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ООО "БИОНИКА МЕДИА"

CONTENTS

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ASYMPTOMATIC BACTERIURIA IN PREGNANT WOMEN – THE NORMAL CONDITION OF HEALTHY WOMEN URINE

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Aim: to study the dynamics of the microbiota of a freshly excreted middle portion of urine in primigravida at different times of all three trimesters of pregnancy.
Materials and methods. A single-center prospective observational cohort study was conducted with a consecutive enrollment of 30 women at different gestational ages: I – 8–12 weeks, II – 22–24 weeks, III – 30–32 weeks. A midstream specimen of morning vesical urine was taken for the study, then it was cultivated using nutrient media for aerobic and anaerobic microorganisms under appropriate conditions. Statistical analysis was performed using SPSS ver.26 (IBM SPSS Inc., Chicago, IL, USA).
Results. The freshly released middle portion of urine in all 30 observations in the I-III trimesters contains aerobic-anaerobic associations of microorganisms. Coagulase-negative staphylococci, Enterococcus spp., Corynebacterium spp., Lactobacillus spp., Eubacterium spp. prevail in the urine during pregnancy. The E. coli, Candida spp. detection frequency decreases by the third trimester, but Lactobacillus spp. detection frequency rises. Significant differences in the detection frequency were found only in Propionibacterium spp. and Lactobacillus spp. The average level of bacteriuria in most cases is 102-103 CFU/ml with significant differences only in E. faecium, Lactobacillus, Propionibacterium spp. in the III trimester.
Discussion. The study of urine at different times of all three trimesters of pregnancy refutes the previous ideas about asymptomatic bacteriuria. The urine microbiota in primigravida during pregnancy has wide spectrum and quite stable until delivery. Such bacteriuria can be considered asymptomatic, but it is a consequence of a healthy state and it is not a disease or its predictor. Conclusion. The term asymptomatic bacteriuria is not correct in the context of risk factor of urinary tract infection in pregnant women.Key words: asymptomatic bacteriuria, pregnant women, urine microbiota

K e y w o r d s: *asymptomatic bacteriuria, pregnant women, urine microbiota*

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Introduction. Over the past two decades, our research group has provided indisputable evidence of the presence of aerobic and anaerobic bacteria, viruses and fungi in urine of healthy young women (⩾18 years) [1–3], although at the beginning of the century the idea of urine sterility was predominated [4]. Studies based on new methodological approaches, namely the use of an extended set (8–12) of culture media, as well as metagenomic next-generation sequencing (NGS), confirmed the presence of a broad bacterial community of urine (>100 bacterial species) [5, 6]. At the same time, a wide range of bacteria in urine is not associated with any symptoms of urinary tract infection, nor with an inflammatory reaction in the form of leukocyturia. Therefore, the concept of asymptomatic bacteriuria (ABU) has become more contradictory. Traditionally, it is still considered that bacteriuria, which is not accompanied by clinical symptoms should be regarded as ABU, irrespective of pyuria [1]. ABU is of particular importance in assessing the pregnant woman due to its role in the development of acute infections of the upper urinary tract and kidneys [7]. However, well-designed randomized clinical trials have not confirmed the benefit of ABU treatment [8]. At the same time, in a number of official documents of the professional medical communities in Russia and the Ministry of Health of the Russian Federation, modern ideas about the microbiota of the urinary tract of healthy women, as well as those with infectious and inflammatory lesions of the urinary tract, are ignored, and ABU treatment during pregnancy is still highly recommended [9].

Aim. To study the dynamics of the microbiota of a middle portion of urine in primigravida at different times of all trimesters of pregnancy.

Materials and methods. A single-center prospective observational cohort study was carried out, which included consecutive 30 women, who undergone to evaluation at different gestational ages: point I at 8-12 weeks, point II at 22-24, point III at 30-32 weeks. Inclusion criteria were as follows: age of 20–32 years, first singleton pregnancy ⩽12 weeks, absence of any cardiovascular, pulmonary, neurological, endocrine diseases, possible history of acute and recurrent urinary tract infections (UTI), absence of lower urinary tract symptoms during pregnancy. Exclusion criteria: anomalies of the urinary tract, taking antibiotics during pregnancy, previous or present sexually transmitted diseases. A midstream urine sample was collected in a hygienic way to prevent contamination as much as possible. Bacteriological

examination of urine was carried out using standard culture media in accordance with the Clinical Guidelines for the Bacteriological Study of Urine (2014) [10], as well as using an additional 10 culture media (HiMedia, India) for cultivating the possible aerobes, anaerobes and fungi (HiCrome Klebsiella Selective Agar Base, HiCrome Enterococci Agar, Streptococcus Selection Agar, Rogosa SL Agar, Anaerobic Agar, Shaedler Agar, Bacteroides Bile Esculinum Agar, Shaedler Broth, Blaurocca, HiCrome Candida Differential Agar). Cultivation was carried out at a temperature of 37°C under aerobic (24–48 h) and anaerobic (48–72 h) conditions. The HiAnaerobic System – Mark III or VI (anaerobiosis indicator HiAnaero Indicator Tablet) was used with a gas mixture consisting of 10% CO_2, 10% H_2, 80% N_2 or AnaeroHiGas Pak (HiMedia, India) in order to create anaerobic conditions. A positive culture was defined as 10^1–10^2 CFU/mL of one or more microorganisms.

Statistical analysis was performed using SPSS ver.26 (IBM SPSS Inc., Chicago, IL, USA). The frequency of occurrence of microorganisms in urine of pregnant and non-pregnant women and descriptive statistics of urine contamination levels (mean, standard deviation, mode, median, quartiles) were calculated. Comparison of the frequencies of occurrence of microorganisms and contamination rates was made using the Mann-Whitney U-test. Differences were considered significant if p was less than 0.05.

Results. The middle portion of urine in all 30 observations in different trimesters of pregnancy contained aerobic-anaerobic associations of 25 bacteria and fungi (Table 1), including 13 aerobes, 10 anaerobes, and 2 fungi. Nineteen species were present at all stages of pregnancy and only 6 were absent either in the first or third trimesters. Thus, the widest range of urine microbiota was noted in the second trimester. The dominant aerobes in urine were multiple species of coagulase-negative staphylococci (COS) and enterococci, as well as Corynebacterium. Moreover, this predominance persists throughout pregnancy. On the contrary, Enterobacteriaceae were present in the first trimester in less than half of the cases and their frequency in urine decreased from trimester to trimester. Among wide spectrum of anaerobes *Lactobacillus* spp. and *Eubacterium* spp. from I to III trimesters were

Table

Urinary microbiota of pregnant women at different gestational ages

Bacteria	I trimester		II trimester		III trimester	
	Detection rate, %	Concentration, lg CFU/ml	Detection rate, %	Concentration, lg CFU/ml	Detection rate, %	Concentration, lg CFU/ml
AEROBES						
CoNS:	**86,7**	**2,15**	**73,3**	**2,27**	**86,7**	**2,27**
S. epidermidis	30,0	2,11	26,7	2,13	26,7	2,00
S. lentus	26,7	2,13	20,0	2,17	30,0	2,22
S. warneri	23,3	2,29	20,0	2,33	16,7	2,20
S. haemolyticus	16,7	2,80	23,3	2,00	20,0	2,67
S. saprophyticus	16,7	2,20	10,0	2,67	10,0	2,33
S. coagulans	3,3	2,00	3,3	2,00	0	0
***Enterococcus* spp.:**	**63,3**	**2,53**	**56,7**	**2,82**	**43,3**	**2,77**
E. faecalis	60,0	2,56	53,3	2,94	36,7	2,55
E. faecium	10,0	2,00	6,7	2,00	23,3	**3,00***
Enterococcus недиф.	3,3	2,00	6,7	2,00	3,3	4,00
***Corynebacterium* spp.**	**60,0**	**2,33**	**36,7**	**2,45**	**50,0**	**2,80**
Enterobacteriaceae:	**43,3**	**3,15**	**36,7**	**3,27**	**23,3**	**3,14**
E. coli	40,0	2,92	33,3	3,10	23,3	3,14
Klebsiella spp.	3,3	6,00	6,7	3,50	0	0
S. aureus	**23,3**	**2,14**	**26,7**	**2,50**	**26,7**	**2,25**
***Candida* spp.:**	**10,0**	**2,00**	**6,7**	**2,00**	**3,3**	**2,00**
C. albicans	6,7	2,00	3,3	2,00	3,3	2,00
C. glabrata	3,3	2,00	3,3	2,00	0	0
ANAEROBES						
Lactobacillus spp.	83,3	3,32	70,0	3,10	93,3**	3,86**
Eubacterium spp.	76,7	3,52	90,0	3,33	86,7	3,65
Veillonella spp.	20,0	2,17	23,3	2,14	6,7	2,00
Bifidobacterium spp.	16,7	2,00	10,0	2,00	20,0	2,33
Peptococcus spp.	13,3	2,00	23,3	2,14	20,0	2,00
Propionibacterium spp.	6,7	2,00	30,0*	2,22	36,7***	2,82***
Fusobacterium spp.	3,3	2,00	3,3	2,00	3,3	2,00
Megasphaera spp.	3,3	2,00	6,7	2,00	0	0
Peptostreptococcus spp.	0	0	3,3	2,00	0	0
Mobiluncus spp.	0	0	3,3	2,00	0	0

*$p<0.05$, significant differences between variables in I and II trimesters, **$p<0.05$, significant differences between variables in II and III trimesters, ***$p<0.05$, significant differences between variables in I and III trimesters.

predominated. It is important to emphasize that there were no significant differences in the frequency of the presence of aerobes in urine during the I–III trimesters, but they were found for two anaerobes (*Propionibacterium* spp. and *Lactobacillus* spp.), whose frequency increased from I to III trimester (<0.005 and < 0.02, respectively).

The average level of most bacteria was initially in the range of 10^2-10^3 CFU/ml, and it remained stable until the end of pregnancy. In fact, the level of bacteriuria by the third trimester increased for *E. coli, Lactobacillus* spp., *Propionibacterium* spp., *Eubacterium* spp. and some species of Enterococcus spp. up to 10^3–10^4 CFU/ml, however, only for *Enterococcus faecium, Lactobacillus* spp. and *Propionibacterium* spp. a level of bacteriuria was significantly higher (p<0.05).

Discussion. The concept of ABU was formed in the era of the standard approach to urine culture that was accepted for many decades and is still recognized as the "gold" standard of bacteriological study [10, 11]. The researchers proceeded and proceed from the concept of sterility of the bladder and urine. Therefore, the detection in urine of the so-called uroculture using MacConkey or blood agar in the absence of symptoms of infection served as convincing evidence of non-sterile urine.

But it must be understood that the standard protocol was developed to detect a small group of individual uropathogens, primarily the uropathogenic E. coli, which allegedly causes the majority of urinary tract infections.

In fact, with this protocol, it was important to detect exactly those microbes that we know as uropathogens. However, the use of a wide range of culture media, which were not previously mentioned in bacteriological studies in urology, led us at the beginning of this century to the understanding that the spectrum of possible uropathogens can be markedly increased. The study of the microbiota of healthy people (children, women and men) convinced us and many others that the bladder and urine are never sterile [1, 2, 5, 12, 13].

The research team of L. Brubaker and A. J. Wolfe (2015) [14] showed that the standard urine culture, compared with the extended culture approach, gives an incredibly high level of false negative results (up to 90%) in women without obvious clinical symptoms [5, 15]. The introduction of bacterial gene sequencing (16S rRNA) of urine into research protocols for the study of various urological conditions became a revolutionary step [16, 17]. This sequencing allowed to reveal many more microorganisms than standard urine culture [5, 15].

The present study of bladder urine at different trimesters during pregnancy again refutes previous ideas about ABU. The urine microbiota, as assessed throughout pregnancy in healthy women, is broad in its spectrum and quite stable up to delivery. Such bacteriuria can be considered asymptomatic, but it serves as a manifestation of healthy condition, not disease and not its predictor.

We would like to emphasize once again that this study included healthy primigravids without any comorbidities. All women had delivery at term and gave birth to healthy children. To elucidate the role of ABU as it is understood today by other researchers, new ideas are needed to design studies, which can identify changes in the quality and quantity of the microbiota that complicate pregnancy for both woman and fetus. Our study, however, did not pursue this goal.

In our opinion, the term ABU, characterized as a pathological condition, is completely outdated. There is no constant level of bacteriuria that can cause an infectious process. It should be assumed that any level of bacteriuria is capable of triggering it. Therefore, the level of bacteriuria of 10^5 CFU/ml, given in the EAU Guidelines 2022 [18], is extremely debatable. It should be noted that this level (10^5 CFU/ml) was taken from the publication of E. Kaas dated 1956 [19]. Therefore, it is important to focus obstetricians on dynamic monitoring of pregnancy, not only to assess bacteriuria and pyuria, but also for early detection of symptoms and signs of UTI. They are the first who look at the "infection", requiring the earliest possible start of treatment. However, the presence of ABU by itself in pregnant woman, from our point of view, is not an indication for the prevention and treatment.

Conclusion. Based on our results, the term ABU is not acceptable as a factor suggesting the risk of urinary tract infection. We can make the following conclusion that the complex composition of the microbiota of urine in a woman in the I-III trimesters of pregnancy is a sign of a healthy state of the body. Most likely, dysbiosis of the urinary microbiota is a pathological factor, but its characteristics require additional studies.

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THE INFLUENCE OF ALFUZOSIN MONOTHERAPY ON THE SEXUAL FUNCTION OF PATIENTS WITH BENIGN PROSTATIC HYPERPLASIA IN REAL CLINICAL PRACTICE (RESULTS OF A RUSSIAN MULTICENTER STUDY)*

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Introduction. The current armamentarium of drugs for lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) is diverse and includes both monotherapy and combination therapy. Indirect and limited direct comparisons have demonstrated that all alpha-1-blockers (a1-ABs) have similar efficacy when used at appropriate doses. Differences in tropism to the prostate of modern α1-ABs are largely responsible for the severity of their side effects, mainly negative influence on sexual function and cardiovascular system.

Aim. To evaluate the influence of Alfuprost® MR 10 mg once daily on sexual function in patients with LUTS due to BPH during 3-months therapy in real clinical practice. The secondary endpoint was an effect on systolic, diastolic blood pressure (BP) and heart rate.

Materials and methods. A total of 537 men with LUTS/BPH were included in the study by urologists from 21 outpatient departments of the Russian Federation. The follow-up included 3 visits: visit of inclusion in the program of patients with a previously prescribed drug of Alfuprost® MR in a dosage of 10 mg once a day (visit "0"), visit 1 at 30 days (±5 days) later, and visit 2 at 90 days (±5 days) after inclusion in the study. At each visit, evaluation of complaints and physical examination was performed. In addition, patients completed questionnaires: International prostate symptom score (IPSS) and quality of life (QoL) index; the full version of the International Index of Erectile Function (IIEF) questionnaire; the Likert scale for the patient and for the physician. Also, laboratory and instrumental studies used in routine clinical practice were recorded: total prostate specific antigen (PSA) in serum; ultrasound examination (US) of the bladder; transrectal ultrasound examination (TRUS) of the prostate; uroflowmetry (maximum urine flow rate (Qmax)); measurement of systolic and diastolic BP; measurement of heart rate.

Results: after 3 months of therapy with Alfuprost® MR in a dosage of 10 mg once a day, significant ($p<0.05$) improvement of all urodynamic parameters was documented, including a decrease in the average IPSS score by 55% and improvement of quality of life by 2.46 points (on the QoL index); increase of Qmax by 53%; reduction of the average postvoid residual to normal values.

In addition to a significant improvement in the quality of urination, changes in sexual function were also positive. Thus, the average total IIEF score increased significantly ($p<0,05$) from 45.35 to 53.18 points. When considering specific domains of male sexual function, positive dynamics in all domains was noted: overall improvement of orgasm function, sexual desire, sexual satisfaction and overall sexual functioning was 11.98%, 15.14%, 19.7% and 18.46%, respectively.

Hemodynamic indices remained stable during the 3-month follow-up; only clinically insignificant decrease in systolic BP by no more than 2 mmHg during the entire follow-up period was observed. At the same time there was no influence on diastolic BP. Changes in heart rate were also clinically insignificant, averaging no more than 1 beat per minute.

Conclusions: The results of observational study allow to recommend Alfuprost® MR as a first-line therapy for BPH, including for sexually active men and patients with various types of sexual dysfunction. Considering minimal and clinically insignificant vasodilatory effects observed during 3 months of therapy, it is possible to prescribe Alfuprost® MR in a dosage of 10 mg once daily, including comorbid patients.

Key words: Alfuzosin, BPH, LUTS, sexual function, blood pressure, Alfuprost® MR

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Introduction. Benign prostatic hyperplasia (BPH) is a progressive disease of aging men, manifested by a gradual increase in the prostate volume due to the growth of its periurethral glandular zone and is accompanied by lower urinary tract symptoms (LUTS), which worsens the quality of life (QoL) and often leads to the need for surgical treatment. Prevalence rate of BPH in men under the age of 50 is 11.3%, increasing to 40% and 80% at age 60 and 80 years, respectively [1]. In 75% of men older than 50 years, LUTS are related to BPH. The increase in life expectancy and the number of elderly and senile men, the improvement in the quality of medical care and socio-economic factors in many countries of the world, unfortunately, contributed to the increase in the number of patients with BPH [2].

In the pathogenesis of BPH, along with other mechanisms, an increase in the activity of 5α- reductase has been established, which leads to a decrease in the concentration of 5α-androstenediol, which represents adrenoreceptors, and contributes to an increase in the level of estrogens, the number and activity of α1-adrenoreceptors (α1-AR) [3]. In BPH, the most common subtype of adrenergic receptors in the prostate is α1A [1]. Their stimulation is clinically manifested by irritative symptoms (increased frequency of urination, urgency, nocturia), and as a result, deterioration in the quality of life. Excessive stimulation of α1A-AR increases the smooth muscles tone of the bladder neck, prostatic urethra and prostate, and also maintains high intraurethral pressure [1]. Since α1-ARs are mainly present in the prostate stroma, both an increase in their number and their activation leads to a dynamic component of bladder outlet obstruction (BOO). As the disease progresses, functional and morphological changes in the detrusor develop with circulatory disorders and tissue hypoxia [4].

The main goal in the treatment of LUTS/BPH is the rapid and effective control of LUTS. Until recently, surgical interventions were the cornerstone of treatment. However, the achievements of fundamental science in studying the main mechanisms of the pathogenesis have been so great, and the success of the pharmaceutical industry in the development of modern drugs is so significant that in 80–90% of cases, drug therapy becomes the first line of treatment [5]. There are short-term and long-term goals of conservative treatment of patients with LUTS/BPH. Short-term aims include elimination of LUTS, improvement in urinary flow rate, improvement in QoL, or preparation of the patient for surgical treatment. Long-term goals include reducing both the risk of complications associated with BOO and the need for surgical intervention, which is especially important in cases of serious comorbidities. The main principles of conservative treatment of patients with BPH have been determined [6].

The modern armamentarium of drug therapy for BPH is diverse and, depending on the indications, allows for both mono- and combination therapy. The choice of drug based on the predominance and severity of emptying or voiding symptoms allows to implement a personalized approach. Based on the pathogenesis of BPH, currently α1-blockers (α1-AB) occupy a leading position. These drugs reduce the tone of the smooth muscles of the prostate and urethra, which leads to a decrease in urethral resistance, elimination of the dynamic component of the BOO, and improving bladder and prostate perfusion. The α1-ABs are considered the "gold" standard of conservative therapy for BPH [7]. However, it should be noted that α1-AB monotherapy in the early stages of BPH is recommended for patients without risk factors for disease progression [8]. With a prostate volume of >40 cc and the presence of other risk factors, combination therapy (α1-AB and 5α -reductase inhibitors) is preferable [9].

Modern α1-ABs have different prostatotropism, which determines the severity of possible side effects (mainly the influence on the cardiovascular system and sexual function). Alfuzosin has the highest index of prostate selectivity (prostatotropism) compared to other α1-ABs, is rapidly washed out of blood plasma and accumulates in the prostate [10, 11].

Manifestations of diabetes mellitus are considered a common problem among patients taking α1-ABs. Effectively relieving LUTS, α1-blockers can cause a number of side effects, including sexual disorders. However, international studies have shown that many patients with LUTS due to BPH consider it important to preserve sexual activity [12]. According to Mondul et al., in the presence of LUTS, the risk of developing erectile dysfunction (ED) was 40% higher. In many patients with BPH, there is a need to correct ED during conservative treatment [12]. According to another study, in 17.4% of patients taking tamsulosin, and 14.2% with silodosin, the development of sexual disorders may even become a reason for treatment refusal [13]. For other α1-ABs, a rate of this complication is about 7–8% [13]. Due to adverse events, the appointment of these drugs requires an individual approach.

Thus, it becomes obvious that drugs registered for the conservative treatment of LUTS in BPH require further study in real practice in order to assess frequency and severity of side effects, the impact on male sexual function, as well as to study the effect of α1-AB on the quality of life.

Aim. To carry out a non-interventional study to assess the effect of Alfuprost® MP 10 mg once a day for 3 months on the sexual function of patients with LUTS due to BPH in real clinical practice.

The objectives of the study included evaluation of LUTS severity and QoL of patients with BPH according to the International Index of Symptoms in Prostate Diseases (IPSS) questionnaire and QoL score, frequency and severity of nocturia, dynamics of maximum urine flow rate (Q_{max}) according to uroflowmetry and the postvoid residual volume (PVR) according to ultrasound during therapy by Alfuprost® MR at a dosage of 10 mg once a day. The main attention was paid to the influence of the drug on the sexual function (according to the International Erectile Function Index, IIEF), as well as the effect on various aspects of sexual function: erectile function, orgasm, sexual desire, intercourse satisfaction and overall satisfaction. We performed an analysis of patient satisfaction with treatment (according to the Likert scale) and an analysis of physician satisfaction with the results of treatment (according to the Likert scale). In addition, the frequency of occurrence, nature, severity, timing of occurrence and duration of adverse events (AEs), as well as the frequency of treatment refusal, were studied. The secondary endpoint was the effect of the drug on systolic blood pressure (BP), diastolic BP and heart rate (HR).

Materials and methods. The non-interventional study included 537 men with BPH who met the inclusion criteria. First of all, Alfuprost® MR should be prescribed for the treatment of LUTS associated with BPH (in accordance with instructions for its use), associated with moderate LUTS (IPSS score of 8-19 points). Other inclusion criteria were age of 50–65 years, prostate volume on ultrasound of 30–80 cc, Q_{max} 6–13 ml/s, preserved sexual activity, PSA level <4 ng/ml, personally signed informed consent to participate in the study.

The presence of ED corresponding to 12 to 16 points (mild/moderate ED) on the IIEF scale did not serve as a contraindication to inclusion (at the discretion of the investigator).

Only patients who had already been prescribed Alfuprost® MR, alfuzosin extended release 10 mg tablets 1 time per day after meals were included in the study. The duration of the follow-up period was 3 months. All patients (100%) signed an informed consent form.

The study was carried out by urologists in 21 outpatient treatment and prophylactic clinics in the Russian Federation. The follow-up included three visits: the baseline entry visit (Visit 0), Visit 1 30 (±5) days after entry into the study, and Visit 2 90 (±5) days after entry into the study (60 [±5] days after visit 1).

Complaints were recorded at each visit, and a physical examination (external genitalia, digital rectal examination) was also performed. The following questionnaires were used: IPSS and QoL; full version of the IIEF score; a questionnaire on patient satisfaction with the treatment (a Likert scale for a patient) and a questionnaire on physician satisfaction with the treatment (a Likert scale for a doctor). The laboratory and instrumental studies used in routine clinical practice were also recorded, including total serum PSA; ultrasound of the bladder (postvoid residual volume, ml); uroflowmetry (Q_{max}); transrectal ultrasound (TRUS) of the prostate (volume, cc), measurement of systolic and diastolic BP, and HR.

Descriptive statistics methods were used to analyze the obtained results. Quantitative data that had a normal distribution, were given using the arithmetic mean (M) and standard deviation (SD), presented as M (SD). When the distribution differed from normal, data were presented as a median (Me) and quartiles Q1 and Q3 as Me (Q1; Q3). Qualitative indicators were shown both in absolute and relative values (%). Samples were checked for normality using the Kolmogorov–Smirnov test. Samples were compared using Student's t-test, Mann-Whitney U-test, and Wilcoxon's t-test. The relationship between the parameters was revealed using the Pearson and Spearman's correlation. An analysis of the difference in the frequencies of factors in independent groups was performed using the McNemar's and Chi-square tests. Also, for a number of factors, the calculation of relative risk indicators according to Mantel-Haenszel (RR) was used. The odds ratio (OR) and confidence interval (CI) were calculated by comparing the frequency of a binary trait in groups using four-field tables. Mathematical and statistical processing of the data was carried out using standard software packages Statistica (V7.0) and SPSS Statistics (V17.0).

Results. The average age of the men included in the study was 58.7 (±4.29) years, which, according to the 2021 World Health Organization (WHO) classification, corresponds to the middle age group. In 358 (66.67%) patients, the PSA level was <2.5 and in 179 (33.33%) it was 2.5–4.0 ng/ml. The initial average prostate volume (visit "0"), according to TRUS, was 53.0 (±12.9) cm^3 (from 28 to 88 cm^3).

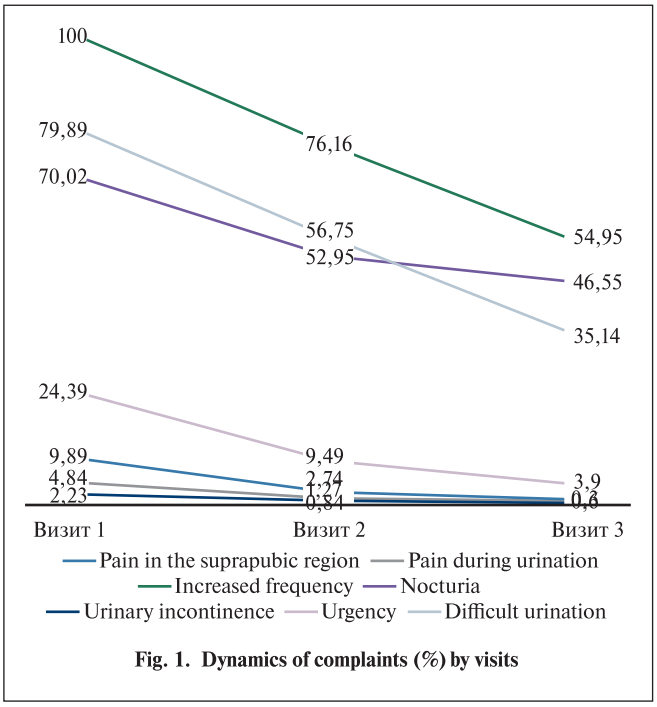

Fig. 1. Dynamics of complaints (%) by visits

The average body mass index was 27.6±3.7 kg/m^2, which, according to the WHO classification (2021), corresponds to overweight. 32.40% of patients had concomitant diseases (*Table 1*), in the structure of which hypertension, chronic gastritis and duodenitis, and chronic obstructive pulmonary disease were prevalent (p<0.05).

Among the complaints of patients at the visit "0", difficult urination was in 429 (79.89%), increased frequency in 537 (100%), nocturia in 376 (70.02%) and urgency in 131 (24.39%) of patients. In addition, 12 men (2.23%) had urinary incontinence (*Fig. 1*). Pain in the suprapubic region and during urination, typical for prostatitis, was in 79 (14.6%) patients at the visit "0". Thus, LUTS at the beginning of therapy, among which increased frequency, nocturia and difficulty urinating predominated, were present in all (100%) patients. At visit 1 (*Fig. 1*), in 11.73% of patients, the number of LUTS significantly (p<0.05) decreased by 39.32% of the total number of complaints. Difficult urination was already noted only 269 (56.75%), increased frequency 361 (76.16%), nocturia 251 (52.95%), urgency 45 (9 .49%) patients, and 4 (0.84%) men reported urinary incontinence. Pain in the suprapubic region and during urination was in 19 (4.01%) patients.

The decrease in the number of complaints was preserved by the visit 2, at which their number decreased by 69.82% compared to the visit 0. Increased frequency decreased by 45%, nocturia by 23.5%, difficulty urinating by 44.8%, urgency by 20.5% and pain by 13.7%.

The average total IPSS score (*Fig. 2*) at visit 0 was 14.9 (±3.2) points (range from 8 to 19), which corresponds to moderate symptoms, at visit 1 it decreased to 10.3 (± 3.4)

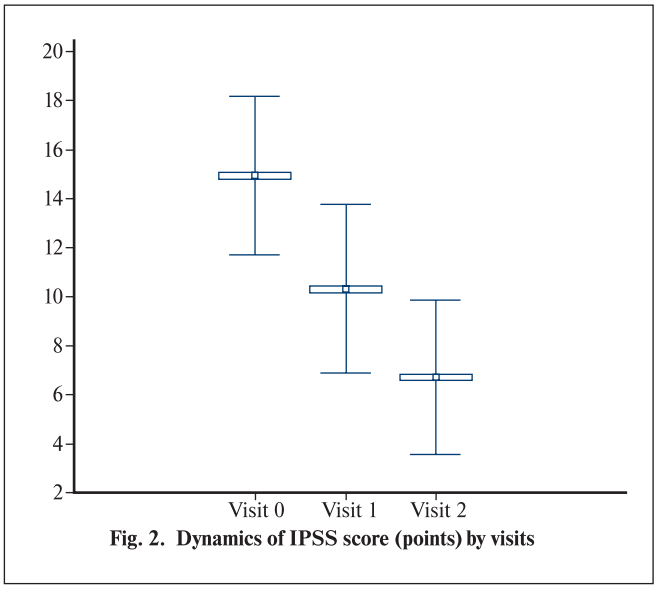

Fig. 2. Dynamics of IPSS score (points) by visits

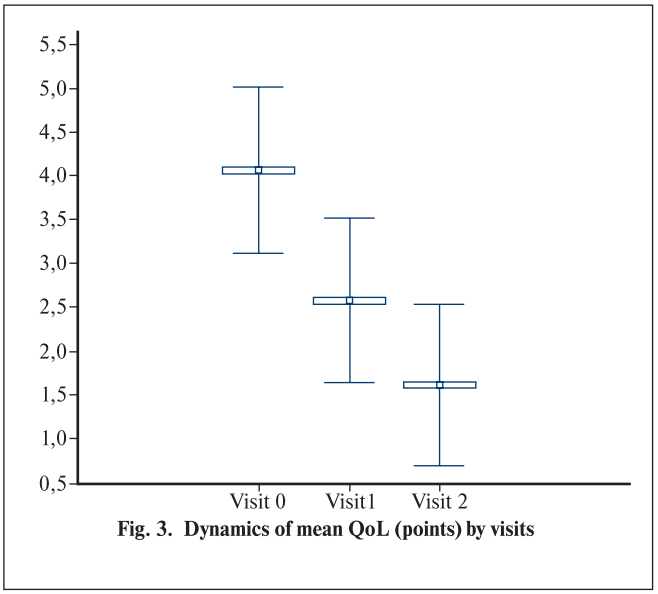

Fig. 3. Dynamics of mean QoL (points) by visits

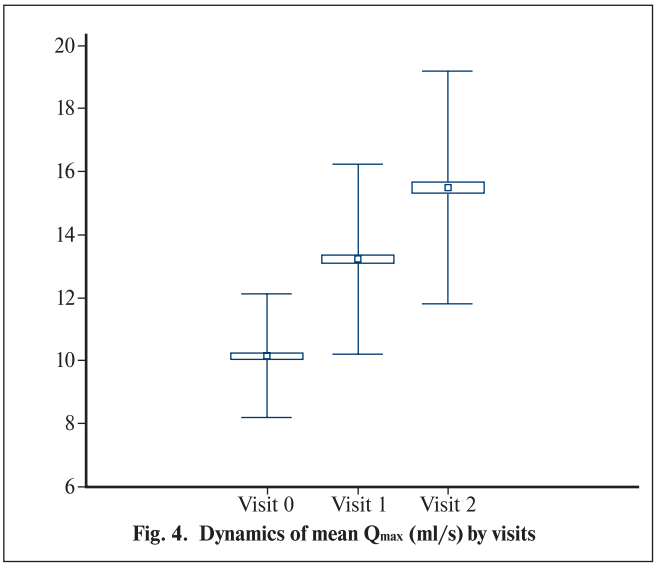

Fig. 4. Dynamics of mean Q_{max} (ml/s) by visits

(1 to 19) with a continuation of downward trend at visit 2 to 6.7 (± 3.1) points (0 to 15), which corresponds to mild LUTS. In total, after 3 months of treatment mean IPSS significantly decreased by 55.04% ($p<0.05$).

The average QoL score (*Fig. 3*) at visit 0 was 4.06 (±0.95) points (1 to 6), which corresponds to the "dissatisfied", compared to 2.58 (±0.92) (0–6) at visit 1, which is between "mostly satisfied" and "mixed about equally satisfied and dissatisfied", and 1.60 (±0.92) points (0–6) at visit 2, which corresponds to "pleased". The total significant ($p<0.05$) improvement of QoL by 2.5 times by the end of the follow-up was documented.

During 3 months of therapy, there was a significant ($p<0.05$) improvement of Q_{max} (*Fig. 4*): at visit 0, the mean value was 10.1(±1.9) ml/s (4–17), but at visit 1 it was already 13.2 (±3.0) ml/s and further increased to 15.5 (±3.7) ml/s by visit 2. In total, the average Q_{max} after 3 months of therapy increased by 5.35 ml/s (by 52.7%).

There was a significant ($p<0.05$) increase in voiding volume over visits: from 209 (±83.6) ml (range from 197 to 660 ml) to 222 (±73) at visit 0, to 236.3 (±74.0) ml at visit 1 and to 230–570 ml at visit 2. Total mean voiding volume after 3 months increased by 12.9%.

During 3 months of therapy, there was a significantly positive trend in the decrease in the average PVR: at visit 0, the mean PVR was 48.4 ml (±32.5; 0–240.0 ml). It decreased significantly to 28.3 ml (±22.2) at visit 1 and to 15.3 ml (±15.1; 0 to 90 ml) at visit 2. Total PVR after 3 months of therapy significantly decreased by 23.05 ml (3 times).

At visit 1, patients reported satisfaction with the treatment. The average Likert score was 3.8 (±0.64), range from 2 to 5 points. At visit 2, patients also noted a significant increase in the average score of satisfaction with the treatment, and the average score increased to 4.3 (±0.56), range from 2 to 5 points.

At visit 1, physicians also mentioned satisfaction with the treatment, and the average score on the Likert scale was 4.05 (±0.64; 2-5 points). The significant increase in the average satisfaction score with the treatment was also found at visit 2, with an increase in average score to 4.41 (±0.6; 2-5 points).

The secondary endpoint was the possible effect of Alfuprost® MR on hemodynamic parameters. Throughout 3 months of therapy they remained stable: there was a clinically insignificant decrease in systolic BP by no more than 2 mmHg: at visit 0, mean score was 131 (±9.6) mmHg (from 130 to 175 mmHg), compared to 127.9 mmHg at visit 1 (±8.4) (130–160) and 130 mmHg (±7.9) (130–170) at visit 2.

In general, positive changes of the main components of male sexual function in our observational study was

Table 1

Concomitant diseases	Number of questionnaires	% of the total number of questionnaires (537)
Yes	174	32.40
No	363	67.60

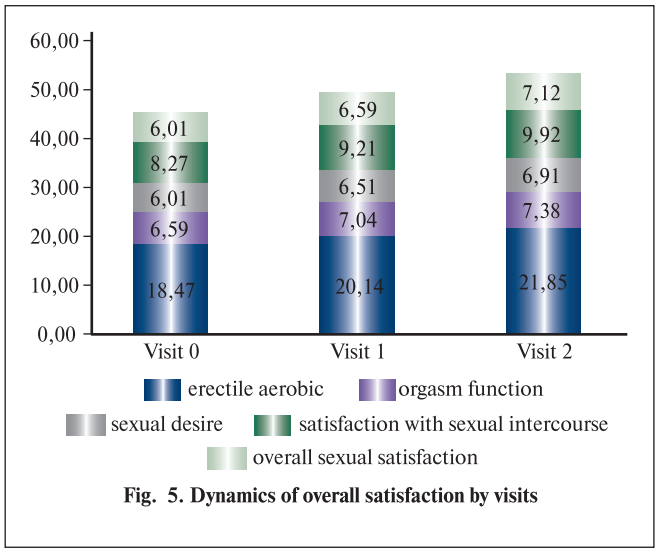

Fig. 5. Dynamics of overall satisfaction by visits

significant ($p<0.05$). The average score of ED was 18.47 (±7.0) points (1 to 30) at visit 0, indicating moderate ED. At visit 1, there was a significant ($p<0.05$) improvement by 2 points (20.14 [±6.58]) and at visit 2, an increase by 21.8 (±6.6) points was seen, which corresponds to a mild ED with an improvement by 18.29%. Orgasmic function significantly ($p<0.05$) improved from 6.59 (±2.7) points at visit 0 to 7.04 (±2.51) at visit 1 and to 7.38 (±2.4) points at visit 2, with an overall improvement of 11.98%. Sexual desire also improved during therapy: from 6.01 (±2.0) at visit 0 to 6.51 (±1.98) at visit 1 and to 6.9 (±1.9) points at visit 2, while the overall improvement was by 15.14%. The treatment also resulted in an improvement in intercourse satisfaction: from 8.27 (±3.3) at visit 0 to 9.21 (±3.29) at visit 1 and to 9.9 (±3.3) points at visit 2; the overall improvement was 19.7%. Overall satisfaction increased from 6.01 (±2.37) points at visit 0 to 6.59 (±2.23) at visit 1 and to 7.12 (±2.2) points at visit 2; the overall improvement was 18.46%. The average total IIEF score significantly ($p<0.05$) increased from 45.35 to 53.18 points (*Fig. 5*).

At the same time, there was no effect of drug on diastolic BP: at visit 0, average value was 85 (±7.3) (80–110 mmHg), compared to 81.76 mmHg (±25.44) (130–160) at visit 1 and 81.9 mmHg (±33) (80–110) at visit 2.

During the 3 months of treatment a clinically insignificant decrease in HR was observed by no more than 1 beat per minute (bpm). Mean value at visit 0 was 76.1 (±6.9) bpm (57 to 98), compared to 75 bpm (±5) (54 to 104) at visit 1 and 75.2 bpm (±5.9) (62–104) at visit 2.

AEs during the follow-up period were observed only in 7 (1.3%) of 537 patients (*Table 2*); at visit 1 4 AEs in 4 (0.7%) patients; at visit 2 there was 4 AEs, while in 4 questionnaires 5 AEs were documented. Retrograde ejaculation during the entire observation period developed only in 1 (0.19%) patient. Arterial hypotension was recorded in 2 (0.37%) patients at visit 1. Dizziness was recorded in 1 (0.19%) man at visit 1 and in 3 (0.56%) at visit 2. Weakness was noted at visit 2 in 1 (0.19%) man.

Discussion. Scientific advances in the study of the pathogenesis of BPH have allowed the pharmaceutical industry to develop effective drugs for symptomatic treatment of LUTS, which remain the first line both in mono- and combination therapy. The efficiency of α_1-AB in case of irritative and obstructive symptoms irrespective of prostate sizes has been confirmed by numerous placebo-controlled studies. However, indirect and limited direct comparisons have shown that all α_1-ABs have similar efficacy when used at appropriate doses. According to the controlled studies, the use of α_1-AB is usually accompanied by a decrease in IPSS from 25 to 40% and an increase in Q_{max} by about 20–25% [14].

The results of this prospective non-interventional study demonstrated the high efficiency of the therapy for 3 months. A decrease in the mean score on the IPSS score by 55%, an increase in Q_{max} by 53%, and a decrease in the mean PVR to normal values were recorded, which improved QoL, according to the results of QoL score, by an average of 2.46 points. Thus, the data obtained in real clinical practice on the use of Alfuprost® MR at a dosage of 10 mg once a day indicate higher efficiency in relieving LUTS than previously published data.

Manifestations of sexual dysfunction are a common problem among patients taking α_1-ABs. Effectively relieving LUTS, α_1-blockers can lead to a number of side effects, including sexual disorders. Meanwhile, international studies have shown that many patients with LUTS due to BPH consider it important to preserve sexual activity [15]. A long-term (2-year), open-label, prospective study of the efficacy and safety of alfuzosin (10 mg once daily) demonstrated clinically significant improvements in Brief Sexual Function Inventory (BSFI) domains such as erection, ejaculation, and intercourse satisfaction from baseline [16]. These improvements were more pronounced in men with severe LUTS at baseline. According to another study, Sol Yoon (2014), the use of alfuzosin (10 mg per day) for 2 years resulted in an improvement in the MSHQ-EjD scale (abridged version of the Male Sexual Health Questionnaire (MSHQ) [17].

According to the results of this prospective non-interventional study, a significant improvement in

Table 2

Structure of AEs by visits

	AEs	Number	% of all patients
Visit 1	Retrograde ejaculation	1	0,19
	Arterial hypotension	2	0,37
	Dizziness	1	0,19
Visit 2	Retrograde ejaculation	1	0,19
	Dizziness	3	0,56
	Weakness	1	0,19
	Total	9	1,7

the quality of urination was accompanied by positive dynamics of male sexual function. When considering its components, a significant ($p<0.05$) positive changes in all domains was noted: the overall improvement in orgasm function, sexual desire, intercourse satisfaction and overall function satisfaction was 11.98%, 15.14%, 19.7% and 18.46%, respectively.

The most common circulatory side effects with α_1-ABs are asthenia, dizziness, and hypotension (orthostatic). Although alfuzosin, doxazosin and terazosin are similar in terms of molecular structure, vasodilatory factors are most pronounced with doxazosin and terazosin and much less common with alfuzosin. In a multicenter open observational study (Sánchez-Chapado et al., 2000) [18], which included 3095 Spanish patients with LUTS associated with BPH, the safety and efficacy of 60-day alfuzosin extended-release tablets (10 mg per day) was evaluated in real clinical practice. Therapy with alfuzosin showed a minimal effect on blood pressure: it decreased by an average of 5–6 mmHg (4%) during treatment with alfuzosin; differences in systolic and diastolic BP were stable throughout the entire follow-up period; asymptomatic orthostatic hypotension (decrease in systolic BP and/or diastolic BP by at least 20 mmHg) was registered in less than 1% (in 28 patients); mean HR was within the normal range throughout the study.

According to our results, hemodynamic parameters dur systolic BP ing 3 months of therapy remained stable: there was a clinically insignificant ($p<0.05$) decrease in SBP by no more than 2 mmHg. At the same time, there was no effect of therapy on diastolic BP ($p>0.05$). Changes in HR during taking of Alfuprost® MR was also statistically ($p<0.05$), but not clinically significant and averaged no more than 1 bpm.

Conclusion. Based on our prospective observational study, the high efficacy and favorable safety profile of Alfuprost® MP 10 mg/day is confirmed in patients with LUTS associated with BPH. In addition, the positive impact on the sexual function after 3 months of therapy was noted.

The results of a non-interventional study allow to recommend Alfuprost® MR as a first-line drug for the treatment of patients with LUTS, associated with BPH, including sexually active men and patients who already have ejaculatory disorders.

Minimal and clinically insignificant vasodilatory effects when using Alfuprost® MR make it also possible to recommend this drug to comorbid patients.

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PILOT STUDY OF THE MANIFESTATIONS OF SYNCHRONY OF THE ANATOMICAL-METABOLIC AND FUNCTIONAL STATE OF THE BRAIN, KIDNEYS AND BLADDER

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Inroduction. The results of clinical observations and scientific studies of recent years indicate that abstinence from urination before the introduction of radiopharmaceuticals for PET / CT procedures is accompanied by a significantly lower flow of it into the bladder than after preliminary urination.
Aim. To carry out the comparative analysis of PET/CT metabolism of 18F-fluorodeoxyglucose at the level of the cingulate gyrus of the brain, different regions of the kidney parenchyma and in the bladder wall in individuals without urological disorders, depending on the phase of the functional state of the bladder.
Materials and methods. The results of PET/CT of the whole body of 30 patients of the radiological center of the Tyumen Regional Oncological Dispensary, including 16 men and 14 women (median age 52.5 (38; 63) years), were analyzed, distributed randomly in three equal study groups: after urination, in the between voiding and immediately after the appearance of the first urge to urinate.
Results. Signs of synchrony were revealed in the anatomical and metabolic activity of the cortical vegetative centers, certain regions of the renal parenchyma and the wall of the bladder in the process of urination, the movement of urine along the urinary tract, the stage of its accumulation in the bladder and preparation for urination.
Conclusion. According to our data, the analyzed regions are equivalent areas of the general regulatory system that provides physiological processes in the organs of the urinary system. However, this fact requires further research and clarification.

K e y w o r d s: PET/CT, synchrony of metabolic manifestations, brain, kidneys, bladder

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Background. In the authoritative scientific American Journal of Nuclear Medicine (JNM) P. Lovrec et al. published in 2014 a review of literature and the results of their own observations of general physiological patterns, chance findings and variants of the distribution of radiopharmaceuticals in the human body, which can be a molecular cellular precursor of various functional, metabolic and already occurred subclinical manifestations of oncological and inflammatory diseases among sick people and healthy volunteers. Based on the results of a comprehensive analysis, the following conclusion was made: the general physiological patterns of the absorption of labeled biomolecules in organs not involved in the pathological process in oncological and somatic patients are similar to those observed in healthy volunteers. In other words, the standard positron emission and computed tomography (PET/CT) of the molecular and cellular metabolism of the human body, regardless of the indications, allows to visualize and mathematically calculate the physiological, functional and, possibly, pathological components of the anatomical and metabolic process in the organs of a particular person during one study [1]. In this regard, the results of a comparative study of the accumulation of radiopharmaceuticals in the bladder during PET/CT of the whole human body with 18F-fluciclovine as part of a clinical examination of patients with suspected oncological disease outside the urinary system are of scientific interest. Patients of one group were asked to empty their bladder before administration of the drug, while patients of the other group did not urinate. The standard indicator of absorption of labeled molecules in the bladder (SUVmax) was significantly higher in patients with empty bladder. This led to the conclusion that abstinence from urination before the administration of radiopharmaceuticals is accompanied by a significantly lower intake of radiopharmaceuticals into the bladder, and it is advisable to conduct diagnostic studies in this phase to exclude functional artifacts [3–5].

It has been proven that the filling phase of the bladder is under the control of the sympathetic part of the autonomic nervous system located in the thoracic spinal cord, the lateral pons nuclei and the anterior cingulate gyrus, and the urination phase is controlled by the

parasympathetic part of the autonomic nervous system with centers in the sacral region, medial nuclei in the brainstem, and presumably in the posterior cingulate gyrus [7–10].

Sympathetic stimulation of the renal vessels leads to an increase in nephron perfusion with an increase in filtration, reabsorption, and secretion, which accelerate the elimination of substances from the body, while parasympathetic dominance reduces the blood flow rate and the efficiency of glomerular filtration with a slowdown in the excretion of metabolites from the body [11–15].

Thus, the results of clinical observations and scientific studies indicate that the neurogenic provision of the daytime period between urination and nighttime abstinence from voiding is accompanied by a reflex decrease in the functional state of the kidneys [16, 17].

Aim. To carry out a comparative analysis of PET/CT metabolism of 18F-fluorodeoxyglucose (18F-FDG) at the level of the cingulate gyrus, different regions of the kidney parenchyma and in the bladder wall in individuals without urological disorders, depending on the phase of bladder cycle.

Materials and methods. The results of PET/CT of the whole body of 30 patients performed in the radiological center of the Tyumen Regional Oncological Dispensary were analyzed. A total of 16 men and 14 women (median age, 52.5 [38; 63] years) were included. PET/CT was carried out to exclude oncological diseases outside the organs of the urinary system. Random selective method formed 3 groups of 10 patients. Patients of the first group were asked to empty the bladder immediately before scanning, in the second participants did not void, while in the third group, the study was performed immediately after the first urge to urinate. The patients were informed about participation in a clinical trial to find the optimal PET/CT regimen, which would allow more accurate assessment of the anatomical and metabolic state of their organs, for which written consent was obtained. The state of energy metabolism of the entire body of patients was assessed by PET/CT using a Biograph apparatus (Siemens). Data analysis was performed by a visual method with 3D image reconstruction. We studied the activity of 18F-FDG metabolism in the areas of interest marked with a dashed line according to the level of isotope uptake (SUVmax) within the framework of physiological deviations of indicators from 4.5 to 17.5 g/ml. Studies were carried out for 30 minutes, including 20 minutes after intravenous administration of 5 ml (200 MBq) of the drug. The 18F-FDG radiopharmaceutical contains no more than 0.5 mg/mL of glucose and is used in practice for life-time assessment of the rate of its metabolism by tissues in which energy metabolism depends on the consumption of carbohydrates [21]. The drug was manufactured at the Tyumen Radiological Center on a compact cyclotron by Scanditronix. PET/CT scanning was performed in standard mode in all cases.

Statistical analysis was carried out in accordance with international requirements for the processing of research data using the Statistica for Windows (version 11.5). Continuous variables are presented as M±m (mean±standard error of the mean). The statistical significance of differences was assessed by Student's t-test.

Results. Initially, the standard procedure for PET/CT with 18F-FDG consisted in scanning the entire human body, regardless of the anatomical area of interest, was carried out (*Fig. 1*).

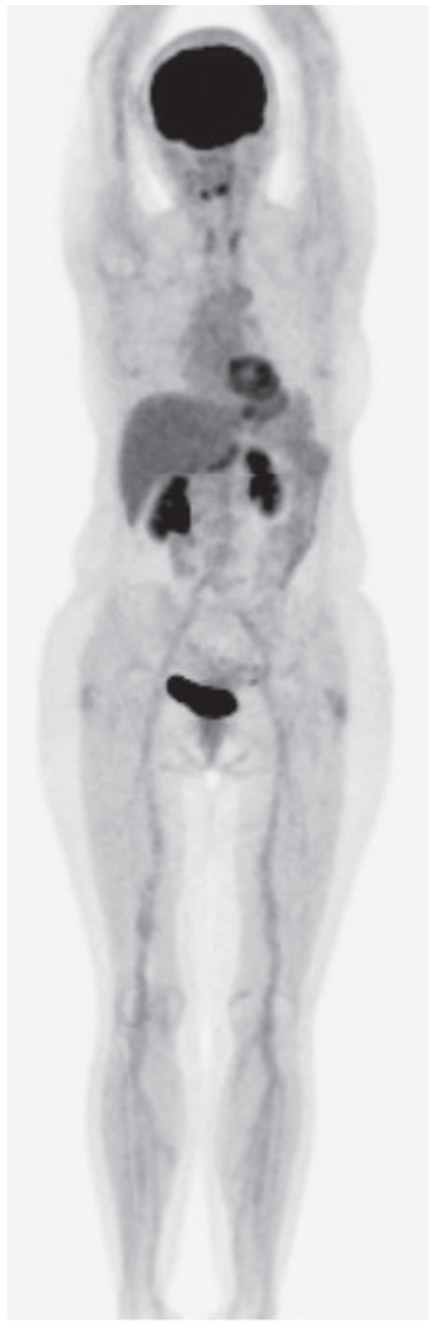
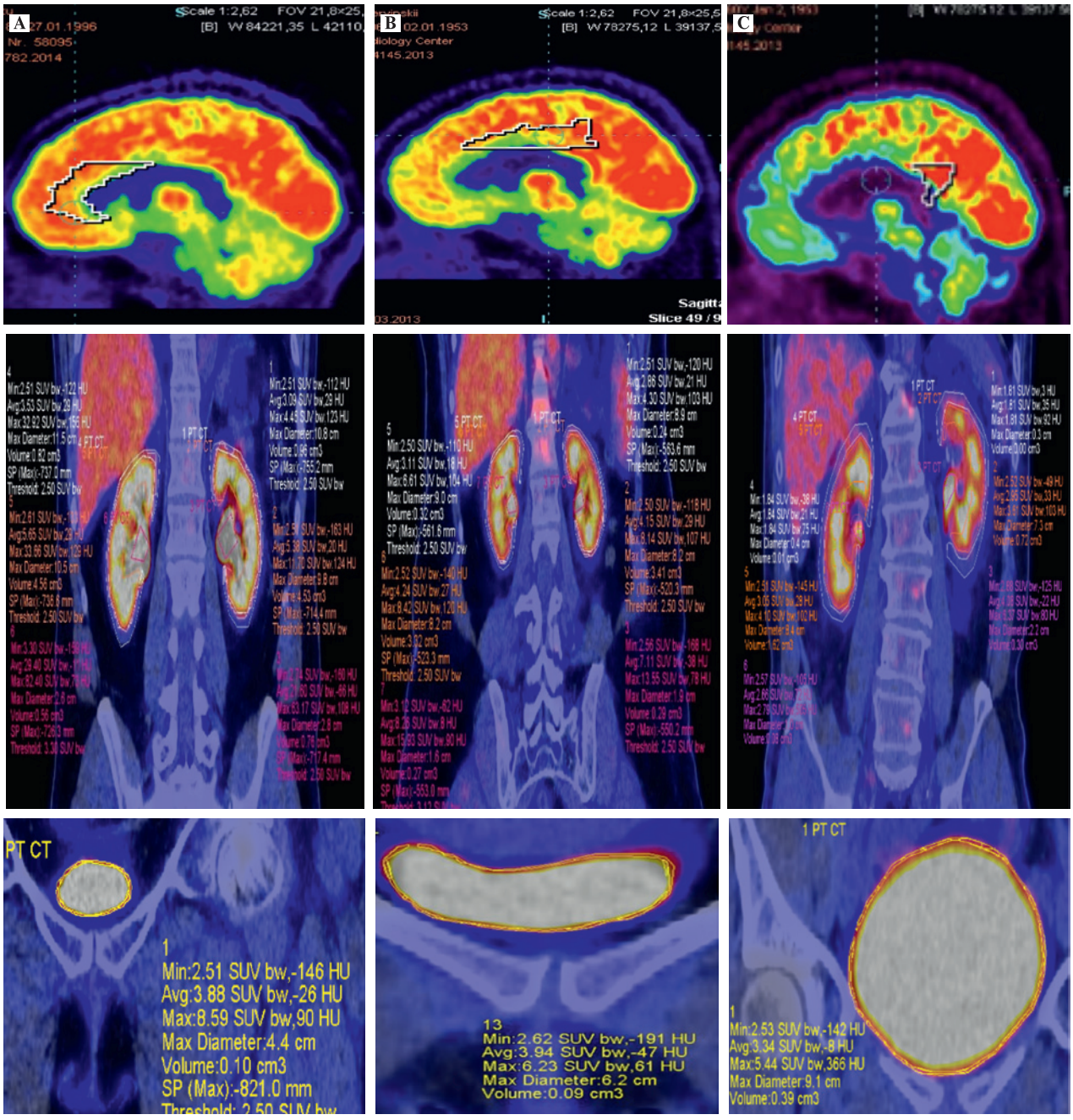


Fig. 1. PET/CT data of a human with 18F-FDG

At the second stage, the visual features of the anatomical and metabolic distribution in tissues of labeled energy-intensive glucose molecules were analyzed with a mathematical calculation of tropism in the regions highlighted by dashed lines (*Fig. 2*).

As a result, it was found that immediately after urination, patients had an increase in the metabolism of energy-intensive glucose molecules mainly in the projection of the anterior cingulate gyrus, while in case of full bladder the activity in the middle part of the cingulate gyrus was found, and at the first urge to urinate it was seen mainly in the posterior cingulate gyrus.



A – immediately after urination; B – without prior urination;
C – after the first urge to urinate.

Fig. 2. Visual and typological picture of PET/CT of anatomical and metabolic synchrony in the physiological axis of brain-kidney-bladder

At the same time, hypermetabolism in the anterior cingulate gyrus coincided with increased tropism for energy-intensive molecules of the cortical and medulla parts of the renal parenchyma. Activity in the middle cingulate gyrus was accompanied predominantly by saturation of the renal medulla, while the posterior cingulate gyrus's activity occurred simultaneously with the maximum accumulation of the isotope in the collecting system.

The next stage of the study was a digital analysis of the results of visual observations (see table).

It was found that the overall metabolic activity in the analyzed regions was the highest immediately after urination (81.7±0.6 g/ml), mainly due to anterior cingulate gyrus (17.6±2.5 g/ml). The lowest total activity was detected in the phase of urine accumulation (51.2±0.7 g/ml, $p<0.05$), with the exception of hypermetabolism in the middle cingulate gyrus (15.6±1.0 g/ml. $p<0.05$), and average metabolic activity (61.4±0.7 g/ml, $p<0.05$) was at the first urge to urinate with metabolic processes in the posterior cingulate gyrus (16.9±0.5 g/ml, $p<0.05$).

At the level of the kidneys, the affinity of parenchyma tissues to energy-intensive glucose molecules, depending on the phase of the study, shifted from the cortical layer in the post-micturition period (12.6±0.5 g/ml, $p<0.05$) to the medulla during the period of urine accumulation

Table

Dynamics of tropism of the tissues of the cingulate gyrus, kidney parenchyma and bladder wall to 18F-FDG (SUVmax in g/ml) depending on the study protocols (M±m)

Area of interest	After voiding	During storage phase	At first desire to void
Cingulate gyrus:			
anterior	17,6±2,5*	10,2±2,0	10,4±1,5
middle	12,5±1,5	15,6±1,0*	12,5±1,5
posterior	14,1±0,5	11,6±0,5	16,9±0,5*
Kidney parenchyma:			
Cortex	12,6±0,5*	1,8±0,5	2,3±0,5
Medulla	3,8±0,5	2,9±0,5*	3,6±0,5
Collecting system	10,9±0,5	2,0±0,3	10,5±0,5*
Bladder wall	10,2±0,5	6,5±0,5**	5,2±0,5**
Total metabolism in the areas of interest	81,7±0,6	51,2±0,7**	61,4±0,7**

Note. Statistical significance of differences ($p < 0.05$): *in the areas of interest, **between different groups, based on a study protocol (Student's t-test).

(2, 9±0.5 g/ml, $p<0.05$) and to the collecting system during the first urge to urinate (10.5±0.5 g/ml, $p<0.05$). At the same time, in the bladder wall, the maximum activity of glucose metabolism occurred in the immediate post-micturition period, it significantly decreased with the accumulation of urine and especially at the first urge to urinate (10.2 ± 0.5; 6.5 ± 0.5 and 5, 2±0.5 g/ml, respectively, $p<0.05$).

Thus, the results of this study did not contradict the previously published data and allows to confirm the presence of a certain synchrony of metabolic processes within the functional physiological axis brain–kidney–urinary bladder.

Discussion. It is known that molecular and cellular metabolism determines the state of viability of human organs in terms of their specialized functions. Neurohumoral regulation ensures the synchronization of these functions and holistic interaction within the composition of the body. However, only the introduction of a non-invasive PET/CT procedure allows to evaluate it in real time fashion. As part of the pilot study, elements of anatomical and metabolic synchrony were identified in the interaction of cortical vegetative centers, certain areas of the renal parenchyma and the bladder wall, which reflect the provision of neural pathways with glucose molecules for the process of urine formation, its movement along the urinary tract, the stage of its accumulation in bladder and preparation for urination. At the same time, it is difficult to determine what is decisive within the framework of the axis, and we can only assume that each analyzed organ is an equivalent part of the general regulatory system that provides the whole variety of physiological processes in a healthy person.

Conclusion. According to our data, the analyzed regions are equivalent areas of the general regulatory system that provides physiological processes in the organs of the urinary system. However, this fact requires further research and clarification.

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EXTENDED CULTURE STUDY AS A KEYPOINT TO RETHINKING ANTIBIOTIC THERAPY FOR CHRONIC BACTERIAL PROSTATITIS

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Objective. To juxtapose the microbiological efficacy of standard and targeted antibiotic therapy (ABT) based on the comparison of the results of extended bacteriology of biomaterial in patients suffering chronic bacterial prostatitis (CBP) before and after treatment.

Materials & methods. Study design: single-centre observational comparative study. Sixty patients with CBP aged 20 to 45 years were included in the study. All patients underwent an initial examination: questioning, Meares-Stamey 4-glass test, extended bacteriology of biomaterial samples, and determination of antibacterial susceptibility (ABS). After the initial examination, the patients were randomly assigned to two groups (30/30 patients). In group (G) 1, antibacterial drugs were prescribed following the EAU guidelines on Urological Infections (monotherapy), in G2, focusing on the results of ABS (mono or combination therapy). Evaluation of the treatment effectiveness and control bacteriology were carried out three months after therapy.

Results. In G1 vs G2, nine vs ten aerobes and eight vs nine anaerobes were identified in the expressed prostate secretion, respectively. The microbial load of the samples in ⩾103 CFU / ml was established in G1 vs G2 for five vs ten aerobes and seven vs eight anaerobes, respectively. The highest ABS of bacteria was determined to moxifloxacin, ofloxacin, and levofloxacin. Cefixime was the most active against anaerobes. After treatment, no significant changes in the bacterial spectrum were observed in both groups. A more reliable decrease in the frequency of microorganism identification and the microbial load of the samples was observed in patients with G2 after the targeted ABT.

Conclusion. Targeted ABT based on extended bacteriology can be considered an effective alternative to standard guideline-approved ABT for the treatment of CBP.

K e y w o r d s: *antibiotics; antibiogram; bacteria; cephalosporins; culture media, extended; fluoroquinolones; macrolides; microbial drug resistance; prostatitis*

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Doi: https: //dx.doi.org/10.18565/urology.2023.1.5-11

Introduction. Traditionally, antibiotic therapy for chronic bacterial prostatitis (CBP) is aimed at suppressing bacterial growth and/or eliminating a narrow spectrum of the most studied and easily isolated uropathogens. This spectrum is represented by various species of family Enterobacteriaceae, single gram-positive pathogens, in some cases, by nonfermenting gram-negative bacteria, in particular, Pseudomonas aeruginosa [1, 2]. It has also been proven that some sexually transmitted pathogens are also involved in the development of the CBP [3].

At the same time, a number of publications provide convincing data on the role of various species of Staphylococcus spp., Streptococcus spp., Corynebacterium spp., some anaerobes, viruses, and fungi in the development of CBP [4, 5]. However, new studies and publications on the etiological structure of CBP do not globally change the paradigm that has existed for many decades about a predominance of Enterobacteriaceae, resulting in following stereotypes: 1) CBP is usually caused only by one of the uropathogens; 2) antibiotic therapy in the vast majority of cases is aimed at eliminating Enterobacteria, which are causative uropathogens of CBP. According to the Guidelines of the European Association of Urology on Urological Infections and the Guidelines of the Association of American Family Physicians, fluoroquinolones are considered the first-line drugs for the treatment of CBP [6, 7]. However, these agents are really effective only in patients with primary CBP.

In turn, in recurrent CBP, the multifactorial pathogenesis and the emergence of multidrug-resistant microflora, in particular carbapenem-resistant (CREB) and ESBL-producing (ESBL) Enterobacteriaceae, multidrug-resistant Escherichia coli and P. aeruginosa, vancomycin-resistant Enterococcus and some other microorganisms, lead to failure of antibiotic therapy [8–12]. In general, the efficiency of antibiotic therapy in CBP is estimated at 60.0% [4].

Therefore, in the treatment of CBP, the search for alternative treatment options using antibacterial drugs continues. In the case of minimal efficacy of standard antibiotic therapy or recurrent episodes of CBP, these alternative regimens can be used in a second or, in some cases, first line to achieve a positive result. At the same time, there is an assumption about erroneous view on the etiology of the disease, based on standard urine culture. The study results demonstrate significant differences between the generally accepted etiological spectrum and

the modern microbial landscape verified in patients with CBP using extended culture media [13, 14]. This leads not only to the verification of a narrow spectrum of pathogens in CBP, but also to the prescription of antibacterial drugs that act specifically on this spectrum of microorganisms.

Aim. To compare the microbiological efficacy of standard and targeted antibiotic therapy based on a comparison of the results of an extended bacteriological study in patients with CBP before and after treatment.

Materials and methods

Study design. Single center observational comparative study was carried out (2012–2019).

Ethical statement. The study was approved by the Ethics Committee of the Rostov State Medical University (protocol No. 17/12 dated December 4, 2012) and complies with the Declaration of Helsinki (as amended by Fortaleza, Brazil, October 2013). All patients signed informed consent to participate in the study and permission to publish personal medical data.

Characteristics of the sample. A total of 60 patients aged 20–45 years with CBP were included in the study.

Inclusion criteria: presence of symptoms typical for prostatitis, lasting more than 3 months; pain in "typical localizations": perineum and/or suprapubic area with irradiation to the scrotum, sacrum, inguinal region; lower urinary tract symptoms (LUTS), leukocyturia, positive culture of post-massage urine with more than 10-fold higher concentration compared to the first or second urine sample of Meares-Stamey test.

Exclusion criteria: acute infections of the lower urinary tract and genital organs; sexually transmitted diseases; prostate cancer; heart/kidney/liver failure; previous surgical interventions on the prostate and lower urinary tract (within 3 months before the study); radiation therapy; drug, alcohol abuse; allergic reactions to antibacterial drugs.

Survey. Each patient underwent initial (at the diagnostic stage) and follow-up examinations (3 months after the end of therapy). Patients completed validated NIH-CPSI, IPSS-QoL, IIEF-5 questionnaires at the first visit. In all cases, a Meares-Stamey 4-glass test was performed. The number of leukocytes was determined in each sample.

Bacteriological examination of urethral, bladder and post-massage urine was performed in all patients on an expanded set (n=12) of culture media for aerobic and anaerobic bacteria (HiMedia Laboratories Ltd., Maharashtra, India), for isolation of aerobes and anaerobes (AnaeroHiGas Pack, HiMedia, HiMedia Laboratories Ltd., Maharashtra, India) in order to identify as much microorganisms as possible. To compare the dynamics of concentration and the detection rate of pathogens, data on post-massage urine culture were used.

The individual antibiograms were analyzed in order to assess the sensitivity of identified microorganisms to 13 antibiotics: 6 fluoroquinolones, 2 macrolides and 1 representative from oral cephalosporins, phosphonic acid derivatives and nitrofurans, tetracyclines and glycopeptides. Minimal inhibitory concentration was determined by disk diffusion method on Mueller-Hinton agar in accordance with the recommendations of the Clinical and Laboratory Standards Institute (CLSI), the European Committee on Antimicrobial Susceptibility Testing, (EUCAST) using standard discs (HiMedia Laboratories Ltd., Maharashtra, India).

Randomization and Therapy

After the initial examination, all patients were randomly divided into two groups. In all patients, therapy was carried out according to the standard scheme: antibiotic therapy (based on the results of urine culture) + α-blocker + non-steroidal anti-inflammatory drug.

In Group 1, fluoroquinolone was prescribed (levofloxacin, ofloxacin, or ciprofloxacin), aimed at suppressing causative uropathogens, considering their sensitivity. In Group 2 either fluoroquinolone monotherapy (levofloxacin or ofloxacin), or a combination with oral cephalosporin (cefixime), or a combination of macrolides (azithromycin) with cephalosporin (cefixime) was used based on the sensitivity of all identified bacteria, thus providing the effect on the whole spectrum of pathogens. The spectrum and frequency of prescribing antibiotics and their combinations in groups are presented in Table 1. Drug therapy was administered for 1 month. All examinations were repeated at the follow-up visit at 3 months after the end of treatment.

Statistical analysis

Statistical processing of the results was carried out using the software package Statistica 10.2 (StatSoft Inc., Tulsa, Oklahoma, USA). The normality of the distribution was determined using the Shapiro–Wilk and Kolmogorov–Smirnov tests. Descriptive statistics of quantitative variables are presented as mean (M) and standard deviations (SD) (M±SD in tables). Comparison of independent variables in groups was performed using student t-test (unpaired and paired t-test for dependent and independent samples) and Pearson`s χ^2-test. The accepted level of significance was $p<0.05$ at a=0.05.

Results. Prior to the initial treatment, in group 1, a total of 9 taxa of aerobic and 8 anaerobic microorganisms were verified in post-massage urine, compared to 10 aerobic and 9 anaerobic in group 2. In group 1, the concentration ⩾103 CFU/ml in post-massage urine was seen for 5 aerobes and 7 anaerobes, while in group 2 for 10 aerobes and 8 anaerobes.

The individual antibiotic susceptibility of microorganisms isolated from post-massage urine in the concentration of ⩾103 CFU/ml in patients of both groups are presented in Table 2.

Antibiotic sensitivity of Enterobacteriaceae to fluoroquinolones was as following (from higher to lower): moxifloxacin → ofloxacin → levofloxacin → lomefloxacin → ciprofloxacin. Almost 50.0% of isolated microorganisms were sensitive to levofloxacin and more than 80.0% to ofloxacin. With regard to anaerobic bacteria, cefixime (91.9%) had the highest activity.

The results of the primary and repeated cultural studies of post-massage urine are given in Table 3. In group 1 patients received only fluoroquinolones. A decrease in the detection rate of five taxa was found, but the difference was significant ($p<0.05$) only for Klebsiella spp. At the follow-up, a change in the spectrum of microorganisms in post-massage urine was noted only due to an increase ($p<0.05$) in the frequency of Citrobacter spp. and the appearance of coagulase-negative staphylococci (CoNS) Staphylococcus xylosus. Among the anaerobic bacteria, the detection rate of most taxa (five out of eight), with the exception of Bacteroides spp. and Fusobacterium spp., was significantly increased ($p<0.05$) for Eubacterium spp.

Table 1

Antibacterial drugs prescribed in two groups

Antibacterial drug	Group 1 (n=30)		Group 2 (n=30)	
	n	proportion (%)	n	proportion (%)
Levofloxacin 500 mg QD	15	50,0	3	10,0
Ofloxacin 400 mg BID	8	26,7	9	30,0
Ciprofloxacin 500 mg BID	7	23,3	–	–
Ofloxacin + Cefixime 400+400 mg QD	–	–	6	20,0
Levofloxacin + Cefixime 500+400 mg QD	–	–	4	13,3
Azithromycin + Cefixime 500+400 mg QD	–	–	8	26,7

and Prevotella spp. Thus, by the 3rd month of follow-up, a significant decrease in the detection rate of 5 aerobes and 4 anaerobes was seen.

In group 2, at the follow-up visit, the spectrum of microorganisms in post-massage urine virtually did not change, with the exception of the elimination of Enterobacter aerogenes and the identification of Staphylococcus equorum. Among 10 aerobes, the detection rate of 6 taxa decreased with reliable values only for 4 microorganisms. A significant (p<0.05) increase in the detection rate was noted only in Staphylococcus haemolyticus, but with a reduction in concentration. In the anaerobic cluster, in comparison with group 1, the detection rate of four bacteria out of eight decreases with significant values for Propionibacterium spp., Prevotella spp. and Eubacterium spp. In addition, there was a significant decrease (p<0.05) in bacterial load in post-massage urine for both aerobes and anaerobes.

Discussion. An extended bacteriological study in two groups revealed 21 taxa of microorganisms in post-massage urine. A total detection rate in descending was as following: anaerobes (100.0%), CoNS (86.7%), Corynebacterium spp. (65.0%), Enterococcus spp. (50.0%), Enterobacteriaceae (45.0%).

Thus, anaerobes and CoNS were main pathogens in post-massage urine in CBP. The data obtained do not correspond with the results of a number of studies on the predominant role of Enterobacteriaceae. A. Trinchieri et al. (2021) studied 1027 isolates from post-massage urine, expressed prostatic secretion (EPS), ejaculate and urethral

Table 2

Antibacterial susceptibility of microorganisms isolated during the initial examination

Antibacterial drug	Microorganisms [families, clusters]				
	Enterobacteriaceae	*Enterococcaceae*	CoNS	*Corynebacteriaceae*	Анаэробы
Fluoroquinolones[a), b)]					
Ciprofloxacin	30,0	–	–	–	–
Levofloxacin	48,4	49,0	51,4	–	–
Ofloxacin	81,7	56,8	82,8	–	–
Lomefloxacin	40,9	–	–	–	–
Moxifloxacin	96,6	91,2	88,6	95,4	94,5
Norfloxacin	–	–	–	–	–
3rd generation cephalosporins[a)]					
Cefixime	73,3	–	57,1	59,0	91,9
Phosphonic acid derivatives[a)]					
Fosfomycin	48,4	41,0	–	–	–
Tetracyclines[b]					
Doxycycline	–	62,6	–	–	83,7
Nitrofuran derivatives[a), b)]					
Nitrofurantoin	–	35,4	–	–	–
Glycopeptides[a)]					
Vancominin	–	46,8	–	–	–
Macrolides[b)]					
Erythromycin	–	–	–	79,4	–
Azithromycin	–	–	–	–	83,7

Note. CoNS, coagulase-negative staphylococci, (-), sensitivity did not exceed 30%.
a), bactericidal activity, b), bacteriostatic activity.

Table 3

Changes in microbial load (lgCFU/ml) and detection rate (%) of microorganisms in two groups before and after antibiotic therapy

Pathogens	Group 1 (*n*=30)				Group 2 (*n*=30)			
	At baseline		3 months after therapy		At baseline		3 months after therapy	
	lgCFU/ml (M±SD)	rate (%)	lgCFU/ml (M±SD)	rate (%)	lgCFU/ml (M±SD)	rate (%)	lgCFU/ml (M±SD)	rate (%)
Aerobes								
(EBC) E. coli	4,7±0,3	40,0	**2,5±0,4**↓	33,3↓	4,5±0,5	33,3	**2,0±0,1**↓	**6,7**↓
(EBC) Klebsiella spp.	2,0±0,1	6,7	**1,0±0,1**↓	**3,3**↓	4,0±0,1	3,3	**2,0±0,1**↓	3,3
(EBC) Citrobacter spp.	3,0±0,1	3,3	**1,5±0,3**↓	**6,7**↑	–	–	–	–
(EBC) E. aerogenes	–	–	–	–	4,0±0,1	3,3	–	–
(Gram+ B) Corynebacterium spp.	3,5±0,5	56,7	3,1±0,4↓	56,7	4,0±0,1	73,3	**1,8±0,3**↓	66,7↓
(CoNS) S. haemolyticus	3,1±0,1	63,3	**2,1±0,3**↓	63,3	3,2±0,2	66,7	2,3±0,4	**76,7**↑
(CoNS) S. epidermidis	2,3±0,4	33,3	1,6±0,5↓	26,7↓	3,6±0,3	26,7	**1,4±0,4**↓	23,3↓
(CoNS) S. warneri	2,5±0,3	26,7	1,6±0,4↓	16,7↓	3,7±0,2	10,0	**2,0±0,1**↓	**3,3**↓
(CoNS) S. lentus	2,7±0,7	20,0	–	–	4,0±0,1	3,3	**2,0±0,1**↓	3,3
(CoNS) S. xylosus	–	–	1,0±0,1	**6,7**↑	3,7±0,7	10,0	**1,0±0,1**↓	**3,3**↓
(CoNS) S. equorum	–	–	–	–	–	–	**1,0±0,1**↑	3,3
(ECC) Enterococcus spp.	3,9±0,3	46,7	**2,3±0,3**↓	53,3↑	3,3±0,2	53,3	**1,8±0,4**↓	**33,3**↓
Anaerobes								
Peptococcus spp.	3,1±0,2	66,7	3,6±0,6↑	70,0↑	3,3±0,4	60,0	**1,8±0,3**↓	56,7↓
Peptostreptococcus spp.	4,0±0,1	60,0	4,2±0,2↑	70,0↑	5,0±0,1	63,3	**1,9±0,5**↓	66,7↑
Propionibacterium spp.	3,7±0,5	50,0	**4,9±0,7**↑	53,3↑	4,4±0,2	76,7	**1,7 ±0,7**↓	**66,7**↓
Eubacterium spp.	4,7±0,3	20,0	4,9±0,6↑	**33,3**↑	5,5±0,3	6,7	**1,0±0,1**↓	**3,3**↓
Prevotella spp.	3,6±0,4	16,7	4,0±0,1↑	**26,7**↑	4,5±0,5	6,7	**2,0±0,1**↓	**3,3**↓
Veillonella spp.	3,8±0,5	16,7	**4,7±0,3**↑	13,3↓	4,2±0,6	20,0	**2,0±0,1**↓	20,0
Bacteroides spp.	1,0±0,1	6,7	**2,5±0,5**↑	6,7	6,0±0,1	6,7	**2,0±0,1**↓	6,7
Fusobacterium spp.	4,0±0,1	3,3	**5,0±0,1**↑	3,3	4,0±0,1	3,3	**2,0±0,1**↓	3,3
Mobiluncus spp.	–	–	–	–	1,0±0,1	3,3	–	–

Note. 1) intragroup significant differences are highlighted in bold ($p<0.05$); 2) ↑/↓, dynamics of changes in variables (increase/decrease); 3) EBC, Enterobacteriaceae, CoNS, coagulase-negative staphylococci, ECC, Enterococcaceae, Gram+B, Gram-positive rods.

swab and revealed E. coli (31.0%) and Enterococcus spp. (22.0%). In addition, K. Stamatiou et al. (2019) in a study of 389 patients with CBP found that in post-massage urine/EPS (465 samples) E. coli (142/465 samples) and E. faecalis (102/465 samples) were predominated. In both studies, obligate uropathogens Klebsiella spp., Proteus spp. and Pseudomonas aeruginosa were isolated much less frequently. However, among other types of pathogens, K. Stamatiou et al. (2019) also significantly often identified CoNS (108/465 samples). It should be noted that anaerobes were not isolated in these works due to the limitations of bacteriological studies [11, 15].

According to the Guidelines of European Association of Urology on Urological Infections, ability of CoNS, Corynebacterium spp. and anaerobes to cause a relevant inflammatory process in the prostate remains debatable [7]. Various studies, which form controversies about the prostatotropic pathogenic potential of individual microorganisms (anaerobes, intracellular pathogens, CoNS, Corynebacterium spp., Peptococcus spp., viruses, etc.) [13–16] are provided by the groups of authors. However, causative uropathogens in patients with typical symptoms of prostatitis are isolated not in all cases, however, debatable microorganisms or bacteria with "unknown prostatotropic pathogenicity" can be also detected [17-19]. In this case, do we need to follow the standard protocols for antibacterial therapy of CBP? We believe that in such cases it is advisable to form an individual treatment strategy, considering antibiotic sensitivity, pharmacokinetics, the principles of antibiotic potentiation/synergy, and the spectrum of antibacterial activity.

To confirm our hypothesis, based on the analysis of antibiograms, we noted four antibiotics with the most pronounced (in frequency) and extensive (in coverage) antimicrobial activity (presented in descending order, max–min) against pathogens verified in the post-massage urine: moxifloxacin (CoNS 88.6%, Enterobacteriaceae 96.6%), cefixime (Enterococcaeae <30%, anaerobes 91.9%), ofloxacin (Corynebacteriaceae/anaerobes <30%, CoNS 82.8%) and levofloxacin (Corynebacteriaceae/anaerobes <30%, CoNS 51.4 %). Indeed, moxifloxacin is the unique antibacterial drug with hybrid bactericidal and bacteriostatic effects, especially against gram-positive cocci and anaerobes. It has ability to accumulate in the tissue and prostatic secretion due to its lipophilicity compared to other fluoroquinolones [20]. However, this respiratory fluoroquinolone cannot be considered as part of the first-line therapy for CBP, due to two main reasons. Firstly, moxifloxacin is not included in the guidelines for the treatment of CBP; moreover, its prescription is off-label [7, 21]. In turn, ofloxacin and levofloxacin are first-line drugs. Cefixime is not included in the list of preferred antibacterial drugs for the treatment of CBP, but it can be used in uncomplicated urinary tract infections [7, 22].

A. Trinchieri et al. (2021), when assessing the frequency of antibacterial resistance of microorganisms from 1027 isolates of post-massage urine, EPS, ejaculate and urethra, found that among Enterobacteriaceae (E. coli, Proteus spp., Klebsiella spp.) resistance to fluoroquinolones and cephalosporines varied within 12.0–31.0%, and to macrolides within 0.0–20.0%. For Enterococcus spp., Staphylococci and Streptococci, the resistance rate to fluoroquinolones was determined at levels of 21.0%, 21.0 and 4.0%, respectively, to cephalosporines 93.0%, 16.0 and 4.0%, and to macrolides 77.0%, 42.0 and 26.0%, respectively [15]. Thus, the study also showed a relatively high resistance of Enterobacteriaceae, Enterococcus and Gram-positive cocci to fluoroquinolones and cephalosporines. Macrolides, which is the first line of therapy for CBP, if intracellular pathogens are isolated, have demonstrated high efficacy against Enterobacteriaceae. The sensitivity of Enterococcus spp., Staphylococci to this group of antibiotics was significantly lower. In our study, the lowest resistance to macrolides was noted in anaerobes (83.7% to azithromycin) and Corynebacteriaceae (79.4% to erythromycin), while the sensitivity of other pathogens to this antibiotic did not exceed 30.0%.

Considering the limited arsenal of antibiotics according to the results of individual antibiograms, drug instructions and guidelines for the treatment of CBP, the following adjustments were made when prescribing drugs in group 2. Firstly, the use of ciprofloxacin was excluded due to the borderline sensitivity. Secondly, combinations of levofloxacin/ofloxacin + cefixime and azithromycin + cefixime were used. Thirdly, the selection of antibiotics for each patient was carried out considering the fact that one or a combination of antibiotics covered the entire spectrum of pathogens identified in the post-massage urine, i.e., with sensitivity to prescribed drugs. Fourthly, the dosage, frequency and duration of antibiotics wasn't changed.

A comparative analysis of bacteriological analysis at diagnostic stage and at the follow-up visit showed the following results. Despite slight significant differences in the detection rate of pathogens in both groups, in group 2 there was a significant decrease in the microbial load by aerobes and anaerobes in post-massage urine below the threshold pathogenic concentration of 103 CFU/ml at follow-up. Accordingly, targeted fluoroquinolones, along with combinations of cefixime with ofloxacin/levofloxacin and azithromycin, covering the entire spectrum of microorganisms, were more effective in reducing the microbial load compared to fluoroquinolones monotherapy aimed only at predominant uropathogens in Group 1. This is due, on the one hand, to the escalation of the bactericidal effect in the combination of cephalosporin and fluoroquinolones or the potentiation of the bactericidal and bacteriostatic effects in the combination of cephalosporin with macrolide, and, on the other hand, to the targeted effect of fluoroquinolones. The complete elimination of bacteria by the follow-up visit was achieved in Group 1 only for Staphylococcus lentus, and in group 2 for E. aerogenes and Mobiluncus spp., which indicates an extremely insignificant elimination of pathogens after antibiotic therapy.

In this regard, an important question arises, whether there is a need to eliminate opportunistic microorganisms from post-massage urine or not, since the elimination of one of the species changes the symbiotic relationships in the biotope. Perhaps it is most preferable to reduce the concentration of pathogens. Regarding combination therapy, V. Magri et al. (2019) noted that the combination of levofloxacin and azithromycin in 90.0% of cases enables to eliminate pathogens compared with levofloxacin monotherapy, which provided eradication in 79.0% of cases [23].

It should be noted that a lot of studies have been published comparing the efficiency of various fluoroquinolones and combinations of fluoroquinolones with macrolides for the treatment of CBP, but oral cephalosporines are ignored [24-26]. We presented data that indicate the efficiency of combinations of oral cephalosporines with fluoroquinolones/macrolides. I.A. Bochkov et al. (2011) also demonstrated a high sensitivity to a number of cephalosporines and fluoroquinolones (74.6–91.0%) of Enterobacteriaceae, except for Klebsiella spp. and Enterobacterium spp., as well as CoNS. Streptococcus spp. had the lowest resistance to macrolides (62.9–77.9%) [27]. In addition, M.S. Bader et al. (2020) provide data indicating the possible use of oral cephalosporines in step-down therapy of urinary tract infections in case of known antibiotic sensitivity [28]. Moreover, V.N. Krupin et al. (2019) believe that the inefficiency of therapy in CBP is largely due to the inadequate intraprostatic penetration and cumulative capacity of many antibiotics [29]. Fluoroquinolones, undoubtedly, are reference in this respect. However, according to the review by B.A. Lipsky et al. (2010), accumulation of cefixime (1.08 mg/g) in the prostate tissue is comparable to ciprofloxacin (0.6-4.18 mg/g) and prulifloxacin (1.9-5.5 mg/g) and slightly inferior to azithromycin (2.54 mg/mL) [30].

Thus, despite the limited data on the use of oral cephalosporins in the treatment of CBP as monotherapy, we should consider them as additional drugs in certain situations in which the prescription of cephalosporins is required based on objective data.

In summary, it is necessary to highlight several key points based on the results of the study:

- Standard antibiotic therapy does not lead to complete eradication of the pathogens.
- Targeted antibiotic therapy does not cause significant changes in the spectrum of microorganisms.
- At the follow-up, a more pronounced decrease (significant and insignificant) in the detection rate and concentration of aerobes was seen after standard monotherapy (Group 1); on the contrary, an increase (significant and insignificant) in the detection rate and concentration for anaerobes was noted.
- At the follow-up visit after targeted monotherapy and/or combination therapy, there was a pronounced (mostly significant) decrease in the detection rate and concetration for both aerobes and anaerobes.
- There were no recurrences of CBP during the follow-up, but it is possible in the long term, especially in those receiving monotherapy.

Conclusion. Currently, antibiotics remain the basis of conservative therapy of urogenital infections, in particular CBP. Nevertheless, the growth of antibiotic resistance dictates the need to choose antibiotic therapy more carefully. There is no doubt that adherence to clinical guidelines is mandatory in the health care systems of various countries, but a number of first-line drugs is not very large. An extended bacteriological study with individual

antibiograms is necessary at the diagnostic stage to obtain reliable data. We believe that the use as initial therapy of both alternative drugs from fluoroquinolones group (non-first line) and combinations of fluoroquinolones with cephalosporines/macrolides, taking into account the antibiotic sensitivity of microorganisms, can be justified, especially in regions with increased resistance of microorganisms to fluoroquinolones. At the same time, it is important to consider the sensitivity of all isolated pathogens, and not rely only on causative or predominant microorganisms. In assessing clinical and laboratory results, one should remember that antibiotics may not always lead to the complete elimination of a potential pathogen. However, we believe that one should not achieve "sterility" in the case of a stable reduction of the clinical manifestations after a full 4-6-week course, provided that there are no intracellular pathogens.

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SURGERY FOR PELVIC ORGAN PROLAPSE BY VAGINAL APPROACH IN A SPECIALIZED CENTER: THE EVOLUTION OF IMPLANTS FROM «XL TO XS»

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Introduction. The use of large vaginal meshes for the treatment of pelvic organ prolapse (POP) combined with insufficient surgeon experience are the important risk factors for serious postoperative complications.
Aim. To find the most safe and effective method of surgical treatment of POP.
Materials and methods. To evaluate the efficiency of surgical techniques, a retrospective study of 5031 medical records from an electronic database was carried out. As the primary endpoint, we assessed the duration of the procedure, the volume of blood loss and the length of stay. As a secondary endpoint, the number of intra- and postoperative complications was assessed. In addition to objective data, we assessed subjective measures using the validated PFDI20 and PISQ12 questionnaires.
Results. The best results in terms of blood loss were shown by unilateral hybrid pelvic floor reconstruction and three-level hybrid reconstruction (33±15 ml and 36±17 ml, respectively). Patients who underwent the three-level hybrid pelvic floor reconstruction technique had the highest result: 33±15 points of the PISQ12 questionnaire, 50±28 points of the PFDI20 questionnaire, which was significant in comparison with other techniques ($p<0.001$). The number of postoperative complications was also significantly lower for this procedure.
Conclusion. Three-level hybrid pelvic floor reconstruction is a safe and effective technique for the treatment of pelvic organ prolapse. In addition, this procedure can be done in a specialized hospital with the appropriate skills of surgeons.

Key words: pelvic organ prolapse, transvaginal mesh implant, hybrid pelvic floor reconstruction

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Introduction. Today it is well known that the use of large vaginal meshes for the treatment of pelvic organ prolapse (POP) in combination with insufficient experience of surgeons are the main risk factors for serious postoperative complications [1, 2]. The first mesh implants for POP repair had four sleeves and a central part. Their main aim was to perform the full reconstruction of the endopelvic fascia [3]. These standardized kits (pre-cut mesh with disposable instruments) were developed with little or no consideration for individual differences in the pelvic anatomy and promoted by manufacturers under the concept of "fits all patients, fits all surgeons". This approach has led to a significant number of complications, a wide public awareness and, as a result, to the uncertain position of meshes in pelvic floor reconstruction in many countries.

In a recent systematic review, Ugianskiene et al. discussed a need to improve the surgical technique for POP repair [4]. The same postulate is supported by the high-quality PROSPECT study [5], and although it reported complications after the use of vaginal meshes, the authors noted that surgical outcomes may be more successful if the intervention is performed in high-volume centers by experienced surgeons who are specialize in pelvic floor reconstructive surgery [5]. Further, in this review, authors evaluated the prospects for the use of vaginal meshes in current difficult situation. They suggested that vaginal meshes should be implanted only in specialized centers by surgeons with experience in both insertion and removal of prostheses [4].

The lack of consensus regarding the choice of the method of surgical treatment of POP among urologists and gynecologists is a problem not only for specialists, but also for patients who cannot receive the optimal medical care.

The main aim of this study is to retrospectively assess of the safety and efficacy of various methods of POP repair using vaginal meshes and to determine the choice of the most optimal method of surgical treatment.

Materials and methods. From 2012 to 2019, in the University Clinic of St. Petersburg State University seven types of POP repair with meshes were used, differing in the amount of implanted material, the presence and type of simultaneous reconstructive surgery with autologous tissues, the method of mesh fixation, and a number of fixation points. Each procedure was performed by transvaginal access.

A retrospective analysis of electronic medical records was carried. For each patient, 12 months follow-up was available. Inclusion criteria for the retrospective analysis: a reconstructive procedure using mesh implants due to the presence of POP of III-IV stages according to the Baden-Walker classification, confirmed by pelvic examination, signed informed consent for the use of

their personal data. Exclusion criteria were cervical elongation, cervical dysplasia, undiagnosed irregular uterine bleeding, endometriosis, and chronic pelvic pain. For unifying the classification of POP, a stage of prolapse was assessed according to the Baden-Walker system [6]. The following factors were assessed: type of operation, duration of procedure, length of stay, intraoperative complications (blood loss, trauma of the bladder or rectum), early postoperative complications (clinically significant hematomas, urinary retention). A clinically confirmed POP of more than stage II according to Baden-Walker, requiring a repeated reconstructive operation, was considered a relapse. The assessment was carried out during follow-up examinations only by the surgeons, after which the data were entered into the electronic medical history.

At postoperative follow-up after 12 months the most common complications and side effects were evaluated, as well as on the anatomical efficiency of treatment and subjective patient satisfaction. To ensure the accuracy and completeness of the data, a physical examination in the gynecological chair was performed and questionnaires validated in Russia (Pelvic Floor Distress Inventory-20 [PFDI-20] and Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire-12 [PISQ-12]) were used.

Statistical processing. Quantitative data are described using the mean ± standard deviation, as well as 95% confidence intervals for the means (95% CI). Absolute frequencies and proportions of the total number of cases were calculated in order to assess different values of categorical data, which are presented using contingency tables and Fisher's exact test. For multiple pairwise comparison, Bonferroni correction was used. ANOVA (one-way analysis of variance) was performed to compare treatment outcomes between groups. Significance level (alpha) is set to 0.05.

Results. The final analysis included 5031 medical records of patients who were treated between 2012 and 2019. All patients were comparable in terms of basic characteristics (*Table 1*). The mean age was 54±9 years. To simplify further description, all procedures are coded from "1" to "7", which is described in detail and shown in *Table 2*.

Significant differences in the most postoperative complications were found (*Table 3*). There were no differences only in the rate of infectious complications (p=0.12). Technique “7” demonstrated a significantly lower risk of bladder injury, pelvic hematomas, erosion of the vaginal walls, and chronic pelvic pain syndrome compared with techniques 1–6. Techniques "5" and "6" showed comparable safety profile compared to technique "7".

In addition to objective data, we also assessed subjective indicators using the PFDI20 questionnaire prior to and one year after surgery, which has a fairly high sensitivity and can be used to measure the degree of influence of lower urinary tract symptoms, lower gastrointestinal tract symptoms and manifestations of POP on quality of life [7]. At baseline, there were no significant differences in PFDI20 scores between all groups (p=0.2). The average score for all patients was 188±31 points. We found a significant decrease in the severity of POP symptoms one year after surgery in all groups compared to baseline (p<0.001). According to the post-hoc analysis, there was a significant decrease in the severity of symptoms in patients who were treated according to the technique "5" (52±31), "6" (51±34), "7" (52±31) compared with other groups (75±54, 66±46 and 63±44 for techniques "1", "2" and "3", respectively). Meanwhile, there was no significant improvement in these groups (p=0.3). PISQ-12 is a validated and reliable short form questionnaire that assesses the sexual function in women with urinary incontinence and/or POP [8]. All patients fill it out at admission and during postoperative follow-up. The analysis did not reveal significant differences in the results of the PISQ12 questionnaires at baseline. The average score was 21±12 points (p=0.7).

However, during the follow-up, a significant decrease in the mean score on the questionnaire was observed in patients who underwent technique "1" by 16±15 points (p<0.001). The average score in group of technique “7” was 33±15, which was significantly better compared to other techniques (p<0.001). In addition, all groups were comparable in terms of the number of POP recurrences (p=0.5). Relapses in the apical region did not exceed 3.3%, regardless the technique.

Discussion. It is known that the most common type of POP is cystocele in combination with apical prolapse [9, 10]. Traditional techniques such as anterior and posterior colporrhaphy may restore only pelvic support of level II according to DeLancey [11]. It is not surprising that

Table 1

Baseline characteristics of patients included in the analysis

Factor	1, N = 60[1]	2, N = 317[1]	3, N = 129[1]	4, N = 375[1]	5, N = 1,928[1]	6, N = 972[1]	7, N = 1,250[1]	P-value[2]
Age	54±10	54±10	55±9	54±9	54±9	54±9	54±9	0.9
BMI	32,6±3,3	31,3±4,0	30,2±4,4	31,5±4,5	31,4±4,4	31,3±4,1	31,4±4,3	0,024
POP stage (Baden-Walker)								0,8
II (%)	9 (15)	44 (14)	18 (14)	57 (15)	255 (13)	157 (16)	182 (15)	
III (%)	45 (75)	229 (72)	93 (72)	258 (69)	1,410 (73)	678 (70)	884 (71)	
IV (%)	6 (10)	44 (14)	18 (14)	60 (16)	263 (14)	137 (14)	184 (15)	
Menopause (%)	22 (37)	112 (35%)	34 (26)	120 (32)	595 (31)	333 (34)	418 (33)	0,2
PFDI score	195±33	190±31	185±32	187±31	187±31	187±32	189±31	0,2
PISQ12 score	20±12	21±12	22±12	21±12	20±12	21±12	20±12	0,7

[1] Mean ± standard deviation; *n* (%).
[2] One-way ANOVA (one-way analysis of variance); Pearson's chi-squared test.

Table 2

Characteristics of surgical treatment of POP

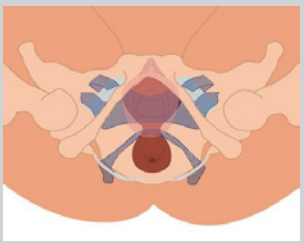
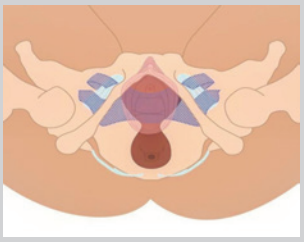
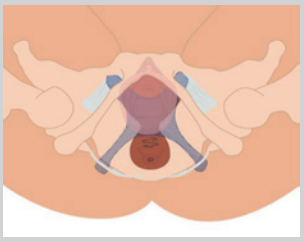
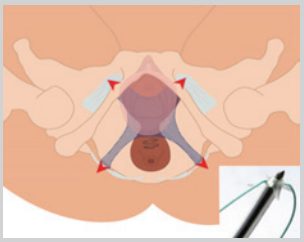
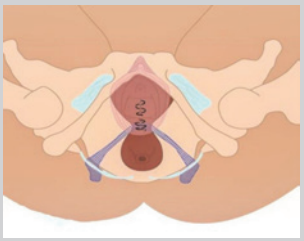
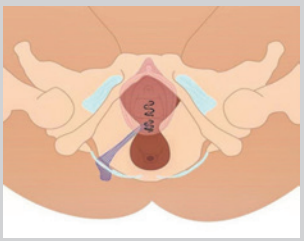
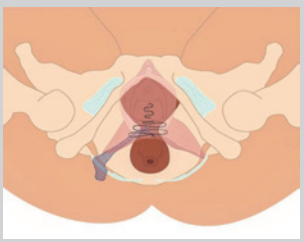
Method (code)	Description	Number of fixation points of the prosthesis	Scheme of the procedure
Total pelvic floor reconstruction using prosthesis («1»)	Mesh "Pelvic Anterior" (Lintex, St. Petersburg) was put under the pubocervical fascia, and "Pelvic Posterior" under the rectovaginal fascia. There were 6 fixation points according to the trocar technique (anterior part of the mesh was sewed by two sutures to the obturator membranes, while the posterior part bilaterally to the sacrospinous ligaments)	6	
Anterior mesh reconstruction of the pelvic floor with trocar transobturator fixation («2»)	Mesh "Pelvic Anterior" was put under the pubocervical fascia. Four fixation points were used according to the trocar technique (anterior and posterior arms to the obturator membrane)	4	
Anterior mesh reconstruction of the pelvic floor with trocar bilateral sacrospinous fixation and posterior subfascial colporrhaphy ("3");	Mesh "Pelvic Anterior" was put under the pubocervical fascia. Four fixation points were used according to the trocar technique (anterior arms to the obturator membrane, posterior arms to the sacrospinous ligaments). The defect of rectovaginal fascia was repaired by local flaps	4	
Anterior reconstruction of the pelvic floor with harpoon bilateral sacrospinous fixation and posterior subfascial colporrhaphy using prosthesis ("4")	Similar to the previous technique, but the trocar method of mesh fixation was used at four points	4	
Hybrid pelvic floor reconstruction with bilateral trocar sacrospinous fixation («5»)	The UroSling-1 mesh (Lintex, St. Petersburg) was used for the apical defect. There were two fixation points to both sacrospinous ligaments, while defects in pubocervical and recto-vaginal fascias were repaired using subfascial colporrhaphy	2	
Hybrid pelvic floor reconstruction with unilateral trocar sacrospinous fixation («6»)	The technique is different from previous by only one fixation point of UroSling-1 mesh to the right or left sacrospinous ligament	1	
Three-level hybrid pelvic floor reconstruction with unilateral trocar sacrospinous fixation («7»)	With this technique, apical support of the level I was carried out using a mesh "UroSling-1", fixed unilaterally to the sacrospinous ligament according to the trocar technique (also one fixation point); anterior and posterior defects of the level II were repaired by subfascial colporrhaphy, while for level III (perineum) perineoplasty was done	1	

Table 3

The results of surgical treatment of pelvic organ prolapse (POP)

Factor	1, N=60[1]	2, N=317[1]	3, N=129[1]	4, N=375[1]	5, N=1,928[1]	6, N=972[1]	7, N=1,250[1]	P-value[2]
Length of stay, days	4,82±1,66	4,03±1,56	3,27±1,15	2,73±1,29	2,00±0,77	1,59±0,59	1,69±0,70	<0.001
Duration of operation. min	81±14	54±10	46±13	42±13	37±11	40±14	52±17	<0.001
Blood loss. ml	172±26	106±22	56±18	50±20	39±18	33±15	36±17	<0.001
Pelvic hematoma (%)								<0.001
Yes	5 (8,3)	2 (0,6)	2 (1,6)	4 (1,1)	4 (0,2)	3 (0,3)	3 (0,2)	
No	55 (92)	315 (99)	127 (98)	371 (99)	1,924 (100)	969 (100)	1,247 (100)	
Bladder injury (%)								<0.001
Yes	6 (10)	14 (4,4)	4 (3,1)	4 (1,1)	8 (0,4)	2 (0,2)	3 (0.2)	
No	54 (90)	303 (96)	125 (97)	371 (99)	1,920 (100)	970 (100)	1,247 (100)	
Rectal injury (%)								<0.001
Yes	11 (18)	0 (0)	1 (0.8)	0 (0)	1 (<0,1)	0 (0)	1 (<0,1)	
No	49 (82)	317 (100)	128 (99)	375 (100)	1,927 (100)	972 (100)	1,249 (100)	
Infectious complications (%)								0.12
Yes	1 (1,7)	0 (0)	0 (0)	1 (0,3)	1 (<0,1)	1 (0,1)	2 (0,2)	
No	59 (98)	317 (100)	129 (100)	374 (100)	1,927 (100)	971 (100)	1,248 (100)	
Postoperative acute urinary retention (%)								<0.001
Yes	11 (18)	29 (9,1)	8 (6,2)	22 (5,9)	24 (1,2)	15 (1,5)	29 (2,3)	
No	49 (82)	288 (91)	121 (94)	353 (94)	1,904 (99)	957 (98)	1,221 (98)	
Stress urinary incontinence (%)								<0.001
Yes	15 (25)	70 (22)	22 (17)	70 (19)	112 (5.8)	56 (5,8)	46 (3,7)	
No	45 (75)	247 (78)	107 (83)	305 (81)	1,816 (94)	916 (94)	1,204 (96)	
Chronic pelvic pain (%)								<0.001
Yes	5 (8.3)	10 (3.2)	3 (2,3)	17 (4,5)	5 (0,3)	2 (0,2)	3 (0,2)	
No	55 (92)	307 (97)	126 (98)	358 (95)	1,923 (100)	970 (100)	1,247 (100)	
Vaginal wall erosion (%)								<0.001
Yes	2 (3,3)	4 (1,3)	1 (0,8)	2 (0,5)	6 (0,3)	2 (0,2)	0 (0)	
No	58 (97)	313 (99)	128 (99)	373 (99)	1,922 (100)	970 (100)	1,250 (100)	
Relapses of POP (%)								0.5
Yes	2 (3,3)	6 (1,9)	2 (1,6)	6 (1,6)	22 (1,1)	13 (1,3)	14 (1,1)	
No	58 (97)	311 (98)	127 (98)	369 (98)	1,906 (99)	959 (99)	1,236 (99)	
Total PFDI20 score after 1 year	75±54	66±46	63±44	61±44	52±31	51±34	50±28	<0.001
Total PISQ12 score after 1 year	16±15	22±17	23±17	22±16	22±11	22±11	33±15	<0.001

[1] Mean ± standard deviation; *n* (%).
[2] One-way ANOVA (one-way analysis of variance); Fisher's exact test.

the lack of proper apical fixation leads to anatomical recurrence in a significant number of patients within the first year (up to 58%) [12]. On the contrary, even an isolated surgical correction at level I according to DeLancey eliminates the prolapse of the anterior vaginal wall in half of the patients [13]. One of the most studied and effective methods of apical repair is sacrospinous fixation [14].

In 1997, in an attempt to reduce trauma and achieve a more physiological position of the vaginal axis, a posterior vaginal sling was proposed [7]. Despite the high efficiency and good functional results, this technique did not received development due to the poor quality of the implant (multifilament microporous mesh) and the subsequent data on infectious complications [8, 15–17]. The apical sling represents a further development of this technique. Despite its high efficiency, apical sling has a number of disadvantages: fixation the prosthesis can lead to chronic pain and dyspareunia, and suturing the implant to weakened tissues of the vaginal fornix can reduce efficiency [18, 19]. However, up to 80% of patients with apical prolapse have associated pelvic floor defects such as cystocele, rectocele, or enterocele [20, 21]. All this indicates a need to search for new methods of simultaneous correction of levels I, II and III of pelvic support for effective and safe treatment.

The closest alternative to our technique was Prolift System®. According to Fatton et al., the most common complications associated with Prolift were contracture (17%), extrusion (4.7%), granuloma without extrusion (2.8%), and vaginal synechiae (0.9%). Early postoperative complications included urinary tract infection (11.8%), urinary retention (11.8%), and hematoma requiring revision (1.8%) [22]. Our results partly match these data. Since total pelvic floor reconstruction is associated with wide tissue dissection, it is logical that the main complications are associated with pelvic organs dysfunction.

Another mesh with similar specifications to ours is the OPUR six-arm transvaginal mesh (Abiss, Saint-Étienne, France). Kluz et al. described the result of using this mesh in 39 patients [23], which were consistent with ours regarding the prevalence of stress urinary incontinence (SUI) at 1 year follow-up. However, the frequency of hematomas, urinary retention, and rectal trauma

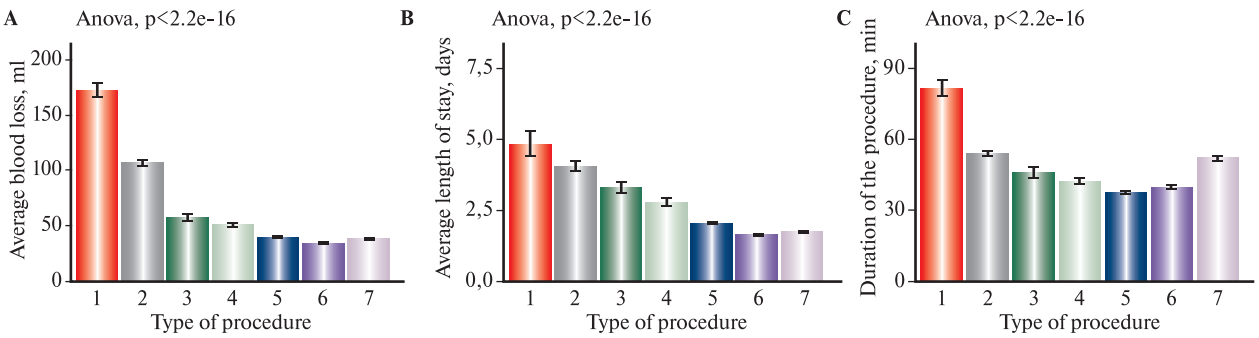


Figure. Study's Primary Endpoint

The mean value is presented on the Y-axis; X-axis shows the type of procedure. The range represents the 95% CI for the mean value. A, average blood loss, B, average length of stay, C - duration of the procedure.

was different, since the authors did not observe these complications in the postoperative period.

Among the implants for simultaneous repair of the apical and anterior compartment, large mesh sets, such as Elevate Anterior/Apical (AMS) is the closest to the one used by us. Like our implant, this mesh contains 4 fixation points. Its efficiency after a 12-month follow-up is about 90–98%; adverse events include extrusion in 3–5% and urinary retention in 11.9% of cases [24]. In our study, we observed these complications less often than SUI. In addition, in a significant number of cases, chronic pelvic pain syndrome was not observed.

Accumulating considerable surgical experience, we draw the conclusion that our hybrid technique of apical sling placement with subfascial colpoperineorrhaphy is the most optimal in terms of safety and efficiency. It is important to note that this technique differs from the one, which we presented in previous publication [25]. The main difference is that the fixation of the mesh is carried out not to two sacrospinous ligaments, but to one (unilateral fixation). We consider that sacrospinous fixation is characterized by a displacement of the vaginal axis. To minimize this retroflexion effect, we used the implant as a "bridge" between fixation points. In addition, subfascial colporrhaphy was performed, which allowed to repair most of the defects of the pubocervical fascia [26]. Owing to these technical maneuvers, it was possible to reduce the frequency of relapses at a 12 months follow-up. In addition, an important difference is the repair not only of the levels I or II of pelvic support, but also level III, which is represented by the urogenital diaphragm [20]. The most common postoperative complication of sacrospinous fixation is the high incidence of de novo prolapse in the anterior region (20–33%) [27].

In our study, we didn't have a long follow-up period, and SUI was a common "late" complication. It is known that the presence of SUI is characteristic of patients with POP. Until now, there is no single approach for the simultaneous sling procedures during POP repair [28]. One of our guiding principles with regard to SUI was not to simultaneously put a suburethral sling. All patients with complaints of SUI during 1 year follow-up were invited for surgical treatment. The most common early postoperative complication was urinary retention (up to 18%), which was eliminated by placing a urethral catheter for 1 week.

We obtained important data on the quality of sexual life after surgical treatment, depending on the type of procedures. The greatest satisfaction was noted after the "7" type. Probably, it is associated with the simultaneous repair of the posterior wall of the vagina and the perineum. It should be noted that our data are in contrast with some authors who associate the development of postoperative dyspareunia with the technique of fixation of the sacrospinous ligament [29].

Limitations. Our study had a number of limitations. These include retrospective nature and a relatively short follow-up period (12 months). However, there are a number of studies demonstrating that the most of postoperative complications after placing the intravaginal mesh developed in the first 12 months [30, 31]. In addition, we consider incomplete data on the presence of SUI before surgery as an important limitation, and therefore we did not include some patients in the analysis. Thus, it is unclear how many patients initially had SUI. Currently, the POP-Q system is generally accepted for classification of POP, however, we started to use it in our center in 2014. In order to unify the data on POP degree, we decided to stage it according to the Baden-Walker system. Another limitation for replicating study results in another clinic is that all procedures were performed by experienced surgeons in a high-volume center, in which more than 2500 pelvic floor reconstructions are performed per year.

Conclusion. Our data confirm the global trends towards a decrease in the amount of meshes in favor of autologous slings. Three-level hybrid pelvic floor reconstruction is a safe and effective surgical technique that can be offered to patients with POP in a specialized hospital with the appropriate experience of surgeons.

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IMPACT OF THE SARS-COV-2 VIRUS ON THE URINARY BLADDER

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Introduction. There are publications about the impact of a new coronavirus infection (COVID) on the lower urinary tract, including the development of overactive bladder (OAB) or COVID-associated cystitis. The cause of dysuria in patients with COVID is not fully understood.

Material and methods. A total of 14 consecutive patients after COVID with complaints of frequent urination with urgency were included in the study. The main inclusion criterion was the development or worsening of OAB symptoms after resolution of COVID, confirmed by the eradication of SARS-CoV-2 by a polymerase chain reaction. The severity of OAB was assessed using the International Scale of Symptoms (Overactive Bladder Symptom Score, OABSS).

Results. Three (21.4%) out of fourteen patients had OAB symptoms prior to COVID, while in 11 (78.6%) patients OAB symptoms developed in post-COVID period. In 4 patients (28.6% of the entire cohort and 36.4% of patients in de novo group) urge urinary incontinence and urgency developed. The average score on the OABSS scale in patients with baseline OAB was 6.7±0.8, which corresponded to the moderate severity. In this group, one patient developed urge urinary incontinence and urgency, which were not present prior to COVID. In a retrospective evaluation of symptoms before the COVID, their average score on the OABSS scale was 5.2±0.7, i.e., past COVID led to an increase in OAB symptoms by 1.5 points.

In patients with OAB de novo, the symptoms were less pronounced, with a score of 5.1±0.6 points, that is between mild and moderate OAB. At the same time, urinalysis in 9 patients did not have signs of inflammation: in 5 cases, 5–7 white blood cells per field of view was seen only once. A follow-up urine test was normal, suggesting contamination. None of the cases revealed bacteriuria over 102 CFU/ml.

All patients were prescribed trospium chloride at a dose of 30 mg per day. The choice of the drug was due to the absence of a negative effect on the central nervous system, which is very important both during COVID and in post-COVID period, since the neurotoxicity of SARS-CoV-2 has been proven.

Conclusion. A past history of COVID led to an increase in OAB symptoms by 1.5 points in patients who had OAB prior to infection. In 11 patients, after the treatment of COVID, the moderate symptoms of OAB developed de novo.

Our small study showed the importance of focusing the attention of internists and infectious disease doctors on urination disorders in patients with COVID and timely referral to a urologist. For the treatment of post-COVID OAB, trospium chloride is the drug of choice, as it does not aggravate the potential neurotoxicity of SARS-CoV-2.

K e y w o r d s: *overactive bladder, OAB, COVID, new coronavirus infection, dysfunction, cognitive abilities, antimuscarinics, trospium chloride, spasmex, SARS-CoV-2, bladder*

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Introduction. The typical symptoms of the novel coronavirus (COVID-19) are well known and include fever, dry cough, shortness of breath and severe weakness. The intensity of symptoms varies from mild to severe up to the development of organ failure [1]. Along with respiratory symptoms, many patients have complaints, which are associated with pathology of other organs and systems, and it can be difficult to understand whether they are caused by the influence of the SARS-CoV-2 or exacerbation of comorbidities [2]. There are some data that COVID-19 can influence on the lower urinary tract, causing the development of overactive bladder (OAB) or COVID-19-associated cystitis (CAC) [3–6]. The exact cause of dysuria in patients with COVID-19 is not clear, since large-scale studies have not been carried out for obvious reasons; only case series describing the effect of SARS-CoV-2 on the bladder have been published [3, 5–6]. We analyzed seven patients with COVID-19 who, along with typical respiratory complaints, also had urination disorders [3]. The reasons for more frequent urination could not be established. There were no signs of bacterial inflammation in the lower urinary tract or

a prostate. The authors suggested the development of CAC as a reason of dysuria. Again, it is not clear yet, whether it is caused by to the direct replication of SARS-CoV-2 RNA in urothelial cells, or these secondary effects are caused by local or systemic inflammation, such as endothelitis [7]. Three patients had microhematuria, which may further support the hypothesis of CAC when urothelial cells are infected.

Angiotensin-converting enzyme-2 (ACE-2) expression has been found to be highest in the lungs, intestines, and kidneys, but it is also present in 2.4% of urothelial cells, potentially increasing their susceptibility to SARS-CoV-2 and creating prerequisites for the development of CAC [8]. Meanwhile, viral RNA was detected in urine of patients with COVID-19 [9].

However, it is not been established, are the receptors expressed in luminal or basal urothelial cells. SARS-CoV-2 infects the urothelium and causes CAC either through viremia, infecting basal cells, or via urine, affecting luminal urothelium cells. In addition, it is postulated that endotheliitis, which is typical feature of patients with COVID-19 [7], may contribute to local inflammation in the bladder.

Materials and methods. A total of 14 consecutive patients who admitted to a urologist after undergoing an CT with complaints of urinary frequency and urgency were included in the study. The main inclusion criterion was the development or worsening of OAB symptoms after eradication of SARS-CoV-2, confirmed by a molecular genetic method. All patients were discharged from the infectious hospital 10–12 weeks prior to visiting a urologist. The age of the patients ranged from 48 to 69 years (59.7±4.2). The severity of OAB symptoms was assessed using the international Overactive Bladder Symptom Score (OABSS). This questionnaire consists of the domains of the daytime frequency (0–2 points) and nighttime frequency (0–3 points), urgency (0–5 points), and the number of urgent incontinence episodes (0–5 points) for 48 hours [10]. OAB was diagnosed if the total score was three points or more, and urgency score was at least two points. OAB severity was assessed as mild (3-5 points), moderate (6-11 points) or severe (⩾12 points). This scale has been tested and supported by many researchers [11–13].

Results. Three (21.4%) out fourteen women had OAB symptoms prior to COVID-19 and received solifenacin (1) and trospium chloride (2). In 11 (78.6%) patients, OAB symptoms developed after COVID-19. After discharge, the predominant complaint was pronounced weakness, while other symptoms might be overlooked. However, within 2 months urgency increased, while in 4 patients (28.6% of the entire cohort and 36.4% of patients with OAB de novo) urgency with urinary incontinence (urgent) developed de novo, which prompted them to visit a urologist. The average score on OAB-SS scale in patients with pre-COVID-19 OAB was 6.7±0.8, which corresponded to the moderate severity. In this group of patients, one developed urge incontinence, which was not present initially. Patients were asked to retrospectively assess their symptoms prior to the development of COVID-19; their average score on the OABSS scale was 5.2±0.7, i.e., COVID-19 led to an increase in OAB symptoms by 1.5 points.

In patients with OAB de novo, the symptoms were less pronounced (5.1 ± 0.6), that corresponds to mild/moderate severity. At the same time, urinalysis in 9 patients did not have signs of inflammation, while five people had leukocyturia only one time (5–7 cells/HPF). Follow-up urinalysis was normal, suggesting contamination. There was no case of bacteriuria over 102 CFU/ml.

All patients (both with newly diagnosed OAB and pre-COVID-19 OAB) were prescribed trospium chloride at a dose of 30 mg per day. The choice of the drug was due to the absence of a negative effect on the central nervous system (CNS), which is very important both for patients with COVID-19 and for those in the post-COVID period, since the neurotoxicity of SARS-CoV-2 has been proven.

Discussion. The pathophysiology of COVID-19 is generally understood. This disease develops due to the attachment of the viral spike protein to ACE-2 receptors, which are present in many organs [8]. The causal relationship between COVID-19 and the development/aggravation of OAB is obvious, but this can be either a direct effect of the virus on the urothelium containing ACE-2 receptors or a manifestation of the post-COVID-19 syndrome [3].

SARS-CoV, a related virus, has been found to be excreted in urine [14]. SARS-CoV-2 was also detected in urine, but not in all patients [15-18]. In addition, an increase in pro-inflammatory cytokines has been found in those with de novo urinary symptoms, suggesting that inflammation associated with COVID-19 may lead to bladder dysfunction [6].

It was not long time ago, when viral cystitis was denied by formal medicine, but now the viral etiology of bladder inflammation is not in doubt. In particular, the human immunodeficiency virus creates the prerequisites for bladder damage by an opportunistic infection, and also has a direct neurotoxic effect, which can lead to neurogenic bladder dysfunction [19–21]. A recent study showed a dynamic decrease in bladder capacity in young patients with COVID-19 in the acute period [22].

A number of works demonstrated the development or exacerbation of urinary tract symptoms, primarily OAB [3–4]. The authors analyzed self-report questionnaires in those with de novo or pre-COVID-19 symptoms of OAB several months after recovery [19]. A total of 350 patients, including 140 women and 210 men, who developed new or worsened pre-existing OAB symptoms 10 to 14 weeks after COVID-19, were interviewed. All these patients were referred to a urologist after being discharged from an infectious hospital. Among them, 100 patients reported a history of OAB symptoms, and in 250 cases urinary symptoms developed de novo. The authors emphasize the need for timely initiation of OAB therapy in after COVID-19 [19].

There are many studies confirming the neurotoxicity of SARS-CoV-2 and its ability to cause cognitive impairment and more serious neurological disorders after COVID-19 [23–28]. Neurological symptoms associated with COVID-19 include headache, dizziness, depression, anosmia, encephalitis, stroke, epileptic seizures [29], as well as loss of the sense of taste and smell, stroke, delirium, and neuromuscular symptoms [30].

SARS-CoV-2 can enter the CNS directly through the olfactory nerve, blood circulation, ACE-2 receptors in the brainstem and neural pathways, leading to neurological disorders [31]. CNS damage is associated with a poor prognosis and worsening of the clinical manifestations [29]. The neurotoxicity of SARS-CoV-2 leads to the

avoidance of prescribing drugs that penetrate the blood-brain barrier to patients with COVID-19. In this regard, trospium chloride has an undisputed advantage, since it demonstrates the efficacy and safety in patients who simultaneously received several neurotoxic drugs [32].

Conclusion. In addition to the damage to respiratory tract, SARS-CoV-2 involves other organs and systems, including the lower urinary tract, and causes not only inflammation, but also functional disorders, in particular OAB. Recent COVID-19 led to an increase in OAB symptoms by 1.5 points in patients who had OAB at baseline. In 11 patients, the moderate symptoms of OAB developed after the treatment of COVID-19.

Our small study showed the importance of increased awareness of internists and infectious disease specialists of urination disorders in patients with COVID-19 and timely referral to a urologist. For the treatment of post-COVID OAB, trospium chloride is the drug of choice since it does not aggravate the potential neurotoxicity of SARS-CoV-2.

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MEAN FEATURES OF THE NEPHRON-SPARING SURGERY IN OLDER PATIENTS WITH LOCALIZED RENAL CELL CARCINOMA

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Background. Imaging diagnostics becomes more widespread, the incidence of incidental renal cell carcinoma (RCC) among older adults is increasing each year. Although nephron-sparing surgery are the standard of care for localized RCC, the potential risk of perioperative complications and readmission rates are higher among older patients.

Aim. To compare the main perioperative indicators, as well as oncological and functional results in the treatment of localized RCC in in older patients and middle-aged patients

Materials and methods. From 2016 to August 2021 in the urological clinic of the N. I. Pirogov Russian National Research Medical University on the basis of the City Clinical Hospital No. 1. we performed 134 laparoscopic partial nephrectomies. The 1st group included patients from 55 to 69 years old – 96 (71.6%) and 2nd group – 70 years and older - 38 (28.4%). The physical status was assessed according to the ASA (American Society of Anesthesiologists) classification and the Charlson comorbidity index (IC) was calculated. Glomerular filtration rate (GFR) was estimated using the MDRD (Modification of diet in renal disease) formula.

Results. Length of the operation in patients in 1st group was 133.1 minutes. (60–250), in 2nd group 139.3 (50–240), the median time of warm ischemia was 12.4 (7–33) and 12.7 (6–22) minutes, the median blood loss volume was 123.3 and 135.1 ml, respectively. Complications, according to the Clavien-Dindo classification, were in 21 (21.9%) cases in patients from 55 to 69 years old and in 9 (23.7%) in patients 70 years and older. The median GFR for MDRD in the postoperative period for groups I and II was 57.4 and 50.5 ml/min/1.73 m2. The median follow-up time was 26 (4–66) months. A positive surgical margin was observed in 2 (2.1%) cases in the 1st group and in 1 (2,6%) in 2nd group. The median follow-up time was 26 (4–66) months.

Conclusion. Nephron-sparing surgery is safety in patients 70 years and older and the main intraoperative and oncological results are comparable to the group of middle-aged patients. Age itself is not a contraindication to surgical treatment.

K e y w o rd s: renal cell carcinoma, kidney tumor, laparoscopic partial nephrectomy, nephron-sparing surgery, older patients

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Introduction. According to the World Health Organization, the population over 60 years old is expected to increase to 2 billion people by 2050 [1]. In the Russian Federation, the average life expectancy among women is 75 years, while in men is 63 years [2]. Most cases of renal cell carcinoma (RCC) are diagnosed in patients aged 60 to 70 years [3]. With the aging of the population and the widespread use of imaging studies, the incidence of asymptomatic RCC among older people is increasing every year. Although nephron-sparing surgery (NSS) is the standard of care for localized RCC, the potential risk of perioperative complications and readmission rates is higher in older patients.

Aim. To compare the main perioperative parameters and early functional outcomes in older and middle-aged patients with localized RCC.

Materials and methods. The study included patients with RCC, who undergone to laparoscopic partial nephrectomy (PN) from 2016 to August 2021 in the urological clinic of the N. I. Pirogov Russian National Research Medical University on the basis of the City Clinical Hospital No. 1. Inclusion criteria were as follows: localized RCC and tumor size ⩽10 cm (clinical stage cT1aN0M0, cT1bN0M0 and cT2aN0M0). Patients with insufficient data on preoperative tumor features were excluded from

the final analysis. A total of 134 patients were included in the study. Depending on the age, they were divided into two groups: from 55 to 69 years old (n=96, 71.6%), and 70 years and older (n=38, 28.4%). All patients underwent contrast-enhanced computed tomography with staging according to the TNM classification and assessment of complexity of PN by the RENAL score. General physical status was evaluated using ASA (American Society of Anesthesiologists) score and Charlson comorbidity index (CCI). Glomerular filtration rate (GFR) was assessed using the MDRD formula (Modification of diet in renal disease). Detailed characteristics of both groups are presented in table 1.

Statistical analysis was performed using Microsoft Excel and the Prism 8 for Windows (GraphPad Software, Inc). All history, clinical, laboratory and instrumental data were entered into a Microsoft Excel spreadsheet developed by the author and processed by the method of variation statistics. For each quantitative factor, the mean value (M), standard deviation (δ), error of the mean (m), median (Me), and 95% confidence interval were determined, while for qualitative data the frequency was obtained (%). To compare numerical data (after checking for normal distribution), Student's t-test was used. To compare nonparametric data, pairwise comparison was performed using the Mann–Whitney test (for two groups) for independent groups. Differences were considered significant if p was less than 0.05 (95% significance level).

Results. The median operative time in patients aged 55 to 69 years was 133.1 (60–250) minutes, while among patients 70 years and older it was 139.3 (50–240) minutes. The median time of warm ischemia in groups I and II was 12.4 (7–33) and 12.7 (6–22) min, the median blood loss was 123.3 and 135.1 ml, respectively. Opening of the collecting system with subsequent suturing was performed in 15 (15.7%) patients aged 55–69 years and 6 (15.8%) patients aged 70 years and older.

To assess early and late postoperative complications, the Clavien–Dindo scale was used. In group I, complications were observed in 21 (21.9%), in group II in 9 (23.7%) cases. A rate of complications of Clavien I–II in those aged 55–69 years was 12.5% compared to 18.4% in patients of 70 years and older. Complications of Clavien III–IV were observed in 9 (9.4%) and 2 (5.3%) cases, respectively.

In the postoperative period, blood transfusion was necessary in 3 (3.1%) patients aged 55–69 years. Superselective embolization of renal artery branches was performed only in 2 (2.1%) cases in 55–69 years old group. In 2 (2.1%) cases in Group I and in 1 (2.6%) case in Group II, delayed nephrectomy was done due to bleeding.

The median GFR in the postoperative period, calculated using the MDRD formula, was 57.4 in group I and 50.5 ml/min/1.73 m^2 in group II. The decrease in GFR in groups I and II was 5.1 and 6.9%, respectively.

Table 1

The characteristics of patients in both groups prior to surgical treatment

Factor	55–69 years		70 years and older	
	Number (*n*)	%	Number (*n*)	%
Total Patients	96	100	38	100
Number of men	45	46,9	14	36,8
Number of women	51	53,1	24	63,2
Average age (years)	63,1		73,9	
Average BMI (min-max)	28,9 (17,3–42,5)		30,2 (22,2–46,7)	
Comorbidities:				
- coronary artery disease	23	23,9	16	42,1
- arterial hypertension	70	72,9	33	86,8
- Non-insulin-dependent (type II) diabetes mellitus	22	22,9	9	23,7
- gastrointestinal disorders	37	38,5	20	52,6
- acute cerebrovascular accident (past)	5	5,2	5	13,2
- COVID-19 (past):	10	10,4	1	2,6
- no comorbidities	13	13,5	1	2,6
Surgical risk (ASA score):				
-ASA II	41	42,7	5	13,2
-ASA III	55	57,3	321	84,2
-ASA IV	0	0		2,6
Mean CCI	3,6		5,3	
GFR (ml/min/1.73 m^2), calculated using MDRD score preoperatively	63,8		58,7	
TNM stage:				
-cT1aN0M0	59	61,5	30	78,9
-cT1bN0M0	31	32,3	8	21,1
-cT2aN0M0	6	6,2	0	0
Mean tumor size (cm)	2,8		2,2	
Side of the tumor:				
- left	42	43,8	16	42,1
- right	54	56,2	22	57,9
RENAL score:				
-4–6	36	37,5	15	39,5
-7–9	44	45,8	17	44,7
-10–12	16	16,7	6	15,8

The median follow-up time was 26 (4–66) months. Functional and oncological outcomes were available for 39 (40.6%) patients aged 55–69 years and 18 (47.4%) patients aged 70 and older. According to ultrasound data, there were no changes in 31 (79.5%) cases in group I and in 14 (77.7%) cases in group II. A cystic lesion in the tumor bed was noted in 3 (7.7%) and 2 (11.1%) cases, respectively, a decrease in blood flow during color Doppler mapping in 2 (5.1%) and 1 (5.6%) case, respectively. Contrast-enhanced computed tomography was performed annually in 30 patients aged 55–69 years and 14 patients aged 70 years and older. The conclusion according to computed tomography data after PN was regarded as the absence of any pathology in 26 and 10 cases, while cysts in the tumor bed were present in 4 and 2 patients, respectively. Annual dynamic renal scintigraphy was performed in 15 patients of group I and 11 in group II. A decrease in perfusion and the amount of functioning parenchyma >15% was observed in 1 and 3 cases, respectively.

One year after surgery, GFR using the MDRD formula in the group of patients aged 55–69 years was 60.9, while in the group of patients aged 70 years and older it was 54.1 ml/min/1.73 m^2.

The number of hospitalizations in patients of groups I and II during the follow-up was as follows: 2.1 vs. 7.9% in the department of internal medicine, 0% vs. 10.5% in surgical department, 1% vs. 5.3% in urological department, 0% vs. 2.6% in nephrological department and 2.1 vs. 2.6% in traumatological department, respectively.

According to the pathologic study, a negative surgical margin was found in 97.9% patients aged 55–69 years and in 97.4% patients of 70 years and older. A positive surgical margin was seen in 2 (2.1%) and 1 (2.6%) case, respectively. The clear cell RCC was diagnosed in 83 (86.4%) cases in group I and in 29 (76.3%) cases in group II. A chromophobe RCC was observed in 7 (7.3%) and 1 (2.6%), papillary RCC in 4 (4.2%) and 8 (21.1%), another type of RCC in 2 (2.1%) and 0 cases, respectively. Among patients aged 55–69 years, two had local recurrence and one had progression, while among patients aged 70 and older, there was no local recurrence or progression, including those with a positive surgical margin.

The 1-year cancer-specific survival rate in both groups was 100%, while overall survival was 97.9% and 97.4% in group I and II, respectively. Detailed characteristics of patients of both groups are presented in table 2.

Discussion. In the Russian Federation, about 25,000 new cases of RCC are registered annually, and when assessing age-specific incidence rates between people in the Russian Federation and the United States younger than 70 years, there are no differences, while an increase in the incidence among residents of the United States has been noted [4].

Due to the widespread use of imaging studies, RCC is detected more often at the T1a stage [5, 6]. Despite the fact that laparoscopic PN is the standard of care for localized T1 RCC, it carries the risks of postoperative complications and readmission, especially for debilitated patients [7, 8]. For elderly people, the choice of optimal treatment strategy can present a difficult dilemma. The presence of cardiovascular, neurological, and pulmonary diseases, the use of anticoagulants and nephrotoxic drugs, and a decrease in the patient's physical status all increase the surgical risk compared to the natural course of the disease [9–13]. On the example of our study, concomitant diseases in patients aged 55–69 years were observed in 86.5% of cases, while among patients 70 years and older its rate was 97.4%.

Watchful management is an appropriate strategy for elderly patients with decompensated comorbidities who have not been considered for surgery [14]. A. Kutikov et al. suggested using a nomogram of competing risks, while R. Abouassaly et al. revealed a median age threshold of 74 years for patients eligible for active surveillance [15, 16]. However, a group of authors led by S.P. Hillyer performed robot-assisted PN in patients with a mean age of 74.5 years. The rate of peri- and postoperative complications did not significantly differ from those in young patients [17]. In the works of Russian authors for

Table 2

Main intraoperative parameters of both groups

Factors	55–69 years		70 years and older	
	Number (*n*=96)	%	Number (*n*=38)	%
Median operative time, min	133,1 (60–250)		139,3 (50–240)	
Median warm ischemia time, min	12,4 (7–33)		12,7 (6–22)	
Median volume of blood loss, ml	123,3		135,1	
GFR on the first day, ml/min/1.73 m^2	57,4		50,5	
Opening of the collecting system:				
- yes	15	15,7	6	15,8
- no	81	84,3	32	83,2
Drainages:				
- yes	88	91,7	33	86,8
- no	8	8,3	5	13,2
Hemostatic drugs:				
- yes	9	9,4	1	2,6
- no	87	90,6	37	97,4
Surgical margin				
Positive	2	2,1	1	2,6
Negative	94	97,9	37	97,4
Early complications according to Clavien–Dindo score:				
I–II	12	12,5	7	18,4
III–IV	9	9,4	2	5,3
No	75	78,1	29	76,3

2020–2021, regarding NSS, the average age was 53.7 (22–79) years (V.B. Matveev et al.) and 61.48 (53–67) years (S.A. Rakul et al.) [18, 19]. In our study, the average age was slightly higher: 63.1 years vs. 73.9 years in group I and II, respectively.

CCI is a popular indicator for assessing age and the presence of comorbidities. Average age in the study of A. Becker et al. was 74 years, and CCI was 2.1 [20]. Among patients aged 55–69 years, the CCI was 3.6, compared to 5.6 among patients of 70 years and older. The CCI in our study was significantly higher, even among patients of the middle age group.

The ASA score is used to calculate the risk for each individual patient. Among those aged 70 years and older, ASA score III-IV was observed in 58% of cases, while the average tumor size was 2.7 cm. The most common stage was T1a (71.4%) [17]. According to our data, among patients 70 years of age and older, ASA score III-IV was in 86.8% patients, tumor size was 2.2 cm, and T1a was found in 78.9% of cases.

Regarding concerns about postoperative complications, the implementation of a "minimal invasive" NSS for the treatment of RCC contributed for faster recovery [21]. The safety of laparoscopic PN is discussed in the publications of T. Deklaj et al. and A.A. Thomas et al., who confirmed its safety in a carefully selected group of elderly patients [22, 23]. In our work, the rate complications in those >70 and <70 years was not significantly different (21.9 vs. 23.7%, respectively).

In a study by S. P. Hillyer et al. the length of stay was twice as high among patients of advanced age [17]. However, in our study, this trend was not observed, and in groups I and II, the length of stay was 7.6 and 8.1, respectively. Back in 1996, A. Bufalari et al. noted that ASA II–V score and presence of two comorbidities was an independent risk factor for postoperative complications and mortality [24]. It should be noted that along with age, not only on the presence of concomitant diseases is of importance, but also the degree of their compensation.

Conclusion. NSS is a safe option for patients 70 years of age and older, and major intraoperative and oncological outcomes are comparable to those of middle-aged patients. Age itself is not a contraindication to surgical treatment. The laparoscopic PN in older patients is associated with an increase in the number of complications requiring conservative treatment, and the rate of readmissions due to concomitant diseases.

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EJACULATORY DISORDERS AFTER SURGICAL TREATMENT OF BENIGN PROSTATIC HYPERPLASIA

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Introduction. Ejaculation disorders occur in 62-75% of patients after surgical treatment for benign prostatic hyperplasia (BPH). Despite the development and widespread introduction into clinical practice of laser procedures, which have reduced the overall incidence of complications, the frequency of ejaculatory disorders is still high. This complication negatively affects the quality of life of patients.

Aim. To study the nature of ejaculation disorders in patients with BPH after surgical treatment. In this work, we did not compare the effect of various surgical methods and techniques in patients with BPH on ejaculation. At the same time, we selected the most widely used procedures in routine urological practice and assessed the presence and development of ejaculatory dysfunction prior to and after surgery. It should be emphasized that we determined the disorders that occurred in the same patients in whom ejaculatory function was evaluated prior to surgery.

Materials and methods. A prospective study of the ejaculatory function of 224 sexually active men aged 49 to 84 years with LUTS/BPH before and after surgical treatment was performed. From 2018 to 2021, thulium laser enucleation of prostatic hyperplasia (ThuLep) was done in 72 patients, conventional TURP in 136 patients, and 16 patients underwent open transvesical simple prostatectomy. Surgical treatment was carried out by certified urologists with extensive experience. ThuLep and conventional TURP were not ejaculatory-sparing. All patients underwent a standard examination for LUTS/BPH pre- and postoperatively, including IPSS score, uroflowmetry to determine the maximum urine flow rate (Qmax), PSA, urinalysis, transrectal ultrasound examination with a calculation of prostate volume, postvoid residual. The erectile function was assessed according to the IIEF-5 score. Ejaculation function was evaluated according to the Male Sexual Health Questionnaire (MSHQ-EjD) preoperatively and at 3- and 6-months follow-up. For the diagnosis of premature ejaculation, CriPS questionnaire was used. For the differential diagnosis of retrograde ejaculation and anejaculation after surgical treatment, patients underwent an analysis of post-orgasmic urine for the presence and quantity of spermatozoa.

Results. The average age of patients was 64 years. At baseline, various ejaculatory disorders were detected in 61.6% of cases. In 48.2% of patients (n=108) a decrease in the ejaculate volume was found, while 47.3% (n=106) noted a decrease in the intensity of ejaculation. In 15.2% of cases (n=34), acquired premature ejaculation was detected, and 17% (n=38) men reported pain or discomfort during ejaculation. In addition, 11.6% (n=26) had delayed ejaculation during intercourse. There were no patients with anejaculation at baseline. The average score on the IIEF-5 scale was 17.9, and on the IPSS scale 21.5 points.

Three months after surgical treatment, the following disorders of ejaculation were documented: retrograde ejaculation in 78 (34.8%), anejaculation in 90 (40.2%) patients. In the remaining 56 (25%) men, antegrade ejaculation was preserved. Among those with antegrade ejaculation, an additional survey was carried out, which showed a decrease in ejaculate volume and in the intensity of ejaculation in 46 (20.5%) and 36 (16.1%) cases, respectively. Pain during ejaculation was noted by 4 (1.8%) men, however, there was neither premature nor delayed ejaculation after surgical treatment.

Conclusion. In patients with BPH, the predominate types of ejaculation disorders before surgical treatment were as following: a decrease in ejaculate volume (48.2%), a decrease in the speed (intensity) of ejaculation (47.3%), painful ejaculation (17%), premature ejaculation (15.2%), and delayed ejaculation (11.6%). After surgical treatment, retrograde ejaculation (34.8%, n=78) and anejaculation (40.2%, n=90) prevailed.

K e y w o r d s: ejaculatory dysfunction, benign prostatic hyperplasia, lower urinary tract symptoms

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Introduction. Ejaculation disorders are one of the main problems in relatively young (35–60 years) patients with bladder outlet obstruction, which is a consequence of benign prostatic hyperplasia (BPH) or sclerosis. Despite the recent development and widespread introduction into clinical practice of laser technologies, which reduced the overall incidence of complications of the surgical treatment of BPH, the frequency of ejaculatory disorders is still high [4–7]. According to the literature, surgical procedures lead to ejaculation disorders in 62–75% of cases [2]. In our opinion, such a high percentage of postoperative ejaculation disorders requires study, evaluation and correction. At the same time, the information available in the literature on ejaculation disorders and the sexual functioning in patients undergoing surgical treatment of BPH is extremely scarce and contradictory. Most publications are devoted to retrograde ejaculation, but there are no studies on other types of ejaculatory dysfunction. In a number of studies, the development of retrograde ejaculation after surgical treatment of BPH is questioned; it is believed that anejaculation develops due to damage to the musculus ejaculatorius [8].

In patients with BPH, the following types of ejaculation disorders may occur after surgical treatment: premature ejaculation, delayed ejaculation, retrograde ejaculation, anejaculation, decrease in the speed (intensity) of ejaculation or ejaculate volume, painful ejaculation and hemospermia. The loss of ejaculation can lead to orgasmic disorders, the development of erectile dysfunction (ED), accompanied by psychosocial issues and the inability to have children naturally [3]. In addition to the risk of bleeding and the development of other intra- and postoperative complications, the loss of antegrade ejaculation remains the main reason why patients refuse to perform surgical treatment, despite the indications [26].

The aim was to study the nature of ejaculation disorders in patients with BPH after surgical treatment. In our work, we did not compare the effect of various methods of surgical treatment on ejaculation. Instead, we selected the most widely used procedures in daily urological practice and assessed the presence and development of ejaculatory dysfunction disorders in the same patients pre- and postoperatively. We would like to emphasize that we determined the disorders that occurred in the same patients in whom we assessed ejaculatory function prior to surgery.

Materials and methods. A prospective study of the ejaculatory function in 224 sexually active men aged 49 to 84 years with lower urinary tract symptoms (LUTS) due to BPH (BPH/LUTS) was performed before and after surgical treatment.

Patients with prostate cancer, bladder stones, urethral stricture or bladder neck stenosis were excluded, as well as those with severe ED, and having no sexual activity. Inclusion criteria were moderate or severe LUTS due to BPH; regular sexual life; intellectual level and education sufficient to understand the nature of sexual dysfunction, consent of patients to take part in the study and the decision of the Ethics Committee of Sechenov University (decision of the Ethics Committee No. 01-21 of 01/22/2021).

From 2018 to 2021, we performed endoscopic thulium laser enucleation of the prostate (ThuLep) (n=72), mono- and bipolar transurethral resection (TUR) of the prostate (n=136), and open simple transvesical prostatectomy (n=16).

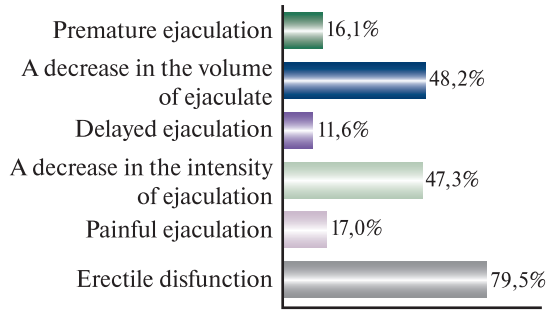

Fig. 1. Structure of sexual disorders in patients with LUTS/BPH before surgical treatment

Statistical analysis was carried out using the StatTech v. 2.8.8 (developed by Stattech LLC, Russia). Quantitative indicators were tested for normal distribution using the Shapiro-Wilk test (number of subjects <50) or the Kolmogorov-Smirnov test (number of subjects >50). Quantitative indicators that had a normal distribution were described using arithmetic means (M) and standard deviations (SD) with 95% confidence interval (95% CI). In the absence of a normal distribution, quantitative data were presented using the median (Me), lower and upper quartiles (Q1–Q3). The direction and strength of the correlation between two quantitative indicators were assessed using the Pearson correlation coefficient (with a normal distribution of the indicators).

Results. Ejaculation disorders prior to surgical treatment of BPH. Various disorders of ejaculation were found in 61.6% of cases. There might be a combination of several types in one patient: 108 (48.2%) men noted a decrease in ejaculate volume and 106 (47.3%) had a decrease in the intensity (speed) of ejaculation. In 16.1% (36) of patients, acquired premature ejaculation was detected, 17% (n=38) reported pain/discomfort during ejaculation, while 11.6% (n=26) were complaining of delayed ejaculation (Q5 of MSHQ-EjD) (*Fig. 1*). There were no patients with anejaculation at baseline. Premature ejaculation was established by CriPS questionnaire, and all patients indicated the presence of a period of sexual activity with a normal duration of coitus. Pain/discomfort during ejaculation was most often localized in the penis, perineum and lower abdomen. The severity of pain ranged from mild discomfort to debilitating pain that reduces satisfaction with sexual intercourse.

According to the IPSS questionnaire, 224 patients had moderate and severe LUTS in 86 (38.4%) and 138 (61.6%) cases, respectively, at baseline. The mean IPSS score was 21.5.

Surgical treatment was carried out by certified urologists with extensive experience. During endoscopic thulium laser enucleation and traditional TURP non-ejaculatory-sparing technique was used.

All patients underwent a traditional examination pre- and postoperatively, including IPSS score, uroflowmetry with the determination of the maximum urine flow rate (Qmax), a serum prostate-specific antigen level (PSA), urinalysis; transabdominal and transrectal ultrasound examination of the prostate with a measurement of the postvoid residual volume. The erectile function was

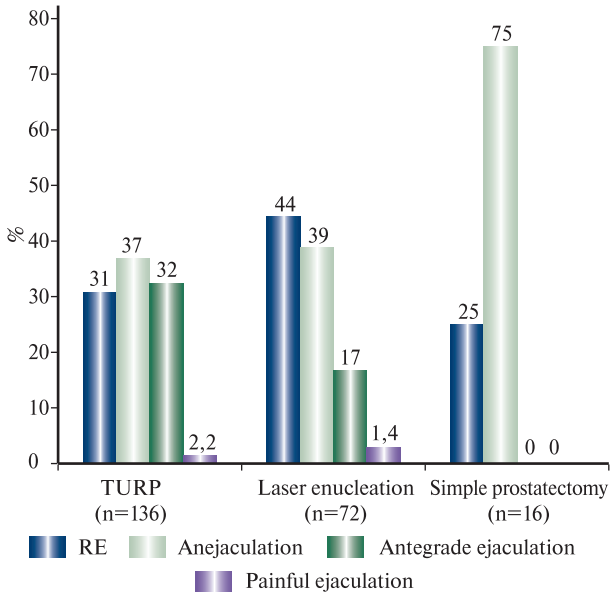

Fig. 2. Ejaculatory disorders at 3 months after surgical treatment (n=224)

assessed using the IIEF-5 questionnaire. Ejaculation function was evaluated using Male Sexual Health Questionnaire (MSHQ-EjD) at baseline and 3 and 6 months after surgical treatment. For the diagnosis of premature ejaculation, CriPE questionnaire was chosen (criteria for premature ejaculation, N.D. Akhvlediani, 2008). For differential diagnosis of retrograde ejaculation and anejaculation at 3 months after surgical treatment, post-orgasmic urine was analyzed for the presence and quantity of spermatozoa.

We found a significant relationship between the severity of LUTS according to IPSS score and a decrease in the intensity of ejaculation (p=0.001), as well as a decrease in ejaculate volume (p<0.001). Thus, patients with severe LUTS (IPSS score 20-35) were 3.7 times more likely to have a decrease in the intensity of ejaculation (95% CI: 1.663-8.602) and 4 times more likely to have a decrease in ejaculate volume (95% CI: 1.764 - 9,154) than patients with moderate LUTS (IPSS 8-19) (Table 1).

Painful ejaculation was also more common among men with more severe LUTS (IPSS >20) (p=0.026). The probability of having painful ejaculation in the group of patients with severe LUTS were 4.025 times higher than in the group of patients with moderate LUTS: the odds difference was significant (95% CI: 1.097–14.764).

When analyzing the rate of premature ejaculation and delayed ejaculation, depending on the severity of LUTS, we were unable to identify significant differences (p=0.124, p=0.557, respectively). Premature ejaculation occurred with almost the same frequency in patients with moderate or severe LUTS (Table 1).

Ejaculation disorders after surgical treatment of BPH. After 3 months, the following ejaculation disorders were revealed in 224 patients: retrograde ejaculation (n=78, 34.8%) and anejaculation (n=90, 40.2%). In the remaining 56 (25%) men, antegrade ejaculation was preserved. Among them, an additional survey was carried out, which showed a decrease in an ejaculate volume and intensity of ejaculation in 46 (20.5%) and 36 (16.1%) cases, respectively. Also, four of them were complaining of painful ejaculation (1.8%), however, there were no cases of premature ejaculation and delayed ejaculation (*Fig. 2*).

The ejaculatory function was evaluated 6 months later. After TURP, retrograde ejaculation, persistent anejaculation and antegrade ejaculation were found in 38 (27.9%), 50 (36.8%), and 48 (35.3%) patients, respectively. Thus, in four patients after TURP, restoration of antegrade ejaculation was observed. Among patients who underwent ThuLEP and open simple prostatectomy, there were no differences in the ejaculatory function after 3 and 6 months (*Figures 2* and *3*).

We evaluated the association of ejaculation disorders with the various patients' characteristics. There were no significant differences in ejaculatory dysfunction, depending on the age of patients. The probability of ejaculatory dysfunction (retrograde ejaculation, anejaculation) after surgical treatment was assessed depending on the preoperative prostate volume (*Table 2*).

There were significant differences in the rate of anejaculation and antegrade ejaculation, depending on the prostate volume (p<0.001). The larger was the prostate volume/volume of resected tissue, the more likely was anejaculation or an absence of antegrade ejaculation. When evaluating the frequency of retrograde ejaculation depending on the prostate volume, there was no significant difference (p=0.976), as well as when

Table 1

Analysis of the group "Ejaculation Disorders" depending on IPSS score

Type of dysfunction	Category	LUTS (IPSS)		*P*
		Moderate symptoms	Severe symptoms	
Painful ejaculation	No	80 (93,0)	106 (76,8)	0,026*
	Yes	6 (7,0)	32 (23,2)	
Intensity (speed) of ejaculation	Normal	62 (72,1)	56 (40,6)	0,001*
	Decreased	24 (27,9)	82 (59,4)	
Ejaculate volume	Normal	62 (72,1)	54 (39,1)	< 0,001*
	Decreased	24 (27,9)	84 (60,9)	
Premature ejaculation	No	78 (90,7)	110 (79,7)	0,124
	Yes	8 (9,3)	28 (20,3)	
Delayed ejaculation	No	74 (86,0)	124 (89,9)	0,557
	Yes	12 (14,0)	14 (10,1)	

* - differences are statistically significant (p<0.05).

comparing the painful ejaculation depending on the prostate volume (p=0.912).

We performed an analysis of ejaculatory dysfunction after surgery, depending on the preoperative Q max (Table 3). When analyzing the retrograde ejaculation and anejaculation, the significant differences was found (p=0.007, p=0.008, respectively). However, there were no significant differences in the rate of antegrade ejaculation depending on Qmax (p=0.954).

Discussion. The scientific literature provides various data on the prevalence of ejaculation disorders in men undergoing surgical treatment for BPH. Ejaculation dysfunction are best studied after TURP, which is still the "gold" standard of treatment. According to an analysis of 30 studies, the incidence of retrograde ejaculation after TURP was 66.1% [10]. Several studies compared the effects of bipolar and monopolar TURP on ejaculatory function and confirmed the absence of a significant difference between two techniques [13-15]. Other studies compared TURP vs. active surveillance, and some trials evaluated the effect of the volume of resected tissue and type of the electrode on the frequency of ejaculation disorders. At the same time, there is no study, dedicated to the association of the ejaculatory dysfunction and preoperative data, such as patient age, Qmax, postvoid residual volume, prostate volume, or the presence of chronic prostatitis.

Considering that in recent years, endoscopic laser enucleation of the prostate has occupied a leading position among surgical treatment of BPH and, according to the Guidelines of European Association of Urology (EAU), is the method of choice in those with a prostate volume of more than 80 cm3, there have been an increasing number of studies evaluating the effect of holmium and thulium laser enucleation on the ejaculatory and erectile function.

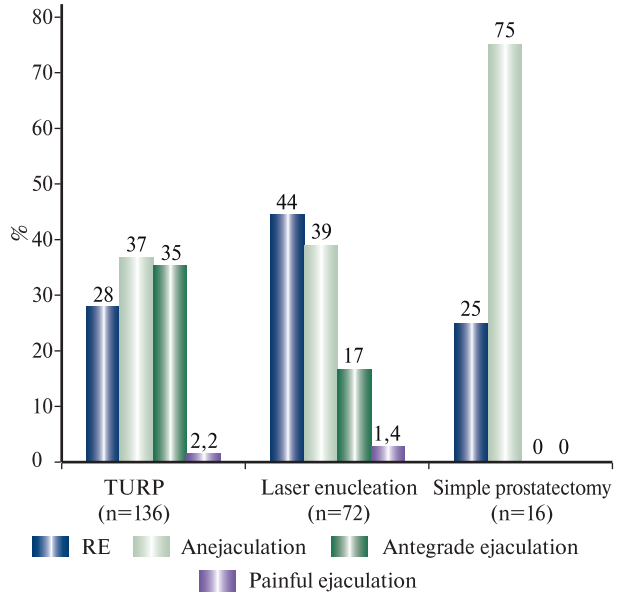

Fig. 3. Ejaculatory disorders at 6 months after surgical treatment (n=224)

The most publications showed the comparable frequency of ejaculatory disorders after laser enucleation vs. TURP [12, 16]. We did not find any publications in which the ejaculation function after open simple prostatectomy was evaluated. Only one prospective study assessed sexual satisfaction before and after simple prostatectomy, but no studies assessed ejaculation as separate indicator [11].

Conclusion. Before surgical treatment, patients with BPH had the following ejaculatory disorders: decrease in

Table 2

Анализ показателя «нарушения семяизвержения» после операции в зависимости от объема простаты

Index	Category	Prostate volume, cc			*P*
		Me	$Q_1 - Q_3$	N	
Retrograde ejaculation	No	68	55 – 80	146	0,976
	Yes	70	54 – 80	78	
Anejaculation	No	65	54 – 76	134	< 0,001*
	Yes	75	65 – 100	90	
Antegrade ejaculation	No	71	60 – 88	168	< 0,001*
	Yes	59	46 – 68	56	

* - differences are statistically significant (p<0.05).

Table 3

Analysis of the "ejaculatory dysfunction after surgery", depending on the preoperative Q max

Index	Category	Qmax, ml/s			*P*
		Me	$Q_1 - Q_3$	N	
Retrograde ejaculation	No	9	8 – 10	146	0,007*
	Yes	8	7 – 9	78	
Anejaculation	No	8	7 – 10	134	0,008*
	Yes	9	8 – 11	90	
Antegrade ejaculation	No	9	7 – 10	168	0,954
	Yes	9	7 – 10	56	

* - differences are statistically significant (p<0.05).

the ejaculate volume (48.2%), a decrease in the intensity of ejaculation (47.3%), painful ejaculation (17%), premature ejaculation (16.1%) and delayed ejaculation (11.6%). A significant relationship was found between two complaints, namely a decrease in the ejaculate volume and a decrease in the intensity (speed) of ejaculation. In addition, there was a significant association between LUTS severity, a decrease in the intensity of ejaculation, and a decrease in ejaculate volume. For example, patients with severe LUTS (IPSS 20–35) were more likely to have decreased ejaculatory intensity (3.7 times) and decreased ejaculate volume (4 times) than patients with moderate LUTS (IPSS 8–19). Painful ejaculation was also more frequent in men with severe LUTS.

After surgical treatment, retrograde ejaculation (34.8%, n=78) and anejaculation (40.2%, n=90) prevailed in the same patients. In a quarter of men (n=56), antegrade ejaculation was preserved. The painful ejaculation was noted by 4 (1.8%) patients, while before surgical procedure 38 (17%) patients had this complaint. The main factors influencing the development of ejaculation disorders postoperatively were the prostate volume, the presence of chronic prostatitis, and a decrease in baseline Qmax. However, the patient age and baseline LUTS severity did not significantly affect the frequency and structure of ejaculation disorders. Anejaculation can be predicted at a prostate volume ⩾89 cc. Interestingly, it was possible to predict the persistence of antegrade ejaculation after surgical treatment only if the prostate volume was <68 cc.

A significant association between retrograde ejaculation/anejaculation and Qmax was found (p=0.007, p=0.008, respectively). Retrograde ejaculation and anejaculation after surgical treatment can be predicted at a Qmax <8.8 ml/s and ⩾10 ml/s, respectively.

Ejaculation disorders, such as retrograde ejaculation, anejaculation, painful and premature ejaculation in patients after various surgical procedures for BPH, including transurethral enucleation of the prostate, laser and electrosurgical enucleation and open simple prostatectomy, represent significant problems. Often, patients, especially those who are young, consider preserving of antegrade ejaculation so important, that refuse a procedure aimed at improving voiding. The search for surgical methods, which allows to preserve ejaculatory function, and the use of minimally invasive technologies, such as Urolift, Rezum, iTUND in patients, who are interested in maintaining ejaculatory function, is a promising direction in urology.

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PUNCTURE ACCESS WITH A NEW ATRAUMATIC NEEDLE MG FOR MINI-PERCUTANEOUS NEPHROLITHOTOMY

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Introduction. An important aspect of the prevention of complications in percutaneous nephrolithotomy (PCNL) is to reduce the likelihood of injury to the adjacent structures and perirenal tissues.
Aim. To determine the efficiency and safety of renal puncture during mini-PCNL with a new atraumatic needle MG.
Materials and methods. A total of 67 patients who underwent mini-percutaneous nephrolithotomy at the Institute of Urology and Human Reproductive Health of Sechenov University were included in the prospective study. For the purpose of homogeneity of the groups, those with staghorn nephrolithiasis, nephrostomy, a history of prior kidney surgery (including PCNL), renal and collecting system anomalies, acute pyelonephritis, and blood clotting disorders were not included. The main group consisted of 34 (50.7%) patients who underwent atraumatic kidney puncture with a new needle MG (MIT, Russia), while in the control group there were 33 (49.3%) patients, who underwent standard puncture with Chiba or Troakar needles (Coloplast A/S, Denmark). The outer diameter of all needles was 18 G.
Results. In patients with a standard access, a hemoglobin decrease in the early postoperative period was more pronounced (p=0.024). The incidence of complications according to the Clavien-Dindo classification did not differ significantly (p=0.351), however, a JJ stent was placed in two patients from the control group due to impaired urine flow and the development of urinoma.
Conclusion. Together with a similar stone-free rate, atraumatic needle allows to reduce a hemoglobin drop, as well as less development of severe complications.

Key words: *urolithiasis, mini-percutaneous nephrolithotomy, complications of percutaneous nephrolithotomy, kidney puncture.*

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Introduction. Urolithiasis is a common disease, and its prevalence varies depending on the region and can reach 25% of all urological disorders [1]. In our country, the incidence of urinary stone disease is 5.7%, while over the past 15 years there has been the annual increase in new cases by 16.2% [2, 3].

Percutaneous nephrolithotomy (PCNL) occupies an important place in the treatment of patients with urinary stone disease. Over its long history, its technique has been repeatedly modified, and at the same time it still remains the method of choice for those with complex and large kidney stones [4, 5].

Like any surgical procedure, PCNL is not without complications, the frequency of which reaches 23.3%. The most common are intrarenal problems, such as severe bleeding, perforation of the collecting system, and acute infectious complications [6].

The most important aspect of the prevention of intrarenal complications is the correct choice of the puncture access and the low-traumatic puncture itself. As part of our clinical study, it was proposed to modify a technique of mini-percutaneous nephrolithotomy (mini-PCNL) using a new atraumatic puncture needle MG.

Aim. To determine the efficiency and safety of renal puncture during mini-PCNL using a novel atraumatic needle MG.

Materials and methods. A total of 67 patients who underwent mini-PCNL from September 2019 to March 2021 were included in the prospective study. Surgical procedures were carried out on the basis of the Institute of Urology and Human Reproductive Health of Sechenov University. The study included patients over 18 years of age who underwent mini-PCNL using single access. In order to provide group homogeneity, the study did not include patients with staghorn nephrolithiasis, nephrostomy drainage, a history of kidney surgery (including PCNL), kidney anomalies, acute pyelonephritis, and blood clotting disorders.

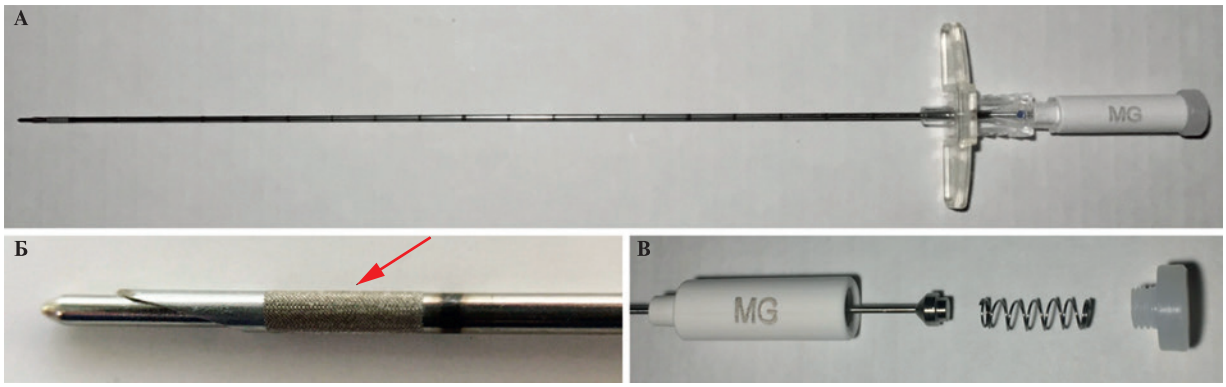

Рис. 1. (А) Новая малотравматичная игла MG; (Б) дистальный конец иглы с остроконечной канюлей и выходящим за её пределы атравматичным мандреном-бульбом; (В) павильон иглы с пружинным механизмом. Красной стрелкой показана ультразвуковая насечка

The main group included 34 (50.7%) patients who underwent mini-PCNL with an atraumatic puncture with a new needle MG (MIT, Russia). In the control group there were 33 (49.3%) patients who underwent standard puncture with Chiba or Troakar needles (Coloplast A/S, Denmark). All puncture needles used in the study had an equal outer diameter of cannula of 18 G.

Blood and urine tests, ultrasound and computed tomography data were analyzed. In those with positive urine culture, antibiotic therapy was performed as part of the preoperative preparation, so all patients had negative results of urine culture by the time of surgery.

There were 44 (65.7%) males and 23 (34.3%) females. The average age was 50 (20–72) years, the mean body mass index was 27.1±3.5 kg/m2, the average stone size was 17±5 mm, and the median density was 1155 (800–1365) HU. In 43 (64.2%) patients there was a single kidney stone, while 24 (35.8%) had multiple ones. Most of the stones were localized in the pelvis (45.9%) and lower calyx (40.8%), while the remaining 13.3% in the middle and upper calyxes; 36 (53.7%) patients underwent surgery in the prone position, the rest 31 (46.3%) had supine PCNL.

Statistical analysis was carried out using the StatTech v. 2.5.4 (Stattech LLC, Russia).

Mini-PCNL technique with atraumatic puncture needle MG

Under endotracheal anesthesia in supine position, cystoscopy was performed with the placement of a ureteral catheter. Subsequently, the cystoscope was removed, and the bladder was drained with a Foley catheter.

Puncture access was performed using an atraumatic needle MG. It consists of a pointed cannula and an atraumatic bulb mandrel extending beyond it without cutting edges. The bulb mandrel has reciprocating movements due to a spring mechanism hidden in the mandrel pavilion (*Fig. 1*). The distal tip (cannula and mandrel) has ultrasonic markings (red arrow in *Fig. 1*), which, reflecting the ultrasound signal in different projections, enhance the “echogenicity” on the monitor, which contributed to an increase in puncture accuracy.

When performing a puncture of the collecting system, the needle touches a number of anatomical structures of different thickness and density. If the structures cannot be displaced (to dilate), bulb mandrel extends beyond the pointed cannula, and the latter pierces the structure (*Fig. 2*). As soon as the needle passes through dense structures owing the cutting tip of the cannula, the atraumatic tip automatically returns to its original position. Passage of the needle allows for spreading soft

Table 1

Baseline patient characteristics

	Main group 34 (50,7)	Control group 33 (49,3)	*P*-value
Age, M (min-max), years	50 (24–71)	50 (20–72)	0,903
Gender, *n* (%)			
Male	20 (58,8)	24 (72,7)	0,231
Female	14 (41,2)	9 (27,3)	
BMI (M±SD) kg/m^2	27,2±3,4	27,1±3,6	0,908
Stone size (M ± SD), mm^2	16,8±5,1	16,6±5,8	0,905
Stone density (Q1-Q3), HU	1209 (802–1452)	1105 (800–1270)	0,188
Solitary stone, n (%)	22 (64,7)	21 (63,6)	0,927
Multiple stones. n (%)	12 (35,3)	12 (36,4)	
Stone location, *n* (%)			
Pelvis	23 (46)	22 (45,8)	0,932
Lower pole	21 (42)	19 (39,6)	0,727
Middle/upper pole	6 (12)	7 (14,6)	0,765

tissue, which makes it possible to minimize trauma during puncture.

At the end of the puncture, the mandrel was removed and pyelography was performed through the cannula to verify access. After passing the working guidewire, a safety hydrophobic guidewire was advanced along the two-way introducer to the ureter.

One-step dilation was carried out along the working guidewire and a mini-nephroscope access sheath (Karl Storz, Germany) of 16.5 Fr was placed. After connecting the irrigation fluid, the collecting system was inspected for visualizing the stone.

Then laser lithotripsy was performed using a thulium fiber laser FiberLase U2 (NTO IRE-Polus, Russia). Initially, (energy 0.5 J, frequency 30 Hz, power – 15 W) the stone was crushed in the dusting mode to 4-5 mm fragments, which were further crushed to fine dust in the popcorning mode (energy 0.15 J, frequency 200 Hz, power 30 W). The resulting dust was washed through an access sheath due to the vacuum cleaner effect.

Upon completion of the removal of stone fragments, a nephrostomy drainage was put followed by antegrade pyelography.

Results. The baseline data (age, gender, BMI, stone localization and size) was not significantly different between groups ($p>0.005$) and are shown in *Table 1.*

According to the analysis, the stone-free rate was similar ($p>0.005$). The frequency of complications did not significantly differ as well ($p>0.005$), however, there were two patients in the control group in whom JJ stent was postoperatively placed due to impaired urodynamics and the development of urinoma, confirmed by contrast-enhanced computed tomography. The decrease in hemoglobin level was significant in the control group who underwent a standard puncture (6.8% [3.8–11.4]) compared with patients of the main group (3.55% [2.2–5.9]). The study results are presented in *Table 2.*

Discussion. PCNL has become a method of choice for the treatment of kidney stones >2 cm [5]. Taking into account its specific features, PCNL is associated with the risk of complications, of which the most severe is bleeding.

In 1997, in order to reduce trauma to the kidney parenchyma, it was proposed to miniaturize the instrumentation by performing PCNL with a pediatric nephroscope (mini-PCNL) [7]. By decreasing the size of the working channel from 24F to 18F, the surface area of the access sheath is reduced by 78%, which has a beneficial effect on the parenchyma preservation [8].

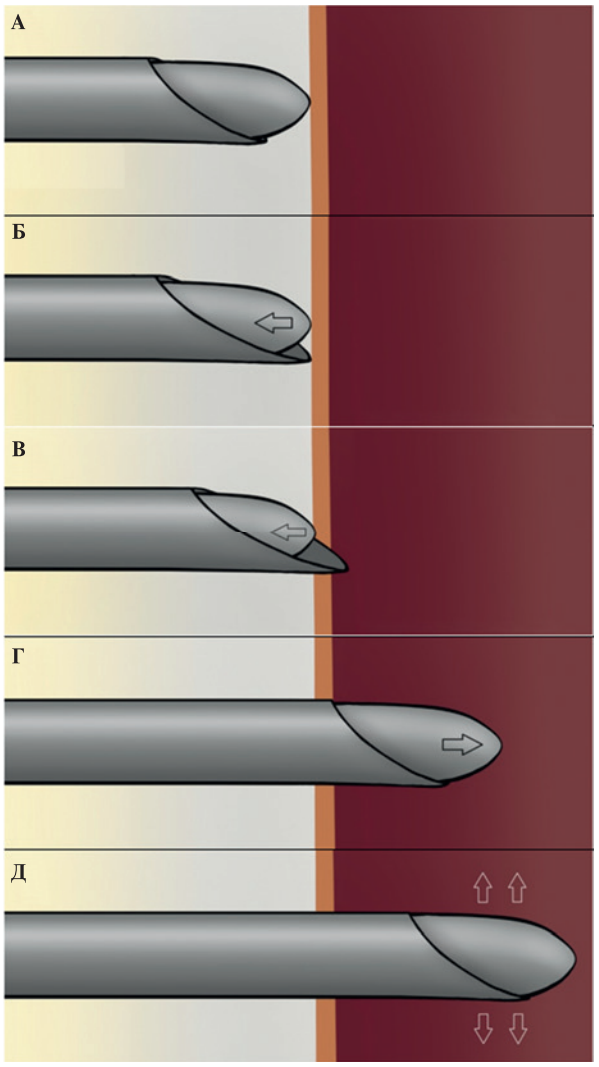

Рис. 2. Схема работы малотравматичной иглы MG. (А) Игла встречает плотную структуру; (Б) мандрен-бульб уходит за острую канюлю; (В) игла прокалывает плотную структуру; (Г) возвращение мандрена в исходное положение; (Д) бужирование мягких тканей

Table 2

Analysis of the study results

	Total (n=67)	Main group (n=34)	Control group (n=33)	P-value
Duration of the procedure (Q1–Q3), min	75 (67,5–90)	77,5 (70-90)	70 (60-90)	0,133
Time to nephrostomy tube removal (Q1–Q3), days.	3 (3-5)	3,5 (2-5)	3 (3–5)	0,339
Stone-free rate, n (%)	55 (82,5)	28 (82,4)	27 (81,8)	1,000
Pain according to VAS (M±SD), points	4,5±1,4	4,2±1,4	4,8±1,4	0,174
Complications according to Clavien-Dindo classification, n (%)				
I grade	10 (14,9)	4 (11,8)	6 (18,2)	0,351
II grade	7 (10,4)	3 (8,8)	4 (12,1)	
IIIa-grade	2 (3,0)	0 (0,0)	2 (6,1)	
Hemoglobin drop (Q1–Q3), %	4,5 (2,6–8,5)	3,55 (2,2–5,9)	6,8 (3,8–11,4)	0,024*

*differences in variables are significant ($p<0.05$).

Despite the 20-year history of mini-PCNL, existing meta-analyses comparing its efficacy and safety with standard-PCNL have been characterized by high heterogeneity, together with an insufficient number of randomized trials [9]. In 2021 G. Sharma et al. performed a strict meta-analysis of the results of studies comparing the efficiency of standard and mini-PCNL [10]. Despite a similar stone-free rate, smaller instrumentation contributed to less pronounced kidney injury. Since it is difficult to reliably determine the exact amount of blood loss during PCNL, the authors analyzed indirect indicators: the frequency of blood transfusion and the level of hemoglobin loss. As in our study, by reducing the trauma, the level of hemoglobin loss was lower. In addition, the mini-PCNL group showed a decrease in the frequency of severe bleeding resulting in blood transfusions by 56%.

One of the critical stages of PCNL is puncture access. A correctly chosen trajectory not only contributes to the stone-free rate, but also reduces the likelihood of complications. Owing good perfusion, the kidneys have a developed system of blood vessels containing up to 25% of the cardiac output. Most of the segmental vessels are located on the ventral side; therefore, a very important condition for safe puncture is access through the avascular plane of Brodel, which is located along the axis of the posterior calyxes [11, 12]. Another component of safe and effective puncture is the proper preoperative planning, which consists in a detailed analysis of kidney and collecting system anatomy (assessment of the length of the calyx infundibulum, the number of calyxes and the angle of their deviation from each other), which allows to choose a safe and effective trajectory of the puncture. The access must pass strictly trough the papilla (top of the pyramid), avoiding getting into columns of Bertini (with trauma of the vessels) [13, 14].

Currently, many techniques have been proposed to provide safe puncture, including robotic needle guidance systems, electromagnetic tracking systems, as well as augmented virtual reality devices, aimed at increasing puncture accuracy [15].

One of the main puncture needles with proven efficiency in PCNL is the needle, developed in the Japanese University of Chiba for performing percutaneous transhepatic cholangiography [16]. Initially, the needle had an outer cannula diameter of 22G (0.8 mm), but for urologists' purposes the diameter was increased to 18 G. Chiba needles 22 G are used in percutaneous surgery only by novice specialists. Due to the small diameter of the cutting area, the needle less injures (cuts) the renal structures. However, such thin needles have a number of disadvantages, the main of which is their rigidity. When encounters dense structures (in patients with well-developed subcutaneous fat or in those with perirenal fibrosis), the 22G needle may deviate from the intended trajectory and disappear from the ultrasound field of view, increasing the likelihood of hitting large vessels.

In experimental study, the atraumatic puncture needle MG demonstrated an advantage over standard needles (Chiba and Troakar). A comparative morphological study on porcine kidneys, presented in a previous publication, showed that the needle MG with a standard diameter of 18 G allows for maintaining the integrity of perirenal structures due to the bougienage effect [17].

Conclusion. Our results demonstrate the efficiency and safety of puncture with a novel atraumatic puncture needle MG for mini-PCNL. Due to the atraumatic bulb-mandrel, MG needle spreads soft tissues during puncture, allowing for preserving their integrity, while special echogenic markings at the distal end allows good visualization of the needle. With a similar stone-free rate, atraumatic puncture needle MG helps to reduce a hemoglobin loss and the risk of complications. Due to the wide possibilities of using the new atraumatic puncture needle MG, further research is required.

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CASE REPORT

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PERCUTANEOUS NEPHROLITHOTOMY IN A PATIENT AFTER LIVER TRANSPLANTATION

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The work is devoted to the description of percutaneous nephrolithotomy in a patient who previously underwent liver transplantation. In case of immunodeficiency of any etiology, one-stage non-severe kidney injury is less dangerous compared to infectious and inflammatory complications, which naturally have more severe course compared to in those with intact immune system. Based on these considerations, the patient underwent percutaneous nephrolithotomy, which allowed to remove the stone of 2.5 cm in size without any complications. The choice of surgical treatment and management tactics for this category of patients are described in detail in the article.

K e y wo r d s: percutaneous nephrolithotomy, liver transplantation

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One of the main problems of modern clinical medicine is the treatment of comorbid patients. A huge number of combinations of different diseases can present in one patient, and it is hardly advisable to consider them all. Cases where one disease significantly restricts the treatment of another are of the greatest relevance.

Modern urology is developing by improving minimally invasive techniques that allow to treat those patients who previously underwent surgery only for absolute indications. In addition, our patients are being changed. For example, kidney and liver transplant recipients are not infrequent in routine clinical practice. High-quality selection of a transplant and proper immunosuppressive therapy allow to achieve a high degree of rehabilitation for many years, and sometimes decades. However, comorbidities, including urological disorders, are still of importance.

Urological care for patients after organ transplantation undoubtedly has its own characteristics, unawareness of which sometimes forces to completely abandon the elective procedure due to fear of complications.

In the literature, scant data are available on urological care for patients with immunodeficiency, including those after organ transplantation. There is a large number of publications devoted to urological complications of kidney transplantation, primarily describing reconstructive procedures for necrosis or stricture of transplanted ureter [1–3]. Almost all of these interventions are performed on the basis of transplant clinics, which have their own hemodialysis, as well as the possibility of laboratory analysis of cyclosporine and tacrolimus level, which is not available in most urological clinics. However, urological procedures in liver or lung transplant recipients are practically not described [4, 5]. Therefore, the follow-up of a patient after successful surgical treatment of nephrolithiasis who has previously undergone liver transplantation, is of particular scientific and practical interest.

Many questions regarding the surgical treatment of nephrolithiasis in a liver transplant recipient can be divided into three main topics:

1. What are the limitations and contraindications to the surgical treatment of nephrolithiasis?

2. What are the features of choosing a method for stone removal, taking into account the presence of liver transplant and drug-induced immunodeficiency?

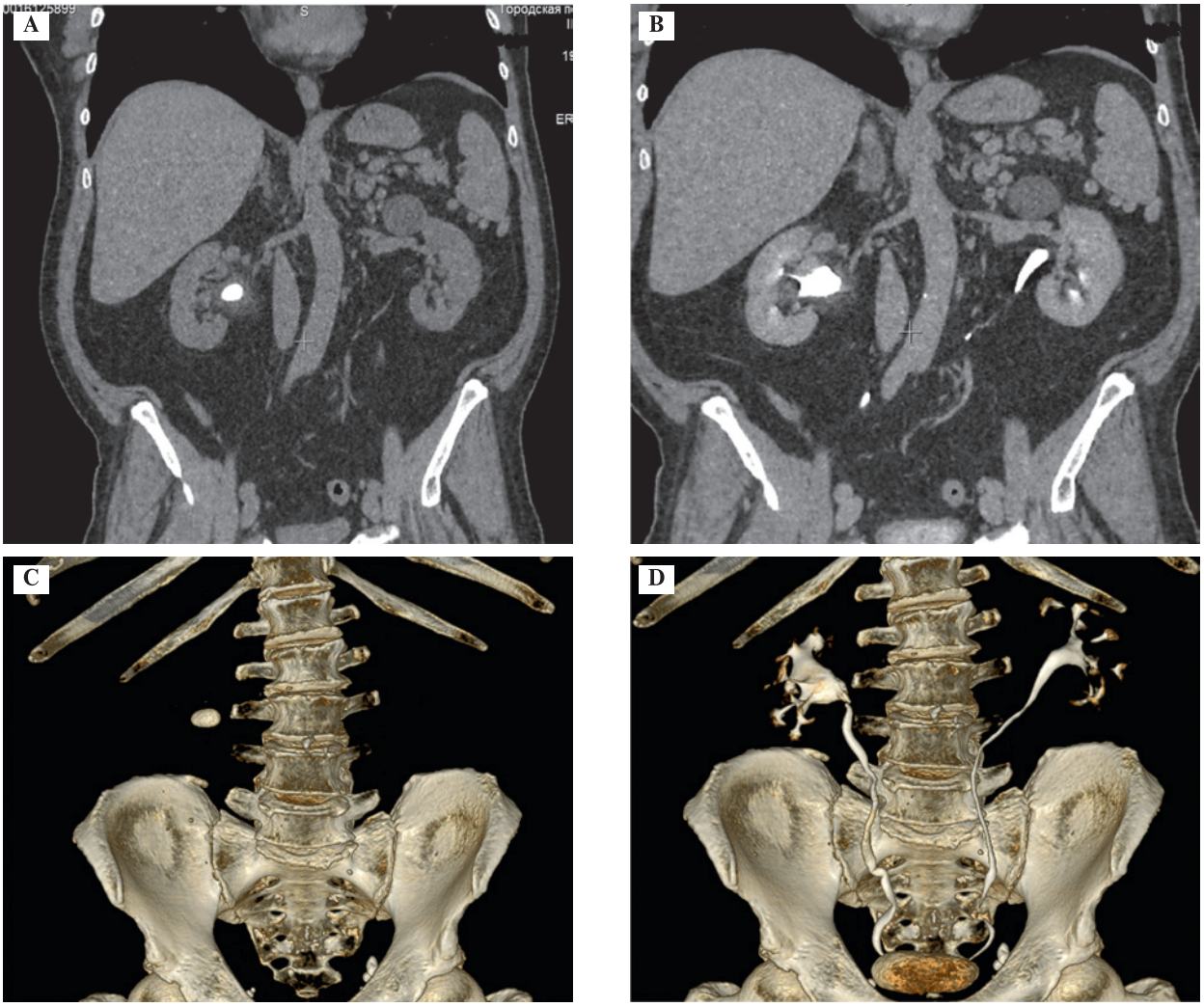

Fig. 1. Multispiral computed tomography of the kidneys (A – scout, B – after contrast injection, C – 3D reconstruction of scout image, D – 3D reconstruction after contrast injection. A stone in the right renal pelvis up to 2.3 cm in size

3. What is the tactics of drug therapy?

Detailed answers to these questions with a description of our clinical observation are presented below.

In 2021, 63-year-old patient S. admitted in the 2nd urological department of the City Clinical Hospital named after D.D. Pletnev, with complaints of nagging right lumbar pain. In December 2019 he underwent orthotopic liver transplantation (OLT) for liver cirrhosis caused by chronic viral hepatitis B and hepatocellular carcinoma of stage II, T2N0M0, BCLC-A. The patient had received immunosuppressive and antiviral therapy according to the scheme: Tacrolimus 0.5 mg 1 QD, Everolimus 1 mg BID, Entecavir 0.5 mg QD. He also took Metformin 850 mg 1 tablet BID for type 2 diabetes mellitus that developed after OLT.

The patient underwent a routine preoperative clinical and laboratory examination. Complete blood count, urinalysis, as well as the serum biochemistry were within the normal range. There were no signs of liver failure (total bilirubin 4.5 μmol/l, albumin 31 g/l, ALT 33 U/l, AST 27 U/l, alkaline phosphatase 44 U/l) or changes in blood clotting parameters (APTT 35 s, fibrinogen 3.74 g/l, INR 0.96, prothrombin time 11.1 s, platelets $187x10^9$/l). Urine culture showed no bacteriuria. Biochemical recurrence of liver cancer was also excluded (alpha-fetoprotein 5.2 IU/ml).

According to the results of ultrasound examination of the urinary tract and contrast-enhanced computed tomography of the kidneys, a stone of 2.5 cm in size with a density of 500 HU was detected in the right kidney pelvis, which caused the upper urinary tract obstruction (*Fig. 1*).

Based on complaints, medical history, laboratory and instrumental data, the diagnosis was as follows: urolithiasis, right kidney stone, chronic pyelonephritis in remission phase; OLT on December 6, 2019 due to liver cirrhosis as a result of chronic hepatitis B, hepatocellular carcinoma of stage II, T2N0M0, BCLC A, bridge therapy (transarterial embolization + sorafenib), type 2 diabetes mellitus.

Ciprofloxacin 400 mg was prescribed preoperatively as antibacterial prophylaxis 2 times a day intravenously. Enoxaparin sodium, 4000 Anti-XA IU (0.4 ml) subcutaneously once a day, was chosen for a prevention of thromboembolic complications.

Percutaneous nephrolithotripsy (PCNL) was performed on X-ray operating table under endotracheal anesthesia.

After cystoscopy with retrograde placing of 6 F ureteral catheter, retrograde pyelography, which confirmed a filling defect in the right kidney pelvis, corresponding to the stone, was performed. Then, in prone position, a puncture of the collecting system was performed under the X-ray guidance through the lower group of calyxes (*Fig. 2*). The access tract was dilated using Teflon bougies up to a size of 24 F using a guidewire.

Further Amplatz sheath was placed. During inspection of the pelvis a single stone of 2.5 cm was found. Ultrasonic lithotripsy with removal of fragments was performed. X-ray and endoscopic control revealed no residual stones. Intraoperative blood loss was minimal. The right kidney was drained with a nephrostomy tube 20 F with a 5 ml balloon. The ureteral catheter was also left. The operation time was 35 min.

The postoperative period was uneventful. On the 1st POD, a plain X-ray was performed, according to which there were no suspicions on residual fragments (*Fig. 3*). Both ureteral and urethral catheters were removed on the same day. The next day, the patient underwent blood tests, which showed no inflammatory changes. On the 3rd day, the patient started clamping the nephrostomy tube. Since no complications were noted, it was removed. Nephrostomy tract healed completely. At the follow-up ultrasound there were neither urinary tract obstruction, nor residual fragments. On the 4th day, the patient was discharged from the hospital in a satisfactory condition under outpatient surveillance.

Recurrent renal colic and pyelonephritis are absolute indications for surgical treatment of renal stones. Therefore, only the type of procedure can be discussed, whether percutaneous, retrograde, extracorporeal shock-wave lithotripsy, laparoscopic or retroperitoneoscopic pyelolithotomy is preferable. Such a wide range of interventions can be significantly simplified if we consider that some procedures allow to completely remove the stone, but are accompanied by mechanical trauma to the kidney, while others involve the destruction of the stone without mechanical trauma, but are associated with an increased risk of obstruction and pyelonephritis due to migration of residual fragments. With immunodeficiency of any etiology, including drug-induced, mild kidney injury during one-session procedure is significantly less dangerous compared to infectious and inflammatory complications, which may have more severe consequences compared to patients with an intact immune system. For the same reasons, multi-stage treatment is less preferable to one-stage, but more traumatic. Non-severe mechanical trauma to the kidney (kidney trauma, by definition, cannot be severe, otherwise the method will become more dangerous than the disease) almost never lead to nephropathy, particularly progressive intestinal fibrosis.

Extracorporeal shock-wave lithotripsy is the least invasive surgical method in kidney stones, however, repeated sessions are often required, which can be complicated by kidney hematomas, as well as the formation of steinstrasse, predisposing to the development of renal colic and attacks of pyelonephritis, which are very undesirable for immunosuppressed patients [6-8].

With retrograde intrarenal surgery, the risk of inflammatory complications is always higher due to an increase in intrapelvic pressure when using active irrigation intraoperatively [9].

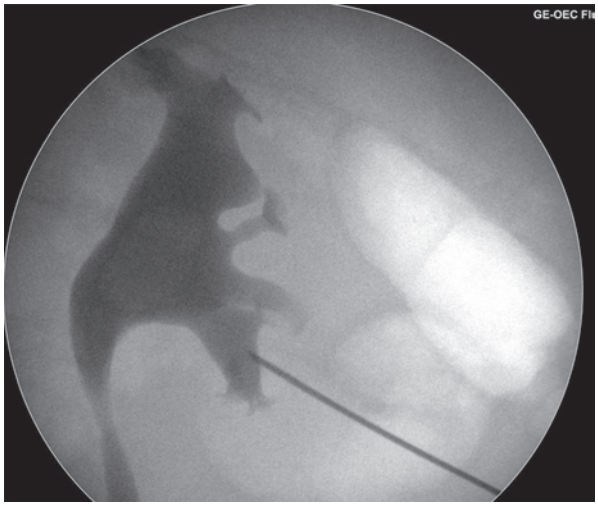

Fig. 2. Fluoroscopy (intraoperatively, in the prone position): retrograde pyelography was performed. In the right renal pelvis, a filling defect is determined, corresponding to a stone up to 2.3 cm in size. A puncture needle during a puncture of through the lower calyx

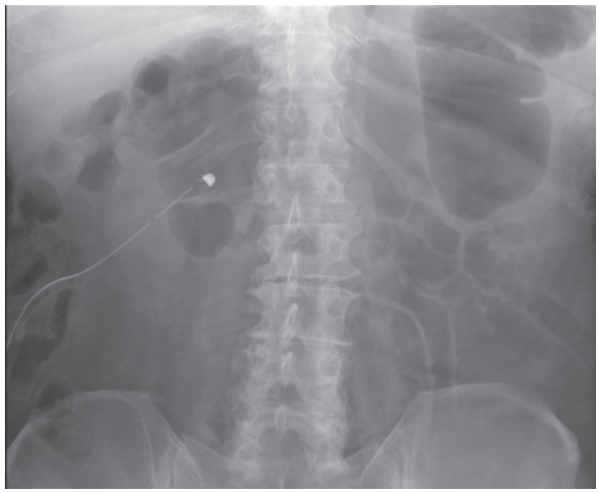

Fig. 3. Plain radiography (postoperatively): in the area of the right kidney, the shadow of the nephrostomy drainage is visualized. There are no shadows suspicious of stones

According to the European Association of Urology Guidelines, the standard method for the surgical removal of kidney stones larger than 2 cm, is PCNL. Although retrograde intrarenal surgery can be also suggested, the likelihood of repeated sessions and stenting is higher [10]. Based on these considerations, the patient underwent PCNL, which allowed to remove the stone at one procedure.

A normally functioning liver transplant does not impose any restrictions on urological tactics. Problems begin if the graft function is reduced. Thus, preoperative assessment of the level of bilirubin, serum albumin, clotting parameters (including the international normalized ratio [INR]) for evaluation of graft function, transaminases (to exclude cytolysis and hepatitis activity) and alkaline phosphatase (to assess cholestasis) is obligatory.

To determine the risk of surgery in patients with impaired liver function, a number of scales incorporating clinical and laboratory parameters have been developed. The Child-Turcott and Child-Turcott-Pugh scores include an assessment of five indicators: bilirubin, albumin, prothrombin time, severity of ascites, stage of hepatic encephalopathy. Depending on the severity of changes, each indicator is scored from 1 to 3 points. A score of less than 6 points according to Child-Turcott-Pugh is corresponds to group A on Child-Turcott score, and indicates the absence of liver failure and preservation of the liver protein synthesis. Such patients can undergo elective surgical treatment of nephrolithiasis.

Somewhat less known in general clinical practice, but widely used in liver transplantation, is the MELD score (Model for End-Stage Liver Disease), which is a mathematical formula that includes three indicators: bilirubin, creatinine and INR. A MELD index of 10–19 is roughly equivalent to the Child–Turcott A group. With high MELD index, planned surgery for nephrolithiasis is undesirable.

Liver transplantation involves lifelong immunosuppressive therapy, which in most cases is three-component and includes a calcineurin inhibitor (cyclosporine, tacrolimus), mycophenolate, and a glucocorticoid (usually methylprednisolone). The first component has a narrow therapeutic window, which, combined with biliary excretion, involvement of cytochrome P-450 system, and an abundance of drug interactions, makes it potentially dangerous. Overdose is associated with numerous side effects, the most significant of which is nephrotoxicity. The deficiency can result in the development of a graft rejection. Such risks require regular monitoring of the serum concentration of these drugs with dosage adjustment if necessary. Currently, the vast majority of patients receive tacrolimus, which is associated with better safety profile compared to cyclosporine. A serum tacrolimus concentration of 6–8 ng/mL is considered normal. It is recommended to check it preoperatively, since this indicates normal function of the graft in the postoperative period. Certainly, it is very hard to change the scheme of immunosuppression, even if the patient develops infectious and inflammatory complications.

Considering pharmacological features of calcineurin inhibitors, it is extremely undesirable to prescribe drugs that compete the same enzymatic systems, including such antimicrobial agents as macrolides and azoles. A tacrolimus can generally be classified as a macrolide, as it is a polycyclic lactone. However, neither azoles nor macrolides are the drugs of choice for the prevention and treatment of postoperative pyelonephritis, so the restrictions seem to be formal.

The severity of immunosuppression in patients receiving maintenance therapy (but not induction or anti-crisis) is rather moderate. Therefore, there is no risk of rare and unusual uropathogens and inflammatory diseases of the genitourinary system like in severe immunodeficient state. Antibacterial prophylaxis should be carried out with the same drugs as for patients with an intact immune system. Of course, in this situation, urine culture is highly recommended, which will minimize the risk of ineffective prophylaxis.

However, there are still two limitations: it is not recommended to prescribe cefotaxime and cefoperazone. The former undergoes hepatic metabolism with the formation of an active metabolite. With an adequately functioning liver transplant, this drug is not contraindicated, but in our clinical case it is impossible to predict what percentage of the drug is transformed into the active form. Moreover, this is an additional burden on the graft, which can be completely avoided. The cefoperazone is the only one of the cephalosporins that has almost complete biliary excretion, and it may also potentiate the effects of anticoagulants. Although there are no formal contraindications in liver transplant recipients, it seems to be an additional burden on the graft and an unnecessary risk of hemorrhagic complications.

In conclusion, we can give some practical recommendations:

- in immunodeficient state, the main risks are not associated with kidney injury, but with acute pyelonephritis, especially recurrent episodes. Single-stage procedure with more mechanical trauma is preferable than multi-stage treatment with less mechanical trauma, but a greater risk of obstructive pyelonephritis.
- At the preoperative stage, it is necessary to ensure the adequacy of the graft function, the absence of liver failure, check viral hepatitis activity and the adequacy of immunosuppressive therapy, which is not changed postoperatively unless absolutely required.
- Antibacterial prophylaxis should be carried out according to urine culture. Preference is given to drugs that are excreted by the kidneys and do not undergo hepatic metabolism.

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LITERATURE REVIEWS

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MODERN ASPECTS OF DIAGNOSTICS AND TREATMENT OF RENAL INFARCTION

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One of the causes of acute kidney injury is the renal artery thrombosis. Clinical manifestations depend on the level of thrombus. This pathology is characterized by non-specific clinical manifestations in the early period, the complexity of differential diagnosis, often delayed verification of the diagnosis and unfavorable prognosis in case of prolonged (5-7 days) anuria.

There is no generally accepted protocol for the diagnosis and treatment of renal artery thrombosis. To clarify the diagnosis, intravenous urography, radionuclide renography, and contrast-enhanced computed tomography are recommended. Until recently, patients with suspected renal artery thrombosis were treated with anticoagulant therapy and renal replacement therapy with hemodialysis, which is required constantly as renal function was usually irreversibly impaired. Surgical treatment is effective only in the first hours. The outcome is often unfavorable, the probability of hemorrhagic complications is high. Due to the rare frequency of detection and verification of renal infarction, no consensus has been reached regarding the diagnosis or treatment of this condition.

K e y w o r d s: renal infarction, renal artery thrombosis, diagnosis, treatment.

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Acute kidney injury (AKI) is a serious interdisciplinary problem of modern medicine, due to its wide prevalence and association with adverse consequences for the patient. Recent studies have identified the development of AKI in 3.2-9.6% of patients treated in hospitals in developed countries. At the same time, hospital mortality was 20%, and in intensive care units, it reaches 50% [1–3]. Approximately 5-6% of patients in intensive care units develop AKI, which requires hemodialysis, and in such cases hospital mortality increases to 60% [4-6].

Acute renal artery thrombosis ranks 5th among thromboses of any localization, and renal artery embolism ranks second after pulmonary embolism.

As a result of thromboembolism, a renal infarction develops, the severity of which depends on the thrombus size and the diameter of the vessel. Often, unilateral renal vascular thrombosis is not diagnosed due to subtle clinical manifestations and compensation by the contralateral kidney [7, 8].

Renal infarction is a rare disease that occurs due to occlusion of the blood vessels [9]. Its incidence ranges from 0.004 to 0.007% of patients presenting to the emergency department [10]. However, when studying the results of autopsies, renal infarction was detected in 1.4% of cases [11]. This suggests that the incidence of renal infarction is higher than previously estimated. It may be due to non-specific symptoms, which are typical for both acute pyelonephritis and renal colic.

Renal infarction most often occurs in patients of the middle age group (30-50 years). No gender differences were described or predominant involvement of the right or left renal artery.

The non-specific clinical manifestations make it difficult to establish a diagnosis [12]. The study of modern aspects of the diagnosis and treatment of renal artery thrombosis is of relevance, considering the global COVID-19 pandemic, since a number of studies report that renal artery thrombosis may be secondary to coronavirus infection. [15]

The aim of this review was to describe modern aspects of the diagnosis and treatment of renal infarction.

Despite the rare occurrence in the general population, frequency of renal infarction can be relatively high in patients at risk, including those with oncological diseases, severe atherosclerotic lesions of the aorta and renal arteries, and cardiac arrhythmia. Thrombus may form both in the main renal arteries and in their branches.

Etiology of renal infarction

According to numerous studies, cardiovascular diseases lead to the development of renal infarction in most cases (up to 95%) [7, 9, 10]. Atrial fibrillation is particularly

common among the risk factors for renal artery thrombosis. Other causes are bacterial endocarditis, renal artery injury, and hypercoagulability [13, 14]. In addition, rare cases of renal infarction have also been reported, including vasculitis, systemic lupus erythematosus, sickle cell anemia, and fibromuscular dysplasia of the renal arteries.

Despite the variety of possible causes, exact etiology cause cannot be determined in approximately 30% of cases [15].

In 2013 M. Bourgault et al. suggested four main etiologic factors of renal infarction [9]:

- cardiac diseases;
- damage to the renal artery (vascular forms);
- hypercoagulability;
- idiopathic.

This classification not only describes the possible causes of renal infarction, but also details the approaches to its diagnosis. It is important to assess the coagulation profile, blood circulation, cardiac muscle, heart cavities and valvular apparatus. Concerning the "vascular forms", A-L. Faucon et al. [16] emphasize the importance of studying several vascular beds (carotid arteries, contralateral renal artery) to clarify the exact etiology and reduce the incidence of pseudo-idiopathic form.

Clinical manifestations

Most patients with renal infarction have abdominal pain, although some do not experience any subjective symptoms. Subfebrile temperature, nausea and vomiting may also be observed [9, 14]. Hematuria is also common. Often the clinical manifestations can be subtle and develop gradually as perfusion of the renal parenchyma decreases.

Thus, renal infarction may be misdiagnosed initially as renal colic or acute pyelonephritis [9]. In a retrospective study of 14 patients, renal infarction was initially misdiagnosed as renal colic [17]. The diagnosis of renal infarction is often made more than 48 hours after the onset of symptoms [18].

Examination

Given the non-specificity of the clinical manifestations of renal infarction, it is critical to highlight specific changes in routine investigations performed in patients with presumed renal colic or pyelonephritis that may raise a suspicion of a possible renal infarction. Thus, renal infarction is associated with an increased level of lactate dehydrogenase in more than 90% of cases, which can help to differentiate this disease from renal colic and pyelonephritis [9].

Many patients with renal infarction may be initially misdiagnosed as having renal colic, and therefore undergoing a non-contrast-enhanced computed tomography (CT) scan of the urinary tract. The sensitivity of this study for renal infarction is low [19]. Therefore, if urolithiasis is ruled out and clinical suspicions of renal infarction persist, it is recommended to supplement the CT with injection of intravenous contrast [20].

Contrast-enhanced CT is the optimal diagnostic tool for diagnosing renal infarction [21]. The blood supply to the kidneys is usually assessed in the vascular phase, which is about 15–25 s after intravenous administration of a contrast agent [22]. The appearance of the kidney parenchyma is determined by the size of the thrombus, its location, and the duration of the disease. The key feature for the diagnosis is the absence of enhancement of renal tissue in the arterial phase [23].

In a local renal infarction, ultrasound shows a cone-shaped area of increased echogenicity, which is directed by the base to the kidney capsule [9].

Invasive diagnosis of renal infarction, including angiography and endovascular ultrasound have changed approaches to therapy by better assessing the etiology of this condition. In addition, invasive diagnostic studies have improved treatment outcomes by increasing the use of antiplatelet therapy and decreasing the use of oral anticoagulant therapy. Invasive diagnostic studies of 59 patients led to a change in the antithrombotic strategy in 56% of cases with an increase in the prescription of antiplatelet therapy. Only 2 (8%) patients had persistent chronic kidney disease. The authors showed that an invasive imaging of the renal artery can improve the long-term prognosis in renal infarction [25]. In contrast to angiography, intravascular ultrasound allows not only to detect renal artery thrombosis, but also to directly assess atherosclerotic lesions and arterial wall remodeling [24]. Therefore, it is more sensitive than angiography to detect vascular lesions, provided that the affected artery is available for invasive catheterization.

Therapy Options

The scientific basis for the treatment approaches in renal infarction is extremely scant, as it is based only on small studies or case series. While a consensus has been reached in the diagnosis and acute treatment, the view of the professional community on the problem of delayed treatment remains controversial.

Options for conservative treatment include antithrombotic therapy and systemic or selective thrombolysis. The optimal combination of these methods is currently also controversial due to the lack of data, but it is certain that the earlier treatment is provided, the less ischemic damage to the parenchyma occurs. Some researchers recommend using a predominantly anticoagulant strategy for unilateral lesions, as well as in case of a low baseline renal function [26].

Systemic anticoagulant therapy with heparin in the acute period is the standard of care and is aimed at reducing mortality [27]. There are no clear criteria for its duration, and the decision is often based on individual basis. A scheme of prolonged conservative therapy largely depends on the etiology of renal infarction and the mechanism of thrombosis. If thrombosis was caused by thromboembolism from the left heart chambers, including those with atrial fibrillation, oral anticoagulants (warfarin, apixaban, rivaroxaban, dabigatran) are indicated [28]. In atherosclerotic lesions, the use of antiplatelet agents (acetylsalicylic acid, clopidogrel) is desirable [29]. Anticoagulant therapy for idiopathic thromboembolic conditions in patients without atrial fibrillation remains unclear. In a large retrospective cohort study, M. I. Khayat et al. (2019), which compared long-term outcomes of anticoagulant and non-anticoagulant therapy in patients with idiopathic renal infarction (n=103), there was no significant difference in the frequency of recurrence of

Table

Cohort studies of patients with renal infarction

Author, studied period	Average age of patients (years)	Past atrial fibrillation (%)	ESRD	All-cause mortality rate	Relapse	Treatment		
						AC	AT	AC+AT
Bourgault et al. [9], 1989–2011	53	18	5% (30 days	0% (30 days)	–	38	35	0
Huang et al. [28], 1991–2016	56	56	7%[b] (48 months)	30% (6 months)	12% (48 months)	44	0	0
Oh et al. [13], 1993–2013	60	45	2.1% (20 months)	5% (20 months)	2.8%	48,2	37,2	14
Bae et al. [35], 1995–2012	59	40	–	–	–	70	6	0
Mesiano et al. [36], 1999–2015	59,8	28	5.6% (15 months)	–	–	44	33	0
Rhee et al. [34], 2000–2009	56	25	–	19.7% (40 months)	–	–	–	–
Faucon et al. [16], 2000-2015	53	4	–	–	–	–	–	–
Yun [37], 2006–2012	61,3	53	2% (41 months)	36% (5 years)	19% (20 months)	100 (3-6 months)	0	0
Cerba et al. [38], 2013–2015	57	–	0% (6 months)	9% (6 months)	0% (6 months)	64	36	0,9
Eren et al. [39], 2015–2018	53	30	3% (14 months)	5% (14 months)	–	41	0	–

Note. ESRD – End-Stage Renal Disease; AC – anticoagulants; AT – antithrombotic agents

arterial thrombosis between treatment groups after 4.3 years of follow-up (p=0.46) [30].

Since being introduced into clinical practice, thrombolytic therapy has been actively used for the treatment of renal infarction, including systemic thrombolysis and endovascular interventions, which are increasingly performed as selective therapy. Fibrinolytic enzymes (strepokinase, urokinase), tissue plasminogen activators (alteplase) are also used [31]. Data on the efficacy and safety of this method of therapy are based mainly on clinical cases, which generally demonstrate sufficient safety and good clinical efficacy even in the case of prolonged ischemia [26, 32].

It is important to mention that in some patients a combination of different antithrombotic strategies is required. In any case, the duration of treatment and the choice of drug are variable and depend on the overall health, patient comorbidities, individual risk of bleeding and should be determined by a multidisciplinary team. It is also important to focus not only on the treatment of renal infarction, but also on the identification and therapy for predisposing conditions.

Thus, drug treatment of renal infarction is a challenging with little evidence. Randomized controlled comparative trials are needed to assess the benefits of one or another method of treatment.

In cases of traumatic renal artery thrombosis, surgical treatment is highly effective, including endovascular thrombolysis, data on which are limited. Other options for percutaneous endovascular procedures may be thrombectomy or angioplasty with or without renal artery stenting.

Successful thrombolysis allows to improve blood supply, but does not fully restore kidney function. Thrombolysis is most effective when performed as soon as possible after a renal infarction.

All patients who have undergone renal infarction need long-term prevention of recurrent arterial thrombosis according to generally accepted protocol, including the combined use of oral anticoagulants and antiplatelet drugs.

The table provides an analysis of the prescribing of antithrombotic drugs immediately after diagnosis of renal infarction, which have been reported in the literature and consist mainly of oral anticoagulants.

The prognosis of patients with renal infarction, on the one hand, depends on both the severity of kidney damage and the etiology of the disease. It should be noted that in those with renal artery thrombosis, the risk of repeated life-threating thrombosis of another localization, both arterial and venous, is significantly increased.

In the immediate period after renal infarction, the highest mortality rate was found: for example, during the first 30 days, it was 11.8% [23]. Consequently, more than 50% of patients achieve a complete or more often partial recovery of kidney function.

Thus, renal artery thrombosis is a rare pathological condition that requires special attention due to the high risk of loss of kidney function. As with all diseases, timely diagnosis and proper treatment is an important aspect. It is advisable to choose the treatment tactics based on the degree of thrombosis. In the case of incomplete thrombosis, conservative anticoagulant therapy shows good results (decrease in kidney function after 2.5 years by 9%), while for complete thrombosis, endovascular thrombectomy is required (decrease in kidney function after a year by 27%) [26].

According to current data, renal artery thrombosis is one of the causes of acute renal failure, and its clinical manifestations depend on the severity of the lesion.

The features of this condition are the complexity of early diagnosis (less than 30% of patients) and the

apparent futility of treatment in patients for long-term (57 days) anuria. There is no generally accepted protocol for the diagnosis and treatment of renal artery thrombosis. To clarify the diagnosis, intravenous urography, radionuclide renography, and contrast-enhanced computed tomography are recommended [29]. Until recently, when renal artery thrombosis was suspected, patients were prescribed anticoagulant and renal replacement therapy with hemodialysis, which became chronic, since kidney function, as a rule, was irreversibly impaired. Surgical treatment is effective only in the first hours. The outcome is often unfavorable, and there is a high probability of hemorrhagic complications [40].

Due to the rare frequency of renal infarction, no consensus has been reached regarding its diagnosis or treatment. Therapeutic measures include thrombolysis, anticoagulants, and sometimes surgical treatment, depending on the duration of the symptoms. To improve the prognosis of patients with renal artery thrombosis, timely identification and elimination of causes and predisposing factors, as well as adequate individualized treatment based on etiology, is obligatory.

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MODERN METHODS FOR DETERMINING THE POSITIVE SURGICAL MARGIN DURING RADICAL PROSTATECTOMY

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Determining and evaluation of predictors of biochemical recurrence (BCR) is one of the essential aim, which may help to achieve the most effective treatment of prostate cancer. Obviously, positive surgical margins represent an independent risk factor for BR following radical prostatectomy. The development of methods determining the status of the surgical margin during surgery is an important direction which can upgrade the effectiveness of prostate cancer treatment.Moreoverit is relevant to review modern methods for diagnosing the status of the surgical margin during radical prostatectomy.
This article presents a systematic review carried out at the Department of Urology and Andrology of Pirogov Russian National Research Medical University. In September 2021, we performed a PubMed/Web of Science search to include articles published in 1995–2020 evaluating the key words «prostate cancer», «surgical margin», «radical prostatectomy», «biochemical recurrence», «methods for determining the surgical margin». Nowadays the following technologies have been developed and being actively studied: the usage of aminolevulinic acid, optical coherence tomography, optical spectroscopy, confocal laser microscopy, 3D augmented reality, 3D modeling, the study of frozen samples.

K e y w o r d s: prostate cancer, surgical margin, prostatectomy, method for determining the surgical margin

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Currently, the main treatment method for prostate cancer (PCa) is still radical prostatectomy (RP). Despite the increase in the proportion of patients with localized PCa, the widespread introduction of minimally invasive surgery, the evolution of surgical techniques and high efficiency of RP, up to 30% of patients have the biochemical recurrence. It is associated with a less favorable prognosis [1], namely significantly higher risk of disease progression and death [2]. Development of predictors of the biochemical recurrence is one of the fundamental tasks, which is necessary in order to provide the most effective treatment for PCa. Although numerous nomograms are developed, which combine such parameters such as clinical stage, Gleason index, seminal vesicle invasion, has certain advantages, their predictive value remains unsatisfactory. One of the most studied predictors of biochemical recurrence is positive surgical margins (PSM). It is defined as the presence of tumor cells at the outer border of the specimen, detected by microscopic examination. The separate methods for staining tissues with hematoxylin and eosin were discovered in the second half of the 19th century. In 1878, Busch combined these methods, which made it possible to create a "gold" standard for histological examination [3]. The optimal requirements for determining a status of surgical margin are the possibility of in vivo analysis, the minimum range of additional surgical equipment, the high speed of the study (per min), the reduction in the time of procedure, high sensitivity and specificity, a large area of the examined area of the prostate (3– 5 cm3), and minimization of false-negative and false-positive results due to surgical procedure by itself (including tissue coagulation). Finally, the method must be intuitive and safe for both the patient and medical staff, and the tissue sample must be delivered to the pathology department with minimal artifacts in order to allow proper histological examination.

Therefore, it is important to review modern diagnostic methods for detecting PSM when performing RP.

At the Department of Urology and Andrology of N.I. Pirogov RNRMU on the basis of the City Clinical Hospital No. 1 named after N.I. Pirogov a descriptive scientific review was prepared. In September 2021, a comprehensive literature search was carried out in PubMed and Web of Science for 1995–2020 on intraoperative methods for determining the status of surgical margins during RP. The key phrases were as following: "prostate cancer", "surgical margin", "radical prostatectomy", "biochemical recurrence", "methods for determining the status of surgical margin". The following technologies are being under investigation for assessing the status of the surgical margin: the use

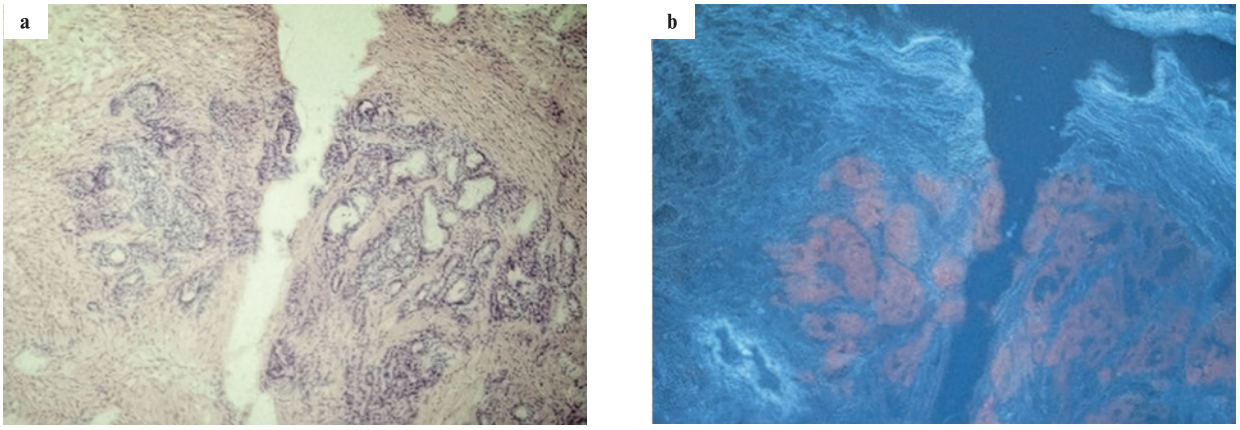

Fig.1. Photomicrograph of an acinar adenocarcinoma of Gleason score 6 (3+3). Magnification: 20X.
Fig. 1a. A staining with hematoxylin and eosin. Fig. 1b. Accumulation of protoporphyrin IX in tumor cells.

of aminolaevulinic acid, optical coherence tomography (OCT), optical spectroscopy, confocal laser scanning microscopy (CLSM), 3D augmented reality with 3D modeling and intraoperative frozen sections.

Experimental methods (1–5)

1. Use of aminolaevulinic acid

δ-Aminolevulic acid (delta- or 5-aminolevulinic acid, or 5-ALA) is an organic acid, the primary component in the synthesis of tetrapyrroles, porphyrins and corrins in animals, and chlorophyll in plants. 5-ALA is a naturally occurring compound, the early intermediate in the heme biosynthesis pathway. Its excessive introduction into the body (or into the specific tissues) leads to the inhibition of the last stage of heme synthesis and the accumulation of its precursor, endogenous protoporphyrin IX (PpIX), mainly in tumor cells and foci of inflammation [4]. The use of photodynamic diagnosis (PDD) using 5-ALA has been described in a number of scenarios as an innovative method for intraoperative detection of malignant tissue. Scientific papers have been published on using this technique for diagnosing ovarian, pharynx and larynx cancer, glioma, breast cancer, and metastases to the lymph nodes. The main area of using PDD in urology is the diagnosis of superficial urothelial bladder cancer [5]. Zaak et al. described for the first time the selective accumulation of PpIX in the prostate after RP [6] (*Fig. 1*).

Currently, several scientific papers have been published on the use of 5-ALA to detect PSM during RP [7–10]. Ganzer studied 24 patients with localized PCa who took aminolevulinic acid (orally 20 mg per 1 kg of body weight) 3 hours before laparoscopic nerve-sparing RP. Intraoperatively, at various stages the status of surgical margins was determined in white and PDD modes. Suspicious areas found on PDD were marked with white ink to determine sensitivity and specificity during the final pathological examination. According to the results, white light endoscopy detected no suspicions area of PCa. Six out of eight PSM were confirmed by PDD. In two cases, positive areas detected by PDD were found to be negative. In two other cases, PCa was not detected during PDD (1 in bladder neck, 1 in lateral part of the prostate). The overall sensitivity and specificity of the method were 75% and 88.2%, respectively. In another study, Fukuhara et al. performed RP (retropubic and laparoscopic) using PDD in 52 patients. A suspicious area detected by PDD was found in 1 of 52 patients, which was confirmed during the final pathological examination. However, in two other cases, PCa was missed by PDD. According to the authors, the reason was the short length of PSM and thermal injury of tissues, which led to false negative results (*Fig. 2*).

Summarizing the studies on the use of 5-ALA in the diagnosis of PSM during RP, the sensitivity of the method ranged from 75 to 82%, and the specificity from 68 to 88%.

The main advantage of the 5-ALA method:

- Ability to perform in vivo (specific equipment is required).

The main disadvantages of the 5-ALA method:

- Learning curve.
- Influence of heat (due to tissue coagulation) on the result.
- Preparation time.
- Side effects of the drug.

Side effects of 5-ALA are photodermatosis, nausea, vomiting, increased levels of alanine aminotransferase and aspartate aminotransferase.

2. Optical coherence tomography

OCT is a non-invasive imaging technique that provides real-time imaging of tissue microstructure [11]. The physical principle of OCT is similar to ultrasound, with the only difference that OCT uses near-infrared light to probe tissue (~1 μm) rather than acoustic waves [12]. In a study by Dangle et al., OCT was used in 100 patients who underwent robot-assisted radical prostatectomy (RARP) [13]. The authors used OCT to assess the status of the surgical margin, the presence of extraprostatic extension and tumor invasion into the seminal vesicles. During the study, 20 OCT images were obtained for each case (the base of the seminal vesicles, the prostate apex and bladder neck, the posterolateral area of the prostate, and any palpable nodule). A total of 2000 OCT images were acquired. At the final pathological examination, 85 patients had stage pT2 and 15 had pT3. PSM was detected in 10 cases. Based on the obtained OCT data (before the result of pathological study), the authors expected to find 21 PSM, of which 7 were indeed positive, 14 were false positive. The authors expected to find 79 negative surgical margins, of which 76 were indeed negative and 3 were false negatives. The sensitivity and specificity of the method in assessing the status of the surgical margin were

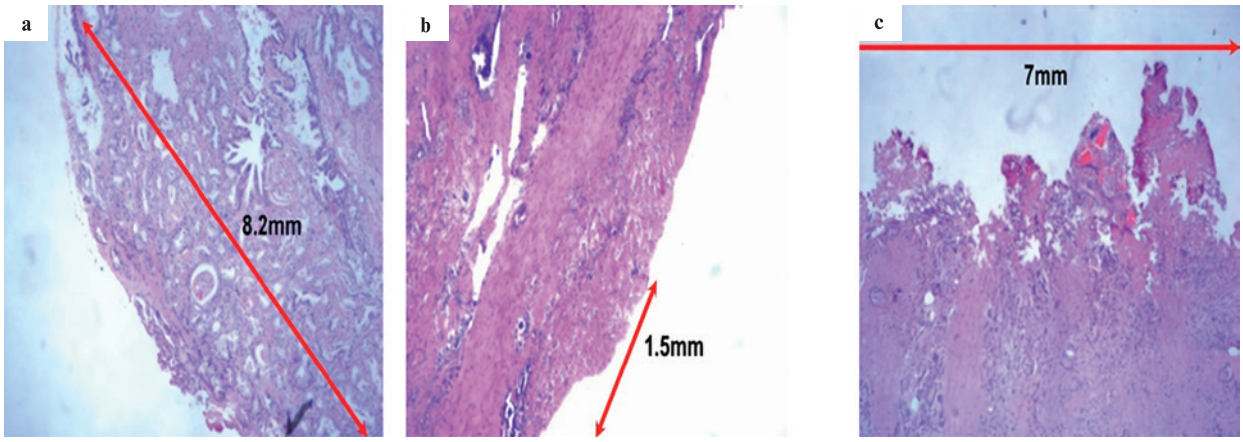

Fig. 2. Photomicrograph of an acinar adenocarcinoma. The relationship between histological examination and the sensitivity of photodynamic diagnosis. Magnification: 20X
Fig. 2a. Red fluorescence (+), PSM length more than 5 mm. Fig. 2b. Red fluorescence (-), PSM length less than 5 mm.
Fig. 2c. Red fluorescence (-), thermal tissue degeneration.

70 and 84%, respectively. Positive and negative predictive value was 33 and 96%, respectively (*Fig. 3*).

The main advantages of OCT:

- Ability to perform in vivo (equipment required).
- Evaluation of the entire surface of the prostate, including the neurovascular bundle.
- Rapid result (about 5-10 minutes).

The main disadvantages of OCT:

- Learning curve.
- Influence of blood and other tissues on the accuracy.
- Small imaging area (2.7 mm).
- A small number of scientific papers.

3. Optical spectroscopy

The method of optical spectroscopy is based on the interpretation of specific interactions between electromagnetic radiation and tissue. Healthy and tumor cells are characterized by different tissue properties, including nucleus size and cell density [14]. Optical spectroscopy measures the intensity and spectrum of reflected and backscattered light. In studies on PCa, various types of spectroscopies were used: fluorescence spectroscopy [15], Rayleigh (elastic) spectroscopy [14, 16, 17], and Raman (inelastic) spectroscopy [18–20].

According to the most recent systematic review, which included 5 studies, the overall sensitivity and specificity of optical Raman spectroscopy are 0.89 (95% CI: 0.87–0.91) and 0.91 (95% CI: 0.89–0.93), respectively [21].

Main advantages of spectroscopy:

- Unequivocal result.
- Minimal effect of blood on the result.

The main disadvantages of spectroscopy:

- Small visualization area (1 mm).
- Time for data processing.
- Cannot not used in vivo.

4. Confocal laser microscopy

CLSM is a type of light optical microscopy that enables to increase contrast and spatial resolution compared to classical light microscopy, which is achieved by using a pinhole aperture located in the image plane; the image is obtained from the focal plane only, limiting background scattered light [22]. CLSM is a non-invasive imaging tool that allows real-time visualization of cells and structures

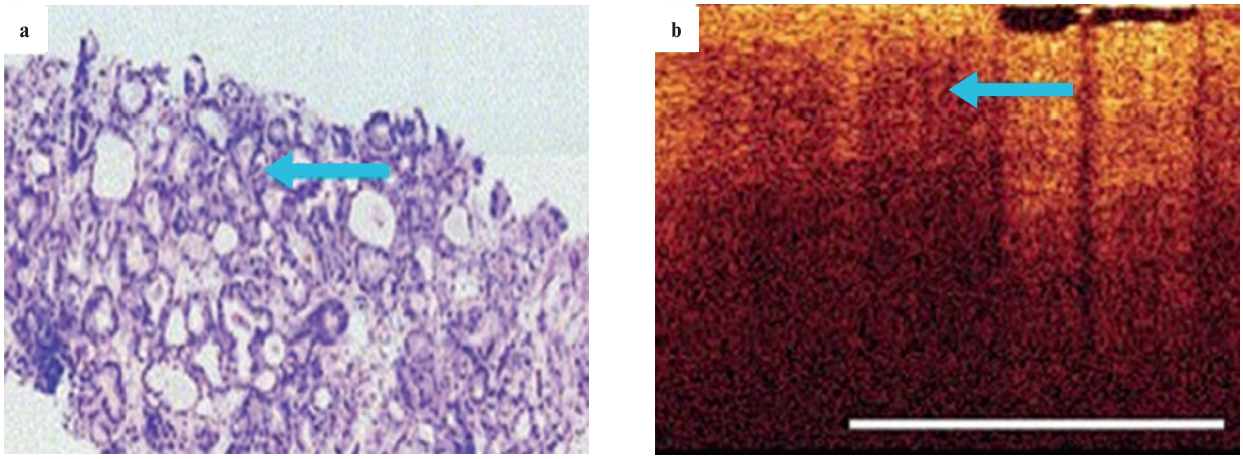

Fig. 3. Photomicrograph of an acinar adenocarcinoma. Magnification: 20X
Fig. 3a. A staining of the positive surgical margin of the prostate with hematoxylin and eosin.
Fig. 3b. A similar section of prostate tissue under the influence of OCT.
Heterogenous columns with a low level of scattering, characteristic of the tumor are indicated by the arrow [13]

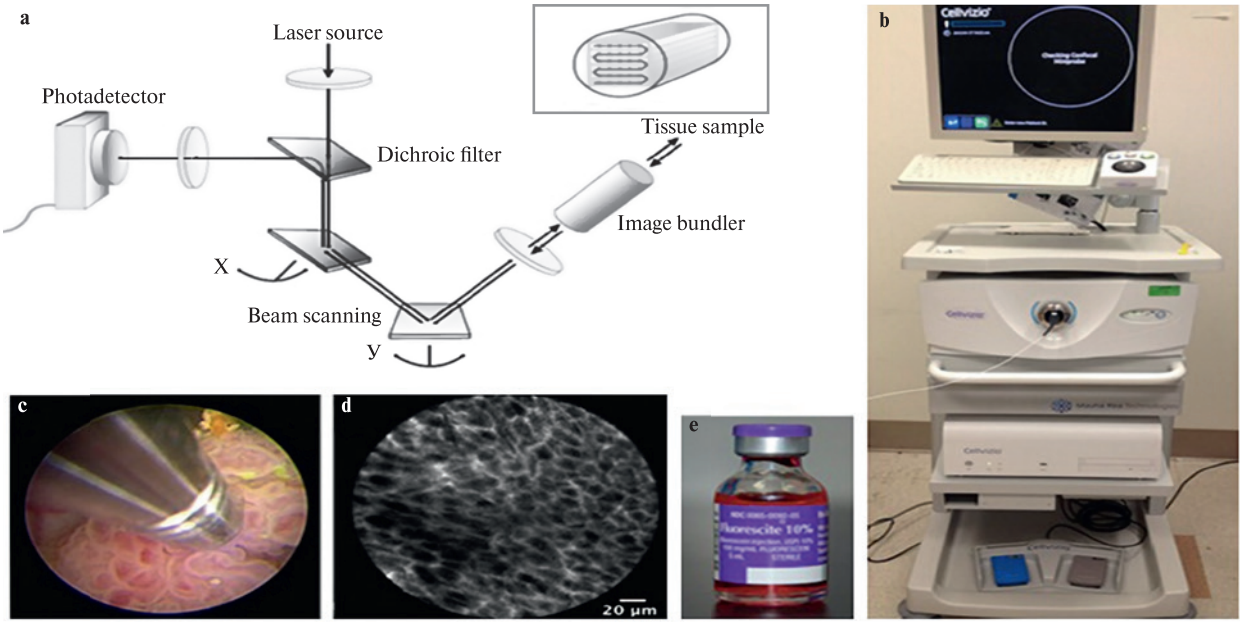

Fig. 4. A physical principle of confocal laser microscopy in the diagnosis of bladder cancer
Fig. 4a. Schematic representation of the physical principle of confocal microscopy. Fig. 4b. An apparatus for confocal laser microscopy (Cellvizio). Fig. 4c. Intraoperative probing of bladder tumor. Fig. 4d. An imaging of the similar area obtained using KLM. Fig. 4e. The drug fluorescein sodium.

in vivo at near histological resolution. The method was first invented in 1957 and used for research purposes to develop new tools [23]. CLSM can be performed in two modes: reflection and fluorescence. It has been successfully used for the diagnosis of bladder cancer and upper urinary tract tumors in vivo [24] (*Fig. 4*).

In a study by Lopez et al. the CLSM was used to visualize PCa in vivo and ex vivo [25]. A 488 nm laser and the drug Fluforor (sodium fluorescein), which was administered 20 minutes before surgery, were used. The sensitivity and specificity of the method are not specified. There was no PSM. In another work, Panarello et al., based on their own data, created an atlas that allows comparing and interpreting images obtained with CLSM and the final histological examination. This allows to study the efficiency of this technology in determining the status of the surgical margin during RP [26]. Another type of CLSM is fluorescence confocal microscopy (FCM). It combines two types of lasers, which allows to study tissue samples in two modes. This technology is characterized by a vertical resolution of 4 µm, a penetration depth of 200 µm and a magnification of up to 550 x. Notably, the penetration depth can be increased by changing the laser power and/or the incubation period of the sample in the dye. In addition, digital processing allows to send the results in electronic form to the pathologist. FCM is used in various medical areas and has shown promising results [23]. With this method, the pathological examination of the prostate nay be performed in real time (ex vivo). The method showed high sensitivity and specificity (91 and 93.3%, respectively) [27].

5. 3D augmented reality and 3D modeling.

Augmented reality is the result of adding any sensory data into the visual field in order to supplement information about the environment and change its perception. Interest in the use of projection displays in surgery arose in the 1990s. [28, 29].

Currently, this technique has proven to be reliable in many medical fields [30–32]. According to the largest systematic review, more than 25 scientific papers have been published on the use of 3D modeling/3D augmented reality in the treatment of PCa [33]. The value of this technology can be divided into three areas: simulators, preoperative planning, intraoperative navigation. For example, Ukimura et al. created a 3D model of the prostate based on transrectal ultrasound/magnetic resonance imaging and biopsy data [34]. Their initial experience showed that 9 out of 10 patients (90%) had a negative surgical margin. The limiting factor of the described model is the inability to overlay a 3D model on an organ in vivo. At the moment, innovations in the field of digital technology allows to use new modifications of augmented reality. Porpiglia et al. reported the successful use of an elastic virtual reality 3D model superimposed during procedure. The elasticity of the model allowed it to bend and stretch depending on the intraoperative picture. The authors reported that this method allows to predict extracapsular invasion in 100% [35].

6. Intraoperative frozen sections

The intraoperative frozen section was introduced at the end of the 19th century when William Welch first examined a specimen taken from breast tissue during surgery. However, Thomas Cullen was the first to publish a description of the intraoperative study in 1895 [36]. The technique is based on the concept of rapid freezing of tissues in a cryostat (from -16 to -20°C), which leads to conversion of the water component into ice, allowing the tissue to be cut into several samples. After tissue cutting, a standard histological examination is performed using hematoxylin and eosin [37]. Currently, the intraoperative frozen section is the most common method for assessing

Table 1

Publications on frozen section during RP from January 2000 to March 2019

Summary						
Localization	Number of studies (authors [s], year)	Number pf patients (*n*)	Surgical approach	PSM rate (*frozen section*), %	Sensitivity, %	Specificity, %
Prostatic apex	Shah O. et al., 2001	95	ORP	4,2	57	100
	Ye H. et al., 2011	1669	n.a.	6,7	59.1	99,8
	Wambi C.O. et al., 2013	329	RARP	2,7	67	99
Neurovascular bundle	Goharderakhshan R.Z., 2002	101	n.a.	14,9	69	95
	Fromont G. et al., 2003	100	LRP	24	96	100
	Heinrich E. et al., 2010	130	ORP	6,9	n.a.	n.a.
	Lavery H.J. et al., 2010	177	RARP	6	n.a.	n.a.
	Schlomm T. et al., 2012	2567	All approaches	27,2	93.5	98.8%
	Beyer B. et al., 2014	1040	RARP	29,6	n.a.	n.a.
	Petralia G. et al., 2014	134	RARP	13,4	n.a.	n.a.
	Vasdev N. et al., 2015	40	RARP	25	75	75
	Hatzichristodoulou G., 2015	471	ORP	29,1	n.a.	n.a.
	Bianchi R. et al., 2016	254	RARP	29,1	n.a.	n.a.
	Mirmilstein G. et al., 2017	120	RARP	Н.Д.	82.4	91%
	Preisser F. et al., 2019	156	RARP	Н.Д.	n.a.	n.a
BN	Nakamura K. et al., 2007	51	n.a.	6%	n.a.	n.a.
Other areas	Lepor H. et al., 2003	500	ORP	6.9	57.7	98.2
	Dillenburg W. et al., 2005	198	LRP	13	70 (apex)	97
	Tsuboi T. et al., 2005	259	n.a.	8,9	42	100
	Gillitzer R. et al., 2010	178	ORP	10,7	11.5–29.2	97.4
	Fasolis G. et al., 2006	259	ORP	24,3	n.a.	n.a.
	Emiliozzi P. et al., 2010	270	LRP	24,8	n.a.	n.a.
	Kakiuchi Y. et al., 2012	1128	RARP	5,3	n.a.	97.3
	Akin Y. et al., 2013	66	RARP	34,8	n.a.	n.a.
	Almeida G.L., 2013	128	RARP	18,7	n.a.	n.a.
	Von Bodman C. et al.2013	236	ORP	22	n.a.	n.a.
	Nunez A.L. et al., 2016	71	RARP	15,5	85	100
	Obek C. et al., 2018	170	LRP	33	n.a.	n.a.
	Pak S. et al., 2018	2013	RARP	10,6	78.1	97.8

Note. ORP, open retropubic radical prostatectomy, RARP, robot-assisted radical prostatectomy, LRP, laparoscopic radical prostatectomy, BN, bladder neck, n.a.. – not available.

the status of the surgical margin. The table provides a summary of studies published since 2000 [38].

It is known that the prostate is covered by a fibromuscular tissue known as the prostate capsule. However, the capsule covers the prostate unevenly, becoming thinner in some parts of the prostate, including the apex. This makes it difficult to dissect tissue in this area due to the proximity of the urethral sphincter, which must be preserved. The urethral stump (apex of the prostate) is one of the most common sites for PSM. Several works are devoted to the analysis of intraoperative frozen sections from the prostate apex. According to literature, the sensitivity and specificity of the method ranged from 57 to 67% and from 99 to 100%, respectively [39–41]. Ye H. et al. compared the 5-year recurrence-free survival of patients with negative and positive surgical margins after re-excision of the initially PSM (as determined by intraoperative frozen sections). In the group of patients with the negative surgical margin after re-excision, the 5-year disease-free survival was 93.75% versus 80% in those with PSM without re-excision [42]. The second most common location for PSM is the posterolateral surface of the prostate (the neurovascular bundle). Since Walsh described the nerve-sparing technique in 1983, there has been a standardization of the technique for patients with localized PCa in order to improve functional outcomes. A recent systematic review and meta-analysis showed that nerve-sparing (unilateral or bilateral) RP was not associated with a significant increase in the risk of PSM in patients with stage pT2 or pT3 [43]. However, these conclusions remain contradictory. According to the largest meta-analysis, which included 32 cohort studies involving 141,000 patients, a negative prognostic effect of PSM on oncological outcomes was revealed. The presence of PSM significantly worsens relapse-free ($p<0.001$), cancer-specific ($p=0.001$) and overall survival ($p=0.014$) [44]. At present, a significant number of publications devoted to the studying of intraoperative frozen sections from the posterolateral surface of the prostate have been published [45–47]. In 2012, Schlomm et al. from Martini-Klinik (Germany) developed a protocol of neurovascular structure-adjacent frozen-section examination (NeuroSAFE), which has been validated in their own cohort [48]. The authors provided data on 11,069 open RP and RARP performed with NeuroSAFE. An increase in the total number of nerve-sparing RP from 81% to 97% was reported. The number of PSM decreased from 22 to 15% among all clinical stages. This technique demonstrates high sensitivity and specificity, which was 93.5 and 98.8%, respectively. However, long-term oncological results remain debatable, since the disease-free survival in NeuroSAFE group did not significantly differ from the group of patients without NeuroSAFE. This technique has become quite widespread in other urological centers. Studies of Beyer et al. and Mirmilstein et al. showed that the use of NeuroSAFE allowed to reduce the incidence of PSM (from 24 to 16% and from 17.8 to 9.2%, respectively). In

addition, the technique allowed to increase the number of nerve-sparing RP (from 81 to 97% and from 69 to 75.1%, respectively) [49, 50]. Despite this, a number of studies have been published showing that using intraoperative frozen sections for obtaining negative surgical margin at the posterolateral surface of the prostate does not significantly affect disease-free survival [51, 52].

On the other hand, the analysis of intraoperative frozen sections in the prostate base (bladder neck) demonstrated the ability to reduce PSM rate to 0% [53].

Surgical treatment is still the gold standard in patients with localized PCa. One way to improve oncological and functional outcomes is to modify surgical approaches, including intraoperative determination of PSM. Although intraoperative frozen sections have a history of more than 100 years, this technique, despite its limitations, remains the generally accepted method for determining the status of surgical margins. Modern development in fields related to medicine allows to propose new methods for determining PSM, many of which show promising results. However, most of them are still experimental and not used in routine clinical practice. Further researches are needed in this area.

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