (struvites),
- bacteriuria,
- leukocyturia,
- history of urinary infection,
- presence of residual fragments,
- intraoperative increase in intrarenal pressure (IRP) ⩾40 cm H_2O,
- volume and flow rate of irrigation fluid [10, 12, 17–22].

The development of infectious complications is associated with the increased IRP [23]. This leads to the development of pyelovenous reflux, which results in the release of the contents of the collecting system directly into the bloodstream. In an experimental study by Loftus et al. on an animal model, it was shown that elevated IRP increases the likelihood of bacteremia and contamination of parenchymatous organs such as the kidneys, liver, and spleen with microorganisms contained in the irrigation fluid [24]. According to a randomized study by Omar et al., high IRP leads to an increase in the frequency of a systemic inflammatory response by approximately 30% [25].

A number of authors showed that the IRP during flexible URS is significantly higher compared to percutaneous procedures and varies in the range of 40.8–199.35 cm H_2O [26]. Normal IRP fluctuates within 0–20 cm H_2O, and its increase depends on many factors. Thus, even the passage of a ureteroscope into the collecting system without irrigation can lead to an increase in IRP by 30 cm H_2O due to obstruction of the ureteral lumen, and active irrigation with a manual pump can lead to an increase in IRP from 156.4 to 557.6 cm H_2O depending on its intensity [27]. As indicated earlier, a specific role in the development of infectious complications belongs to the pyelovenous reflux. According to experimental studies, it occurs with a persistent increase in IPP to 74 cm H_2O and higher for 20 minutes [28]. Thus, the most rational way to control infectious complications seems to be the control of IRP as the main pathogenetic mechanism. One of the effective methods for controlling IRP is the use of a ureteral access sheath (UAS). The study of Tokas et al. showed that when using UAS, IRP usually does not exceed 30 cm H_2O with an irrigation fluid pressure of ⩽100 cm H_2O [25]. The use of UAS reduces IRP, while improving the visibility, which increases the efficiency of the procedure [29–31]. UAS allow to maintain a stable IRP in safe range even when using a hand pump. According to the Rehman et al., UAS of 12–14 Fr or more allows for stabilization of IRP <20 cm H_2O [32, 33], which in turn leads to a decrease in the incidence of infectious complications [34].

Another significant risk factor for infectious complications is the duration of procedure. The study by Xu et al. showed that the risk of infectious complications increases by 11.1 times if intervention lasts more than 60 min [35]. Accordingly, with a large stone, the duration of procedures increases, which is associated with a high risk of infectious complications.

No less significant risk factors for infectious complications and sepsis are asymptomatic bacteriuria, the presence of obstruction or a ureteral stent [20, 36, 37]. According to the study by Wang et al., the use of flexible URS in patients with upper urinary tract obstruction is associated with a higher risk of sepsis than with percutaneous access [20]. Such risks can be explained by the impaired urine passage and, as a result, misleading results of urine culture, indicating sterility, while the pelvis can be contaminated with pathogens. Other authors completely dispute the value of bacteriological examination of urine from the bladder, demonstrating much greater sensitivity of the results of urine from the renal pelvis and the stone [38].

A ureteral stent, being a foreign body, is also considered by many authors as a risk factor for infectious complications. According to a large multicenter study, the dwelling time more than 2 months increases the risk of developing infectious complications, and duration of stenting more than 4 months triples the risks [39]. In the study of Nevo et al., an increased risk of sepsis was demonstrated in patients with a ureteral stent; in addition, the risks of sepsis depended on the dwelling time. Thus, an increased probability of sepsis was observed in cases where the duration of stenting was more than 1 month [40].

One of the most popular preventive measures is the preoperative antibacterial therapy. A number of studies have shown that preoperative antibacterial prophylaxis with a single dose leads to a decrease in the incidence of bacteriuria, leukocyturia and infectious complications. Intravenous antibiotic prophylaxis is not superior to oral in terms of reducing the incidence of urinary tract infections [41, 42]. Zisman et al. mentioned a higher risk of developing urosepsis in patients with a positive urine culture, suggesting as a preventive measure an augmentation of antibacterial therapy (adding a second antibiotic) [43]. Thus, based on the analysis of modern literature, the following recommendations can be given to ensure the safety of RIRS: selection of patients based on risk factors, mandatory use of UAS to maintain IRP at a level of less than 40 cm H_2O, limiting the duration of the procedure to 1 hour in high-risk patients, minimizing

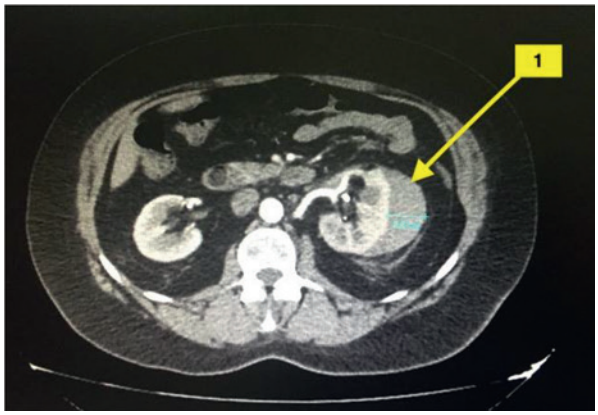

Fig. 2. Contrast-enhanced computed tomography of the urinary system, 1 – subcapsular hematoma of the left kidney after flexible URS

the dwelling stent time before intervention (less than 1 month), routine use of antibiotic prophylaxis, elimination of upper urinary tract obstruction as the first stage of treatment using the results of pelvic urine culture and stone culture in those with impaired urine passage.

Hemorrhagic complications. The most common hemorrhagic complications of RIRS include hematuria and a subcapsular hematoma (*Fig. 2*). According to the literature, hematuria is observed in 7-10% of patients, while the incidence of hematomas does not exceed 0.5% [44-46].

In most patients, subcapsular hematoma is asymptomatic, but it can present with pain and a palpable mass in the lumbar region, fever and a decrease in hemoglobin levels.

In their analysis, Bai et al. showed that the incidence of renal subcapsular hematoma was 0.4% (in 11 patients out of 2848) [41]. Chiu et al. reported a similar incidence, 0.36% (4/ 1114 patients) [40]. In a meta-analysis of 7 randomized studies that included 8929 patients, which was carried out by L. Whitehurst et al., subcapsular hematoma in the postoperative period was found in 0.45% of cases (0.15–8.9%) [47]. At the same time, surgical intervention was required in only 7 (17.5%) patients. In the remaining cases, the hematoma resolved with conservative therapy, which consisted of antibiotics and blood transfusions (22.55%). Percutaneous drainage of the hematoma was performed in 27.5% of cases. Among the 7 patients who required surgical treatment, two underwent angiography, one of whom subsequently had nephrectomy, while in three patients open revision with drainage of the paranephric hematoma was done. The authors noted one lethal outcome. Risk factors for renal hematoma include:

- chronic kidney disease [42, 48],
- ureteral obstruction due to hydronephrosis (ex vacuo bleeding during renal decompression),
- duration of the procedure longer than 41 min,
- patient body mass index <18.5 kg/m^2,
- renal parenchyma thickness less than 1 cm,
- anticoagulant use,
- high IRP ⩾30–40 cm H_2O,

Minor transient hematuria is the most common hemorrhagic complication after flexible URS. According to literature, the incidence of this complication ranges from 7.1 to 19.1% [7, 34]. Predisposing factors include stone size greater than 1.5 cm, high stone density, and use of a large-size UAS. In most cases, patients with transient hematuria do not require active treatment. Hematuria that presents for more than 3 days is classified as persistent and requires examination to identify its source.

The main mechanisms for the development of hemorrhagic complications include forniceal rupture, trauma to the ureteral mucosa or renal papilla during laser lithotripsy. As noted above, forniceal rupture occurs due to high IRP. According to animal studies, it may occur at IRP values of 81.6–95.2 cm H_2O in rabbits and at 272 cm H_2O in pigs [49]. Thus, the main efforts aimed at preventing hemorrhagic complications should be a maintain of a safe IRP level in order to prevent forniceal rupture.

Traumatic complications. The main types include ureteral damage and stricture [50].

The main mechanism of ureteral damage is the passage of an instrument or UAS, especially in case of ureteral deviation and edema, or at level of anatomical narrowings. Due to the narrowness of the ureteral lumen, a surgeon sometimes does not have the ability to pass the instrument or UAS without resistance, and forcing the passage in such cases almost inevitably leads to ureteral trauma.

The most frequently used classification of ureteral damage is proposed by Traxer et al., which is based on the endoscopic picture [51]. According to this classification, there are 5 degrees of ureteral damage. Grade 0 indicated no lesion or only mucosal petechiae, grade 1 represented mucosal erosion or a mucosal flap without smooth muscle injury, grade 2 involved both the mucosa and smooth muscle while sparing the adventitia, grade 3 denoted ureteral perforation encompassing the full thickness of the ureteral wall, including the adventitia, and grade 4 indicated complete ureteral avulsion with a disruption of its continuity. The same group of authors demonstrated that ureteral pre-stenting can reduce the risk of its damage by about 7 times, which is associated with passive dilation and a decrease in tissue resistance. Another study of Jessen et al. also demonstrated the positive role of ureteral pre-stenting [52]. From 565 patients who underwent flexible URS, pre-stenting was performed in 323 cases, while 242 patients did not have a stent preoperatively. According to the results, pre-stenting had a positive effect on the stone-free rate (86% vs. 74%) and the frequency of complications (6.5% vs 14.5%), while the duration of the procedure did not differ significantly (55 ± 36 min vs. 61 ± 35 min). In the group without pre-stenting, ureteral injuries were detected significantly more often (10.7% vs. 3.1%).

In addition to reducing the frequency of ureteral injuries, a number of authors note that pre-stenting reduces the time of procedure, which is associated with a reduction of manipulations during passage ureteroscope to the kidney [53]. Even ureteral injuries lead to the formation of strictures, data from a number of authors show that the incidence of strictures in patients with grade 3 ureteral injuries caused by the passage of UAS does not differ from patients without ureteral injuries and is 1.8% [54]. A study of Aykanat showed that the use of 12/14 Fr UAS increases the risk of ureteral injury without influencing on the incidence of ureteral stricture [55]. Authors of a systematic review of 28 studies concluded

that there is no relationship between ureteral injuries and ureteral strictures.

Available meta-analyses support the pre-stenting, confirming its positive role in reducing the risk of ureteral injury and increasing the likelihood of successful instrument passage [56–58]. The dwelling stent time required for passive dilation remains a controversial issue. According to animal studies, ureteral aperistalsis occurs as early as the fifth day of stent placement [59]. Thus, modern literature supports pre-stenting before stone removal for preventing ureteral damage.

RIRS is an effective and minimally invasive option for treating upper urinary tract stones. In order to minimize the risk of complications, it is necessary to assess risk factors preoperatively and carefully select patients. The current literature demonstrates a positive role in preventing complications of such measures as stone and pelvic urine culture, using UAS, pre-stenting of the ureter, minimizing dwelling stent time and limiting the duration of the procedure.

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Information about authors

Malkhasyan V.A. – M.D.; Professor of the Department of Urology, Russian University of Medicine, Head of Urology Department №67, Botkin City Clinical Hospital Moscow, Russia; e-mail: vigenmalkhasyan@gmail.com. https://orcid.org/0000-0002-2993-884X

Martov A.G. – Corresponding member of the Russian Academy of Sciences, M.D., Professor, Head of the Department of Urology and Andrology of A.I. Burnazyan SRC FMBC, FMBA of Russia, senior researcher of the Medical Research and Educational Center of Lomonosov Moscow State University, Moscow, Russia; e-mail: martovalex@mail.ru. https://orcid.org/0000-0001-6324-6110

Gadzhiev N.K. – M.D., Deputy Director for the Medical part (Urology) of the High Medical Technologies Clinic named after N.I. Pirogov St. Petersburg State University, St. Petersburg, Russia. https://orcid.org/0000-0002-6255-0193

Sukhikh S.O. – Ph.D., urologist of Botkin City Clinical Hospital, Moscow, Russia; e-mail: docsukhikh@gmail.ru. https://orcid.org/0000-0002-3840-0259

Grigoryan B.L. – Resident of the Department of Urology, Russian University of Medicine, Moscow, Russia; e-mail: bagybaga97@gmail.com. https://orcid.org/0000-0002-7698-0653

Pushkar D.Yu. – Academician of the Russian Academy of Sciences, M.D.; Professor, Head of the Department of Urology of the Russian University of Medicine, Moscow, Russia. Head, Moscow Urological Centre, Botkin City Clinical Hospital, Moscow, Russia; e-mail: pushkardm@mail.ru. https://orcid.org/0000-0002-6096-5723

CONSIDERATIONS

A.M. Dymov[1], Yu.A. Lee[1], M.P. Korchagin[2,3], A.R. Dzharimok[4], A.Z. Vinarov[1], M.A. Gazimiyev[1]

BCG-THERAPY FOR NON-MUSCLE-INVASIVE BLADDER CANCER: OVERVIEW OF THE CURRENT TRENDS

[1]Institute for Urology and Human Reproductive Health of FGAOU I.M. Sechenov First Moscow State Medical University, Moscow, Russia; [2]GBUZ "MNPC for the fight against tuberculosis DZM" Moscow, Russia; [3]Department of Urology of FGBOU VO "Russian University of Medicine", Moscow, Russia; [4]Medical Institute of Maykop Technological University, Republic Adygea, Maykop, Russia

Corresponding author: A.M. Dymov – Ph.D., MD, Institute for Urology and Human Reproductive Health of FGAOU I.M. Sechenov First Moscow State Medical University, Moscow, Russia; e-mail: alimdv@mail.ru

Introduction. Recurrence of non-muscle-invasive bladder cancer (NMIBC) occurs in 70% of cases, and the risk of progression to muscle-invasive bladder cancer is 20%. Intravesical BCG therapy is indicated in order to increase relapse-free survival in patients with intermediate and high-risk NMIBC. We carried out a survey of Russian urologists on the use of intravesical BCG therapy in the treatment of NMIBC, and also presented the regulatory framework for the use of BCG for the treatment of bladder cancer.
Aim. To evaluate the use of intravesical BCG therapy among urologists of the Russian Society of Urology.
Results. According to the results of a survey of 145 urologists, 46 (32%) do not prescribe BCG therapy to patients with NMIBC. Most of them (63%) have more than 10 years of experience. The main reasons why urologists do not recommend BCG therapy are the lack of conditions (74%), an absence of the drug (20%), fear of adverse reactions or development of tuberculosis infection of themselves and medical staff (2%), absence of recommendations for BCG therapy from an oncological dispensary (2%). The most commonly prescribed drugs for intravesical instillation areImuron-vac (69%), Uro-BCG-medac (29%), OncoTICE BCG (2%). Only 8% of doctors did not report difficulties during therapy. The most common reason for the refusing from BCG therapy was the lack of conditions in the medical facilities.
Conclusions. According to the survey, one third of doctors do not prescribe BCG therapy due to the lack of conditions or a shortage of the drug. An increase of relapse-free survival of patients with NMIBC is possible by providing conditions for intravesical immunotherapy.

K e y w o r d s: *bladder cancer; BCG therapy; survey; oncourology*

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Introduction. Recurrence rate of non-muscle invasive bladder cancer (NMIBC) reaches 70%, and the risk of progression to muscle-invasive cancer is 20% [1]. According to the clinical guidelines, in order to increase recurrence-free survival, patients with intermediate and high-risk NMIBC are prescribed intravesical BCG therapy [2]. It is one of the most effective adjuvant treatment methods for these patients. A meta-analysis that included 9 studies and 2820 patients showed a 32% reduction in the risk of NMIBC recurrence with intravesical BCG therapy compared to a course of Mitomycin C instillations [3]. In 2020, the superiority of BCG therapy over Mitomycin C was confirmed by a Cochrane systematic review [4]. Higher efficacy of BCG therapy was noted in comparative studies with epirubicin [5] and a combination of epirubicin with interferon [6]. In addition to a lower recurrence rate, the risk of NMIBC progression during BCG therapy was 27% lower than in the control group, which included intravesical chemotherapy and other types of immunotherapies [7]. It is worth noting that BCG therapy is the only organ-preserving treatment indicated for patients with carcinoma in situ (CIS) [7]. According to the results of retrospective studies, a complete response in patients with CIS after BCG therapy was achieved in 75–87% of cases, compared to only 48% after chemotherapy [8, 9]. Definitely, in addition to proper adjuvant therapy strategy, the efficiency of NMIBC treatment also depends on the quality of the primary removal of a bladder tumor and on the immediate single instillation of a chemotherapy drug. However, the key role of both patient and physician adherence in the outcome of therapy should not be forgotten. A 2011 study showed low physicians' compliance with clinical guidelines for the treatment of NMIBC. Factors complicating the use of adjuvant therapy were the need to choose from several drugs and variability in the technique of the procedure itself. Despite the proven efficiency of

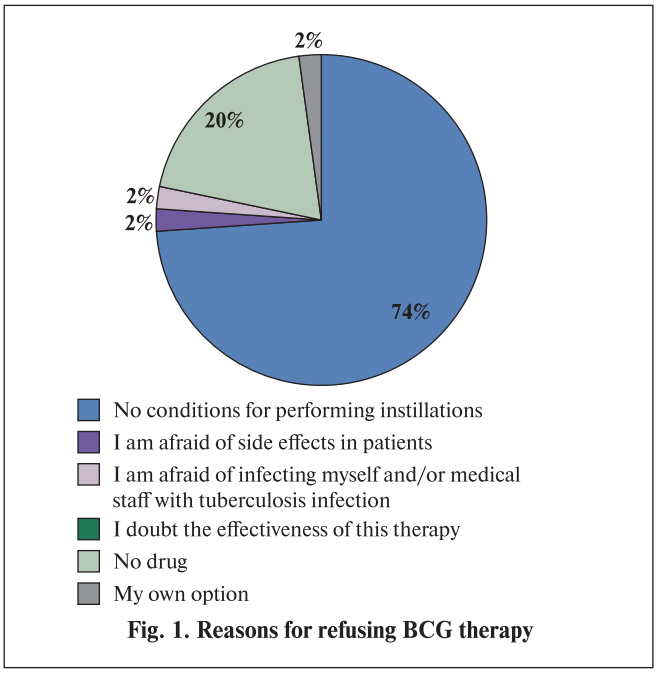

Fig. 1. Reasons for refusing BCG therapy

BCG therapy, physician adherence to its administration was only 26% [10].

Definition of BCG therapy

BCG vaccines are a family of heterogeneous live attenuated vaccines. More than 14 BCG strains are used worldwide. A 2020 comparison of licensed BCG vaccines by Angelidou et al. demonstrated significant differences in the immunological response to the drug, namely in the level of induced cytokines, which must be taken into account when comparing the efficiency of BCG drugs [11]. In the Russian Federation, two vaccines, which are lyophilisates for the preparation of a suspension, are registered for intravesical therapy of NMIBC, including the Russian drug Imuron-vac based on the M. bovis BCG-1 substrain (M. bovis BCG-1, Russia) and the German drug Uro-BCG-medak based on the RIVM strain (Netherlands Vaccine Institute). According to the manufacturers, one vial of the Imuron-vac lyophilisate contains from 2.4x108 to 4.5x108 viable cells, while Uro-BCG-medak from 2x108 to 8x108 viable cells. Such a difference in the quantitative content of viable cells can affect the induced immune response and subsequently the efficiency of the therapy, which means that comparative clinical studies are needed.

Mechanism of action of BCG immunotherapy

The mechanism of triggering the immune response to the tumor remains unclear. Most likely, the principle of action of the BCG vaccine against bladder cancer is a complex of various direct and immune-mediated effects [12].

The action of BCG immunotherapy begins with the attachment of the drug molecules to the urothelium through physicochemical interaction with the damaged layer of glycosaminoglycans or by attachment to fibronectin through a ligand-receptor bond, which causes the penetration of BCG molecules mainly into tumor cells. As a result, both local and systemic immune responses are induced. Activation of antigen-presenting cells results in active secretion of cytokines and chemokines (IL-1β, IL-8, IL-15, IL-18, CXCL10, GM-CSF, CCL2 and CCL333), which are signaling molecules for immunocompetent cells [13]. The main role in the destruction of tumor cells belongs to CD4 and CD8 T lymphocytes, as well as NK cells. Cytotoxic T lymphocytes and NK cells are the main agents that destroy tumor cells during intravesical BCG immunotherapy [14].

The severity of the delayed hypersensitivity reaction can be assessed by a positive reaction to the Mantoux skin test with injection of two tuberculin units before BCG therapy. A positive reaction indicates the presence of T-cell immunity, and therefore, directly correlates with the intensity of the response to BCG immunotherapy [15]. In individuals previously vaccinated with BCG or with a history of tuberculosis infection, as well as active or latent tuberculosis infection, a better 5-year relapse-free survival was noted [16]

Aim. To assess the frequency of prescribing intravesical BCG therapy to patients with urothelial carcinoma of the bladder.

Results

The place of BCG therapy in the treatment of patients with NMIBC in Russia

We carried out a survey of Russian urologists on the use of intravesical BCG therapy and associated difficulties, as well as a review of the regulatory framework in order to provide an algorithm of actions for a urologist regarding epidemiological safety when performing intravesical BCG therapy for oncological patients in healthcare facilities. The survey involved 145 physicians. Of them, 42% are certified urologists, 48% are urologists and oncologists, and 10% are only certified oncologists. Among the physicians treating NMIBC, 99 have over 10 years of experience, 27 have 5 to 10 years of experience, and 19 are young specialists with less than 5 years of experience. According to the survey, 46 (32%) of the 145 physicians do not prescribe BCG therapy to patients with NMIBC. Among them, the majority (63%) have over 10 years of experience. According to our data (*Fig. 1*), most physicians do not prescribe BCG therapy due to the lack of conditions for carrying out BCG therapy. At the same time, 87% of the respondents work in either oncology and urology hospitals or oncology dispensaries. It should be noted that the lack of conditions for BCG therapy was the leading reason not only for refusing to prescribe therapy, but also for referring patients to other healthcare facilities (81%). 68% (n=99) of respondents use BCG therapy for the treatment of patients with NMIBC. The most frequently prescribed drug is Imuron-vac (69%). 29% of respondents use Uro-BCG-medac, and 2% OncoTICE, which is not registered in the Russian Federation.

Only 8% of doctors who perform BCG therapy in their healthcare facilities do not report any difficulties (4% work in private medical centers, 4% in urological hospitals). Most often, doctors report a shortage of the drug (*Fig. 2*). Among the physicians who stated that they have the ability to perform BCG therapy in their healthcare facilities, 11% perform intravesical instillation on outpatient bases, 14% in oncology hospitals, 21% in oncology dispensaries, and 46% in urology hospitals.

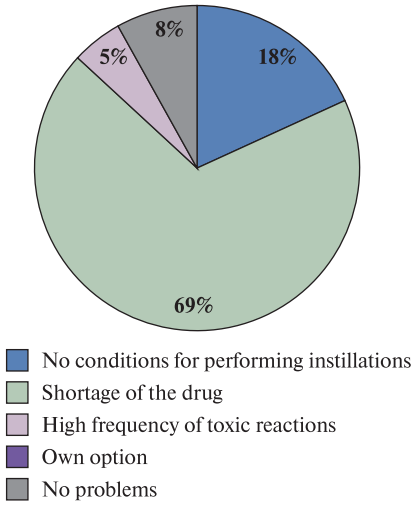

Fig. 2. Difficulties in carrying out BCG therapy

Discussion

Sanitary and epidemiological requirements for BCG therapy

The survey showed that the most common reason for refusing BCG therapy is the belief of doctors in the absence of conditions for BCG therapy in their healthcare facilities, which is due to insufficient awareness of existing sanitary and epidemiological requirements.

According to the Federal Law of the Russian Federation of 04.05.2011 No. 99-FZ «On licensing of certain types of activities» (Chapter 2, paragraph 46; paragraph 19), there is no license required to carry out BCG therapy in a healthcare facility; the law permits the use of immunological drugs for therapeutic purposes.

Requirements for BCG therapy are presented in the sanitary and epidemiological requirements, guidelines, and instructions applied to the use and administration of the BCG vaccine, namely:

1. Order of the Russian Ministry of Health dated March 21, 2003 No. 109 «On improving anti-tuberculosis measures in the Russian Federation», Instructions for vaccination and revaccination against tuberculosis with BCG and BCG-M vaccines (Appendix No. 5).
2. Resolution of the Chief State Sanitary Doctor of the Russian Federation dated January 28, 2021 No. 4 on approval of sanitary rules and regulations SanPiN 3.3686-21 «Sanitary and Epidemiological Requirements for the Prevention of Infectious Diseases» (as amended on May 25, 2022).
3. Sanitary rules and regulations SanPiN 2.1.3684-21. Section X, «Waste Handling Requirements», paragraphs 157-266.
4. SanPiN 3.3686-21. Sanitary Rules and Norms «Sanitary and Epidemiological Requirements for the Prevention of Infectious Diseases», paragraphs 4200-4251.
5. SanPiN 3.3686-21. Sanitary Rules and Norms «Sanitary and Epidemiological Requirements for the Prevention of Infectious Diseases», paragraphs 4252–4378.

Procedure Room Requirements

According to sanitary and epidemiological requirements No. 3.3686-21, registered on 15.02.2021, intravesical BCG instillation can be performed in a manipulation/urology room, which must have:

- a separate sink for instrument processing;
- a pharmaceutical refrigerator for storing BCG vaccine;
- marking of all objects, tables, cabinets, boxes, instruments, etc. related to the manipulation being performed;
- emergency and anti-shock therapy kits;
- emergency HIV and parenteral hepatitis prophylaxis means.

Requirements for storage, transportation, accounting and destruction of BCG vaccine for intravesical immunotherapy

- The vaccine must be stored in a pharmaceutical refrigerator at a temperature of +2 to +8°C. Storage of other drugs in this refrigerator is prohibited.
- Transportation must be carried out in compliance with the cold chain in thermal containers.
- Each batch of BCG vaccine must have a temperature indicator.
- Unloading of BCG vaccine must be carried out in the shortest possible time (5-10 minutes).
- Monitoring of the vaccine storage temperature regime must be carried out 2 times a day. Thermometer and temperature indicator readings must be recorded in the temperature registration log.
- Destruction of ampoules and vials of BCG vaccine and their remains is carried out by physical or chemical methods. BCG vaccine in a closed system (Uro-BCG medac) is not subject to unpacking. The drug is disposed of in accordance with sanitary and epidemiological requirements for handling class B medical waste.

Requirements for the use of BCG vaccine for intravesical immunotherapy of bladder cancer

According to the order of the Ministry of Health of the Russian Federation dated March 21, 2003, No. 109 «On improving anti-tuberculosis measures in the Russian Federation», the procedure is carried out on strictly designated days and hours. Manipulations are not allowed in rooms, as well as by the same employees who are involved in the preparation of cytotoxic drugs for parenteral administration.

In order to ensure epidemiological safety in terms of tuberculosis, before prescribing intravesical immunotherapy, each patient undergoes:

- taking of an epidemiological anamnesis, which includes the examination of the patient's relatives for tuberculosis, data on chest X-ray of adults and immunodiagnostics of children over the past 6 months);
- 3–11 days before immunotherapy, the patient undergoes an intradermal Mantoux skin test with injection of two units of purified tuberculin in a standard dilution or an intradermal test (Diaskintest) in accordance with the instructions to determine specific sensitization to Mycobacterium tuberculosis and the activity of tuberculosis infection. BCG therapy is contraindicated if the local reaction to the intradermal injection of tuberculin is over 17 mm or if a hyperergic reaction with a vesicle and lymphangitis develops. A positive/doubtful Diaskintest is also be a contraindication to BCG therapy.

The patient's medical chart should reflect:

- a detailed record is made indicating the results of thermometry on the day of intravesical immunotherapy;

• status praesens;
• the appointment of the BCG vaccine, indicating the dose, series, number, expiration date and manufacturer of the drug;
• the passport of the drug must be personally read by the doctor on the packaging and on the ampoule;
• registration of local and systemic reactions after intravesical instillation.

To avoid contamination on the day of BCG immunotherapy, it is prohibited to carry out any other parenteral manipulations, including administering of drugs, taking blood, carrying out invasive examinations.

Requirements for organizing disinfection measures

According to the sanitary and epidemiological rules SanPiN No. 3.3686-21, medical devices, equipment, furniture, surfaces and class B medical waste, as well as cleaning equipment are subject to disinfection and pre-sterilization cleaning with solutions of disinfectants that have an antimicrobial effect against Mycobacterium tuberculosis.

Liquid class B waste and biological fluids of patients after intravesical BCG immunotherapy may be discharged without prior disinfection into the centralized sewage system. The spilled preparation is neutralized using a 5% chloramine solution. In accordance with SP 3.3.2.1120-02, waste and used materials can be disposed of by physical (steam sterilization under a pressure of 0.15 MPa at a temperature of 126±2°C for 90 min (SP 1.3.2322-08) or chemical (in a 5% chloramine solution for 6 hours) methods.

Requirements for the organization of work of medical personnel and conditions for compliance with safety precautions

It should be taken into account that medical workers with acute respiratory diseases or having open wounds on their hands, purulent lesions of the skin and mucous membranes regardless of their location, as well as those with immunosuppression, are excluded from procedures using the BCG vaccine.

If the drug gets on skin, it must be washed with a swab soaked in a 0.5% chloramine solution and then rinsed with warm water and soap.

Technique of BCG therapy

The standard algorithm includes:

1) The patient refrains from taking liquids for 4 hours before the procedure;
2) Emptying the bladder immediately before the procedure;
3) Introduction of the drug through a urethral catheter under low pressure;
4) Clamping the catheter for 2 hours;
5) Moving the patient during the procedure, either active or passive (turning the patient from supine to prone position and vice versa every 15 minutes);
6) Removing the urethral catheter;
7) Voluntary emptying of the bladder in a sitting position;
8) Refraining from taking liquids for 2 hours after the procedure;
9) Maintaining a state of hyperhydration for 48 hours after the procedure by increasing fluid intake.

In a retrospective study by Nagai et al., which included 173 patients, it was demonstrated that reducing the exposure time to 1 hour did not reduce the incidence of side effects and did not affect the recurrence rate [17]. Andius et al. reduced the exposure time of the drug to 30 min in the study of 51 patients, and showed a significant decrease in the incidence of side effects in those who had previously had significant adverse effects during BCG therapy [18].

Conclusion. The high efficacy of intravesical BCG therapy in the treatment of patients with intermediate- and high-risk NMIBC has been proven and is beyond doubt, but rates of recurrence and progression of bladder cancer in general population remain high. According to our survey, a third of doctors do not prescribe BCG therapy due to the lack of conditions for the procedure or a shortage of the drug. Consequently, the treatment of a third of patients with NMIBC does not fully comply with the guidelines, largely due to administrative and legal restrictions, which can often be overcome with a detailed study of the regulatory framework for the implementation of BCG therapy in healthcare facilities.

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Author information:

Dymov A.M. – Ph.D., MD, Institute for Urology and Human Reproductive Health of FGAOU I.M. Sechenov First Moscow State Medical University, Moscow, Russia; e-mail: alimdv@mail.ru

Lee Yu.A. – student, Institute for Urology and Human Reproductive Health of FGAOU I.M. Sechenov First Moscow State Medical University, Moscow, Russia; e-mail: julee1806@gmail.com

Korchagin M.P. – GBUZ "MNPC for the fight against tuberculosis DZM", Department of Urology of FGBOU VO "Russian University of Medicine", Moscow, Russia; e-mail: mihailsun@mail.ru

Dzharimok A.R. – Ph.D., urologist, Medical Institute of Maykop Technological University, Republic Adygea, Maykop, Russia; e-mail: a.dzharimok@yandex.ru

Vinarov A.Z. – Ph.D., MD, urologist, Institute for Urology and Human Reproductive Health, Moscow, Russia

Gazimiev M.A. – Ph.D., MD, urologist, Institute for Urology and Human Reproductive Health, Moscow, Russia; e-mail: gazimiev_m_a@staff.sechenov.ru