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

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ООО «БИОНИКА МЕДИА ИННОВАЦИИ»

CONTENTS

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LONG-TERM RESULTS OF URETERAL REPLACEMENT USING SMALL BOWEL IN PATIENTS WITH LONG STRICTURES: 9-YEAR SINGLE-CENTER EXPERIENCE

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Introduction. When reconstructing long ureteral strictures, the optimal substitution material is reconfigured pelvis or bladder flaps. However, it is not always possible to use them due to involvement in the pathological process or insufficient length to replace the defect. In such cases, substitution of the ureter by ileal segment is successfully used.

Materials and Methods. A total of 25 patients, 10 men (40%) and 15 women (60%), who undergone to reconstructive procedure during the period from 2012 to 2021 with a follow-up period of at least 6 months (mean 51.26 months) were included in the retrospective analysis. Additionally, a comparative analysis was carried out between the laparoscopic and open access according to a set of criteria. The endpoints in the study were the functional state of the kidneys, repeated procedures and development of metabolic disorders.

Results. The average length of the stricture was 10.7 cm (5-20 cm). Eleven patients underwent open approach (44%), while in 14 cases laparoscopic approach was used (56%). Primary procedure was performed in 16 (64%) patients, repeated intervention due to stricture recurrence was performed in 7 (28%) cases, and two patients (8%) underwent bowel substitution of the ureter, implanted into the ileal conduit after radical cystectomy. The average duration of the procedure was 240 min (Q1-186 min, Q3-307 min). For laparoscopic access it was 230 min (Q1-186 min, Q3-292 min) compared to 240 min (Q1-202 min, Q3- 312 min) for open access. Complications of the Clavien I grade developed in 5 cases (20%). With a minimally invasive approach, the length of stay in hospital was 6 days (5-6), including 0.7 days (0-1) in the intensive care unit. The average number of drains after laparoscopic procedure was 1.3 (0-2), and the drains were removed in average after 4.4 days (3-5). With open access, the median length of stay was 8 (5-11), including 2 days (1-5) in the intensive care unit. The number of drains was 1.6 (1-2), and the drains were removed in average after 4 days (3-5). Thirteen patients were undergone to follow-up examination until discharge. Regression of dilatation of the pelvicaliceal system was noted in 12 patients (92.3%). Among them, renal function stabilized in 8 (61.5%), improved in 4 (30.8%) and deteriorated in 1 case (7.7%). Clinically significant metabolic acidosis was detected in 1 patient (7.7%).

Conclusion. Substitution of the ureter by ileal segment showed satisfactory results in long-term follow-up.

Key words: reconstruction of the ureter using small bowel, a comparison between laparo scopic and open approaches, functional results, analysis of complications, classification of Clavien-Dindo

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Introduction. Long ureteral strictures remain a challenging problem in the urology. During the last two decades a steady increase in its prevalence has been found, which is associated with more widespread surgical procedures, wider indications for surgical treatment of oncologic diseases in gynecology and surgery, and introduction of endoscopic and laparoscopic techniques into clinical practice, which results in an increase in the number of complications. A long ureteral defect may be a complication of radiation therapy, as well as due to retroperitoneal fibrosis. The method of choice for the treatment of long ureteral strictures is reconstructive surgery using an isolated ileal segment.

Materials and methods. A retrospective study in order to assess long-term results of treatment of patients with long ureteral stricture who underwent replacement using small bowel was carried out. A total of 25 patients was included in the study, of whom 10 (40%) were men and 15 (60%) women. They underwent ureteral replacement using small bowel at the Urology Clinic of the Russian National Research Medical University named after N.I. Pirogov from 2012 to September 2021, followed by assessment of functional results with a follow-up period of at least 6 months. The average age of the patients was 59 (38–80) years. Radiation therapy was etiologic factor in four cases (n=4; 16%), retroperitoneal fibrosis in one (n=1.4%), while the remaining (n=20.80%) ureteral strictures were iatrogenic. In eleven cases, reconstructive surgery was performed on the right side (44%), and in 13 patients, on the left (52%). In one patient, simultaneous bilateral substitution with one intestinal graft was done (4%). The average length of the defect was 10.7 (5–20)

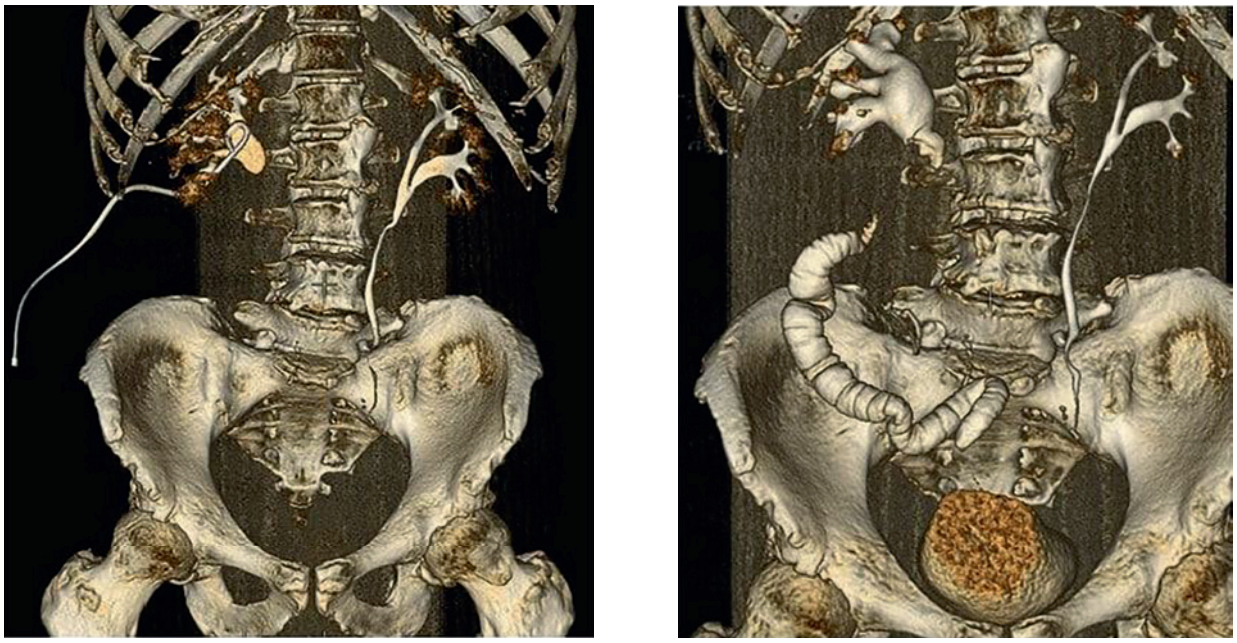

Fig. 1. Contrast-enhanced computed tomography prior to and after surgical treatment

cm. Eleven patients underwent open procedure (44%), and in 14 cases laparoscopic reconstruction was done (56%). Primary and repeat reconstruction was performed in 16 (64%) and 7 (28%) patients, respectively. Two (8%) patients underwent substitution of the ureter using small bowel, which was anastomosed with the ileal conduit after radical cystectomy. Isoperistaltic bowel segments were used. All anastomoses were performed without reflux protection. An anastomosis between bowel segment and proximal ureter was done in 15 (60%) patients, while in 10 cases (40%), an anastomosis between the pelvis and the proximal part of the ileal graft was created. The parameters studied included gender, age, etiology and length of stricture, affected side, methods of drainage before procedure, options for proximal anastomosis, as well as the number of previous procedures. The duration of the operation, the frequency of intra- and postoperative complications, the length of stay, including admission to intensive care unit, the number of opiate analgesics used during the recovery period, number of drains and timing of their removal were compared between open and laparoscopic approaches. Thirteen patients underwent a complete follow-up examination, while the remaining had only a telephone survey. The follow-up period for these patients averaged 51.26 (6–109) months. The main criteria for assessing functional outcomes were deterioration of renal function, repeated procedures and metabolic disorders. Renal function deterioration was defined as an increase in the stage of chronic kidney disease (CKD). CKD stages were defined based on estimated glomerular filtration rate (eGFR): stage 1, eGFR $\geqslant$ 90; stage 2, eGFR of 60-89; stage 3, eGFR of 30-59; stage 4, eGFR of 15-29; and stage 5, eGFR < 15. GFR was calculated using the MDRD (Modification of Diet in Renal Disease) equation. In addition, all patients underwent dynamic scintigraphy in order to assess renal function.

A total of 24 (96%) patients had nephrostomy tube before the reconstruction, while in 1 (4%) patient double drainage (nephrostomy + ureteral stent) was used. If the patient had an internal ureteral stent preoperatively, the latter was removed followed by the putting of a nephrostomy tube within an average of 1 month prior to ureteral substitution.

To assess the anatomical and functional state of the upper urinary tract, contrast-enhanced computed tomography (CT) of the abdominal organs and retroperitoneal space was performed before and after treatment (*Fig. 1*).

All patients underwent a blood test to determine the acid-base status and biochemistry parameters. In those with recurrent pyelonephritis, voiding cystography was performed in the postoperative period to exclude reflux through the intestinal graft. The contrast agent was retrogradely injected into the bladder, then the patients remained in a horizontal position for 1 hour, after that the study was done.

Statistical processing of the results was performed using MS Excel and GraphPad Prism 8. To check the normal distribution of the continuous variables, the Shapiro–Wilk test was used. In the case of normal distribution, data were presented as the mean (M) with standard deviation (SD) in the format M±SD, while in other cases, the median with an interquartile range (Me [Q1; Q3]) was provided. Differences were considered significant at $p<0.05$ using the Student's t-test or the Mann–Whitney U test, respectively.

Results. The mean number of interventions before intestinal reconstruction was 2.4 (range 1 to 7). The median duration of the procedure was 240 minutes (186; 307). In the laparoscopic group it was 230 minutes (186; 292), compared to 240 min (202; 312) in the group of open approach ($p>0.05$). One patient after laparoscopic reconstruction had one intraoperative complication. After mobilization of the intestinal graft, its non-viability was revealed. After that, the intestinal graft was removed and a new bowel segment was harvested.

After open reconstruction, postoperative Clavien grade I complications, such as recurrent pyelonephritis, were observed in 2 (18.2%) patients. In the laparoscopic group,

Clavien grade I complications were identified in 3 (21.4%) cases. In this group, after a full course of antibiotic therapy, an X-ray examination to exclude reflux along the intestinal graft was done (*Fig. 2*). This study showed the presence of passive and active reflux only up to the level of the middle third of the neoureter.

With laparoscopic access, the average hospital stay after treatment was 6 (from 5 to 8) days, including 0.7 (from 0 to 1) days in the intensive care unit. The use of opiate analgesics in the postoperative period was required in 4 (28.5%) patients. The average number of drains after laparoscopic surgery was 1.3 (from 0 to 2 emergency drains), the average time for removal of drains was 4.4 (from 3 to 5) days. The drainage volume was minimal.

With open access, the median postoperative bed days was 8 (range 5 to 11) days, including 2 days (range 1 to 5) in the intensive care unit. In almost all cases, with the exception of one patient, the use of narcotic analgesics was required to relieve pain symptoms (91%). The number of drainages was on average 1.6 (from 1 to 2), the average time till drainage removal was 4 (from 3 to 5) days. The drainage volume was from 20 to 180 ml per day. All patients successfully underwent ureteral reconstruction using bowel segment. Thirteen patients were undergone to inpatient follow-up examination. The remaining were interviewed by telephone. One patient died 4 years after surgery from pulmonary embolism. Another patient died 2 years later due to progression of the cancer.

In the long-term, stabilization (n=8; 61.5%), improvement (n=4; 30.8%) and deterioration (n=1; 7.7%) of renal function was found, characterized by stage of CKD and dynamic scintigraphy.

When assessing electrolyte disturbances, hypokalemic metabolic acidosis was noted in 3 (23%) patients. Hyperchloremic metabolic acidosis was detected in 2 (15.4%) cases. One (7.7%) patient after bilateral reconstruction was prescribed to take alkaline solutions due to decompensated hyperchloremic acidosis that developed postoperatively. Another patient (7.7%), treated 6 months ago, had hypokalemic hyperchloremic acidosis. The follow-up period for patients with electrolyte abnormalities after reconstructive surgery was no more than 24 months, with the exception of one patient treated in 2018 (38 months). This patient had low renal function at baseline (eGFR of 20 ml/min/1.73 m^2, CKD 4) due to diabetic nephropathy, and despite slight improvement of the functional state (GFR of 25 ml/min/1.73 m^2, CKD 4), it was not possible to correct renal deterioration.

In 1 (7.7%) patient, after reconstruction of the left ureter with implantation of the bowel segment into the ileal conduit (after Bricker procedure), decompensated metabolic alkalosis was found. In addition, this patient had an alkaline urine pH.

One patient, who suffered from type 2 diabetes mellitus and the initial CKD 4 (5.3%), was subsequently started hemodialysis therapy. It is not possible to determine the reason for the progression of CKD to a terminal state due to the comorbidities (stroke in the third year of hemodialysis). It is known that the progression to renal replacement therapy occured by the end of the first year after reconstruction.

During repeated hospitalization for the examination, patients who had undergone anastomosis between pelvis and ileal segment, complained of periodic discomfort in the lumbar region on the ipsilateral side.

Fig. 2. Voiding histogram

According to ultrasound, intravenous urography, and contrast-enhanced CT, no urodynamic abnormalities were identified, with the exception of one patient. He underwent retrograde radiography of the neoureter (*Fig. 3*) and antegrade fibropyeloscopy, during which the anastomotic stricture was diagnosed.

In the remaining patients, moderate dilatation of the renal pelvis persisted in the long-term period, and its size directly correlated with preoperative parameters.

During the follow-up CT, gallstones were detected for the first time in one patient, who was treated 9 months ago, which were not visualized on CT before treatment. According to the results of acid-base test, no metabolic disorders were revealed, however, the formation of stones in a short-time after reconstruction was associated with metabolic disorders, which requires further examination.

Discussion. A ureteral defect at any location can lead to hydronephrosis with subsequent loss of renal function. Currently, iatrogenic damage and radiation-induced strictures are becoming predominant [1–4]. In our study, the causes of strictures requiring intestinal reconstruction of the ureter in 96% of cases were post-radiation and iatrogenic. The etiological factors of long ureteral strictures, according to the literature, are presented in *Table 1.*

Oliver Engel et al. compared open, laparoscopic and robotic procedures using the Da Vinci surgical system. The authors pointed to comparable results in case of sufficient surgeon experience [14]. A.D. Kochkin et al. demonstrated the efficiency and safety of laparoscopic reconstruction in a cohort of 40 patients [15]. Robert J. Stein et al. demonstrated a significant advantage of laparoscopic substitution of the ureter with a decrease in the use of narcotic analgesics, and a tendency to reduce the length of stay [16]. Our study also revealed

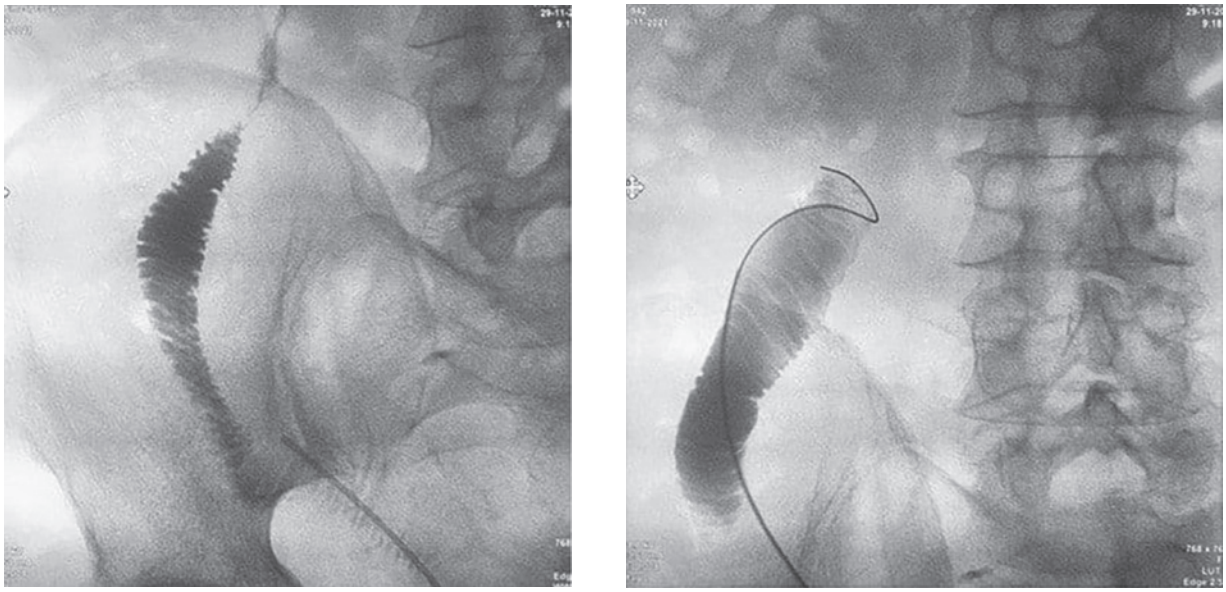

Fig. 3. Retrograde ureterography

a significant advantage in postoperative recovery in the laparoscopic group. There was a reduction in postoperative bed days from 8 to 6. The less traumatic procedure is also demonstrated by the number of drains (average 1.3 in the laparoscopy group, 1.6 in the group of the open approach), the minimum drainage volume and the timing of their removal.

The difficulty of reconstruction with an isolated intestinal segment, in addition to the technical aspects of the procedure itself, is associated with fibrotic process due to repeated previous interventions or radiation therapy [12]. In our work, the average number of procedures performed before reconstruction was 2.1 (1–8), including upper urinary tract drainage, endoscopic surgery for ureteral and renal stones, and previous failed reconstruction. The number of previous interventions correlates with the degree of ischemic, post-inflammatory and fibrotic changes in the retroperitoneum, which can negatively affect long-term results.

In one of the largest studies evaluating functional outcomes, Arkadius Kocot et al. provided long-term results of 157 reconstructive procedures using small bowel [5]. Improvement of renal function was observed in 84.6% of cases, stabilization in 10.3%, and deterioration in 5.1%. In our study, in patients, who were followed, stabilization of the CKD was noted in 75%, while improvement in 25% of cases. Imaging methods also confirm the preserved function of the renal parenchyma on the ipsilateral side. The results of other diagnostic methods are presented in *table 2*.

The results of ureteral reconstruction with intestinal segment directly depend on the experience of the surgeon, the hospital volume and careful selection of the patient. It is necessary to take into account factors that can influence the surgical outcomes. Patients with CKD 4 and higher should be treated with caution, taking into account the low compensatory capacity of the kidneys and preexisting renal dysfunction. A relative contraindication

Table 1

Etiological factors of long ureteral strictures

Authors	Patients (*n*)	Etiology (*n*)				
		Yat	RT	RF	Tumor	Other
Komyakov et al. [1]	165	91	42	10	–	22
Kosot et al. [5]	157	–	43	–	–	114
Roth et al. [4]	108	24	84	–	–	–
Monn et al. [6]	104	-	23	–	–	81
Sandra A. et al. [7]	91	43	17	11	5	15
Benjamin I. et al. [8]	56	23	2	7	2	22
Xu et al. [9]	41	18	–	17	3	3
Kim et al. [10]	31	26	–	–	2	3
Kotov et al. [own data]	25	20	4	1	–	-
Zong et al. [11]	23	15	2	–	1	5
Wolff et al. [12]	17	7	1	1	2	6
Pamecha et al. [13]	14	6	5	–	–	3

Note. Yat, iatrogenic trauma, RT, radiation therapy, RF, retroperitoneal fibrosis.

Table 2

Renal function after ureteral substitution by the small bowel (according to literature)

Authors and year of publication	Number of patients	Follow-up period (months)	Renal function		
			Improvement (%)	Stabilization (%)	Detirioration (%)
Arcadius Kocot et al. (2017) [5]	157	54.1 (1-219)	84.6	10.3	5.1
Roth et al. (2017) [4]	108	51 (22-112)	32.3	52.8	14.9
Monn et al. (2018) [6]	104	47 (26-105)	–	98.1	1.9
Sandra A. et al. (2009) [7]	91	46.8 (2-88)	–	74.7	25.3
Xu et al. (2016) [9]	41	(34-51)	22	78	–
Kim et al. (2018) [10]	31	23.6 (6.5-43.2)	16.1	77.4	6.5
Kotov et al. (2022) [own data]	25	51.3 (6-109)	30.8	61.5	7.7
Zong et al. (2019) [11]	23	45	–	95.7	4.3
Pamecha et al. (2018) [13]	14	12	–	100	–
Gomez-Gomez et al. (2016) [17]	9	17 (1-40)	–	88.9	11.1
Takeuchi et al. (2014) [18]	8	60 (42-73)	–	87.5	12.5
Ou et al. (2018) [19]	8	109	37.5	37.5	25
Zong et al. (2017) [20]	3	(13-24)	–	100	–

to intestinal reconstruction was concomitant urination disorders, which contributed to an increase in intravesical pressure and, consequently, the development of reflux, which can lead to worsening metabolic disorders and infectious complications.

The likelihood of metabolic changes after ileal reconstruction is closely related to baseline renal function [5]. In properly selected patients, the risk of developing long-term hyperchloremic metabolic acidosis is low. According to D. Joshua et al., it was 1.8% in a cohort of 108 patients [4]. The prevalence of hyperchloremic metabolic acidosis is significantly higher in patients with GFR 4. A number of studies have emphasized that preoperative assessment of renal function is a decisive prognostic factor in ureteral substitution [11]. Chung demonstrated that 50% of patients with serum creatinine less than 2.0 mg/dL experienced progression of renal dysfunction after bowel reconstruction [21]. Wolff et al. demonstrated a 90% efficiency of ureteral reconstruction in patients with preoperative creatinine levels above 1.7 mg/dL [12].

In our study, two patients had a creatine level of 0.22–0.28 mg/dL at baseline, which corresponds to CKD 4. One patient progressed to hemodialysis therapy, while the second had a slight improvement in renal function without changing the stage of CKD. In addition, he had hyperchloremic metabolic acidosis. In the remaining patients with an initial creatinine level above 1.48 mg/dL, there was a tendency toward correction of electrolyte disturbances in the postoperative period.

The surface area of the intestinal segment used, the concentration of solutes in urine, renal function, urine pH, and the duration of mucosal contact with urine are factors that determine the various metabolic disorders after ileal reconstruction. To minimize the length of the iliac graft, Wenlong Zhong et al. provided clinical examples of using ileal segment in combination with Boari repair and the psoas-hitch technique for the reconstruction of a panureteral stricture [22]. Y. Pamecha et al. proposed reducing the absorbed surface area by narrowing the intestinal lumen to 12 Ch [13]. There are also a lot of publications demonstrating satisfactory results of reconstructive procedures in long strictures by reconfiguring the intestinal graft using the Yang-Monti technique [23–25].

Based on the literature and our own research, it may be necessary to offer patients with CKD 4 alternative options for reconstruction in order to reduce the length of the bowel segment, and, consequently, the area of intestinal mucosa capable of absorbing urine, which potentially allows to decrease the risk of metabolic disorders.

Conclusion. The use of the ileal segment for ureteral substitution with careful selection of patients provides satisfactory long-term outcomes. In our opinion, the use of laparoscopic access provides an advantage in postoperative recovery without compromising functional results and can be considered the gold standard for the reconstruction of long ureteral strictures.

ЛИТЕРАТУРА/REFERENCES

1. *Komyakov B.K., Al-Attar T.H., Guliyev B.G.* Intestinal and appendicular reconstruction of the ureters. Urologiia. 2021;2:14–20. Russian (Комяков Б.К., Ал-Аттар Т.Х., Гулиев Б.Г.. Кишечная и аппендикулярная реконструкция мочеточников. Урология. 2021;2:14–20).
2. *Loran O.B., Sinyakova L.A., Seregin A.V. and others.* The use of isolated intestinal segments in the surgical treatment of radiation injuries of the urinary tract. Urologiia. 2012;2:20–24. Russian (Лоран О.Б., Синякова Л.А., Серегин А.В. и др. Использование изолированных сегментов кишечника в оперативном лечении лучевых повреждений мочевыводящих путей. Урология. 2012;2:20–24).
3. *Shengwei Xiong, Weijie Zhu, Xinfei Li, Peng Zhang, He Wang and Xuesong Li.* Intestinal interposition for complex ureteral reconstruction: A comprehensive review. International Journal of Urology 2020; 27(5):377–386. Doi: 10.1111/iju.14222.
4. *Joshua D. Roth, M. Francesca Monn, Konrad M. Szymanski, Richard J. Bihrle, Matthew J. Mellon.* Ureteral Reconstruction with Ileum: Long Term Follow-Up of Renal Function. Urology 2017104:225–229. Doi: 10.1016/j.urology.2017.02.026.
5. *Arkadius Kocot, Charis Kalogirou, Daniel Vergho and Hubertus Riedmiller.* Long-term results of ileal ureteric replacement: a 25-year single-centre experience. BJU Int 2017; 120(2):273–279. Doi: 10.1111/bju.13825.
6. *Monn M.F., Roth J.D., Bihrle R., Mellon M.J.* Long term outcomes in the use of ileal ureter for radiation-induced ureteral strictures. Int. Urol. Nephrol. 2018; 50(8):1375–1380. Doi: 10.1007/s11255-018-1904-z.
7. *Sandra A. Armatys, Matthew J. Mellon, Stephen D.W. Beck, Michael O. Koch, Richard S.* Foster and Richard Bihrle. Use of Ileum as

Ureter Replacement in Urological Reconstruction. The journal of Urology. 2009; 181(1):177–181. Doi: 10.1016/j.juro.2008.09.019.
8. *Benjamin I. Chung, Karim J. Hamawy, Leonard N. Zinman and John A.* Libertino. The Use of Bowel for Ureteral Replactmtnt for Complex Ureteral Reconstruction: Long-Term Results. The journal of Urology. 2006; 175(1):179–183; discussion 183-4. Doi: 10.1016/S0022-5347(05)00061-3.
9. *Xu Y.-M., Feng C., Kato H., Xie H., Zhang X.-R.* Long-term outcome of ileal ureteric replacement with an iliopsoas muscle tunnel antirefluxing technique for the treatment of long-segment ureteric strictures. Urology. 2016; 88:201–206. Doi: 10.1016/j.urology.2015.11.005.
10. *Aram Kim, Wook Nam, Sang Hoon Song, In Gab Jeong, Bumsik Hong.* Use of the Ileum for Ureteral Stricture and Obstruction in Bilateral, Unilateral, and Single-Kidney Cases. Urology. 2018; 111:203–207. Doi: 10.1016/j.urology.2017.08.008.
11. *Wenlong Zhong, Peng Hong, Guangpu Ding, Kunlin Yang, Xuesong Li, Junsheng Bao, Guochang Bao, Liang Cui, Changping Men, Zhe Li, Peng Zhang, Ning Chu and Liqun Zhou.* Technical considerations and outcomes for ileal ureter replacement: a retrospective study in China. BMC Surgery. 2019; 18;19(1):9. Doi: 10.1186/s12893-019-0472-1.
12. *Wolff B., Chartier-Kastler E., Mozer P., et al.* Long-term functional outcomes after ileal ureter substitution: a single-center experience. Urology. 2011; 78(3):692–695. Doi: 10.1016/j.urology.2011.04.054.
13. *Pamecha Y., Shelke U., Patil B, Patwardhan S, Kini S.* Use of ileum for complex ureteric reconstruction: assessment of long-term outcome, complications, and impact on renal function. Urol. Ann. 2018; 10(4):369–374. Doi: 10.4103/UA.UA_5_18.
14. *Oliver Engel, Michael Rink, and Margit Fisch.* Management of iatrogenic ureteral injury and techniques for ureteral reconstruction. 2015; 25(4):331–335. Doi: 10.1097/MOU.0000000000000175.
15. *Kochkin A.D., Gallyamov E.A., Popov S.V., Biktimirov R.G., Sanzharov A.E., Sergeev V.P., Sevryukov F.A., Orlov I.N., Novikov A.B.* Laparoscopic replacement intestinal ureteral plastic surgery. Results of the first 40 operations. Urology. 2018;5:5–12. Russian (Кочкин А.Д., Галлямов Э.А., Попов С.В., Биктимиров Р.Г., Санжаров А.Е., Сергеев В.П., Севрюков Ф.А., Орлов И.Н., Новиков А.Б. Лапароскопическая заместительная кишечная пластика мочеточников. Результаты первых 40 операций. Урология. 2018;5:5–12).
16. *Robert J. Stein, Burak Turna, Neil S. Patel, Christopher J. Weight, Mike M.* Nguyen, Gaurang Shah, Monish Aron, Amr F. Fergany, Inderbir S. Gill and Mihir M. Desai. Laparoscopic Assisted Ileal Ureter: Technique, Outcomes and Comparison to the Open Procedure. J Urol. 2009 Sep;182(3):1032–1039. Doi: 10.1016/j.juro.2009.05.013.
17. *Gomez-Gomez E., Malde S., Spilotros M., Shah P.J., Greenwell J., Ockrim J.L.* A tertiary experience of ileal-ureter substitution: Contemporary indications and outcomes. Scand. J. Urol. 2016; 50(3):192–199. Doi: 10.3109/21681805.2015.1106579. E
18. *Takeuchi M., Masumori N., Tsukamoto T.* Ureteral reconstruction with bowel segments: experience with eight patients in a single institute. Korean J. Urol. 2014;55(11):742–749. Doi: 10.4111/kju.2014.55.11.742.
19. *Ou Y.-C., Hu C.-Y., Cheng H.-L., Yang W.-H.* Long-term outcomes of total ureterectomy with ileal-ureteral substitution treatment for ureteral cancer: a single-center experience. BMC Urol. 2018; 18(1):73. Doi: 10.1186/s12894-018-0389-5.
20. *Zhong W., Du Y., Yang K .et al.* Ileal ureter replacement combined with boari flap-psoas hitch to treat full-length ureteral defects: technique and initial experience. Urology. 2017; 108:201–206. Doi: 10.1016/j.urology.2017.07.014.
21. *Chung B.I., Hamawy K.J., Zinman L.N., Libertino J.A.* The use of bowel for ureteral replacement for complex ureteral reconstruction: long-term results. J Urol. 2006; 175(1):179–183; discussion 183–184. Doi: 10.1016/S0022-5347(05)00061-3.
22. *Wenlong Zhong, Yicong Du, Kunlin Yang, Steven Meng , Rongcheng Lin, Xuesong Li, Liyan Zhuang , Lin Cai, Haoran Cui, Zhisong He, Liqun Zhou.* Ileal Ureter Replacement Combined With Boari Flap-Psoas Hitch to Treat Full-Length Ureteral Defects: Technique and Initial Experience Urology. 2017; 108:201–206. Doi: 10.1016/j.urology.2017.07.014.
23. *Steffens J.A., Anheuser P., Reisch B., Treiyer A.E.* Harnleiter rekonstruktion mit rekonfigurierten Ileumsegmenten nach Yang-Monti. Urologe A 2010;49(2):262–267. Doi: 10.1007/s00120-009-2177-z.
24. *Thomas Maigaard.* Hans Joergen Kirkeby. Yang–Monti ileal ureter reconstruction. Scand J Urol. 2015;49(4):313–318. Doi: 10.3109/21681805.2014.882980.
25. *Jun Sheng Bao, Qiqi He, Yuzhuo Li, Wei Shi, Gongjin Wu, Zhongjin Yue.* Yang-Monti Principle in Bridging Long Ureteral Defects: Cases Report and A Systemic Review. Urol J. 2017 Jul 2;14(4):4055–4061.

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CARBOXYCRYOBIOPSY AND CARBOXYCRYOEXTRACTION OF BLADDER TUMOR. EXPERIMENTAL STUDY

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Aim. To evaluate the possibility of performing transurethral carboxycryobiopsy (CCB) and carboxycryoextraction (CCE) of a bladder tumor for pathomorphological examination, as well as to perform a comparative analysis of the safety (quality) of biopsy material (tumor tissue) during standard transurethral biopsy and carboxycryobiopsy.

Materials and methods. In the first experiment in vitro, CCE of bladder tumor fragments obtained after transurethral resection was performed. In the second pilot study, cystoscopy followed by CCB and CCE in a patient with multiple bladder tumors was done. The procedure was performed by transurethral access. During cryopreservation of the bladder tumor, a biopsy was performed. After freezing, the tumor was removed from the bladder and sent for histological examination.

Results. The first experiment showed that cryoextraction of the fragments of a bladder tumor using carbon dioxide (CCE) in vitro is a feasible procedure and allows the evacuation of tumor tissues of various sizes. According to the second experiment, CCB and CCE of the bladder tumor using carbon dioxide allows to obtain a biopsy of a bladder tumor of sufficient size without compression or coagulation artifacts, which contributes to a more accurate histological evaluation.

Conclusion. Our experiments showed that CCB and CCE of a bladder tumor using carbon dioxide are feasible procedures that contribute to obtaining better biopsy material for pathomorphological examination, and also allows to evaluate the effect of low temperatures of carbon dioxide on the biopsy material (tumor tissue).

K e y w o r d s: *carboxy cryobiopsy, carboxy cryoextraction, carbon dioxide, bladder tumor, TUR biopsy*

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Introduction. The use of modern medical equipment in clinical practice not only increases the efficiency of existing treatment methods, but also contributes to the emergence and rapid development of new, more effective diagnostic and treatment tools. One of the new trends in the field of surgical treatment is the effect of low temperatures on biological tissues (cryotherapy and cryosurgery). Technological progress has led to the creation of several types of cryodevices that use the effect of gas throttling. Liquid nitrogen, carbon dioxide, nitrous oxide, helium or argon are most common gases, which allows to obtain low temperature. In modern urological practice, cryoablation is performed for kidney and prostate cancer using argon and helium as a coolant. For this purpose, cryogenic installations of the third and fourth generations are used [1–3]. The effect of these gases on kidney and prostate tissue has also been studied in detail [4–6]. In foreign literature, there is data on the performance of cryobiopsy and cryoablation based on carbon dioxide in coloproctology, thoracic surgery and gastroenterology [7–10]. However, the possibility of using carbon dioxide as a refrigerant in urological practice and its effect on bladder tissue remain unexplored.

Aim. To assess the possibility of performing transurethral carboxycryobiopsy and carboxycryoextraction of a bladder tumor for pathomorphological examination, as well as to carry out a comparative analysis of quality of biopsy material (bladder tumor) during classical transurethral electroresection and carboxycryobiopsy.

Materials and methods. At the Institute of Urology and Human Reproductive Health of the Clinical Center of Sechenov University the experimental study was carried out. Carboxycryobiopsy and carboxycryoextraction of a bladder tumor was performed using a flexible cryoprobe Erbecryo-2 ErbeElectromedizin (Germany), which was designed and registered for use in thoracic surgery for cryoextraction (tumor, tissue biopsy, removal of foreign bodies, blood clots and mucus plugs), cryorecanalization, as well as for cryodevitalization [11–13].

For performing carboxycryobiopsy and carboxycryoextraction of a bladder tumor, a flexible Erbecryo-2 cryoprobe with a diameter of 2.4 mm and a length of 1.15 m was used. The freezing effect of Erberyo-2 is based on the Joule–Thomson effect. The Joule-Thomson effect consists of a change in gas temperature as a result of its slow flow under the influence of a constant pressure drop through a throttle, which is a local obstacle to the gas flow, for example through a porous partition. The physical freezing point of carbon dioxide is minus 78.5°C [14].

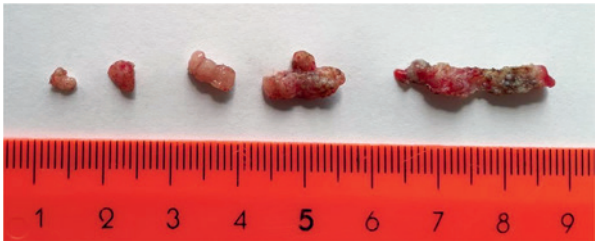


Fig. 1. Tumor fragments after transurethral resection

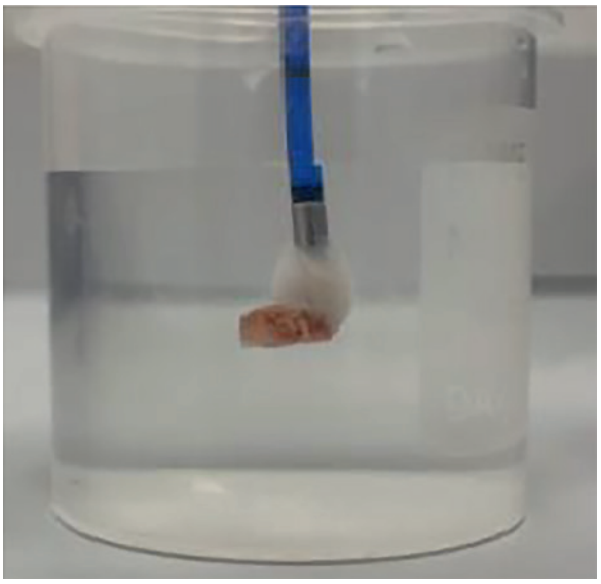
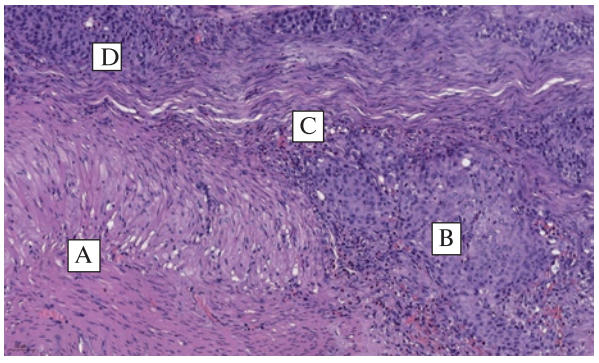


Fig. 2. A fixation of tissue fragment to the tip of the probe



A – muscle layer of the bladder with scant lymphoid infiltration and thin-walled vessels.
B – invasion of urothelial cancer G3 (high-grade) into muscle layer.
C – abundant infiltration of lymphocytes, macrophages and plasma cells along the periphery of the area of tumor invasion.
D – tumor invasion into superficial muscle bundles.

Fig. 3. Microphotograph of a bladder tumor. Hematoxylin and eosin staining, image length of 50 µm

High-pressure carbon dioxide is supplied from a gas cylinder to the cryoprobe through a cryosurgical unit.

The cryoalbation device allows to regulate the flow of carbon dioxide and freezing time. Passing through the narrow tube, carbon dioxide enters the hollow tip of the probe. At the moment of passing from the narrow part of the cryoprobe tube to the wide part of the tip, carbon dioxide undergoes rapid decompression due to the large pressure difference. At that moment, due to the Joule–Thomson effect, the gas very quickly cools the tip of the probe. Depending on the CO2 pressure in the system and the size of the probe at the tip of the flexible cryoprobe, it is possible to create a temperature from minus 35°C to minus 50°C.

At the first stage, fragments of a bladder tumor obtained during transurethral resection of the bladder tumor were used in order to evaluate the possibility of performing carboxycryoextraction in the experiment.

Clinical observation No. 1. In patient V., 65 years old, a bladder lesion measuring 45x24 mm, located the right lateral wall, was detected on ultrasound examination and magnetic resonance imaging. In order to verify the diagnosis and remove a bladder tumor, the patient underwent transurethral resection.

An in vitro experimental study was carried to evaluate the feasibility of cryoextraction at low carbon dioxide temperatures.

After completing the surgical procedure, fragments of bladder tumor tissue of various sizes were obtained. Carboxycryoextraction was performed using 5 fragments of bladder tumor from 4 mm to 23 mm (*Fig. 1*). After placing the tissue fragments in a container with a normal saline at room temperature, the tip of the cryoprobe was advanced, followed by cryofreezing. The cryofreezing time was 5–7 s. During the process, a tissue fragment was fixed to the tip of the cryoprobe with subsequent extraction (*Fig. 2*).

As a result of the experiment, cryoextraction of all five tissue fragments was performed. It has been demonstrated that carbon dioxide can be effectively used as a coolant for cryoextraction.

According to the pathomorphological study, all fragments of the bladder tumor had coagulation artifact (due to loop resection), tumor cells with pronounced signs of atypia and nuclear polymorphism in some areas were clearly visible, as well as peritumoral inflammatory infiltration. The basement membrane was not visible due to infiltrating tumor growth (*Fig. 3*).

Clinical observation No. 2. Patient B., 57 years old. According to the ultrasound and magnetic resonance imaging, three bladder tumors were identified. The first lesion measuring 19x14 mm was located along the posterior wall, the second of size 12x12 mm along the right lateral wall, and third of size 12x8 mm along the left lateral wall without signs of invasion into the muscular layer. For the purpose of morphological verification, removal of bladder tumors, as well as preventing the progression, the patient was undergone to transurethral procedure. A prerequisite for the experimental study was the presence of informed consent from the patient.

Under epidural anesthesia, the cystoscope was passed through the urethra to the bladder. A Karl Storz 25 Ch cystoscope with a working channel with a diameter of 4 mm (12 Ch) was used. Cystoscopy revealed three soft villous lesions with narrow base along the right, left and posterior walls of the bladder. Next, a flexible cryoprobe with a diameter of 2.4 mm was passed through the working channel of the cystoscope. A carboxycryobiopsy of

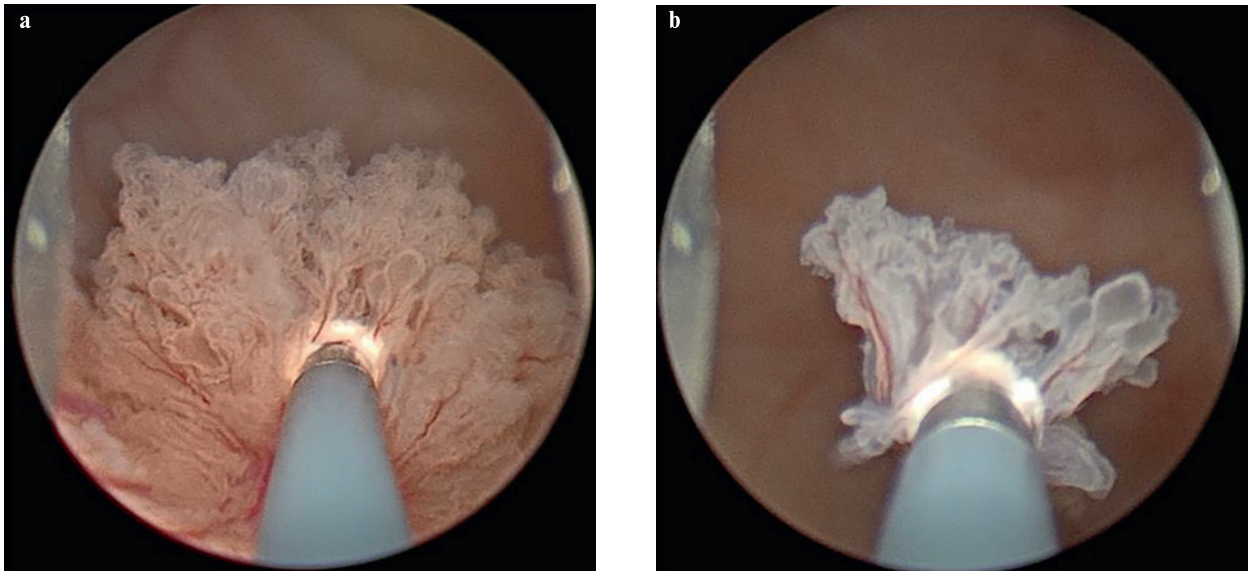


Fig. 4. Endoscopic carboxycryobiopsy of a bladder tumor (a –cryobiopsy of a bladder tumor, b – fragment of a bladder tumor fixed on the tip of a cryoprobe)

the tumor along the right lateral wall was performed. The cryoprobe was advanced and the tumor was frozen for the purpose of biopsy. The time for direct cryo-freezing and fixation of the tumor fragment to the tip of the probe was 15 s. To avoid defixation (loss) of the biopsy specimen when it was removed along the instrument tube, cryofreezing continued until the flexible cryoprobe along with the biopsy specimen was completely extracted out of the body.

Technique for carboxycryobiopsy of the bladder tumor. After advancing the cryoprobe tip to the tumor located along the left lateral wall (close contact of the cryoprobe tip with the tumor tissue was required), cryofreezing was performed with an exposure time of 15 s (*fig. 4a*), after which the tumor was tractioned (as with a pinch biopsy) until a fragment was fixed to the tip of the probe (*fig. 4b*).

Next, cryobiopsy with traction of a large fragment of the tumor in the same patient to assess the possibility of carboxycryoextraction was performed (*Fig. 5*).

For comparative analysis, the fragment of the tumor located along the posterior wall was removed using a bipolar loop (*Fig. 6*). After obtaining a biopsy, the patient underwent classical bipolar transurethral resection of the tumor, followed by hemostasis. Upon completion of the experiment, the specimen was sent for pathomorphological study (*fig. 7*)

Results. According to the pathomorphological study, in the specimens after carboxycryobiopsy and carboxycryoextraction (*Fig. 8. 9*), papillary structure of tumor tissue with signs of mild nuclear polymorphism was clearly visible. There were no signs of coagulation of the epithelial and stromal components. The epithelium was partially desquamated due to the soft consistency and villous structure of the tumor itself. A predominantly preserved surface layer of cells was seen. The stroma of the tumor papillae was loose, edematous, with multiple thin-walled vessels and mild lymphoid infiltration. A basement membrane was preserved and had a clear border. The submucosa had thin-walled vessels with lymphoid and macrophagic infiltration. In high-power filed after carboxycryoextraction, the composition of the cellular infiltrate was possible to assess. In addition, cellular elements such as erythrocytes and leukocytes were clearly visible in the blood vessels.

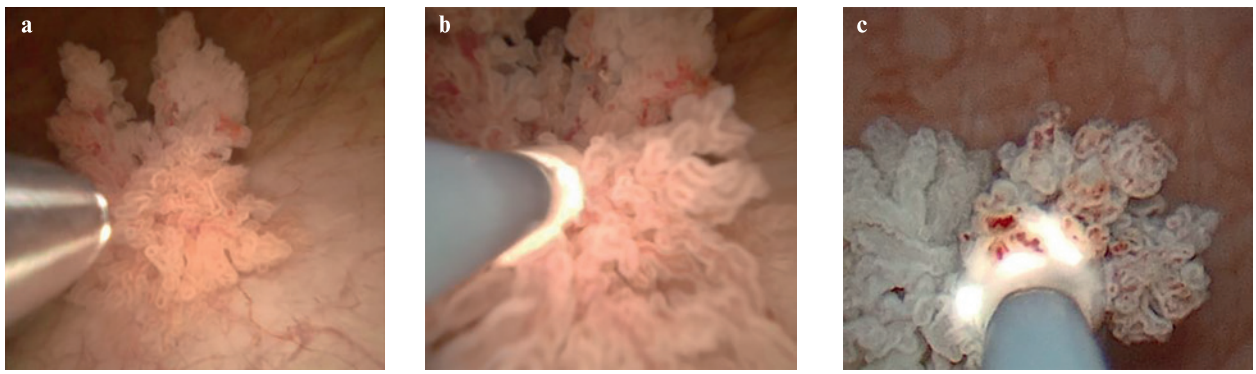


Fig. 5. Endoscopic carboxycryoextraction of a bladder tumor (a – the cryoprobe is advanced to the bladder tumor, b – carboxycryoextraction of the bladder tumor, c – fragment of the bladder tumor fixed on the tip of the cryoprobe)

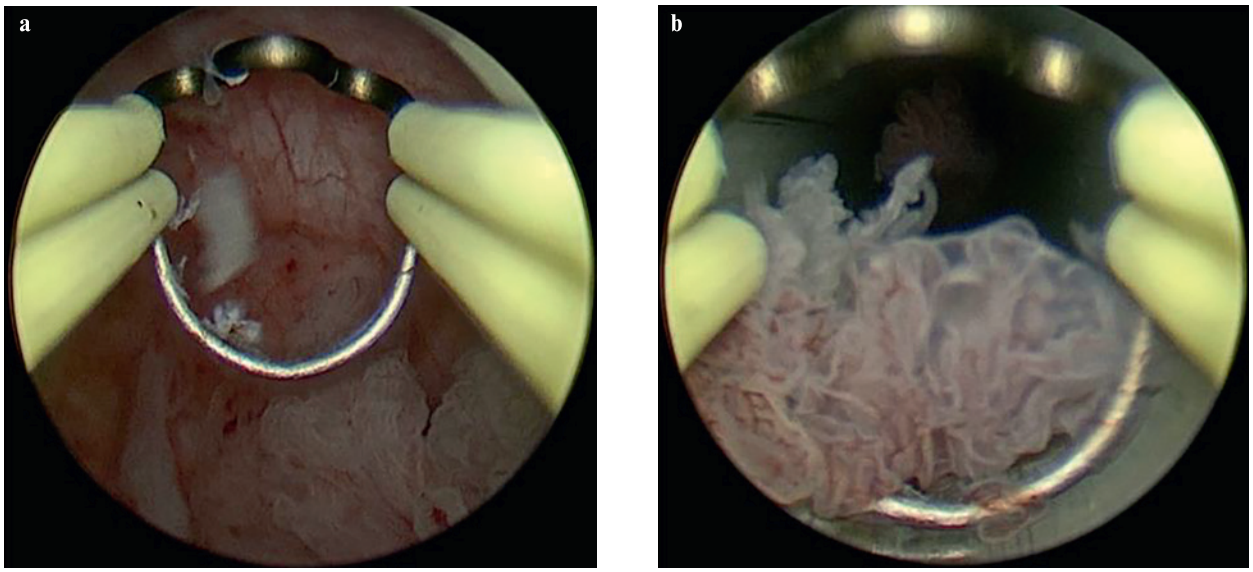


Fig. 6. Endoscopic image of the TUR biopsy of the bladder tumor (a – the loop is advanced to the bladder tumor, b – biopsy of the bladder tumor)

In the specimen obtained by transurethral resection (*Fig. 10*), papillary tumor structures with a partially desquamated surface layer of the urothelium and signs of coagulation were determined. The submucosa had signs of fibrosis and pronounced phenomena of tissue coagulation along the periphery. The tumor papillae were close to each other, with separate hemorrhages and vessels in-between. Compression artifacts were also noted.

Discussion. Transurethral resection is still the gold standard and the most commonly used method in the diagnosis and treatment of non-muscle-invasive bladder cancer [15]. However, this procedure has significant disadvantages, namely intra- and postoperative complications, such as activation of obturator reflex, which can lead to uncontrolled bladder perforation [16]. In addition, the disadvantages include the impact on the quality of the biopsy material, which manifests in cautery and thermal effects, the presence of artifacts from compression and destruction of tumor tissue. These artifacts can significantly complicate the assessment of tumor cells grade due to their necrosis and to preclude a reliable pathomorphological examination and verification of the diagnosis

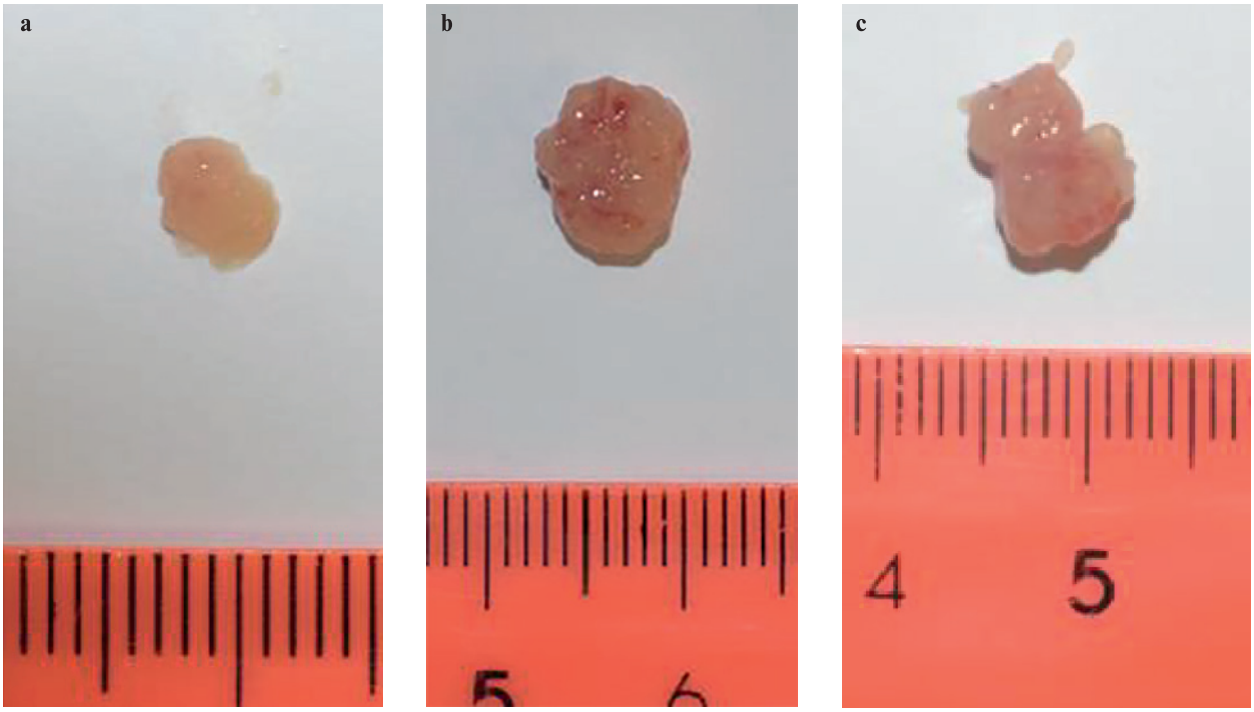
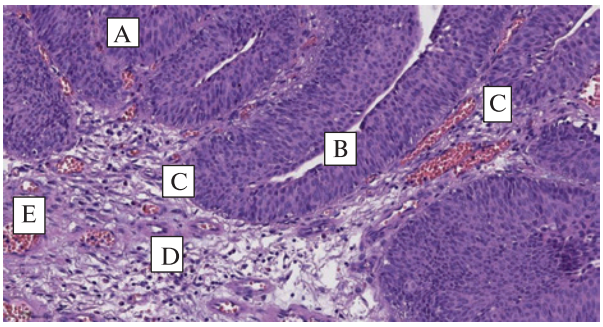
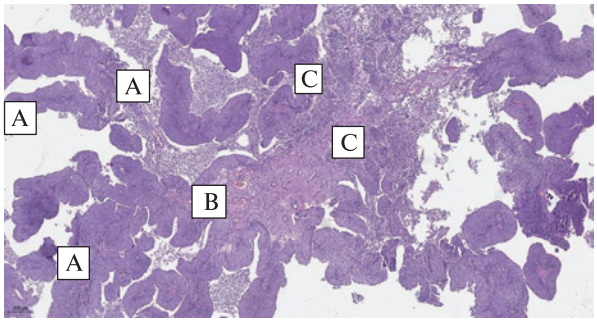


Fig.7. Fragments of a bladder tumor (a – along the right bladder wall (carboxycryobiopsy), b – along the left bladder wall (carboxycryoextraction), c – along the posterior bladder wall (resection biopsy))



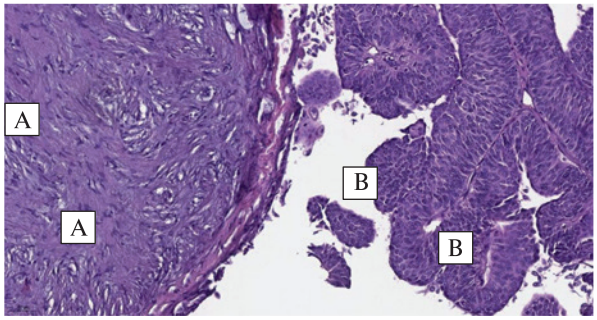
A – papillary tumor structures; B – unaffected urothelium; C – layer of basal cells that form the basement membrane of the urothelium; D – submucosal layer with edema and lymphoplasmacytic infiltration; E – thin-walled vessels; F – leukocytes into the blood vessels.

Fig. 8. Microphotograph of a bladder tumor (carboxycryobiopsy). Hematoxylin and eosin staining, image length of 50 μm



A – papillary tumor structures;
B – intact submucosa with vessels;
C – tumor structures are partially desquamated due to density

Fig. 9. Microphotograph of a bladder tumor (carboxycryoextraction). Hematoxylin and eosin staining, image length of 200 μm



A – submucosal layer with area of fibrosis;
B – pronounced coagulation artifact along the periphery;
C – papillary tumor structures with coagulation artifact;
D – tumor structures are desquamated..

Fig. 10. Microphotograph of a bladder tumor (TUR biopsy). Hematoxylin and eosin staining, image length of 50 μm

[17]. All these factors have led to the search for new, more effective and gentle methods for obtaining and removing biopsy material from bladder tumors. Our study showed that the use of carboxycryobiopsy and carboxycryoextraction of the tumor does not lead to its destruction and allows for a full histological examination and diagnosis.

Conclusions. There was no experience in the world with the use of carboxycryobiopsy and carboxycryoextraction of a bladder tumor using the Erbecryo-2 at the time of this experiment. In our study, we performed carboxycryobiopsy and carboxycryoextraction of a bladder tumor for the first time, and believe that researches aiming to creation a domestic cryosystem based on carbon dioxide has clinical prospects.

Carboxycryobiopsy and carboxycryoextraction allows to obtain and extract a bladder tumor without signs of tissue coagulation and compression artifacts, as in the case of transurethral resection. In addition, with carboxycryobiopsy, there is no obturator syndrome, and removal of tumor tissue from the bladder (carboxycryoextraction) allows for better preservation of the biopsy material for pathomorphological study and verification of a diagnosis. Our experiments showed that cryobiopsy and carbon dioxide-based cryoextraction were feasible procedures and allowed us to evaluate the effect of low temperatures of carbon dioxide on bladder tissue.

ЛИТЕРАТУРА/REFERENCES

1. *Exterkate L., Peters M., Somford D.M., Vergunst H.* Functional and oncological outcomes of salvage cryosurgery for radiorecurrent prostate cancer. BJU Int. 2021;128(1):46–56. Doi: 10.1111/BJU.15269.
2. *Sanda M.G. et al.* Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline. Part II: Recommended Approaches and Details of Specific Care Options. J. Urol. 2018;199(4):990–997. Doi: 10.1016/J.JURO.2018.01.002.
3. *Campbell S, et al.* Renal Mass and Localized Renal Cancer: AUA Guideline. J Urol. 2017;198(3):520–529. Doi: 10.1016/J.JURO.2017.04.100.
4. *Falconieri G., Lugnani F., Zanconati F., Signoretto D., Di Bonito L.* Histopathology of the frozen prostate. The microscopic bases of prostatic carcinoma cryoablation. Pathol. Res. Pract. 1996;192(6):579–587. Doi: 10.1016/S0344-0338(96)80109-9.
5. *Chin J.L. et al.* Serial histopathology results of salvage cryoablation for prostate cancer after radiation failure. J. Urol. 2003;170(4 Pt 1):1199–1202. Doi: 10.1097/01.JU.0000085620.28141.40.
6. *Tayal S., Kim F.J., Sehrt D., Miano R., Pompeo A., Molina W.* Histopathologic findings of small renal tumor biopsies performed immediately after cryoablation therapy: a retrospective study of 50 cases. Am. J. Clin. Pathol. 2014;141(1):35–42. Doi: 10.1309/AJCP6Y3FHDLMILKT.
7. *Xue H.B.et al.* A pilot study of endoscopic spray cryotherapy by pressurized carbon dioxide gas for Barrett's esophagus. Endoscopy. 2011;43(5):379–385. Doi: 10.1055/S-0030-1256334.
8. *Pittrof R., Majid S., Murray A.* Transcervical endometrial cryoablation (ECA) for menorrhagia. Int. J. Gynaecol. Obstet. 1994;47(2):135–140. Doi: 10.1016/0020-7292(94)90353-0.
9. *Lewis J.R., Itzkowitz S., Zhu H., Ward S.C., Anandasabapathy S.* Sequential downgrading of dysplasia in ulcerative colitis using carbon dioxide-based cryotherapy. Endoscopy. 2012;44(Suppl 2). Doi: 10.1055/S-0032-1306788.
10. *Chou C.L. et al.* Role of flexible bronchoscopic cryotechnology in diagnosing endobronchial masses. Ann. Thorac. Surg. 2013;95(3):982–986. Doi: 10.1016/j.athoracsur.2012.11.044.
11. *Schumann C.et al.* Endobronchial tumor debulking with a flexible cryoprobe for immediate treatment of malignant stenosis. J. Thorac. Cardiovasc. Surg. 2010;139(4):997–1000. Doi: 10.1016/J.JTCVS.2009.06.023.

12. *Hetzel J.et al.* Cryobiopsy increases the diagnostic yield of endobronchial biopsy: a multicentre trial. Eur. Respir. J. 2012;39(3):685–690. Doi: 10.1183/09031936.00033011.
13. *Fruchter O., Kramer M.R.* Retrieval of various aspirated foreign bodies by flexible cryoprobe: in vitro feasibility study. Clin. Respir. J. 2015;9(2):176–179. Doi: 10.1111/CRJ.12120.
14. *Lentz R.J. et al.* Transbronchial cryobiopsy for diffuse parenchymal lung disease: a state-of-the-art review of procedural techniques, current evidence, and future challenges. J. Thorac. Dis. 2017;9(7):2186–2203. Doi: 10.21037/JTD.2017.06.96.
15. *Pastuszak A., Zdrojowy R., Poletajew S., Adamowicz J., Krajewski W.* Technical developments in transurethral resection of bladder tumours. Contemp. Oncol. (Poznan, Poland). 2019;23(4):195–201. Doi: 10.5114/WO.2019.91530.
16. *Bolat D., Gunlusoy B., Aydogdu O., Aydin M.E., Dincel C.* Comparing the short - term outcomes and complications of monopolar and bipolar transurethral resection of bladder tumors in patients with coronary artery disese: A prospective, randomized, controlled study. Int. Braz J Urol. 2018;44(4):717–725. Doi: 10.1590/S1677-5538.IBJU.2017.0309.
17. *Herrmann T.R.W., Wolters M., Kramer M.W.* Transurethral en bloc resection of nonmuscle invasive bladder cancer: trend or hype. Curr. Opin. Urol. 2017;27(2):182–190. Doi: 10.1097/MOU.0000000000000377.

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THE COMPARATIVE ANALYSIS OF SURGICAL PROCEDURES A IN PATIENTS WITH BENIGN PROSTATIC HYPERPLASIA AND TYPE 2 DIABETES MELLITUS

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Aim. To compare the efficiency of two surgical methods, holmium laser enucleation of prostate (HoLEP) and laparoscopic retropubic simple prostatectomy with clamping of internal iliac arteries and vesicourethral anastomosis [LPA+CIIA+VUA]) for treating of patients with benign prostatic hyperplasia (BPH) and type 2 diabetes mellitus (T2DM).
Materials and methods. A total of 56 men with T2DM who underwent surgical treatment of BPH in the National Research Centre for Endocrinology of the Russian Ministry of Health (director – corresponding member of RAS Mokrysheva N.G..) in a period from 2021 until 2022 were included in the study. Patients with T2DM received two types of antidiabetic drugs: basal-bolus insulin therapy and metformin (1000 mg/day per os). Patients were divided into the group of LPA+CIIA+VUA (n=28) and HoLEP (n=28). Preoperative, intraoperative and postoperative examinations with an evaluation of intraoperative and early postoperative complications (I, II, III, IV grades according to the Clavien-Dindo scale) were performed. After 1 year of follow-up, International Prostatic Symptom Score (IPSS), "Quality of Life" score (QoL), International Index of Erectile Function-5 score (IIEF-5), maximal urine flow rate (Qmax), and postvoid residual volume (ml) were assessed. Efficiency of surgical procedures was estimated according to "trifecta": absence of postoperative complications, urine continence, maximal urine flow (Qmax) >15 ml/sec.
Results. In the group of HoLEP, shorter postoperative bladder catheterization time but higher risk of urinary incontinence, bladder neck contracture and urethral strictures was found. LPA+CIIA+UVA leaded to a two-fold decrease in intraoperative hemoglobin loss with no necessity of repeat procedures.
Conclusions. Our preliminary results demonstrated higher efficacy of LPA+CIIA+VUA for treatment of BPH in patients with T2DM than HoLEP. Patients who underwent LPA+CIIA+VUA were more often achieved the "trifecta". In order to implement LPA+CIIA+VUA into clinical practice, multi-center, large-scale, double-blind, placebo-controlled ("scar-surgery") randomized studies are required.

K e y w o r d s: *benign prostatic hyperplasia, comparative analysis, urology, surgery, diabetes mellitus*

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Introduction. Benign prostatic hyperplasia (BPH) is a histological diagnosis associated with proliferation of smooth muscle and epithelial cells in the transition zone of the prostate [1]. The histological prevalence of BPH increases at age 40 years, reaching 60% at 60 years and 80% at 80 years [2]. BPH is characterized by an increase in prostate volume, which can ultimately cause bladder outlet obstruction. During this age period the prevalence of type 2 diabetes mellitus (T2DM) also increases. According to the registry of patients in the Russian Federation, the proportion of men over 65 years with T2DM (as of January 1, 2021) was 60.5% (2,681,908 people) of all patients with diabetes [3]. Hyperinsulinemia and insulin resistance observed in T2DM can be a trigger for hyperactivation of sympathetic fibers of the urogenital tract in men, promoting hyperproliferation of prostate cells up to the development of severe lower urinary tract symptoms (LUTS) [4]. In addition, LUTS have a negative, complex impact on quality of life in terms of daily living, productivity at work, and even psychological well-being [5].

The gold standard for surgical treatment of BPH is transurethral resection of the prostate (TURP), which has been used since the 1940–1950s. [6]. Owing to the development and active implementation of laser techniques (in particular, holmium laser enucleation of the prostate [HoLEP]) in the 1990s., a role of TURP as standard has been contradictory. Currently, the use of TURP has decreased, and laser enucleation is becoming more common [7]. Laser techniques in the treatment of BPH

involves tissue destruction, coagulation or vaporization, which allows to enucleate the transition zone within the anatomical layer with good hemostasis and preservation of functional structures [8].

Another reliable method of treating BPH, which allows to significantly reduce the prostate volume and accelerate rehabilitation ("fast track surgery") in topographical and anatomical way, is laparoscopic retropubic simple prostatectomy (LRSP; Millin technique), which has been used since the 2000s [9]. As part of research to prevent massive blood loss due to the anatomic features and surgical technique, as well as to reduce postoperative risk of bladder neck sclerosis and urethral strictures, the authors of this article propose to supplement the standard technique with temporary clamping of the internal iliac arteries and the formation of vesicourethral anastomosis. An almost similar technique without vesicourethral anastomosis in a robotic modification was previously described by F Sergi et al. (2014) with subsequent decrease of blood loss and improvement of IPSS and uroflowmetry. In addition, they did not have vascular complications [10].

The lack of high-quality evidences comparing modern methods of treating BPH, namely LRSP with temporary clamping of the internal iliac arteries and vesicourethral anastomosis and HoLEP is an urgent issue in urology.

Aim. To compare the efficiency of two surgical treatment methods, HoLEP and LSRP in patients with BPH and T2DM.

Materials and methods. An open, single-center, randomized comparative study in parallel groups using the "random sampling" method, approved by the ethics committee of the "National Medical Research Center of Endocrinology" of the Ministry of Health of the Russian Federation was carried out. A total of 56 patients with T2DM, who underwent surgical treatment of BPH (28 in the HoLEP group, 28 in LSRP group) in the period from 2021 to 2022, were included. The diabetes history was identical in both groups. The duration of T2DM averaged 10.6 years (CI 95%: 5.4–15.8), while HbA1c level was 8.4±1.7% (6.7–10.1%). Both groups were divided into subgroups depending on glucose-lowering therapy received (in accordance with national clinical guidelines): basal-bolus insulin therapy with multiple injections of insulin analogues vs. monotherapy with oral hypoglycemic drugs (metformin 1000 mg/day). Selection of glucose-lowering therapy was carried out depending on the difference between the actual and target level of HbA1c.

The data selection was carried out on the basis of electronic databases of patients who were on basal-bolus insulin therapy with multiple injections of insulin analogues (n=14 in each group) and received oral hypoglycemic therapy (n=14 in each group). Before the surgical treatment, the average age (in years), prostate volume (cm^3), International Prostate Symptom Score (IPSS), quality of life index (QoL), erectile function (IIEF-5) was evaluated, as well as maximum urinary flow rate (Q_{max}), postvoid residual (ml), level of prostate-specific antigen (PSA), and presence/absence of cystostomy tube. Patients with a diagnosis of prostate cancer or a history of surgical treatment of BPH with a prostate volume of less than 80 cm3 were excluded from the study.

Intraoperatively, the following parameters were assessed: the average duration of the procedures (minutes), the average mass of tissue removed (g), the average duration of catheterization (days), the average length of stay (days), a decrease in hemoglobin level (g/l), the average duration of bladder irrigation.

Intraoperative and immediate postoperative complications were assessed using the Clavien–Dindo score (I–IV). At one year, IPSS, QoL, IIEF-5 scores, Q_{max} and postvoid residual were assessed. In addition, number of patients with urethral strictures and bladder neck sclerosis was evaluated. At 1-year follow-up, the efficiency of two surgical procedures was compared (HoLEP, LSRP) in accordance with the "trifecta": absence of postoperative complications (urethral stricture, bladder neck sclerosis), urinary incontinence and Q_{max}>15 ml/s.

Statistical analysis

Statistical data processing was carried out using the software package IBM SPSS Statistics 26 (SPSS. Inc, Chicago, IL, USA). Quantitative indicators were assessed with Shapiro–Wilk test in order to test deviation from normal distribution. Categorical data were described using absolute values and percentages. Comparison of percentages in multifield contingency tables was performed using the Pearson chi-square test. Quantitative indicators with a normal distribution were described using means (M) and standard deviations (SD) with 95% confidence interval (95% CI). Student's t test or one-way analysis of variance was performed for continuous variables, and the chi-square test was used for categorical variables. All p values were two-sided and differences were considered significant if $p < 0.05$.

Operative technique of HoLEP

HoLEP was performed using a modified Gilling technique. After dividing the prostate into anatomical lobes, each lobe was enucleated in a retrograde fashion using a holmium laser (50 W) via a 550 mm SlimLine fiber optic (Boston Scientific Auriga XL) through a 26F continuous flow resectoscope. For morcellation and tissue extraction, a 26F nephroscope with a Karl Storz UNIDRIVE S III tissue morcellator was used.

Operative technique of LSRP

LSRP was performed under general anesthesia. A carboxyperitoneum was created using a Veress needle introduced in the paraumbilical area; then an optical port was introduced. Laparoscopy was performed. Four working trocars were put in the right and left iliac areas. The peritoneum was dissected near to the bifurcation of the external iliac artery and the internal iliac artery on the right, and in the area of the intersection of the common iliac artery and the ureter. The internal iliac artery was mobilized using vessel sealing devices. The internal iliac artery was taken using a silicone holder. Hemostasis was performed. The peritoneum was dissected near to the bifurcation of the external iliac artery and the internal iliac artery on the left, in the area of the intersection of the common iliac artery and the ureter. The anterior and lateral surfaces of the prostate were dissected to the intrapelvic fascia. Bulldog clamps were applied to the internal iliac arteries in the area of bifurcation. The prostate capsule was dissected in the transverse direction. After identifying the layer between the prostate capsule and the adenomatous node, the latter were dissected in en-bloc fashion. The bladder

Table 1

Preoperative characteristics

Index	HoLEP (*n*=28)	LRSP (*n*=28)	*p*
Mean age, years	66.3 (± 7.9)	68.3 (± 7.1)	0.5
Average duration of type 2 diabetes	10.6 (± 5.2)	10.8 (± 5.0)	0.5
HbA1c level	8.4 (±1.7)	8.2 (±1.9)	0.5
Patients on basal-bolus insulin therapy	14.0 (50.0%)	14.0 (50.0%)	0.5
Patients on metformin monotherapy	14.0 (50.0%)	14.0 (50.0%)	0.5
Prostate volume, cm^3	134.2 (± 43.2)	127.4 (± 38.9)	0.3
IPSS, score	23.1 (± 1.2)	20.9 (± 1.2)	0.1
QoL, score	4.1 (± 0.9)	4.1 (± 0.8)	0.5
IIEF-5. score	11.6 (± 4.1)	10.3 (± 4.8)	0.2
Qmax, ml/sec	6.7 (± 1.8)	7.4 (± 1.8)	0.1
Postvoid residual, ml	71.1 (± 31.8)	73.5 (± 27.9)	0.0
PSA, ng/ml	4.7 (± 3.1)	4.2 (± 2.3)	0.5
Cystostomy tube, *n* (%)	4 (14.2)	6 (21.4)	0.1

neck was dislodged using predominantly blunt dissection. Adenomatous nodes were dissected from the urethra and placed in a container. Vascular clamps were removed from the internal iliac artery. After adequate identification of the bladder neck, an anastomosis was performed with two V-lock 3/0 sutures with the urethra. The anastomosis was performed in a continuous fashion, starting from the posterior wall (6 o'clock) in opposite directions, and ending with the intersection on the anterior wall (12 o'clock). A Foley catheter 20 Ch was put. After that, 150 ml of saline solution was injected into the bladder to check the tightness of the anastomosis. The prostate capsule was sutured with a continuous suture using V-lock 3/0 thread. The container with adenomatous nodes was removed through the supraumbilical approach. A drain was put into the small pelvis via another incision. Then, layer-by-layer suturing was performed. At the end of the procedure, an aseptic patch was applied.

Antibacterial and anti-inflammatory therapy

All patients in both groups received antibiotic prophylaxis. In case of a systemic inflammatory reaction, antibacterial therapy was administered. A nonsteroidal anti-inflammatory drug (diclofenac 75 mg twice daily) was given for 3 days. Thromboembolic prophylaxis was carried out in accordance with the local guidelines on prevention of venous thromboembolic complications dated September 15, 2022.

Results. According to the preoperative examination (*Table 1*), there were no differences in the average duration of T2DM, HbA1c level, the proportion of patients receiving basal-bolus insulin therapy/metformin monotherapy, prostate volume, IPSS, QoL, IIEF-5 scores, Qmax, postvoid residual, serum PSA level, as well as the presence of cystostomy tube.

In the group of patients who underwent HoLEP, in contrast to the LSRP group, duration of bladder catheterization was significant higher. After HoLEP, there was a more than twofold decrease of hemoglobin level and time of bladder irrigation. In both groups, average duration of hospitalization was equivalent, as well as length of stay and the average mass of removed tissue (*Table 2*).

According to the Clavien–Dindo score (see *Table 3*), HoLEP was associated with a higher incidence of grade 1 complications (damage to the ureteric orifices/bladder mucosa, short-term urinary incontinence, urinary retention due to blood clots), grade II (postoperative hyperthermia, acute urinary retention) and grade III (second stage for morcellation, bladder tamponade). Both methods relatively rarely resulted in massive bleeding, urinary extravasation with the need for repeated procedure. None of the methods was associated with Clavien–Dindo group IV complications (pulmonary embolism).

According to the 1-year follow-up (see *Table 4*), there was an equivalent decrease in IPSS, QoL scores and postvoid residual in both groups. In addition, patients in

Table 2

Intraoperative characteristics

Parameter	HoLEP (*n*=28)	LRSP (*n*=28)	*p*
Average duration of procedure (minutes)	105.4 (±11.4)	95.5 (±11.0)	0.1
Average mass of tissue removed (g)	105.2 (± 13.8)	102.2 (±35.3)	0.3
Average duration of catheterization (days)	3.3 (± 0.5)	4.6 (±1.6)	0.1
Average length of stay (days)	4.3 (± 0.6)	5.0 (±2.4)	0.4
Blood loss (ml)	550	250	0.1
Average duration of irrigation (days)	1.2 (± 0.4)	0	0.1
Cystostomy tube	4	5	0.3

Table 3

Intra- and short-term postoperative complications

Parameter	HoLEP (*n*=28)	LRSP (*n*=28)	*p*
Clavien-Dindo grade I complications			
Damage to the ureteral orifices, *n* (%)	2 (7.1)	-	
Damage to the bladder mucosa during morcellation, *n* (%)	3 (10.7)	-	
Short-term urinary incontinence (after removal of the urethral catheter), *n* (%)	20 (71.4)	1 (3.5)	0.01
Urinary retention due to obstruction of the urethral catheter by clots, *n* (%)	8 (28.5)	0	0.01
Clavien-Dindo grade II complications			
Postoperative fever, *n* (%)	3 (10.7)	1 (3.5)	0.01
Acute urinary retention, *n* (%)	4 (14.2)	0	0.01
Clavien-Dindo grade III complications			
Delayed morcellation (due to severe intraoperative hemorrhage), *n* (%)	5 (17.8)	-	
Bladder tamponade, *n* (%)	2 (7.1)	0 (0.0)	0.01
Massive bleeding (loss of 50% of blood volume within 3 hours or blood loss of 150 ml/min with SBP <90 mmHg)	1	1	
Repeated procedures, *n* (%)	2 (7.1)	1 (3.5)	
Urinary extravasation, *n* (%)	-	1 (3.5)	
Clavien-Dindo grade IV complications			
PAE, *n* (%)	0	0	

both groups had stable IIEF-5 scores similar to baseline. Noteworthy is the advantage in increasing of Q_{max} in patients after LRSP (24.3 (± 2.4) v. 15.3 (± 3.6).

In regard to postoperative complications of LRSP (see *Table 5*), the incidence of urethral stricture, stress/urgent urinary incontinence, and bladder tamponade tended to zero. However, in HoLEP group, stress (10.7%) and urge (3.5%) urinary incontinence, urethral stricture (7.2%), and bladder neck sclerosis (10.6%) were documented.

Discussion. Among elderly patients, BPH is the most common benign disease of the genitourinary system, which is associated with different comorbidities [11]. A preparation of patients with diabetes for surgical treatment is relevant issue. Our study demonstrates comparable perioperative results with literature data in patients without concomitant diabetes.

Our aim was to study the results of modern laparoscopic and laser methods of treating BPH in those with T2DM.

We compared the success rates of two surgical methods (HoLEP, LRSP) in patients with T2DM in accordance with the "trifecta" and examined different parameters, including pre- and intraoperative examination, intra- and early postoperative complications and with postoperative follow-up (1-year).

From the authors' point of view, the quality of the study could be improved by increasing the sample of patients, stratifying patients according to the level of glycemia or HbA1c, increasing the number of follow-up examina-

Table 4

Postoperative characteristics 12 months after procedure

Parameter	HoLEP (*n*=28)	LRSP (*n*=28)	*p*
IPSS, score	10.1 (± 2.6)	10.2 (± 2.9)	0.5
QoL, score	1.8 (± 0.6)	1.3(± 0.5)	0.01
IIEF-5. score	11.6 (± 4.1)	10.3 (± 4.8)	0.01
Q_{max}, ml/sec	15.3 (± 3.6)	24.3 (± 2.4)	0.01
Postvoid residual, ml	16.2 (± 10.5)	15.5 (± 13.1)	0.01

Table 5

Postoperative complications 12 months after procedure

Complication	HoLEP (*n*=28)	LRSP (*n*=28)	*p*
Bladder tamponade, *n* (%)	0	0	
Stress urinary incontinence, *n* (%)	3 (10.7)	0	0.01
Urge urinary incontinence, *n* (%)	1 (3.5)	0	0.01
Urethral stricture, *n* (%)	4 (7.2)	0	0.01
Bladder neck sclerosis, *n* (%)	5 (10.6)	1 (3.5)	0.01

tions (3, 6, 18, 24 months, etc.), as well as to provide a comparison with other surgical procedures, for example, monopolar and bipolar TURP. Another way to improve the study would be to use the criteria of "pentafecta" and "octafecta".

Our study has several limitations, including a small sample (n=56) with T2DM and obesity, which may result in a selection bias. Preoperative prostate volume was higher in the HoLEP group. According to our results, LRSP and HoLEP are both effective methods for the treatment of BPH even in those with concomitant T2DM.

Conclusion. LRSP has significant and promising benefits in terms of urethral complications (stricture, bladder neck sclerosis), urinary incontinence, and hemoglobin loss. We cannot ignore the need to carry out researches in order to analyze the safety aspects (including for other socially significant diseases) and decide on the feasibility of their implementation in routine clinical practice.

ЛИТЕРАТУРА/REFERENCES

1. *Lerner L.B., McVary K.T., Barry M.J., Bixler B.R., Dahm P., Das A.K., Gandhi M.C., Kaplan S.A., Kohler T.S., Martin L., Parsons J.K., Roehrborn C.G., Stoffel J.T., Welliver C., Wilt T.J.* Management of Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia: AUA GUIDELINE PART I-Initial Work-up and Medical Management. J Urol. 2021;206(4):806–817. Doi: 10.1097/JU.0000000000002183. Epub 2021 Aug 13. Erratum in: J Urol. 2021 Nov;206(5):1339. PMID: 34384237.
2. *Ng M., Baradhi K.M.* Benign Prostatic Hyperplasia. 2022 Aug 8. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan. PMID: 32644346.
3. *Dedov I.I., Shestakova M.V., Vikulova O.K., Zheleznyakova A.V., Isakov M.A.* Epidemiological characteristics of diabetes mellitus in the Russian Federation: clinical and statistical analysis according to the Federal diabetes register data of 01.01.2021. Diabetes mellitus. 2021;24(3):204–221. https://doi.org/10.14341/DM12759 Russian. (Дедов И.И., Шестакова М.В., Викулова О.К., Железнякова А.В., Исаков М.А. Эпидемиологические характеристики сахарного диабета в Российской Федерации: клинико-статистический анализ по данным регистра сахарного диабета на 01.01.2021. Сахарный диабет. 2021;24(3):204-221).
4. *Opara N.U.* Diabetes mellitus-induced lower urinary tract symptoms and hepatic steatosis in an older male. Endocrinol Diabetes Metab Case Rep. 2022;2022:22–0290. Doi: 10.1530/EDM-22-0290. Epub ahead of print. PMID: 36125050; PMCID: PMC9513662.
5. *Vartolomei L, Cotruș A, Tătaru SO, Vartolomei MD, Man A, Ferro M, Stanciu C., Sin A.I., Shariat S.F.* Lower urinary tract symptoms are associated with clinically relevant depression, anxiety, and stress symptoms. Aging Male. 2022;25(1):62–66. Doi: 10.1080/13685538.2022.2040981. PMID: 35179090
6. *Summner W A.* Transurethral resection; a history and a heritage. Trans West Sect Am Urol Assoc. 1956;23:99–103. PMID: 13401471
7. *Das A.K., Teplitsky S., Humphreys M.R.* Holmium laser enucleation of the prostate (HoLEP): a review and update. Can J Urol. 2019;26(4 Suppl 1):13–19. PMID: 31481144.
8. *Becker B,. Enikeev D,. Netsch C., Gross A.J., Laukhtina E., Glybochko P., Rapoport L., Herrmann T.R.W., Taratkin M.* Comparative Analysis of Vaporization and Coagulation Properties of a Hybrid Laser (Combination of a Thulium and Blue Diode Laser) Vs Thulium and Ho:YAG Lasers: Potential Applications in Endoscopic Enucleation of the Prostate. J Endourol. 2020;34(8):862–867. Doi: 10.1089/end.2020.0009. PMID: 3229204
9. *Pal R.P., Koupparis A..J.* Expanding the indications of robotic surgery in urology: A systematic review of the literature. Arab J Urol. 2018;16(3):270–284. Doi: 10.1016/j.aju.2018.05.005. PMID: 30147957; PMCID: PMC6105341
10. *Sergi F., Falavolti C., Bove A.M., Buscarini M.* Robotic-assisted laparoscopic simple prostatectomy and bladder diverticulectomy with temporary clamping of internal iliac arteries. J Robot Surg. 2014;8(1):81–83. Doi: 10.1007/s11701-012-0390-z. Epub 2013 Jan 10. PMID: 27637244.
11. *Vickman R.E., Franco O.E., Moline D.C., Vander Griend D.J., Thumbikat P., Hayward S.W.* The role of the androgen receptor in prostate development and benign prostatic hyperplasia: A review. Asian J Urol. 2020;7(3):191–202. Doi: 10.1016/j.ajur.2019.10.003. Epub 2019 Oct 19. PMID: 32742923; PMCID: PMC7385520

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SURGICAL TREATMENT OF URINARY INCONTINENCE IN GERIATRIC PATIENTS

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Introduction. Recently, there has been a steady upward trend in life expectancy, so it is extremely important to remember some of the features of the body associated specifically with aging. Thus, an important topic for discussion is the issue of ensuring the quality of life of an elderly woman. The prevalence of urinary incontinence in patients of the older age group leads to significant restrictions in their social life. Surgical treatment using general and regional anesthesia has significant contraindications due to age and comorbidities. In this regard, in some cases, local anesthesia is the method of choice of anesthesia in this category of patients.
Purpose of the study. Evaluation of the possibility of using local anesthesia in the surgical treatment of stress urinary incontinence in geriatric patients.
Materials and methods. We analyzed the results of surgical treatment of stress urinary incontinence in 42 patients. The mean age of the patients was 78±4 years. All patients were treated for urinary incontinence using mini loops under local anesthesia. Pre- and postoperative examination included vaginal examination in mirrors, cough test, cystoscopy (if indicated), uroflowmetry, ultrasound examination of the pelvic organs and bladder, bacterial culture of urine with determination of sensitivity to antibiotics. Taking into account the advanced age of the patients, the protocol of the preoperative examination included the obligatory performance of ultrasound Doppler examination of the veins of the lower extremities and echocardiography.
Results. The duration of the operation averaged 22±5 minutes. Complications requiring a change in the course of the operation were not registered during the operation. 1 month after the operation, at the control examination, the cough test was negative in 40 (95,2%) patients. 2 (4,8%) had a positive cough test. After 6 months, out of 40 (100%) successfully operated patients, 4 (9,52%) had urine leakage during the cough test. The maximum follow-up period for patients was 12 months. Out of 40 (100%) patients with a negative cough test after surgery, it was possible to track the long-term results of treatment only in 33 (82,5%) patients. After evaluating the results of 33 (100%) operated patients after 12 months, it was found that in 30 (90,9%) patients the symptoms of urinary incontinence were completely absent, in 3 (9,09%) there was a recurrence of urinary incontinence.
Conclusions. Surgical treatment of stress urinary incontinence using a synthetic loop under local anesthesia is effective and safe in geriatric patients.

K e y w o r d s: urinary incontinence, old age, local anesthesia, mini-sling

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Introduction. According to the United Nations, population aging is defined as the proportion of people aged 65 or older above 7%. There is a global increase in the elderly people by an average of 3% per year [1]. By 2050, the world's population will consist of 2.1 billion of elderly people [2]. In Russia, 12.9% of population have reached the age of 65 years and older [3]. The number of those over 65 years has increased by 19.9% since 2009 to 2015, and those over 80 years have exceeded 4 million compared to 2.9 million in 2009 [4]. An improvement of treatment methods aimed at improving the quality of life of an elderly patient helps reduce the average number of years with a state of disability and social dependence. Urinary incontinence significantly affects the quality of life of older women, causing discomfort and significantly limiting social and psychological aspects [5]. Urinary incontinence, as a chronic, slowly progressive disorder, is associated with significantly increased treatment costs and a period of poor quality of life characterized by poor health status. When analyzing the prevalence of urinary incontinence in women over 65 years of age, the prevalence of stress, urgency and mixed urinary incontinence was 28.0, 17.0 and 16.0% respectively [6]. Synthetic loops placed through vaginal access have become routine in the practice of urologists and gynecologists and are undoubtedly the "gold" standard for surgical treatment of stress urinary incontinence (SUI). However, the presence of various concomitant diseases in patients of the older age group is associated with a number of limitations while performing this procedure under general or spinal anesthesia. In this regard, the use of local anesthesia is the method of choice for the surgical treatment of SUI in patients of the older age group.

Aim. To evaluate the possibility of using local anesthesia in the surgical treatment of stress urinary incontinence in geriatric patients.

Materials and methods. From 2019 to 2021 in the surgical department of the NIIKEL clinic - branch of the Institute of Cytology and Genetics SB RAS, Novosibirsk, and the Urology Clinic of the A.I. Evdokimov Moscow State Medical University, Moscow, a total of 42 patients with SUI were treated. The study was carried out according to the 2020 guidelines for the treatment of urinary incontinence [7]. The inclusion criteria were the presence of SUI or mixed type of urinary incontinence with a predominance of the stress component. Exclusion criteria was pelvic organ prolapse of the 2nd degree or more according to the POP-Q classification, mixed urinary incontinence with a predominance of the urgent component, confirmed lower urinary tract infection, and a relapse of urinary incontinence after surgical treatment. All patients underwent a preoperative examination, which included a vaginal examination, a cough test, cystoscopy (if indicated), uroflowmetry, ultrasound examination of the pelvic organs and bladder, and urine culture with sensitivity test.

Considering the elderly age, the preoperative examination included mandatory Doppler ultrasonography of the lower extremity veins and echocardiography. In the absence of contraindications, patients were prescribed to menopausal medications after consultation with a gynecologist. The specific features of the anesthesia and surgical procedure were explained in an accessible form, followed by filling out and signing an informed consent form. All patients underwent a thorough allergy history taking, as well as a local anesthetic test the day before surgery. After preparing of the surgical field and vagina, the anesthetic gel "Acryol Pro (lidocaine + prilocaine)" was applied to the mucous membrane of the paraurethral space with exposure for 5–7 minutes. We regard the gel as more preferable due to the fact that lidocaine spray can cause a short-term burning sensation. Local anesthesia was further performed with an injection of a 0.75% solution of ropivacaine in the sub- and paraurethral spaces to the obturator membrane on the both sides. The administration of the ropivacaine solution was carried out according to a first the solution, then the needle general rule, namely first the solution, then the needle. On average, up to 20 ml of 0.75% ropivacaine solution was injected using 0.8x100 mm (21Gx4') needle. After draining the bladder with a Foley catheter 16 Ch, a vertical incision was made in the anterior vaginal wall with a distance of 1–1.5 cm downward from the external urethral opening. Metzenbaum scissors were used to dissect the paraurethral spaces on the both sides with the formation of channels to the descending branch of the pubic bone. "Mini-loops" were used as synthetic mesh. After positioning the loop under the middle third of the urethra, the bladder was filled with 150 ml 0.9% normal saline, the urethral catheter was removed and a standard cough test was performed. One of the advantages of using the local anesthesia is the reliability of the cough test as an intraoperative criterion for the sufficient loop tension. The bladder was drained with Foley catheter for 6 hours.

A gauze swab was used for packing the vagina for the same period of time. After removing the urethral catheter and tampon from the vagina, patients were activated. During the day, a cough test, uroflowmetry, and ultrasound examination of the bladder with determination of the postvoid residual was done. Patients were discharged the next day after procedure.

Results. The average age of patients was 78±4 years. The average duration of the procedure was 22±5 minutes. There were no complications that required conversion to another procedure. No allergic reactions to local anesthesia or directly to the anesthetic itself were noted. In the immediate postoperative period, all patients had no obstructive urinary symptoms, both clinically and according to uroflowmetry. According to bladder ultrasound, in all cases the volume of postvoid residual did not exceed 17.27±3.3 ml. Severe pain syndrome, as well as signs of wound infection, did not occur in any patient. The length of stay was 2 days. Undoubtedly, the ability to perform this procedure under local anesthesia can significantly reduce the length of hospitalization to 1 day. However, taking into account the age of patients, we decided to extend inpatient treatment to assess the immediate results. After 1 month, the cough test was negative in 40 (95.2%) patients, while 2 (4.8%) had a positive cough test. In the immediate postoperative period, 2 (4.8%) patients developed symptoms of an overactive bladder, which were relieved by taking M-anticholinergics. In 1 (2.4%) woman, acute cystitis occurred, requiring antibiotic therapy. After 6 months, in 4 out 40 successfully treated patients (10.0%), urine leakage was found when performing a cough test. The maximum follow-up period was 12 months. Of the 40 (100%) patients with a negative cough test after surgery, long-term results were evaluated only in 33 cases (82.5%). In 30 women (90.9%) urinary incontinence was completely absent, while in 3 (9.09%) a recurrence occurred.

Discussion. With age, the frequency of urinary incontinence steadily increases. Up to 50% of women from 45 to 60 years old have ever noted episodes of urine loss during physical activity [8]. At the Urology Clinic of the First Moscow State Medical University named after I.M. Sechenov an epidemiological study on the prevalence of various forms of urinary incontinence in menopausal women was carried out. According to results, in women over 40 years of age, prevalence of SUI was 68.13%, including 28.9% of respondents of late reproductive age and up to 58.7% of women in the menopause [9]. In 2000 F. M. Cheater et al. published data on the prevalence of urinary incontinence in institutionalized elderly women. A prevalence of urinary incontinence ranged from 17 to 31% [10]. Urinary incontinence in elderly patients has a negative psycho-emotional impact on their personality and can lead to the development of depression [11, 12]. Elderly patients have a significantly higher risk of developing adverse postoperative outcomes compared to young women due to age-related decline in physiological functions, the presence of several comorbidities, cognitive dysfunction, etc. [13]. Taking into account the trend towards increasing a life expectancy, there are more and more elderly patients, which requires an increase in the volume of surgical care [14].

In elderly patients, general anesthesia is associated with the development of transient, and in some cases, persistent cognitive impairment [15]. M.Yu. Gvozdeva et al. [16] described the experience of using "mini-loops" under local anesthesia in 18 patients with SUI, whose average age was 55.5 years. When assessing the results, 16 (88%) had no complaints of urinary incontinence, 1

(5.5%) patient showed significant improvement. In addition, one patient had a relapse of urinary incontinence. The study results showed clinical and economic efficiency of local anesthesia. When analyzing foreign data, the work of Miriam Campos Delgado et al. is of importance [17]. In their study from 2011 to 2013 the use of "mini-slings" in 40 patients was assessed. All procedures were performed under local anesthesia. The average age was 55 years. At a follow-up after 6 months. a complete absence of urine leakage was recorded in 77.5% of patients, 12.5% noted significant improvement, and only in 4 (10%) women urinary incontinence persisted. However, no intraoperative complications were recorded in any cases. The authors noted the presence of acute urinary retention in one patient and two cases of lower urinary tract infection.

Conclusions. Despite significant progress in the treatment of urinary disorders in older women, we must admit that in some cases they refuse surgical treatment due to concomitant diseases and age. This leads to even greater social maladaptation and decreased quality of life. The use of local anesthesia in gerontological patients allows to effectively and safely solve the problem of SUI.

ЛИТЕРАТУРА/REFERENCES

1. *Guedes T.S.R., Guedes M.B.O.G., de Oliveira H.K.M., Soares R.L., da Cunha V.L., Lopes J.M., de Oliveira N.P.D., Jerez-Roig J., de Souza D.L.B.* Urinary Incontinence in Physically Active Older Women of Northeast Brazil. International Journal of Environmental Research and Public Health. 2021; 18(11):58–78. https://doi.org/10.3390/ijerph18115878
2. *Sousa N.F.S., Lima M.G., Cesar C.L.G., Barros M.B.A.* Envelhecimento ativo: prevalência e diferenças de gênero e idade em estudo de base populacional. Cad Saúde Pública 2018;34(11).
3. *Makienko M.A.* Problems and prospects for maintaining the quality of life of the elderly in the Russian Federation. Bulletin of Science of Siberia. 2015;1:16. Russian (Макиенко М.А. Проблемы и перспективы сохранения качества жизни пожилых людей в российской федерации. Вестник науки Сибири. 2015;1:16).
4. *Vovchenko A.* Strategy for the benefit of older citizens should be ready by the spring of 2015. URL: http://www.ageing-forum.org/ru/strategiya-v-interesah-grazhdan-pozhilogovozrasta-dolzhna-byt-gotova-k-vesne-2015-goda. Russian (Вовченко А. Стратегия в интересах граждан пожилого возраста должна быть готова к весне 2015 г. URL: http://www.ageing-forum.org/ru/strategiya-v-interesah-grazhdan-pozhilogovozrasta-dolzhna-byt-gotova-k-vesne-2015-goda [дата обращения: 19.02.2015]).
5. *Fernandes S., Coutinho E., Duarte J., Nelas P., Chaves C., Amaral O.* Quality of life in women with Urinary Incontinence. Rev. Enferm. Ref. 2015;4: 93–99.
6. *Tsen I.J., Chen Y.T., Chen M.T., Kou H.Y., Tsen S.F.* Prevalence of urinary incontinence and intention to seek treatment in the elderly. J Formos Med Assoc. 2000;99(10):753–758.
7. *Kasyan G.R., Gadzhieva Z.K., Zaitsev A.V.* Clinical recommendations: Urinary incontinence. Moscow: Pero Publishing House. 2021; 60 p. Russian (Касян Г.Р., Гаджиева З.К., Зайцев А.В. Клинические рекомендации: Недержание мочи. Москва: Издательство Перо. 2021; 60 с.)
8. *Alyaev Yu.G., Ishchenko A.I., Gadzhieva Z.K., Chushkov Yu.V* Urination disorders in women - an interdisciplinary problem Clinical Nephrology. 2012;5(6):57F.M.63 Russian (Аляев Ю.Г., Ищенко А.И., Гаджиева З.К., Чушков Ю.В. Расстройства мочеиспускания у женщин – междисциплинарная проблема. Клиническая нефрология. 2012;5(6):57–63).
9. *Gadzhieva Z.K.* Funkcional'noe sostoyanie nizhnih mochevyh putej i medikamentoznaya korrekciya narushenij mocheispuskaniya u zhenshchin v klimakterii. Diss. dokt. med. nauk. 2001. S. 57–63, 76–80 Russian (Гаджиева З.К. Функциональное состояние нижних мочевых путей и медикаментозная коррекция нарушений мочеиспускания у женщин в климактерии. Дисс. канд. мед. наук. 2001. С. 57–63, 76–80)
10. *Cheater F.M., Castleden C.M.* Epidemiology and classification of urinary incontinence. Baillieres Best Pract Res Clin Obstet Gynaecol. 2000;14(2):183–205.
11. *Aguilar-Navarro S., Navarrete-Reyes A.P., Grados-Chavarría B.H., GarcíaLara J.M., Amieva H., Avila-Funes J.A.* The severity of urinary incontinence decreases healthrelated quality of life among community-dwelling elderly. J Gerontol A Biol Sci Med Sci. 2012;67(11):1266–1271.
12. *Felde G., Ebbesen M.H., Hunskaar S.* Anxiety and depression associated with urinary incontinence. A 10-year follow-up study from the Norwegian HUNT study (EPINCONT). Neurourol. Urodynam. 2017;36(2):322–328. https://doi.org/10.1002/nau.22921
13. *Zabolotskikh I.B., Gorobets E.S., Grigoriev E.V., Kozlov I.A., Lebedinsky K.M., Musaeva T.S., Ovechkin A.M., Trembach N.V., Khoronenko V.E.* Perioperative management of geriatric patients. draft clinical guidelines FAR Bulletin of Intensive Care named after AI Saltanov. 2018;1:60–74. Russian (Заболотских И.Б., Горобец Е.С., Григорьев Е.В., Козлов И.А., Лебединский К.М., Мусаева Т.С., Овечкин А.М., Трембач Н.В., Хороненко В.Э. Периоперационное ведение гериатрических пациентов. Проект клинических рекомендаций ФАР. Вестник интенсивной терапии им. А.И. Салтанова. 2018;1:60–74).
14. *Briskin B.S., Lomidze O.V.* Influence of polymorbidity on diagnosis and outcome in abdominal surgery in the elderly. Clinical gerontology. 2008;4:30–33. Russian (Брискин Б.С., Ломидзе О.В. Влияние полиморбидности на диагностику и исход в абдоминальной хирургии у пожилых. Клиническая геронтология. 2008;4:30–33).
15. *Ovezov A.M., Panteleeva M.V., Knyazev A.V.* Neurotoxicity of general anesthetics: a modern view of the problem. Neurology, neuropsychiatry, psychosomatics. 2015;7(4):78–82. Russian (Овезов А.М., Пантелее-ва М.В., Князев А.В. Нейротоксичность общих анестетиков: современный взгляд на проблему. Неврология, нейропсихиатрия, психосоматика. 2015;7(4):78–82).
16. *Gvozdev M.Yu., Reva I.A., Tupikina N.V., Pushkar D.Yu.* Local anesthesia in surgery for urinary incontinence in women Gynecology. 2014;16(1):87–90. Russian (Гвоздев М.Ю., Рева И.А., Тупикина Н.В., Пушкарь Д.Ю. Местная анестезия в хирургии недержания мочи у женщин Гинекология. 2014;16(1): 87–90).
17. *Campos-Delgado M., Quetglas-Muñoz C., Barahona-Orpinell M., García-Tejedor A., Ponce-Sebastià J.* Ambulatory MiniArc Precise Sling under Local Anesthesia for Stress Urinary Incontinence: Feasibility and Outcome. Gynecol Minim Invasive Ther. 2019;29(3):113–117. Doi: 10.4103/GMIT.GMIT_104_18. eCollection 2019 Jul-Sep.

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UROTHELIAL MORPHOLOGICAL STUDY FOR DIFFERENTIAL DIAGNOSIS OF CHRONIC RECURRENT LOWER URINARY TRACT INFECTION

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Introduction. Chronic recurrent cystitis (CRC), notwithstanding the advancements of up-to-date uroinfectology, remains an urgent and controversial problem. An important section of this issue is the study of the etiology of the disease, the determination of which defines the success of treatment and the planned scope of prophylaxis.
Objective. To study pathomorphological changes in the bladder urothelium of patients with chronic recurrent cystitis depending on the etiological factor.
Materials and methods. One hundred fifty eight sexually active female patients aged 20–45 years who had previously been diagnosed with recurrent lower urinary tract infection / chronic recurrent cystitis (RLUTI / CRC) during exacerbation were included in this prospective study. Based on the results of bacteriological and PCR studies of urine, urethral and vaginal discharge, patients were divided into four groups depending on the dominant etiological factor (bacteria / HPV / Candida spp. / M. tuberculosis). Bladder biopsy was performed in remission stage of the disease after premedication and general anaesthesia as routine during cystoscopy. Biopsy specimens after standard preparation were subjected to histological study with characterisation of the changes.
Results. The histological study results revealed characteristic specific pathomorphological tissue changes in different groups, which allowed us to define a protocol for differential diagnosis of RLUTI.
Conclusions. One of the guiding methods of differential diagnostics of RINMP / CRC defining the genesis of infectious-inflammatory process in the bladder is histological study of its biopsy specimens.

K e y w o r d s: *recurrent cystitis, bacteria, candida, human papillomavirus viruses, mycobacterium, biopsy*

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Introduction. Despite the achievements of modern urology and microbiology, chronic recurrent cystitis remains urgent and debated problem for specialists involved in its diagnosis and treatment [1, 2]. An important issue is the study of its etiological structure, which determines success of treatment and possible preventive measures. A number of clinical studies have been carried out in recent years, the result of which is the recognition of the paradigm of unsterile urine both in urology and microbiology, as well as in medicine in general [3–5]. Some progress in the study of the etiological structure of chronic recurrent cystitis was the acceptance as possible etiologic factors not only common aerobic microorganisms, but also the anaerobes [4, 6].

A study of the taxonomic structure of anaerobic microorganisms of the urinary tract revealed that these bacteria can be detected in the urinary tract both in normal and certain pathologic conditions, and they are capable of exhibiting their pathogenic properties and causing infectious and inflammatory diseases of the urinary tract and reproductive organs [7]. The possibility of viruses' contribution in the development of chronic recurrent cystitis is actively discussed [8–10]. It is believed that viral cystitis of various etiologies, as well as fungal cystitis, can be diagnosed in patients with complicating factors, such as primary or secondary immunodeficiency, after transplantation or extensive reconstructive procedures, radiation, chemotherapy, etc. [11]. The standard bacteriologic methods do not detect the full spectrum of pathogens, and therefore it is recommended to perform cystoscopy and bladder biopsy in order to clarify the genesis of chronic recurrent cystitis. Verification of difficult-to-diagnose complex infectious agents has high clinical significance, aimed not only at treatment, but also at the prevention of recurrent lower urinary tract infections (rLUTI) [12].

Our analysis of morphological studies of bladder specimens allows to carry out a differential diagnosis of rLUTI based on the etiological factor, as well as to determine the treatment tactics and examinations of patients.

Aim. To study pathomorphological changes in the bladder urothelium of patients with chronic recurrent cystitis depending on the etiological factor.

Materials and methods. Ethical statement. The study was planned and carried out in accordance with Declaration of Helsinki (revised in Fortaleza, Brazil, October 2013) and approved by the Local Independent Ethics Committee of the Federal State Budgetary Educational Institution of Higher Education Rostov State Medical University of the Ministry of Health of Russia based on review of the design and implementation plan (protocol No. 16 /17 dated 10/05/2017). The study was conducted as part of the dissertation work "Optimization of differential diagnosis and selection of first-line therapy for chronic recurrent cystitis in women" and had no sponsorship.

Patients. A total of 158 sexually active female aged 20–45 years who had previously been diagnosed with rLUTI or exacerbation of chronic recurrent cystitis were included in the prospective study. The inclusion and exclusion are shown in *Table 1*.

The initial examination included the taking history, bacteriological examination of the morning midstream urine, PCR (polymerase chain reaction) of morning midstream urine, urethral and vaginal swab, and cytology of 24-hour urine. The survey methodology has been described in detail in previous work [8]. Based on the predominant etiological factor according to bacteriological and PCR studies, urethral and vaginal swab, patients were divided into four groups. In group 1 (n=70), those with bacterial rLUTI were included, while group 2 (n=70), group 3 (n=11) and group 4 (n=7) involved patients with human papillomavirus (HPV), candida and tuberculous rLUTI.

Bladder biopsy. In the remission phase all patients underwent standard cystoscopy under premedication and general anesthesia. "Cold" biopsies were taken from the affected areas. The pathomorphological material was fixed in a solution of neutral 10% buffered formaldehyde "HistoSafe®" (ErgoProduction LLC, St. Petersburg, Russia) with a 24-hour exposure. Histological processing (degreasing and dehydration, clearing, paraffinization) was carried out using standard technology in a tissue histoprocessor. Slices from paraffin blocks 3–5 μm thick were obtained using a Leica RM 2265 rotary microtome (Leica Microsystems GmbH, Wetzlar, Germany) and stained with Hematoxylin-eosin [H&E] (BlikMedicalProduction, Russian Federation).

Microscopic study was carried out using Leica DM2000 microscope (Leica Microsystems GmbH, Wetzlar, Germany) at magnification x100, x200, x400. Photographic recording of pathomorphological featurs was performed with a Leica DFC295 3 Mpx digital camera (Leica Microsystems GmbH, Wetzlar, Germany).

During microscopic study, the state of urothelium was assessed, as well as signs of inflammation, composition of cell infiltrates, signs of remodeling and pathological transformation of tissues. In order to assess and compare the severity of abnormalities, a 4-tier analogue scale was used to record changes in four fields of view at a magnification of x200: (-) – absence of pathological changes (signs); (+) – mild changes (signs); (++) – moderately pronounced changes (signs); (+++) – the most pronounced changes (signs). Registration of tissue changes was carried out using specially designed Microsoft Office Excel 365 spreadsheets (Microsoft Corp., Redmond, WA, USA).

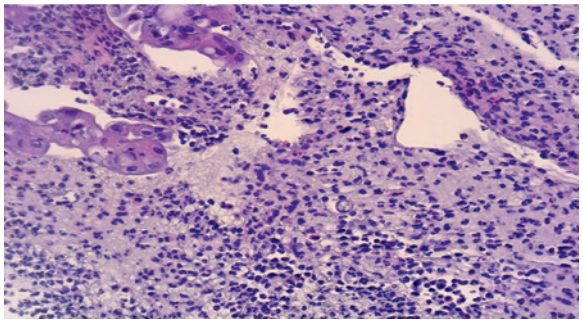

Fig. 1. Microscopic image: chronic severe cystitis with degeneration and desquamation of urothelial cells, pronounced neutrophilic infiltration of the submucosa, lymphocytes and plasmacytes, stromal edema (Hematoxylin-eosin [H&E] staining, magnification x200)

Results. The average age of the patients was 32.3±7.8 years. Based on the histological analysis of bladder wall samples, typical features in tissues were identified in various groups (*Table 2*).

In patients of group 1, thickening of the urothelium, edema of the mucous and submucosal layers, congestion of the capillaries was noted, with a predominance of neutrophils in the cellular infiltrate with a small number of lymphocytes and plasma cells (*Fig. 1*). Also, a chronic

Table 1

Selection criteria in the study

Inclusion criteria	Exclusion criteria
• Age over 18 years • Clinically and laboratory confirmed diagnosis of rLUTI (according to the RSU and EAU guidelines) • Informed consent to participate in the study	• Age over 45 years • Cystitis due to other non-infectious causes (IC/BPS, radiation, chemical, drug-induced, foreign bodies in the bladder) • Proven NLUTD and associated diseases/idiopathic DO • Active STDs • Infectious and inflammatory diseases of the UUT • Infectious and inflammatory diseases of the female reproductive organs • Bladder stones • Bladder outlet obstruction • Concomitant cardiovascular, neurological, endocrine, systemic and other disorders • Hormonal dysfunction associated with female reproductive system • Current or past oncological diseases • Malformation of the urinary tract and female reproductive system • Immunodeficiency states of various origins • Pregnancy/lactation • Menopause • Contraindications to anesthesia

N o t e: UUT – upper urinary tract; DO – detrusor overactivity; STDs – sexually transmitted diseases; IC/BPS – interstitial cystitis/painful bladder syndrome; NLUTD – neurogenic dysfunction of the lower urinary tract; rLUTI – recurrent lower urinary tract infection; RSU – Russian Society of Urologists; EAU – European Association of Urology (European Association of Urologists).

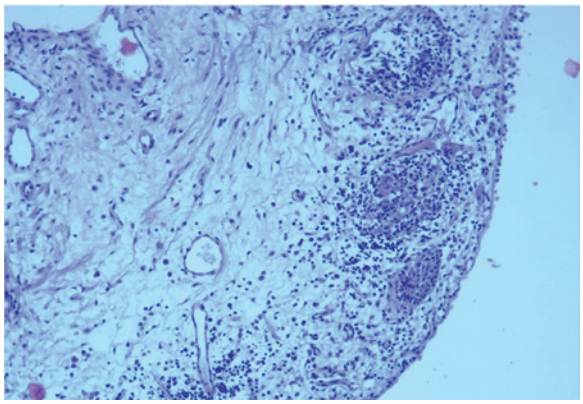

Fig. 2. Microscopic image: chronic superficial cystitis with degeneration and desquamation of urothelial cells (Hematoxylin-eosin [H&E] staining, magnification x100)

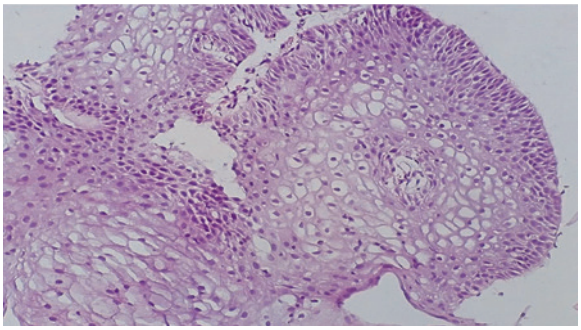

Fig. 3. Microscopic image: remodeling of urothelial cells with papillomatous hyperplasia and signs of HPV infection (koilocytosis, dyskaryosis) (Hematoxylin-eosin [H&E] staining, magnification x200)

infectious-inflammatory process, as well as desquamation of the urothelium was detected (*Fig. 2*).

In all patients of group 2 with signs of HPV lesions in the bladder mucosa with hyperplasia, squamous metaplasia, chronic inflammation, disturbances of vascular architecture and edema, lymphocytic infiltration with an admixture of plasma cells was dominant. In addition, in most cases, squamous cell metaplasia of the urothelium was subtotal or total. All patients had typical koilocytosis of the urothelium (*Fig. 3*).

In 65% of patients, koilocytosis was accompanied by the formation of papillary structures due to pronounced hyperplasia of urothelial cells with signs of HPV infection; in 15%, genital warts were found (Fig. 4).

Koilocytes were usually randomly located in the epithelium and characterized by abnormal, sharply enlarged

Table 2

Pathomorphological features in biopsy specimens from patients in different groups

	Pathomorphological features	Groups			
		Group 1	Group 2	Group 3	Group 4
Epithelium	Thickening	++	+	+	+/++
	Edema	++	+	++	++
	Desquamation	++	+++	++	+
	Koilocytosis	–	+++	–	–
	Squamous metaplasia	–	++	–	–
	Dystrophy	+	+++	+	+
	PIN	–	++	–	–
	Atypical structure	–	–	++ (m*)	–
Submucosal layer	Well-pronounced microvascular bed	++	++	+	++
	Stromal edema	++	+	++	+/++
	Sclerosis	+	+	+	++
	Caseous necrosis	–	–	–	+
Cellular infiltration	neutrophilic	+++	+	++	–
	lymphocytic/plasmatic	+	++++	++	++
	macrophage/histiocytic	++	–	++	+++ (pl*)
	eosinophilic	+	–	–	–
	fibroblastic	+	+	+	++

N o t e: PIN – squamous intraepithelial neoplasia; m* – mycelium; pl* – Pirogov–Langhans cells.
(-) – absence of a sign; (+/++/+++) – weak/moderate/strong feature.

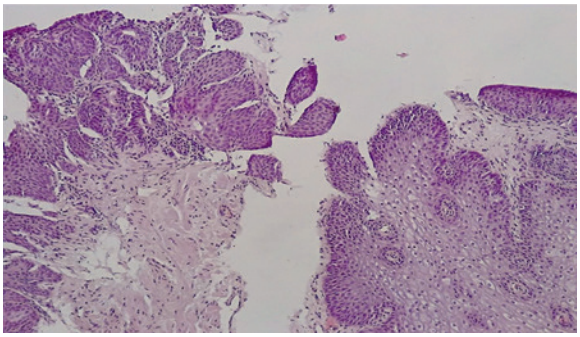

Fig. 4. Microscopic image: chronic superficial cystitis with the formation of papillary structures of hyperplastic urothelium with signs of HPV infection (Hematoxylin-eosin [H&E] staining, magnification x100)

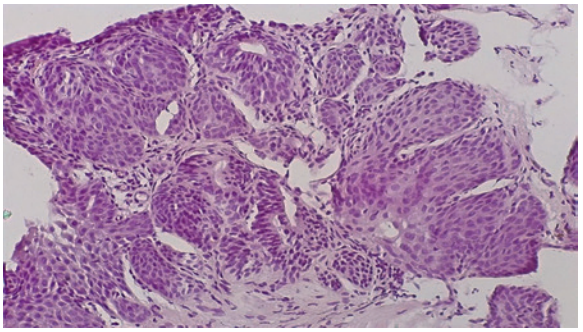

Fig. 5. Microscopic image: chronic superficial cystitis. Papillomatous hyperplasia with the formation of areas of grade 1–2 urinary intraepithelial neoplasia secondary to HPV (Hematoxylin-eosin [H&E] staining, magnification x200)

dark, irregularly shaped nuclei with a folded contour and a perinuclear zone or "halo". In addition, in the majority of affected urothelial cells with HPV, pronounced dystrophic changes in the nuclei were noted, including hyperchromia, hypertrophy, karyorrhexis, karyopyknosis.

In 35% of patients, papillomatous hyperplasia with areas of grade 1–2 intraepithelial neoplasia was recorded in combination with HPV (*Fig. 5*).

In patients of group 3, chronic inflammation with desquamation of the urothelium with moderate lymphocytic and neutrophil infiltration, mycelial proliferation was recorded (*Fig. 6*).

In patients of group 4, vascular congestion, edema of the urothelium and submucosa of varying degrees of severity, sclerosis, and diffuse lymphoid-histiocytic infiltration, typical for the sclerosing process, were revealed. The inflammatory infiltrate consisted of lymphocytes, plasma cells, macrophages, and fibroblasts. In addition, signs of granulomatous inflammation with an accumulation of multinucleated giant cells (Pirogov–Langhans) and areas of caseous necrosis were seen in the bladder wall (*Fig. 7*).

Discussion. The main results of this study are that various infectious pathogens can have different negative effects on the urothelium and on the bladder mucosa. In addition, a constellation of symptoms that is characterized by different clinical and laboratory features, depends on the etiological factor. Identification of the infectious agent responsible for chronic recurrent cystitis is of importance when prescribing etiologic therapy.

Modern bacteriological studies do not always reveal the entire spectrum of possible microorganisms involved in the development of chronic recurrent cystitis, but only a limited range of uropathogens [5]. An important question is what pathogen is the trigger of the inflammatory process leading to chronicity? Verification and differential diagnosis of the pathogen are of high significance, aimed not only at prevention, but also at early diagnosis of chronic recurrent cystitis. Therefore, in recent years there has been a search for methods for identifying all pathogens that can cause cystitis [12, 13]. Morphological examination of bladder biopsies allows to differentiate changes in the urothelium in patients with chronic recurrent cystitis depending on the etiological factor. The results obtained confirm our previous studies demonstrating the importance of the morphological examination of the urothelium in order to differentiate the etiology of chronic recurrent cystitis with high accuracy [11]. However, in the previous study we were limited to the differential diagnosis of bacterial and papillomavirus cystitis. Our results expand the range of possible etiological agents

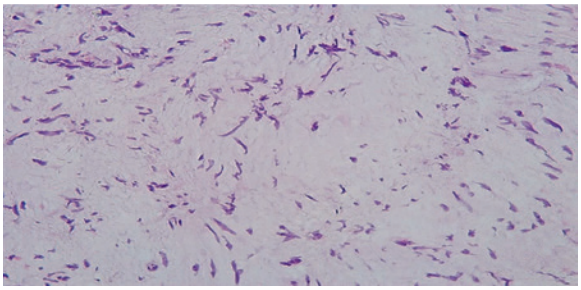

Fig. 6. Microscopic image: candidiasis of the bladder mucosa with signs of chronic cystitis (fungal mycelium in the stroma) (Hematoxylin-eosin [H&E] staining, magnification x200).

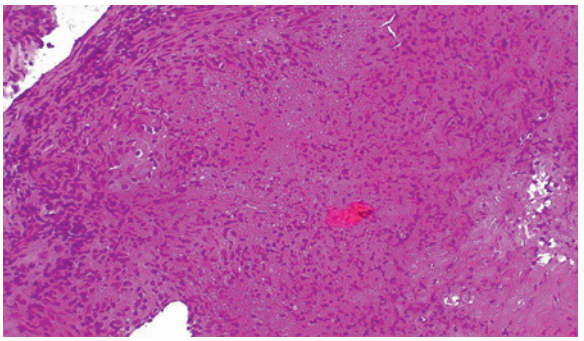

Fig. 7. Microscopic image: chronic granulomatous inflammation of the bladder stroma with an accumulation of multinucleated giant cells (Pirogov-Langhans), areas of caseous necrosis in tuberculosis (Hematoxylin-eosin [H&E] staining, magnification x200)

of chronic recurrent cystitis that can only be identified by morphometric studies.

Conclusion. Chronic recurrent cystitis is a polyetiological disease, and identifying its etiological factor is a difficult and the key to successful treatment. In our opinion, one of the leading methods for the differential diagnosis, which allows to determine the etiology, is the morphological assessment of bladder biopsies, which determines specific changes in the urothelium characteristic of each type of inflammation.

REFERENCES

1. *Sinyakova L.A., Loran O.B., Kosova I.V., Kolbasov D.G., Nezovibatko Ya.I.* Hemorrhagic cystitis in women: diagnosis and treatment. Experimental and clinical urology. 2020;13(5):92–99. Russian (Синякова Л.А., Лоран О.Б., Косова И.В., Колбасов Д.Г., Незовибатько Я.И. Геморрагический цистит у женщин: диагностика и лечение. Экспериментальная и клиническая урология. 2020;13(5):92–99).
2. *Kuzmin I.V., Al-Shukri S.H., Slesarevskaya M.N.* Treatment and prophylaxis of the lower urinary tract recurrent infections in women. Urologicheskie vedomosti. 2019;9(2):5–10. Russian (Кузьмин И.В., Аль-Шукри С.Х., Слесаревская М.Н. Лечение и профилактика рецидивирующей инфекции нижних мочевых путей у женщин. Урологические ведомости. 2019;9(2):5–10).
3. *Kuzmenko A.V., Kuzmenko V.V., Gyaurgiev T.A.* Current trends in the treatment of chronic recurrent bacterial cystitis. Urologiia. 2020;(6):52–57. Russian (Кузьменко А.В., Кузьменко В.В, Гяургиев Т.А. Современные тенденции в лечении хронического рецидивирующего бактериального цистита. Урология. 2020;(6):52–57).
4. *Naboka Y.L., Gudima I.A., Kogan M.I., Ibishev Kh.S., Chernickaya M.L.* Microbial spectrum of urine and bladder biopsy specimens in women with chronic recurrent cystitis. Urologiia. 2013; 4:16–18. Russian (Набока Ю.Л., Гудима И.А., Коган М.И., Ибишев Х.С., Черницкая М.Л. Микробный спектр мочи и биоптатов мочевого пузыря у женщин с хроническим рецидивирующим циститом. Урология. 2013; 4:16–18).
5. *Kogan M.I., Naboka Yu.L., Ibishev H.S., Gudima I.A.* Unsterility of urine of a healthy person – a new paradigm in medicine. Urology. 2014;5:48–52. Russian (Коган М.И., Набока Ю.Л., Ибишев Х.С., Гудима И.А. Нестерильность мочи здорового человека – новая парадигма в медицине. Урология. 2014;5:48–52).
6. *Aliev Yu.G., Arefeva O.A., Asfandiyarov F.R., et al.* Infections and inflammations in urology. Moscow: Medforum, 2019. 888 p. Russian (Инфекции и воспаления в урологии. Аляев Ю.Г., Арефьева О.А., Асфандияров Ф.Р. и др. Москва: Медфорум, 2019. 888 с.).
7. Patent No. 2452773 C1 Russian Federation, IPC C12Q 1/04. Method for determining the bacteriological contamination of urine, prostate secretion, ejaculate: No. 2010147953/10: Appl. 11/24/2010: publ. 06/10/2012 / Yu. L. Naboka, M. I. Kogan, I. A. Gudima [and others]. Russian (Патент № 2452773 C1 Российская Федерация, МПК C12Q 1/04. Способ определения бактериологической обсемененности мочи, секрета предстательной железы, эякулята: № 2010147953/10: заявл. 24.11.2010: опубл. 10.06.2012 / Ю. Л. Набока, М. И. Коган, И. А. Гудима [и др.]).
8. *Ibishev KH.S., Lapteva T.O., Krakhotkin D.V., Ryabenchenko N.N.* The role of human papillomavirus infection in the development of recurrent lower urinary tract infection. Urologiia. 2019;(5):134–137. Russian (Ибишев Х.С., Лаптева Т.О., Крахоткин Д.В., Рябенченко Н.Н. Роль папилломавирусной инфекции в развитии рецидивирующей инфекции нижних мочевых путей. Урология. 2019; 5:134–137).
9. *Ibishyv K.S., Malinovskaya V.V., Parfyonov V.V.* Treatment of persistent infection of the lower urinary tract in women. Attendingphysician. 2014; 9:90–93. Russian (Ибишев Х.С., Малиновская В.В., Парфенов В.В. Лечение персистирующей инфекции нижних мочевых путей у женщин. Лечащий врач. 2014; 9:90–93).
10. *Naboka Yu.L., Kogan M.I., Mordanov S.V., Ibishev Kh.S., Ilyash A.V., Gudima I.A.* Bacterial-viral urine microbiota in uncomplicated recurrent infection of the lower urinary tract: results of pilot study. Vestnik urologii. 2019;7(4):13-19. Russian (Набока Ю.Л., Коган М.И., Морданов С.В., Ибишев Х.С., Ильяш А.В., Гудима И.А. Бактериально-вирусная микробиота мочи при неосложнённой рецидивирующей инфекции нижних мочевых путей (пилотное исследование). Вестник урологии. 2019;7(4):13–19).
11. *Ibishev Kh.S., Krakhotkin D.V., Lapteva T.O. et al.* Endoscopic and morphological signs of chronic recurrent papillomavirus cystitis. Urologiia. 2021; 3:45–49. Russian (Ибишев Х.С., Крахоткин Д.В., Лаптева Т.О. и др. Эндоскопические и морфологические признаки хронического рецидивирующего папилломавирусного цистита. Урология. 2021; 3:45–49).
12. *Mamedov V.K., Krakhotin D.V.* Endoscopic and morphological methods in the differential diagnosis of chronic recurrent cystitis. 8th final scientific session of young scientists of Rostov State Medical University. Rostov-on-Don: Collection of materials. 2021; p. 69–70. Russian (Мамедов В.К., Крахотин Д.В. Эндоскопический и морфологический методы в дифференциальной диагностике хронического рецидивируюего цистита. 8-я итоговая научная сессия молодых ученых РостГМУ. Ростов-на-Дону: Сборник материалов. 2021; С. 69–70).
13. *Ibishev Kh. S., Mamedov V. K., Naboka Yu. L. et al.* Cytological examination of urine in the differential diagnosis of recurrent infection of the lower urinary tract. Urologiia. 2023;2:8–12. Russian (Ибишев Х.С., Мамедов В.К., Набока Ю.Л. и др. Цитологическое исследование мочи в дифференциальной диагностике рецидивирующей инфекции нижних мочевыводящих путей. Урология. 2023;2:8–12).

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REFERENCE VALUES FOR BASIC EJACULATE ANALYSIS FROM FERTILE MEN: RUSSIAN REGIONAL CHARACTERISTICS (MULTICENTER CROSS-SECTIONAL RETROSPECTIVE STUDY)

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Introduction. The current "WHO Manual for the Laboratory Examination and Processing of Human Semen" (6th edition, 2021) states the variability and low predictive ability of traditionally ejaculate parameters (ejaculate volume, sperm concentration, motility and morphology), abandons the concept of "norm", replacing it with 5% and 95% percentiles, and recommends the formation of regional criteria for reference ranges.

Aim. To establish reference ranges for basic indicators of ejaculate analysis from fertile Russian men to improve the clinical and economic efficiency of providing medical care to infertile couples.

Materials and methods. A multicenter cross-sectional retrospective study was carried out. Based on the results of a clinical and laboratory examination, a group of fertile men was formed who met the following criteria:

- *confirmed pregnancy in the wife (regular partner) according to hCG and/or ultrasound;*
- *ejaculate analysis was performed in specialized andrological laboratories according to WHO protocols;*
- *between the date of the study performed and the estimated date of pregnancy there was no more than 3 months (the analysis could be performed before the date of pregnancy, or after the fact of pregnancy was established);*
- *pregnancy in a natural cycle;*
- *absence of any specific treatment at least 3 months before the date of pregnancy;*
- *pregnancy outcome (childbirth, medical abortions, miscarriages, anembryonic pregnancies) was not taken into account.*

In total, the sample included 445 men who was examined in the health care facility where the authors of the article worked regarding sexual dysfunction, chronic prostatitis, or miscarriage.

Results. The reference values of basic ejaculate parameters of fertile Russian men differed from the international data presented in the WHO Guidelines, 6th edition (2021). The lower 5% percentile in Russians was higher for sperm concentration (20 and 16 million/ ml, respectively) and ejaculate volume (1.7 and 1.4 ml, respectively), but less for the proportion of sperm with progressive motility (24 and 30%, respectively). Moreover, our values were very close to those from the WHO Guidelines, 4th edition (1999): 20 million/ml, 2 ml and 25%, respectively. The lower 5% percentile of the number of sperm with progressive motility was 21 million, while the minimum value was 5.2 million. The upper 95% percentile of the percentage of abnormal forms was equal to 99%, which indicates the low predictive ability of this indicator in the assessment possibility of conception. It should be remembered that a "fertile man", i.e. the man who caused the pregnancy is not identical to the concept of a "healthy" man in the reproductive sense, since in 30-40% of cases, anembryonic pregnancy is associated with low sperm quality (ESHRE, 2022).

Conclusion. Our data suggest that for Russian men, the following threshold values foe sperm analysis should be used: for the term "oligospermia", ejaculate volume is <1.7 ml, "oligozoospermia" means the sperm concentration <20 million/ml, for "asthenozoospermia" is defined as <24% progressively sperm motility, and "teratozoospermia" is diagnosed when <1% of morphologically normal sperms with Papanicolaou staining using "strict" criteria. In 95% of fertile men, a number of sperms with progressive motility was at least 21 million, when in 5% it was from 5 to 20 million. A value <5 million indicate a low probability of conception.

K e y w o r d s: *male infertility, sperm, ejaculate analysis, oligozoospermia, asthenozoospermia, teratozoospermia*

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Introduction. In modern clinical practice, to assess male reproductive function, it is recommended [1] to perform a sperm analysis, according to standard protocols described in the WHO Laboratory Manual for the Examination and Processing of Human Semen (in the chapter "Basic tests", 5th edition, 2010 [2], and Basic examination, 6th edition, 2021 [3]). In 2010, the reference values were determined on 400–1900 ejaculate analysis of fertile men from 8 countries on three continents, whose partners were pregnant within 12 months after stopping contraception [4]. At the same time, 5% percentiles obtained by analyzing their distribution were proposed as the minimum reference values: semen volume of 1.5 ml; total number of sperm of 39 million; sperm concentration of 15 million/ml; sperm viability of 58%; progressive sperm motility of 32%; total sperm motility of 40%, proportion of normal forms of 4.0%. These values were close to indicators reported in population studies carried out in Germany, Norway, the USA and other countries [5–7]. Research conducted after 2010 allowed to supplement the World Health Organization (WHO) database with ejaculate parameters from men from 12 countries, including China and African countries (data on fertile men from Russia were not considered), which led to a change in the reference values for concentration, as well as progressive and total sperm motility to 16 million/ml, 30 and 42%, respectively [8]. Sperm concentration (or sperm count) and sperm motility that are less than these are interpreted as "oligozoospermia" and "asthenozoospermia", respectively; absence of sperm in the ejaculate were considered "azoospermia". The authors of the guidelines emphasized that men living in different countries may have regional, ethnic and other factors-related features of the distribution of ejaculate parameters [3].

Specifically, African American men in USA whose wives were pregnant had significantly lower semen volume, concentration, and total motile sperm count compared to white and Hispanic men [9]. Therefore, the authors of the guideline recommended that each laboratory should establish its own reference range, obtained from testing using control materials, based on positive and negative predictive values calculated taking into account the clinical outcome, including pregnancy, miscarriage, etc. (pp. 93, 96, 101, 104) [3]. This is fully consistent with our position, since even a year before the publication of these WHO Guidelines, we found in pilot studies, that in fertile men, who were residents of a metropolis (Moscow), the ejaculate parameters differed markedly from the WHO reference ranges [2, 3].

Clarification of the standard ejaculate indicators in Russia is not only of academic interest, but also determines the need and feasibility of specific treatment, including using expensive assisted reproductive technologies (ART) and, accordingly, the costs of this to the healthcare system.

Aim. To establish reference ranges for basic sperm parameters from fertile Russian men to improve the clinical and economic efficiency of providing assistance to infertile couples.

Materials and methods. Multicenter cross-sectional retrospective study was carried out. Based on the results of a clinical and laboratory examination, a group of fertile men was formed who met the following criteria:

- confirmed pregnancy in the wife (regular partner) according to human chorionic gonadotropin (hCG) (more than 100 mIU/ml) and/or ultrasound (presence of a fertilized egg in the uterus);
- ejaculate examination was performed in specialized andrological laboratories according to WHO protocols;
- between the date of the study and the estimated date of pregnancy no more than 3 months (the analysis could be performed before the date of pregnancy or after the fact of pregnancy was established);
- pregnancy in a natural cycle;
- absence of any specific treatment at least 3 months before the date of pregnancy;
- pregnancy outcome (childbirth, medical abortions, miscarriages, missed pregnancies) was not taken into account.

The analysis of the ejaculate was carried out in accordance with the WHO Laboratory Manual for the Examination and Processing of Human Semen [11]. The volume was assessed using a measuring centrifuge tube. Sperm concentration was determined by hemocytometry; the dilution factor of the ejaculate (1:10; 1:20; 1:50) was determined after a preliminary assessment of the concentration of sperm in the wet (native) preparation processed for counting sperm motility. Sperm counting in a hemocytometer was carried out after dilution with a fixing solution using light microscopy at 400x magnification, assessing the number of sperm in the field determined by the grid of the counting chamber. Only spermatozoa with their heads inside the chamber mesh were considered. Motility was determined in a wet mount by light microscopy at 400x magnification at room temperature according to a standard protocol: each motility was assessed as rapid progressive (category A), slow progressive (B), non-progressive (C) or immobility (D). Two hundred sperms were analyzed. Sperm morphology after Papanicolaou staining was assessed using the strict (Tygerberg) criteria [12]: morphologically normal sperm and the types of defects for each abnormal sperm were documented. Smears were prepared from a drop of sperm with a volume of 20 μl and fixed for at least 5 minutes with absolute ethanol. Slides were analyzed at 1000× magnification (oil immersion brightfield objective) by an experienced laboratory technician. Two hundred sperms were analyzed. A spermatozoon was considered normal if it met the following criteria [2]:

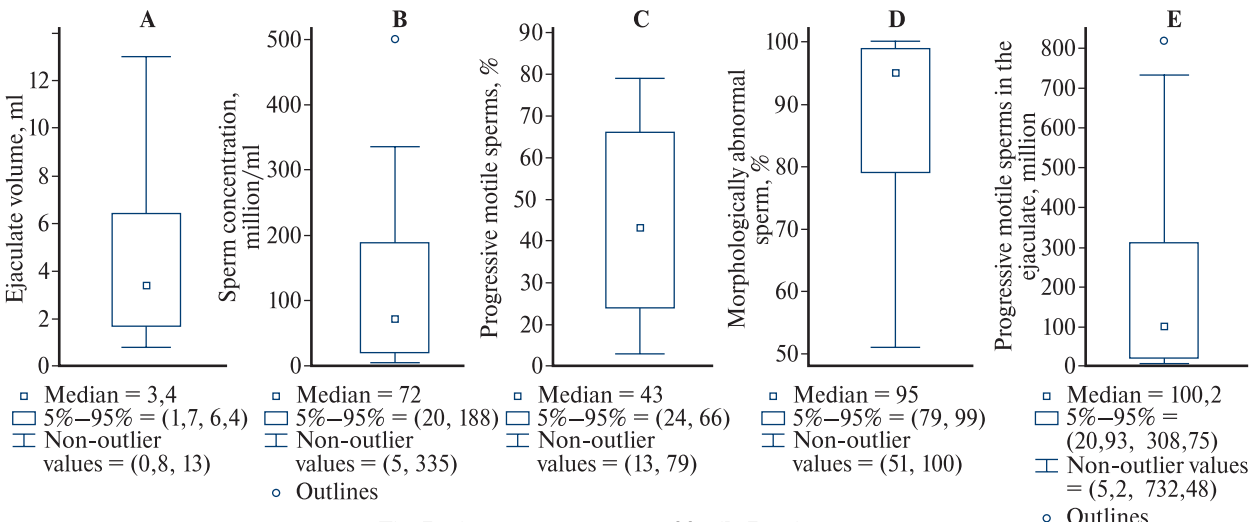

Fig. Basic sperm parameters of fertile Russian men:
A – volume, B – concentration, C – proportion of progressive motile sperms, D – morphology, E – estimated total progressive motile sperm count in the ejaculate.

- the head is smooth, has regularly contours and oval in shape;
- acrosomal region makes up 40–70% of the head without large vacuoles and has no more than two small vacuoles;
- the postacrosomal region does not contain vacuoles;
- the middle part is approximately the same length as the head of the sperm, quite thin and of the same diameter along the entire length;
- the tail has the same diameter along its entire length, is thinner than the middle part and is about 45 microns in length (about 10 times the length of the head);
- residual cytoplasm is considered an abnormality only when there is an abundance, i.e. when it exceeds a third of the size of the sperm head.

Questionable cases, such as "borderline normal sperm", were interpreted as "abnormal."

For an integral assessment of sperm quality, the total progressive motile sperm count in the ejaculate (TPMS) was calculated: volume (ml) x concentration (million/ml) x proportion of progressively motile sperm (%)/100; expressed in million/ejaculate. Data were presented in the table as percentiles, minimum and maximum values; graphically in the form of a range diagram, where "outliers" are values that are more or less than 1.5 times ("contours") and 2 times ("limits") relative to the interquartile range.

Other cellular elements were also recorded but were not included or analyzed in this study. In total, the sample included 445 men who visited the health care facility where the authors of the article worked as part of a medical examination for sexual disharmony, chronic non-infectious prostatitis, or undeveloping pregnancy. Data collection period: 1995–2000 (n=41), 2001–2010 (n=147) and 2011–2022 (n=257). Basic semen testing was supported by the new standard ISO23162:2021 (International Organization for Standardization, 2021) [13], based on the same principles as WHO guidelines.

Results. From the table it can be seen that the average (median) values for volume are 3.4 ml, concentration 72 ml/ml, the proportion of progressively motile sperm 43%, morphologically normal forms 5%. The lower 5% percentile for ejaculate volume was 1.7 ml, sperm concentration 20 million/ml, proportion of progressively motile sperm 24%, proportion of morphologically normal forms 1%. Minimum value of volume was 0.8 ml, concentration 5 million/ml, progressive motility 13%, normal forms 0% (100% of sperm cells were abnormal).

The obtained average values are very close to the data we previously presented analyzing fertile men in Moscow (median) and Ufa (arithmetic mean): volume 3.5 and 3.6 ml, concentration 72 and 70 million/ml, progressively motility 43 and 49%, respectively [10, 14].

In accordance with the WHO guidelines [3], the 5% percentile values should be considered the lower limits of the reference range typical for fertile men, i.e. the lower limit of the "norm" for these ejaculate indicators of Russian men.

At the same time, it is clear from the range diagrams that the minimum "non-outlier" value for ejaculate volume is 0.8 ml (*Fig. 1A*), for concentration 5 million/ml (*Fig. 1B*), for progressive motility 13% (*Fig. 1C*), for the percentage of pathological forms 100% (*Fig. 1E*), which corresponds to the minimum values of these indicators.

The calculated values of the TNMS in the ejaculate of fertile men are shown in the table and *Fig. 1D*: the average (median) value is 100 million in the ejaculate, the lower 5% percentile was 21 million, the minimum value was 5.2 million.

Discussion. Male infertility is a significant problem in urology and the entire healthcare. According to an analysis of population studies published by WHO in 2023 [15], 8.2–21.8% of men are infertile. In recent years, there has been a global trend towards a decrease in the quantitative ejaculate indicators in men living in different countries and on different continents. Between 1973 and 2018, sperm concentration decreased by 51.6%, with the rate of decline occurring after 2000 have doubled and currently amount to 2.64% per year [16]. The similar trends are identified in the Russian Federation: the rate of decline in sperm concentration in ejaculate from 2016 to 2021 is 1.8% per year [17], and the number of men with primary infertility during the period from 2000 to 2018 increased

by 1.8 times. In addition, the total number of men suffering from infertility in our country is equal to 0.1% of the male population of childbearing age, which is significantly lower than similar indicators in other countries, and may indicate the need to improve the diagnosing and reporting [18]. However, the quantitative recording of infertile men is complicated by several circumstances.

Firstly, infertility is a problem of a couple, when it is difficult to clearly establish whose "fault" is the absence of the pregnancy. The low fertility potential of one spouse can be compensated by the high potential of another [19]. There is evidence that in certain situations we may talk about "biological incompatibility of partners", since changing partners allows both persons to achieve the pregnancy [20].

Secondly, strict criteria have not yet been defined on the basis of which we may state a decrease in male fertility, including when we can make a diagnosis of "male infertility" and not "marital infertility". Studies have shown that the basic semen analysis is of little use in distinguishing between success and failure of spontaneous pregnancy, even if population correlations exist between ejaculate parameters and various fertility and infertility outcomes [21, 22].

Formally, the diagnosis of "male infertility" (N 46 according to ICD-10 and GB04.0 according to ICD-11) must be made when no sperm are found in the semen at all. And when they are there, but there are few of them, or they have poor motility, or have an imperfect shape? When to use other diagnoses (according to the new ICD-11 classification): GB04.Y "other specified male infertility" or GB04.Z "unspecified male infertility"? Where are the boundaries of the norm, when a patient should be treated and when not?

Laboratory standards for sperm quality have been revised several times over the past decades, and in the latest WHO Guidelines [3] the concentration, motility and normal morphology of sperm are several times lower than half a century ago.

At the same time, the authors of this guidelines completely abandoned the concept of "norm", limiting themselves to indicating the "statistical range", which 95% of cases belong to. Therefore, when examining for infertility, it should be taken into account that 5% of fertile men had ejaculate values lower than the reference values.

From the data presented in the article (see *Table*) it follows that the reference values of basic ejaculate parameters of fertile Russian men differ from the international data presented in the WHO Guidelines, 6th edition, 2021 [3]: the lower 5% percentile for Russians is higher for sperm concentration (20 and 16 million/ml, respectively) and ejaculate volume (1.7 and 1.4 ml, respectively), while less for the proportion of progressively motile sperm (24 and 30%, respectively). Moreover, our data are very close to the data of the WHO Guidelines, 4th edition, 1999 [11]: 20 million/ml, 2 ml and 25%, respectively. The upper 95% percentile for abnormal morphology was found to be 99%, which confirms the extremely low predictive ability of this indicator in assessing the possibility of conception [23, 24], with the exception of some specific sperm defects (easily detected when 99 or 100% of sperm are affected), which are associated with genetic disorders (globozoospermia, macrocephaly, achephalic spermatozoa syndrome and dysplasia of the fibrous sheath) [25]. When comparing the reference value, we obtained for morphology with those specified in the WHO guidelines [3], it should be remembered that the patients in our group conceived a child in a natural cycle, while those proposed by F. Kruger et al. [26, 27] ranges <4%, 4–14%, >14% are based on the results of in vitro fertilization (IVF) in a standard protocol. The percentage of normal forms, according to them, was 8%, 64 and 88% respectively. However, the number of couples with this morphology was quite modest, 13, 32 and 71, respectively [26, 27].

Lars Björndahl, editor-in-chief of the current WHO Guidelines [3], in his recent article emphasizes that "in the sixth edition, the paradigmatic shift is that the sperm morphology is regarded as a predictor of ART success or failure and should also be used as an indicator of testicular and epididymal function" [21]. When interpreting these data, it is necessary to consider several more important methodological aspects.

Firstly, the interpretation of ejaculate analysis cannot be dichotomous and categorical: "fertile" or "infertile". The normative values do not represent the boundary between fertile and infertile men; it is a description of the distribution of results from a reference population that does not only include highly fertile men. The ranges established on the basis of 5% or 95% percentiles allow to state that in 95% of cases in fertile men, ejaculate parameters will be

Table

Basic indicators of ejaculate from fertile Russian men

Ejaculate indicators	*n*	Percentiles									Range	
		2.5	5	10	25	50	75	90	95	97.5	min	max
Volume, ml	445	1.5	1.7	2.0	2.5	3.4	4.4	5.8	6.4	7.0	0.8	13.0
Concentration, million/ml	445	16	20	27	44	72	103	147	188	245	5	500
Progressive motility, %	445	21	24	27	34	43	52	60	66	70	13	79
Sperms with rapid progressive motility (category A), %	423	2	6	11	20	31	41	49	54	59	0	74
The number of sperms with progressive motility in ejaculate, million	423	14	21	30	54	100	164	248	309	383	5	817
Viability, %	428	52	61	65	76	84	90	93	95	97	22	100
Pathologic forms, %*	257	78	79	83	89	95	97	98	99	99	51	100

Note. n – number of patients; min-max – minimum and maximum; * data for the period from 2011 to 2022: assessment of morphology according to strict criteria in accordance with WHO guidelines 2010 (5th edition); empirical values are rounded to whole numbers.

within these limits. But this does not mean that if the values fall outside this range, then the man will necessarily be infertile [21]. The subject of the analysis was a sample of only fertile men, but not infertile ones, therefore the obtained values do not allow us to judge infertility; on the contrary, they give reason to expect natural conception.

A critical assessment of studies on the likelihood of spontaneous pregnancy carried out several years ago led to the conclusion that determining whether men belong to a classification category, according to WHO reference intervals, is of low value for predicting conception and choosing a treatment method [28]. Perhaps the best reference population may be men in couples who conceived within four cycles of attempts, to reduce the number of couples who achieved conception despite possible male factors [29]. Cornerstones for this are now available in the revised WHO guidelines [3] and the International Organization for Standardization (ISO) standard 23162 for basic semen examination [30].

However, according to the methodology used by the authors of the WHO Guidelines [3], when the value decreases below the 5% percentile, we may suggest the possible contribution of one or more sperm parameters to a multifactorial condition, which is the inability of a couple to conceive a child for a sufficiently long time period of time. This condition is also associated with the female reproductive system dysfunction [31]. The likelihood of such a contribution increases if similar disturbances are documented repeatedly.

But we should not consider a decrease in fertility as a constant, but only about the state at the current moment in time. A decrease in ejaculate parameters below reference values may be transient, caused by some external unfavorable factors influencing for a short time, such as intoxication, overheating, stress, etc. An example of this is COVID-19 [32]. Over time (usually longer than spermatogenesis duration of about 3 months), the ejaculate quality is restored and spontaneous conception may occur. This can explain the pregnancy obtained from men whose ejaculate parameters were significantly worse than the normative values [33, 34]. At the same time, one should not ignore the fact that in almost all such studies there was no genetic confirmation of biological paternity, and, according to available data, from 0.8 to 30% of born children are not biologically related to their official fathers [35].

We can make an almost unambiguous diagnosis of "male infertility" only in a few situations: with repeatedly confirmed "azoospermia" or "cryptozoospermia", total sperm immobility, special forms of teratozoospermia (globozoospermia or acephalic spermatozoa syndrome). In this regard, the International Statistical Classification of Diseases and Related Health Problems, 11th revision (ICD-11), which is planned to be implemented in the Russian Federation in 2024, uses the term "abnormal absence in the measurable level of sperm in semen."

Another challenge in interpreting semen analysis is that multiparametric assessment appears to be more important than interpretation of individual parameters. Thus, combined assessment of sperm production (quantitative [sperm number]; qualitative [motility, viability, morphology]) can provide prognostic information related to fertility success [36].

Therefore, a promising approach for determining the probability of natural conception can be considered the use of a certain integral parameter characterizing the total number of "good" sperm in the ejaculate. We can suggest the TNMS. It may be associated with relatively low motility, but quite high concentration or volume, and vice versa. According to our data (see table), the lower 5% percentile is 21 million. S. Keihani et al. showed a significant decrease in the probability of natural conception within 5 years with TNMS of less than 20 million [29]; this is also accompanied by an increase in the number of cases of severe (>30%) DNA fragmentation (OR = 3.72) [37]. The minimum TNMS value in our sample of fertile men is 5 million (see *Fig. 1D*). Similar results were obtained by J. A. Hamilton et al. [33]. In a prospective study of 1,177 married couples, the likelihood of natural conception from men in whose ejaculate the number of motile sperm exceeded 5 million was significantly higher compared to those in whom TNMS was less than 1 million or varied in the range from 1 to 5 million. Therefore, it can be assumed with high probability that the partners of men whose ejaculate contains more than 5 million motile sperm can expect natural conception.

Thirdly, we should remember that not only a decrease in ejaculate volume, sperm concentration and motility may lead to infertility. There are so-called functional disorders of sperm, which can occur even with normozoospermia [10, 38]. Such functional disorders include disturbances in the acrosome reaction, condensation of sperm chromatin (protamination), sperm DNA fragmentation, the influence of antisperm antibodies, various defects in proteomics and metabolomics, etc.

Finally, it should be noted that a "fertile" man, which partner becomes pregnant is not identical to the concept of a "healthy" man in the reproductive sense, since in up to 30–40% of cases, undeveloping pregnancy is associated with low sperm quality [39, 40]. This can be caused by both congenital genetic defects [41, 42] and acquired defects in chromatin structure, in particular DNA fragmentation, due to influence of reactive oxygen species (oxidative stress), impaired protamination and other still poorly understood factors [39, 40, 43]. Moreover, the higher the percentage of abnormal sperms, the more the disturbances in the chromatin structure are detected (even with normal concentration and motility) [44]. In particular, with 96–99% of pathological forms, protamination and fragmentation are outside the reference ranges in 20 and 27% of cases, respectively, while with 100% of abnormal forms these figures reach 52 and 55%, respectively. But even in those men, who have more than 4% sperms with normal morphology (in this study 5–14%), protamination and fragmentation were abnormal in 12 and 23% of cases, respectively [44].

Conclusion. Based on the sperm analysis of the Russian male population, considering the lower 5% percentile, the following terms should be used:

- "oligozoospermia" – ejaculate volume is less than 1.7 ml;
- "oligozoospermia" – sperm concentration is less than 20 million/ml;
- "asthenozoospermia" – less than 24% sperms with progressive motility;
- "teratozoospermia" – only in 100% of abnormal forms with Papanicolaou staining using strict (Tygerberg) criteria [11].

We consider the calculated TNPS to be important in predicting natural conception. Since in 95% of fertile men

this value exceeded 21 million, in 5% it was in the range from 5 to 20 million, TNPS <5 million can be considered one of the signs of a significant decrease in male reproductive function.

We recommend considering standard ejaculate parameters outside the reference range (5% or 95% percentile) as "subfertility", when the likelihood of spontaneous conception is reduced. In this case, it is recommended to prescribe one or another treatment aimed at increasing the volume, concentration, proportion of sperms with progressive motility, and, as a result, TNPS with a target value of more than 20 million. It should be noted that in a young and reproductively healthy woman and in case of male subfertility, conception in the natural cycle is possible subject to regular sexual activity without contraception for a sufficiently long period of time (1–2 years).

A decrease in fertility can also be observed with normal basic ejaculate parameters ("normozoospermia") in the case of functional sperm disorders, which are revealed when using extended and advanced methods [3], including assessment of DNA fragmentation, protamination, oxidative stress, antisperm antibodies, etc. Further research in this direction, in line with principles of evidence-based medicine, will provide a more complete understanding of their diagnostic and prognostic value, as well as give recommendations for their use.

In addition, specialists in reproductive medicine are discussing the need to designate with an independent code for a man who was unable to achieve conception with his partner within 12 months, and for whom the definition of "male infertility" is proposed. Currently, many physicians use the ICD-10 code "Z31.6 Encounter for general counseling and advice on procreation" in such cases, supplementing it with the words "infertility in marriage (in a couple)", which allows them to perform examination and treatment plans as suggested by current guidelines on male infertility, approved by the scientific and practical council of the Ministry of Health of the Russian Federation. Obviously, in connection with the upcoming implementation on the territory of the Russian Federation of the ICD-11, which provides for the description of the category "male infertility" separate codes for azoospermia (GB04.0), other specified (GB04.Y) and unspecified (GB04.Z) forms will also require the formation of a coordinated position of the professional society on the possibilities of their use in various clinical scenarios for men in infertile couples. At the same time, there is no doubt that every such man, including those with "normozoospermia," should be consulted by a urologist for diagnostics in order to identify possible causes that contribute to a decrease in reproductive function and, if necessary, carry out subsequent treatment aimed at to increase the likelihood of conception and birth of a healthy child.

REFERENCES

1. Clinical recommendations «Male infertility». Russian Society of Urologists. 2021. Available at: Rubricator KR (minzdrav.gov.ru). Russian (Клинические рекомендации «Мужское бесплодие». Российское общество урологов. 2021. Доступно по: Рубрикатор КР (minzdrav.gov.ru).
2. World Health Organization (WHO). WHO laboratory manual for the examination and processing of human semen. 5th ed. Geneva: WHO; 2010.
3. WHO laboratory manual for the examination and processing of human semen, sixth edition. Geneva: World Health Organization; 2021.
4. EAU Guidelines on Sexual and Reproductive Health. A. Salonia (Chair), C. Bettocchi, P. Capogrosso, J. Carvalho, et al. ©European Association of Urology. 2023, p. 151–155, 188.
5. *Cooper T.G., Jockenhoevel F., Nieschlag E.* Variations in semen parameters from fathers. Hum Reprod. 1991;6: 859–866.
6. *Haugen T.B., Egeland T., Magnus O.* Semen parameters in Norwegian fertile men. J Androl. 2006;27:66–71.
7. *Macleod J., Gold R.Z. The male factor in fertility and infertility. II.* Spermatozoon counts in 1000 men of known fertility and in 1000 cases of infertile marriage. J Urol. 1951;66(3):436–449. Doi: 10.1016/S0022-5347(17)74358-3.
8. *Campbell M.J., Lotti F., Baldi E., Schlatt S., Festin M.P.R., Björndahl L., Toskin I., Barratt C.L.R.* Distribution of semen examination results 2020 – A follow up of data collated for the WHO semen analysis manual 2010. Andrology. 2021;9(3):817–822. Doi: 10.1111/andr.12983.
9. *Redmon J.B., Thomas W., Ma W. et al*. Semen parameters in fertile US men: the Study for Future Families. Andrology. 2013;1(6):806–814.
10. *Bozhedomov V.A., Nikolaeva M.A., Ushakova I.V., Bozhedomova G.E., Lipatova N.A., Kamarina R.A., Okhobotov D.A., Kamalov A.A.* The structure of sperm quality disorders in men from infertile couples and the algorithm for managing such patients in specialized institutions of the third level. Obstetrics and gynecology. 2020;11:159–167. Russian (Божедомов В.А., Николаева М.А., Ушакова И.В., Божедомова Г.Е., Липатова Н.А., Камарина Р.А., Охоботов Д.А., Камалов А.А. Структура нарушений качества спермы у мужчин из бесплодных пар и алгоритм ведения таких пациентов в специализированных учреждениях третьего уровня. Акушерство и гинекология. 2020;11:159–167).
11. *Parekattil S.J., Esteves S.C., Agarwal A.* Editors. Male Infertility: Contemporary Clinical Approaches, Andrology, ART and Antioxidants. Second Edition, ©Springer Nature Switzerland AG 2021, p. 28.
12. *Menkveld R., Stander F.S., Kotze T.J., Kruger T.F., van Zyl J.A.* The evaluation of morphological characteristics of human spermatozoa according to stricter criteria. Hum Reprod. 1990;5:586–592.
13. International Organization for Standardization ISO 23162:2021 Basic semen examination – Specification and test methods ISO, Geneva (2021).
14. *Galimov Sh.N., Bozhedomov V.A., Galimova E.F., Pavlov V.N., Sukhoi G.T.* Male infertility: molecular and immunological aspects. Moscow: GEOTAR-Media, 2020. 208 p. Russian (Галимов Ш.Н., Божедомов В.А., Галимова Э.Ф., Павлов В.Н., Сухих Г.Т. Мужское бесплодие: молекулярные и иммунологические аспекты. М.: ГЭОТАР-Медиа, 2020. 208 с.).
15. Infertility prevalence estimates, 1990–2021. Geneva: World Health Organization; 2023. Licence: CC BY-NC-SA 3.0 IGO.
16. *Levine H., Jørgensen N., Martino-Andrade A., Mendiola J., Weksler-Derri D., Jolles M., Pinotti R., Swan S.H.* Temporal trends in sperm count: a systematic review and meta-regression analysis of samples collected globally in the 20th and 21st centuries. Hum Reprod Update. 2023;29(2):157–176. Doi: 10.1093/humupd/dmac035. PMID: 36377604.
17. *Korneyev I.A.* Annual trends in semen parameters among men attending a fertility center between 2016 and 2022. Urology reports. 2023;13(1):23–29. Doi: 10.17816/uroved296569. Russian (Корнеев И.А. Сравнительная характеристика параметров эякулята мужчин, обратившихся в центр репродуктивной медицины с 2016 по 2022 г. Урологические ведомости. 2023;13(1):23–29. Doi: https://doi.org/10.17816/uroved296569)
18. *Lebedev G.S., Golubev N.A., Shaderkin I.A., Shaderkina V.A., Apolikhin O.I., Sivkov A.V., Komarova V.A.* Male infertility in the Russian Federation: statistical data for 2000-2018. Experimental and clinical urology. 2019;4:4–13. Russian (Лебедев Г.С., Голубев Н.А., Шадеркин И.А., Шадеркина В.А., Аполихин О.И., Сивков А.В., Комарова В.А. Мужское бесплодие в Российской Федерации: статистические данные за 2000–2018 годы. Экспериментальная и клиническая урология. 2019;4:4–13).
19. *Nieschlag E.* Scope and Goals of Andrology. Andrology: Male Reproductive Health and Disfunction. 3rd. E.Nieschlag, H.M.Behre, S.Nieschlag (Ed.), 2010; p. 4.

20. *Kekäläinen J.* Genetic incompatibility of the reproductive partners: an evolutionary perspective on infertility. Hum Reprod. 2021;36(12):3028–3035.
21. *Björndahl L.* A paradigmatic shift in the care of male factor infertility: how can the recommendations for basic semen examination in the sixth edition of the WHO manual and the ISO 23162:2021 standard help? Reproductive BioMedicine Online. 2022;45(Issue 4):731–736.
22. *Agarwal A., Tvrda E., Sharma R.* Relationship amongst teratozoospermia, seminal oxidative stress and male infertility. Reprod. Biol. Endocrinol. 2014;12:45.
23. *Blanchard M., Haguenoer K., Apert A., Poret H., Barthélémy C., Royère D., Guérif F.* Sperm morphology assessment using David's classification: time to switch to strict criteria? Prospective comparative analysis in a selected IVF population. Int J Androl. 2011;34(2):145–152.
24. *Rachel B.* Danis, Mary K. Samplaski. Sperm Morphology: History, Challenges, and Impact on Natural and Assisted Fertility. Curr Urol Rep. 2019;20(8):43.
25. *Gatimel N., Moreau J., Parinaud J., Léandri R.D.* Sperm morphology: assessment, pathophysiology, clinical relevance, and state of the art in 2017. Andrology. 2017;5(5):845–862. Doi: 10.1111/andr.12389.
26. *Kruger T.F., Acosta A.A., Simmons K.F. et al.* New method of evaluating sperm morphology with predictive value for human in vitro fertilization. Urology. 1987;30(3):248–251. Doi: 10.1016/0090-4295(87)90246-9.
27. *Kruger T.F., Acosta A.A., Simmons K.F., Swanson R.J., Matta J.F., Oehninger S. Kruger T.F., et al.* Predictive value of abnormal sperm morphology in in vitro fertilization. Fertil Steril. 1988;49(1):112–127. Doi: 10.1016/s0015-0282(16)59660-5.
28. *Esteves S.E. Zini A., Aziz N. et al.* Critical appraisal of World Health Organization's new reference values for human semen characteristics and effect on diagnosis and treatment of subfertile men. Urology 2012;79:16–22.
29. *Keihani S., Verrilli L.E., Zhang C., Presson A.P., Hanson H.A., Pastuszak A.W., Johnstone E.B., Hotaling J.M.* Semen parameter thresholds and time-to-conception in subfertile couples: how high is high enough? Human reproduction (Oxford, England). 2021l;36:2121–2133.
30. International Organization for Standardization. ISO 23162:2021 Basic semen examination – Specification and test methods. ISO, Geneva (2021
31. *te Velde E.R., Eijkemans R., Habbema H.D.* Variation in couple fecundity and time to pregnancy, an essential concept in human reproduction. Lancet. 2000;355:1928–1929.
32. *Fei Chen, Shiheng Zhu, Zhiqing Dai, Lanting Hao, Chun Luan, Qi Guo, Chaofan Meng, Yankun Zhang.* Effects of COVID-19 and mRNA vaccines on human fertility. Hum Reprod. 2021;37(1):5–13. Doi: 10.1093/humrep/deab238.
33. *Hamilton J.A., Cissen M., Brandes M., et al.* Total motile sperm count: a better indicator for the severity of male factor infertility than the WHO sperm classification system. Hum Reprod. 2015;30(5):1110–1121.
34. *Boeri L., Belladelli F., Capogrosso P., Cazzaniga W., Candela L., Pozzi E., Valsecchi L., Papaleo E., Viganò P., Abbate C., Pederzoli F., Alfano M., Montorsi F., Salonia A.* Normal sperm parameters per se do not reliably account for fertility: A case-control study in the real-life setting. Andrologia. 2021;53(1):e13861. Doi: 10.1111/and.13861.
35. *Bellis M.A., Hughes K., Hughes S., Ashton J.R.* Measuring paternal discrepancy and its public health consequences. J Epidemiol Community Health. 2005;59(9):749–754. Doi: 10.1136/jech.2005.036517.
36. *Barratt C.L.R., Björndahl L., De Jonge C.J., Lamb D.J., Osorio Martini F.,McLachlan R., Oates R.D., van der Poel S., St John B., Sigman M., et al.* The diagnosis of male infertility: an analysis of the evidence to support the development of global WHO guidance-challenges and future research opportunities. Human reproduction update. 2017;23:660–680.
37. *Pozzi E., Fallara G., Belladelli F., Corsini C., Raffo M., Candela L et al.* Clinical parameters associated with altered sperm DNA fragmentation index among primary infertile men: Findings from a real-life cross-sectional study. Andrology. 2023;11(8):1694–1701. doi: 10.1111/andr.13380.
38. *Agarwal A., Majzoub A., Parekh N., et al.* A Schematic Overview of the Current Status of Male Infertility Practice. World J Mens Health. 2019: 1–15.
39. ESHRE. Guideline on the management of recurrent pregnancy loss. 2023, p. 91–95.
39. *Inversetti A., Bossi A., Cristodoro M., Larcher A., Busnelli A., Grande G., et al.* Recurrent pregnancy loss: a male crucial factor-A systematic review and meta-analysis. Andrology. 2023 Oct 25. doi: 10.1111/andr.13540. Online ahead of print.
41. *Mikec Š., Kolenc Ž., Peterlin B, Horvat S., Pogorevc N., Kunej T.* Syndromic male subfertility: A network view of genome–phenome associations. Andrology. 2022;10(4):720–732. doi: 10.1111/andr.13167
42. *Brendan J., Riera-Escamilla A., Wyrwoll M.J., Salas-Huetos A., Xavier M.J., Nagirnaja L. et al.* A systematic review of the validated monogenic causes of human male infertility: 2020 update and a discussion of emerging gene–disease relationships. Hum Reprod Update. 2022;28(1):15–29.
43. *Busnelli A., Garolla A., Di Credico E., D'Ippolito S., Merola A.M., Milardi D., Pontecorvi A., Scambia G., Di Simone N.* Sperm DNA fragmentation and idiopathic recurrent pregnancy loss: Results from a multicenter case-control study. Andrology. 2023;11(8):1673–1681. doi: 10.1111/andr.13395
44. *Bozhedomov V., Lipatova N., Bozhedomova G., Kamarina R., Shomarufov A., Kamalov A.* Sperm chromatin integrity in men from infertile couples with teratozoospermia and normozoospermia. Human Reproduction. 2022;37(1): i212.

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TEXTURE ANALYSIS OF 3D MODELS FOR THE PREDICTION OF THE GRADE OF CLEAR CELL RENAL CELL CARCINOMA OF THE KIDNEY (PILOT STUDY)

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Aim. To evaluate the possibilities of textural analysis of 3D models in differentiating the degree of nuclear dysplasia of the clear cell renal cell carcinoma (ccRCC).
Materials and methods. The specimens after surgical treatment of 190 patients with ccRCC were analyzed. In all cases, nephron-sparing surgery (NSS) was performed through laparoscopic access. The clinical characteristics were evaluated, including age, gender, tumor localization (side, surface and segments), absolute tumor volume, Charlson comorbidity index, body mass index, nephrometry scores (RENAL, PADOVA, C-index). Patients were divided into 2 groups. In group 1, there were 119 patients with the ccRCC of Grade 1 or 2, while group 2 consisted of 71 patients with ccRCC of Grade 3 and 4. All patients underwent 3D virtual planning of procedure using the 3D modeling program «Amira». At the first stage, two experienced radiologists performed manual segmentation of 3D models of kidney parenchyma tumors. At the second stage, the tumor shape was analyzed with a mathematical calculation of three indicators and more than 300 textural features of statistics of types 1-2 were extracted. Further, an intellectual analysis was carried out. For the evaluation of tumor grade according to Furman system, the classification problem was solved using the machine learning algorithm Stochastic Gradient Descent and cross-validation k=5.
Results. The accuracy of classification for the two groups of Grade 1 or 2 and Grade 3 or 4 on the F1 metric was 72.2. To build the model, the following parameters were selected: the absolute tumor volume, the Charlson comorbidity index, "Energy", the first quartile and the second decile of the pixel intensity distribution.
Conclusion. The texture analysis of 3D models for the prediction of Fuhrman grade in ccRCC demonstrated satisfactory quality for two groups of Grade 1 or 2 and Grade 3 or 4 nuclear dysplasia.

K e y w o r d s: kidney parenchyma cancer, 3D technologies, texture analysis, machine learning

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Introduction. Every year, more than 400,000 renal parenchymal tumors are diagnosed worldwide, which accounts for about 2–3% of all newly diagnosed cancers [1. 2]. In Russia, renal cell cancer (RCC) statistically ranks 10th among other oncological diseases [3]. At the same time, RCC is the 13th most common cause of cancer death worldwide [1. 2].

To characterize the aggressiveness of clear cell and papillary RCC subtypes, the Fuhrman system of the nuclear gradation is used. According to the classification, RCC is divided into four degrees: grade 1 and 2 refer to highly differentiated tumors (low grade) with a favorable prognosis, while grade 3 and 4 are poorly differentiated lesions (low grade) with an unfavorable course [4. 5]. Fuhrman grade is an independent prognostic factor [6]. However, this information becomes available only after the surgical treatment and does not allow to determine the treatment tactics in advance.

In recent decades, there has been a trend toward an increase in the diagnosis of renal parenchymal tumors up to 4 cm in size (small kidney tumor), which is associated with the widespread use of imaging methods in some diseases or suspected disorders of other organs and systems [7].

Currently, the priority strategy in localized renal parenchymal tumors is surgical treatment, with 10 to 30% of all lesions being verified as benign [8. 9]. The number of “small” kidney tumors removed annually in the United States showed a significant increase among

benign tumors from 2080 to 3393, very low-risk RCC (cT1a G1) from 3352 to 5452 and low-risk tumors (cT1a G2) from 8512 to 13631 during the period from 2000 to 2014 [10]. According to a number of studies, from 30 to 90% of RCC have a low malignancy potential [10–15]. Such a high detection rate of benign and indolent lesions disputes to the appropriateness of surgical intervention for any suspicious lesion, given the number of complications [10. 22].

The use of modern imaging studies shows a high accuracy, specificity and sensitivity in the diagnosis of renal parenchymal tumors. Magnetic resonance imaging (MRI) and contrast-enhanced computed tomography (CT) have approximately the same accuracy of 95–100% [16, 17, 19]. However, it should be noted that these methods have much lower accuracy in verifying the histological type of tumor. Thus, when performing MRI with assessment of various characteristics, the accuracy is no more than 86%, and for CT it is only 79% [17–19]. Positron emission computed tomography (PET/CT) shows an diagnostic accuracy of up to 93.8% with one radiopharmaceutical, and when several series of PET with the introduction of 2–3 radioisotopes are performed, it may reach 100% [20–22]. However, differentiated morphological verification of RCC when performing PET/CT requires the use of a combination of several radiopharmaceuticals, which increases costs, duration of the study and radiation exposure to the patient.

According to the guidelines, preoperative morphological diagnosis of renal parenchymal tumors is not mandatory and is performed for patients with locally advanced RCC to determine the options of drug therapy, when planning ablative treatment methods, and those with multiple malignant tumors to verify the diagnosis [21].

When performing a tumor biopsy, the accuracy of histological study in comparison with the final morphological diagnosis seem insufficiently high; sensitivity, specificity and accuracy are 95.5%; 89.7%; 90.3% respectively [21. 23. 24].

The reliability of determining Fuhrman grade varies from 46 to 85% [21–24]. It is important to remember that a biopsy provides only a "spot" assessment of morphology and does not characterize the entire tumor; its results are erroneous or non-informative in 10–15% of cases due to the heterogeneity of the lesion [21–25]. In addition, a biopsy is not always feasible due to the topographic and anatomical features of the tumor, and the procedure itself is invasive and is accompanied by complications with an incidence of 0.4 to 4.9% [21–25].

In this regard, the need to preoperatively obtain sufficiently complete and reliable information about the tumor morphology without invasive procedures with the risk of complications prevails in order to implement a personalized approach for determination of treatment tactics.

In the last decade, modern radiomics technology has found its application for the non-invasive morphological verification [22. 26].

This technology includes quantitative assessment of imaging methods, namely texture analysis, in comparison with clinical, morphological, genetic and other characteristics using intelligent analysis [22. 26].

For image analysis, intelligent data assessment is performed using computer programs (first, second and higher orders), models (which are characteristic of a particular image), transformation method (descriptive geometry of the general position of a figure relative to the projection plane to a particular one), namely DICOM (Digital Imaging and Communications in Medicine) [22. 26].

Currently, a number of studies have been carried out to evaluate the capabilities of texture analysis of 2D-DICOM data from CT and/or MRI and 3D tumor models in the prognosis of morphological verification [27–29]. There are few studies with texture analysis in predicting the nuclear anaplasia of the clear cell RCC, and their results are contradictory [30–32]. In this regard, further studies are required to analyze the capabilities of texture analysis in determining the Fuhrman grade.

Aim. To evaluate the capabilities of texture analysis of 3D models of the pathological process in differentiating the degree of nuclear anaplasia of the clear cell RCC.

Materials and methods. The retrospective study included 190 patients treated at the Institute of Urology and Human Reproductive Health of Sechenov University for the period from 2018 to 2022 (Table 1). All nephron-sparing procedures were performed using laparoscopic access. The average age of the patients was 57.2±10.8 years. There were 121 men (63.6%) and 69 women (36.4%).

To calculate the absolute tumor volume in mm3, the formula was used: V=4/3πR3. where V is the absolute volume of the tumor, π=3.14. R=(a+b+c):6; a, b, c are three measurements of the tumor, which were made in perpendicular directions according to the CT. In addition to the age and gender, body mass index, Charlson comorbidity index, and nephrometry scores (RENAL, PADOVA, C-index) were considered.

The analyzed group included patients with clear cell RCC. The Fuhrman grade was diagnosed in 67 (35%), G2 in 52 (27%), G3 in 62 (33%), and G4 in 9 (5%) cases.

All patients underwent CT preoperatively on multi-slice computed scanners Toshiba Aquilion One 640 or Toshiba Aquilion multi 320 (Japan). Study protocol 3 Phase Kidneys with the patient in supine position (shooting parameters: spiral study mode, slice thickness 0.5 mm, voltage 120 kV, current 80 mA, tube rotation speed 0.5 s), study area from the dome of the diaphragm to the pubic symphysis) with injection of intravenous contrast. The contrast agent contained an iodine in a concentration of 300–370 mg/ml (omnipaque, ultravist, vizipak). An average volume per study was 80–90 ml with an injection rate of 3.5–4 ml/sec.

All patients, based on DICOM CT data, underwent 3D virtual planning of procedures using the 3D modeling program "Amira" according to a previously described algorithm [33].

Performing texture analysis of 3D models included several stages, presented in fig. 1. Tumor segmentation was performed manually on 3D models by two experienced radiologists. The extracted 3D tumor models were assessed by the tumor shape (Fig. 2) with the calculation of three indicators using formulas 1–3:

Deviation is the ratio of the tumor volume to the volume of the ellipsoid (formula 1).

$$F_1 = \frac{V_t}{V_e}, \quad (1)$$

where Vt is the tumor volume, Ve is the volume of the ellipsoid.

Diameter ratio 1 is the ratio of the minimum length of the ellipsoid semi-axis to the maximum (formula 2).

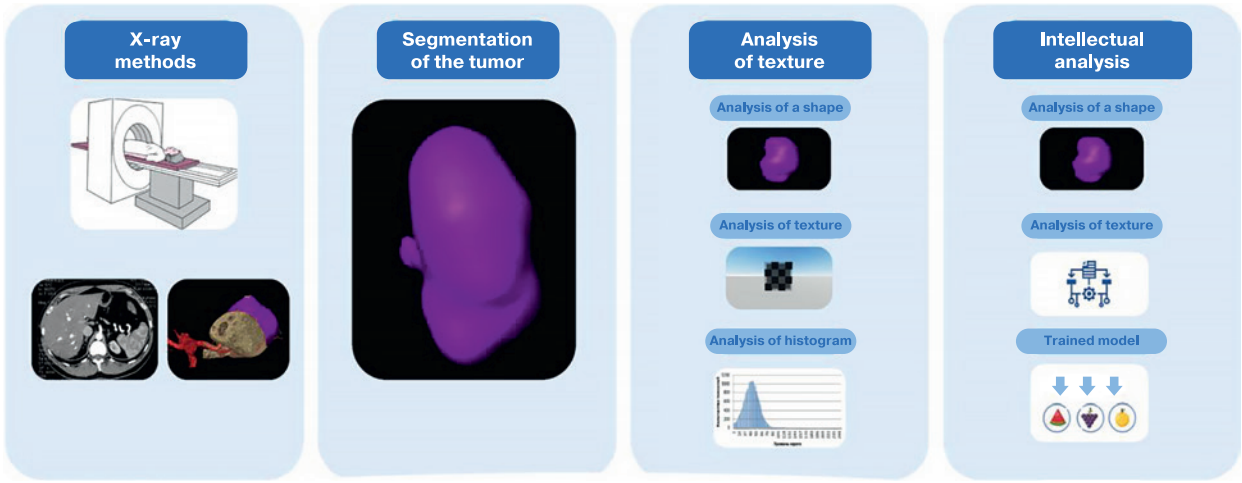

Fig. 1. Scheme of the radiomic process

$$F_2 = \frac{d_{min}}{d_{max}}, \quad (2)$$

where dmin is the minimum length of the semi-axis of the ellipsoid, dmax is the maximum length of the semi-axis of the ellipsoid.

Diameter ratio 2 is the ratio of the intermediate length of the ellipsoid semi-axis to the maximum (formula 3).

$$F_2 = \frac{d_{med}}{d_{max}}, \quad (3)$$

where dmed is the intermediate semi-axis of the ellipsoid along the length, dmax is the maximum semi-axis of the ellipsoid along the length.

Subsequently, texture analysis was performed and 300 texture features were extracted, consisting of first-, second-, and higher-order statistics.

To predict the degree of nuclear anaplasia of renal parenchymal tumors and the accuracy of classification, an intelligent analysis was performed. The prognostic model used the machine learning algorithm, Stochastic gradient descent and cross-validation k=5 with input parameters: first, second and higher order statistics, tumor shape and clinical data.

Results. In the study, patients were initially divided into three groups according to the Fuhrman grade. Patients with G4 tumors were not included in the classification due to the small number of observations (n=9). To build prognosis models, significant features were selected: kutrosis, dissimilarity, difference normalized, difference variance, inverse difference (normalized), homogeneity, contrast. The classification accuracy for the three groups (G1, 2 and 3) was 51.5% according to the F1 metric. Cross-validation k=5 was used. The accuracy of the prognosis is presented in the Table 2.

Due to the low quality of prognosis models and to take into account tumors of G4, patients were divided into two groups: the first group included those with G1/G2 (n=119), while the second group with G3/G4 (n=71).

To build the models, the following features were selected: tumor volume, Charlson comorbidity index, "Energy", first quartile and second decile of pixel brightness distribution. As a result, the accuracy of predicting the Fuhrman grade for two groups G1/2 and G3/4 was 72.2 according to the F1 metric. The accuracy of the prognosis is presented in the Table 3.

Discussion. Interpretation and analysis of DICOM data from imaging studies represents the subjective visual

Table 1

Distribution of patients according to clinical data and tumor grade

Age, years	58.94±11.3	54.67±11.78	57.12±8.63	56±11.34
Gender, m/f	47/20	34/18	40/22	05.апр
Absolute volume, tumors, mm³	33.04±34.43	29.04±37.8	62.86±106.55	42.5±58.95
Charlson index, score	2.02±1.45	1.67±1.35	2.08±1.44	2.6±1.67
Body mass index, kg/m²	29.84±5.52	28.5±5.41	29.5±5.1	28.16± 5.68
RENAL score	7.41± 1.99	7.06±2.17	7.92±1.81	6.8±1.79
PADUA score	8.31±1.54	8.35±2.13	8.92±1.92	
C-index	2.55 ±1.15	2.93±1.42	2.55±1.27	3.64±2.93
Volume of blood loss, ml	228.37±242.54	226.86±271.96	192.31±206.25	350±141.42
GFR prior to surgery, ml/min/m²	77.71±19.85	77.16±19.37	73.85±15.41	70.6±11.59
GFR 24 hours after surgery, ml/min/m²	72.94±17.84	68.47±20.29	65.85±13.9	61.4±21.76
Warm ischemia time, min	8.59±9.3	11.63± 9.25	12.54±7.72	18.8±3.83
Duration of the procedure, min	119.29±63.69	134.41±51.25	121.92±32.96	172±68.43

assessment by a radiologist. In conclusion, the specialist uses a small number of objective parameters that do not have significant differential diagnostic significance, such as the tumor size, topographic and anatomical relationships, the gradient of contrast enhancement in various phases in Hounsfield units (HU) on CT, signal intensity on MRI or standardized uptake value (SUV) on PET [34]. The human eyes recognize the texture of the image as a granular pattern consisting of different intensities of gray dots (pixels). However, images have a number of features of different orders, a certain brightness, color size, roughness, directionality, randomness, smoothness, granulation, etc., the assessment of which is incomplete, insufficiently significant and operator dependent [34].

Texture analysis of images provide much more information about the structural and functional characteristics of biological objects, so the use of radiomics is an important issue in processing and understanding the image.

The Fuhrman classification system is the most widely used by morphologists and is an independent predictor of the "aggressiveness" of clear cell and papillary RCC variants [35]. Accordingly, for G1, 2, 3 and 4, 5-year cancer-specific survival rate was 84.60%, 60.50. 11.54 and 6.40%, respectively [5].

Determining the biological nature of RCC or the likely "aggressiveness" of the cancer at the stage of planning the patient's treatment tactics can provide significant support to the doctor in making a decision on the optimal treatment method: surgical removal and its type (nephron-sparing and/or radical), ablation and/or active surveillance.

Since the accuracy of percutaneous biopsy of renal parenchymal tumors in determining the Fuhrman grade is low due to significant systematic error, preoperative recognition of the biological nature of RCC is still problematic.

In our study, the accuracy of predicting the Fuhrman grade for two groups (G1/2 and G3/4) was 72.2 according to the F1 metric using the machine learning algorithm of Stochastic Gradient Descent and cross-validation k=5. A distinctive feature of our study is the use of texture analysis with 3D models of renal parenchymal tumors. Segmented volumetric tumor models included all CT phases. In a number of studies, one or more phases of CT are used to predict the degree of nuclear anaplasia for texture analysis.

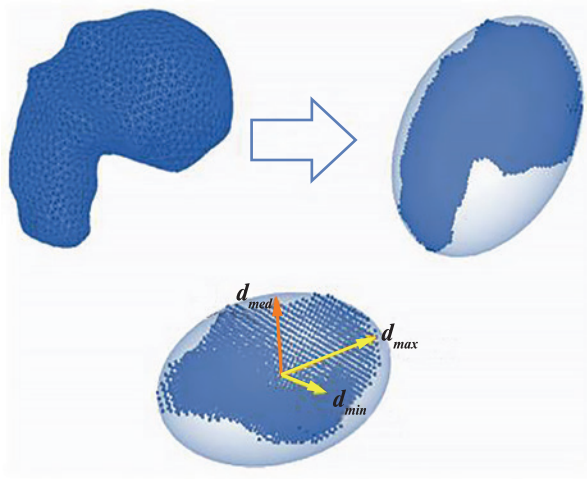

Fig. 2. Finding the minimum volume ellipsoid describing the tumor and its characteristics

For example, in a study of Bektas et al. textural features were extracted from the venous phase in 53 patients with clear cell RCC, divided into 2 groups: 31 low-grade (G1/2) and 23 high-grade (G3/4). The mining used several machine learning algorithms for classification purposes. The highest predictive accuracy was obtained when using the support vector machine algorithm (SVM-support vector machines). SVM-accuracy of the classifier prognosis in two groups (G1/2 and G3/4) was 85.1% [30].

In our opinion, to develop a prognostic model for classifying the degree of nuclear anaplasia of the clear cell RCC, along with textural features, it is necessary to use the tumor shape. We used three calculated values for the shape of tumors. Our assumption is confirmed by the

Table 2

Calculated prognosis accuracy for tumors of G1, G2 and G3

	Clear-cell G1	Clear-cell G2	Clear-cell G3	Σ
Clear-cell G1	30	15	22	**67**
Clear-cell G2	17	26	9	**52**
Clear-cell G3	19	10	42	**71**
Σ	**66**	**51**	**73**	**190**

Table 3

Calculated prognosis accuracy for tumors of G1/2- and G3/4-grade

		Prognosis		
		Clear-cell G1-2	Clear-cell G3-4	Σ
Actual	Clear-cell G1-2	89.1%	10.9%	**119**
	Clear-cell G3-4	52.1%	47.9	**71**
	Σ	**143**	**47**	**190**

work of Luo et al., where texture analysis was performed in the non-contrast and excretory phases of CT in 177 patients with clear cell RCC (124 G1/2. and 53 G3/4), the highest prognostic accuracy of 81% in models with the inclusion of tumor shape [31].

The calculated tumor volume was found to be a significant factor for the Fuhrman nuclear differentiation classifier.

To some extent, our results are consistent with the study of Kierans et al. They performed texture analysis of MRI in 61 patients with clear cell RCC, and multivariate regression analysis found that tumor size (p=0.013), asymmetry (p=0.012) and matrix match correlation (p=0.030) were significant independent predictors of nuclear anaplasia G3/4 [32].

In addition to the tumor volume, we noted the importance of the Charlson comorbidity index in predicting the Fuhrman grade.

The comorbidity index is calculated with a consideration of patient's age and concomitant diseases [36]. Another important point is an evaluation of the Charlson comorbidity index in predicting the Fuhrman grade. Moreover, the majority of concomitant diseases that increase the Charlson comorbidity index are associated with metabolic syndrome: diabetes mellitus, hypertension, coronary heart disease. According to various researchers, these disorders affect the overall survival and "biological potential" of RCC [37–39].

The positive aspects of our study are the implementation of radiomics of 3D tumor models based on the assessment of all four phases of contrast-enhanced CT of the abdominal cavity, and the use of an expanded set of data in prognosis, including clinical and demographic factors, as well as features of renal tumor.

The disadvantages included the small sample and insufficient number of patients with the G4 tumors. In addition, our study was single-center and retrospective.

It is necessary to carry out multicenter studies with a large number of patients in order to validate radiomics in medicine and to determine a personalized approach in choosing treatment tactics for patients with RCC.

Conclusion. The use of texture analysis of 3D models in the predicitng the Fuhrman grade of ccRCC demonstrated satisfactory quality of the models for two groups (G1/2 and G3/4) of cellular anaplasia.

ЛИТЕРАТУРА/REFERENCES

1. *Bhupender S.* Chhikara, Keykavous Parang. Global Cancer Statistics 2022: The Trends Projection Analysis Chem. Biol. Lett. 2023;10(1):451.
2. *Sung H., Ferlay J., Siegel R. et al.* Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71(3):209–249.
3. *Merabishvili V.M., Poltoratsky A.N., Nosov A.K., etc.* The state of cancer care in Russia. Kidney cancer (morbidity, mortality, reliability of accounting, one-year and one-year mortality, histological structure). Part 1. Oncourology 2021;17(2):182–194. Russian (Мерабишвили В.М., Полторацкий А.Н., Носов А.К. и др. Состояние онкологической помощи в России. Рак почки (заболеваемость, смертность, достоверность учета, одногодичная и погодичная летальность, гистологическая структура). Часть 1. Онкоурология 2021;17(2):182–194).
4. *Fuhrman S.A., Lasky L.C., Limas C.* Prognostic significance of morphologic parameters in renal cell carcinoma. Am J Surg Pathol. 1982;6(7):655–663.
5. *Erdoğan F., Demirel A., Polat Ö.* Prognostic significance of morphologic parameters in renal cell carcinoma. Int J Clin Pract. 2004;58(4):333–336
6. *Ljungberg B, Cowan NC, Hanbury DC, Hora M, Kuczyk MA, Merseburger AS, et al.* EAU guidelines on renal cell carcinoma: the 2010 update. Eur Urol. 2010;58:398–406.
7. *Pantuck AJ, Zeng G, Belldegrun AS, Figlin RA.* Pathobiology, prognosis, and targeted therapy for renal cell carcinoma: exploiting the hypoxia-induced pathway. Clin Cancer Res 2003;9:4641–4652.
8. *Davaro F., Roberts J. et al* Robotic surgery does not afect upstaging of T1 renal masses Journal of Robotic Surgery, 2019.
9. *Alyaev Yu.G., Glybochko P.V., Pushkar D.Yu.* Russian clinical guidelines for urology. 2016. M., GEOTAR-Media. 496 p. Russian (Аляев Ю.Г., Глыбочко П.В., Пушкарь Д.Ю. Российские клинические рекомендации по урологии. 2016. М., ГЭОТАР-Медиа. 496 с.).
10. *Patel H.D. Semerjian A. et al.* Surgical removal of renal tumors with low metastatic potential based on clinical radiographic size: A systematic review of the literature. Urologic Oncology: Seminars and Original Investigations. 2019;37:519−524.
11. *Fujii Y., Komai Y., Saito K. et al.* Incidence of benign pathologic lesions at partial nephrectomy for presumed RCC renal masses: Japanese dual-center experience with 176 consecutive patients. Urology. 2008;72:598–602.
12. *Frank I., Blute M.L., Cheville J.C., et al:* Solid renal tumors: an analysis of pathological features related to tumor size. J Urol. 2003;170:2217–2220.
13. *Kim J.H., Li S., Khandwala Y., Chung K.J., Park H.K., Chung B.I.* Association of prevalence of benign pathologic fifindings after partial nephrectomy with preoperative imaging patterns in the United States from 2007 to 2014. JAMA Surg. 2019;154:225–231.
14. *Snyder M.E., Bach A., Kattan M.W., Raj G.V., Reuter V.E., Russo P.* Incidence of benign lesions for clinically localized renal masses smaller than 7 cm in radiological diameter: influence of sex. J Urol. 2006;176:2391–2395.
15. *Zhang L., Li XS., Zhou LQ.* (2016) Renal Tumor Biopsy Technique. Chinese Medical Journal; 2016;20:1236–1240.
16. *Kay F.U., Pedrosa I.* Imaging of Solid Renal Masses. Radiologic Clinics of North America. 2017;55(2):243–258.
17. *Reznek R.H.* CT/MRI in staging renal cell carcinoma. Cancer Imaging 2004; 4(spec no A):S25–S32.
18. *Cornelis F., Tricaud E. et al.* Routinely performed multiparametric magnetic resonance imaging helps to differentiate common subtypes of renal tumours. European Society of Radiology. 2014.
19. *Kang S.K., Zhang A., Pandharipande P.V., et al.* DWI for renal mass characterization: systematic review and meta-analysis of diagnostic test performance. AJR Am J Roentgenol. 2015;205(2):317–324.
20. *Gündoğana C., Çermika TF., et al.* Role of contrast-enhanced 18F-FDG PET/CT imaging in the diagnosis and staging of renal tumors. Nuclear Medicine Communications. 2018;39:1174–1182.
21. *Zhang L., Li X.S., Zhou L.Q.* Renal Tumor Biopsy Technique. Chin Med J. 2016;129:1236–1240.
22. *Roussel E., Capitanio U. et al.* Novel Imaging Methods for Renal Mass Characterization: A Collaborative Review European urology. 2022;81:476–488.
23. *Marconi L, Dabestani S, Lam TB, et al.* Systematic review and meta-analysis of diagnostic accuracy of percutaneous renal tumour biopsy. Eur Urol. 2016;69(4):660–673.
24. *Princea J., Bultman E. et al.* Patient and tumor characteristics can predict nondiagnostic renal mass biopsy findings. J Urol. 2015;193(6):1899–1904.
25. *Haider Rahbar, Sam Bhayani et al.* Evaluation of Renal Mass Biopsy Risk Stratification Algorithm for Robotic Partial Nephrectomy – Could a Biopsy Have Guided Management? The journal of urology. 2014;192:1337–1342.
26. *Ognerubov N.A., Shatov I.A., Shatov A.V.* Radiogenomics and radiomics in the diagnosis of malignant tumors: literature review. Bulletin of the Tambov University. Natural and Technical Sciences series. Tambov, 2017;22(6):1453-1460. Russian (Огнерубов Н.А., Шатов И.А., Шатов А.В. Радиогеномика и радиомика в диагностике злокачественных опухолей: обзор литературы. Вестник Тамбовского университета. Серия Естественные и технические науки. Тамбов, 2017;22(6):1453–1460).
27. *Davnall F., Yip C.S., Ljungqvist G., Selmi M., Ng F., Sanghera B. et*

al. Assessment of tumor heterogeneity: an emerging imaging tool for clinical practice? Insights Imaging. 2012;3 (6):573–589.
28. *Varghese B.A., Chen F., Hwang D.H., Cen S.Y., Desai B., Gill I.S.* и др. Differentiation of Predominantly Solid Enhancing Lipid-Poor Renal Cell Masses by Use of Contrast Enhanced CT: Evaluating the Role of Texture in Tumor Subtyping. AJR Am J Roentgenol. 2018;211(6):W288-W296.
29. *Nie P., Yang G., Wang Z., Yan L., Miao W., Hao D.* и *др.* A CT-based radiomics nomogram for differentiation of renal angiomyolipoma without visible fat from homogeneous clear cell renal cell carcinoma. EurRadiol. 2020;30(2):1274–1284.
30. *Bektas C.T., Kocak B., Yardimci A.H., Turkcanoglu M.H., Yucetas U., Koca S.B., et al.* Clear Cell Renal Cell Carcinoma: Machine Learning-Based Quantitative Computed Tomography Texture Analysis for Prediction of Fuhrman Nuclear Grade. Euro Radiol 2019; 29(3):1153–1163. https://doi.org/10.1007/s00330-018-5698-2
31. *Luo S., Wei R., Lu S., Lai S., Wu J., Wu Z., Pang X., Wei X., Jiang X., Zhen X., Yang R.* Fuhrman nuclear grade prediction of clear cell renal cell carcinoma: influence of volume of interest delineation strategies on machine learning-based dynamic enhanced CT radiomics analysis. European Radiology. 2022;32:2340–2350.
32. *Kierans A.S., Rusinek H., Lee A., et al.* Textural Differences in apparent diffusion coeffificient between low- and high-stage clear cell renal cell carcinoma. Am J Roentgenol. 2014; 203:W637–W644. Doi:10.2214/AJR.14.12570.
33. *Alyaev Yu.G., Sirota E.S., Proskura A.V.* Digitalization of operations for kidney tumors. M.: GEOTAR-Media, 2021. p. 10-35. Russian (Аляев Ю.Г., Сирота Е.С., Проскура А.В. Цифровизация операций при опухоли почки. М.: ГЭОТАР-Медиа, 2021:10–35).
34. *Sirota E.S., Gorduladze D.N., Rapoport L.M., Gridin V.N., Tsarichenko D.G., Kuznetsov I.A., Bochkarev P.V., Alyaev Yu.G.* Noninvasive morphological diagnostics of localized formations of the renal parenchyma (pilot study). REJR 2021;11(4):94–104. Doi: 10.21569/2222-7415-2021-11-4-94-10. Russian (Сирота Е.С., Гордуладзе Д.Н., Рапопорт Л.М., Гридин В.Н., Цариченко Д.Г., Кузнецов И.А., Бочкарёв П.В., Аляев Ю.Г. Неинвазивная морфологическая диагностика локализованных образований паренхимы почки (пилотное исследование). REJR 2021;11(4):94–104. Doi: 10.21569/2222-7415-2021-11-4-94-104).
35. *Minardi D., Lucarini G., Mazzucchelli R. et al.* Prognostic role of Fuhrman grade and vascular endothelial growth factor in pT1a clear cell carcinoma in partial nephrectomy specimens. J Urol. 2005;174:1208–1212.
36. *Charlson M.E., Pompei P., Ales K.L., MacKenzie C.R.* A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–383. Doi: 10.1016/0021-9681(87)90171-8. PMID: 3558716.
37. *Huang H., Chen S., Li W., Wu X., Xing J.* High perirenal fat thickness predicts a poor progression-free survival in patients with localized clear cell renal cell carcinoma. Urol Oncol. 2018;36(4):157.e1-157.e6. Doi: 10.1016/j.urolonc.2017.12.011.
38. *Zheng Y., Bao L., Wang W., Wang Q., Pan Y., Gao X.* Prognostic impact of the Controlling Nutritional Status score following curative nephrectomy for patients with renal cell carcinoma. Medicine. 2018;97:e13409.
39. *Kang H.W., Kim S.M., Kim W.T., Yun S.J., Lee S.C., Kim W.J., Hwang E.C., Kang S.H., Hong S.H., Chung J., Kwon T.G., Kim H.H., Kwak C., Byun S.S., Kim Y.J.* KORCC (KOrean Renal Cell Carcinoma) Group. The age-adjusted Charlson comorbidity index as a predictor of overall survival of surgically treated non-metastatic clear cell renal cell carcinoma. J Cancer Res Clin Oncol. 2020;146(1):187–196. Doi: 10.1007/s00432-019-03042-7.

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PREOPERATIVE FACTORS AFFECTING A RATE OF TRIFECTA AND PENTAFECTA ACHIEVEMENT AFTER PARTIAL NEPHRECTOMY

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Introduction. Trifecta and pentafecta parameters have been described in modern literature to better define success following partial nephrectomy (PN). In this study an association between patient- and tumor-specific variables with achievement of trifecta and pentafecta was examined in order to better predict outcomes following PN.

Aim. To define preoperative parameters that predict achievement of trifecta and pentafecta following PN.

Materials and methods. A total of 1218 open PN were performed by a single experienced surgeon between Jan 2010 and Dec 2019 for localized renal cell cancer in S.P. Botkin Moscow City Clinical Hospital. From prospective database we retrospectively analyzed the patient-related (age, sex, body mass index, hypertension, cardiovascular disease, hemoglobin, estimated glomerular filtration rate [eGFR], preoperative chronic kidney disease stage) and tumor-related (R.E.N.A.L score, renal mass size and intraparenchymal tumor location index) as potential predictive factors.

Results. The outcomes of PN performed in 1114 patients were analyzed. Trifecta was achieved in 705 cases (78.0%). Among the 632 patients with eGFR available at 12 months following robot-assisted PN, pentafecta was achieved in 180 cases (28.5%). Tumor size less then 4 cm (OR= 3.17, 95% CI 1.73–5.84, p<0,001), extraparenchymal tumor location (OR= 2.78, 95% CI 1.54–5.44, p<0,001) and lower R.E.N.A.L. score (6 vs 9) were all associated with increased odds of achieving trifecta (OR 3.37, CI=1,94–6,27, p < 0.001). Preoperative eGFR less then 60 ml/min was associated with pentafecta achievement (OR=2.73, 95% CI 1.62–5.21, p<0,001) as well as above mentioned variables associated with trifecta.

Conclusion: Preoperative R.E.N.A.L score was the only variable associated with achieving trifecta and pentafecta following robot-assisted PN, while kidney function indicators was associated with pentafecta achievement.

K e y w o r d s: renal tumor, trifecta, pentafecta, partial nephrectomy, RCC

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Introduction. Currently, partial nephrectomy (PN) has replaced radical nephrectomy as the gold standard for treatment of localized renal cancer [1–3]. To further improve the quality of treatment for patients with localized tumors, it is necessary to develop an organ-preserving strategy aimed at achieving a better functional result while preserving its oncologic safety. Thus, in order to assess the short- and long-term results of PN, such terms as trifecta and pentafecta have appeared in modern literature. The trifecta involves the short-term results of PN and includes the following indicators: warm ischemia time (WTI) ⩽25 minutes, negative surgical margins, and no serious perioperative complications (Clavien-Dindo >2) [4]. Pentafecta describes long-term postoperative results, including, in addition to the trifecta, preservation of the glomerular filtration rate (GFR) of more than 90% and the absence of an increase in the stage of chronic kidney disease (CKD) at the 12th month [5]. The present study demonstrated the relationship between preoperative patient characteristics, as well as the tumor itself, and trifecta and pentafecta rates in order to identify predictors that influence on the PN outcomes.

Aim. To determine preoperative factors influencing the trifecta and pentafecta rate after PN.

Materials and methods. In the period from January 2010 to December 2019 a total of 1218 nephron-sparing procedures for localized kidney cancer was performed in the urological clinic of the RMANPO on the basis of the City Clinical Hospital named after S.P. Botkin. Exclusion criteria were a history of PN (*n*=24), more than one tumor removed (*n*=37), a tumor of a single kidney (*n*=44), absence of follow-up (*n*=181), and refusal to participate in study (*n*=28). Thus, the final sample included 904 PN. The following prognostic factors were analyzed: age, gender, body mass index (BMI), arterial hypertension, cardiovascular disease, hemoglobin level, GFR, baseline CKD (patient characteristics); R.E.N.A.L score [6], tumor size, endophytic growth (tumor characteristics); warm ischemia time, surgical margin status, postoperative GFR (intra- and postoperative outcomes). Complications were assessed according to the international Clavien–Dindo classification [7]. All procedures were performed by the same surgeon, with 58.2% (*n*=535) using the preventive suture technique

we described previously [8, 9], including 89.5% (n=479) without clamping renal pedicle. The remaining PN were done according to the classical technique (n=369). The tumor size was determined on computed tomography (CT) or, as alternative, magnetic resonance imaging in three sections, after which the largest size was selected. The endo- or exophytic growth was also determined according to CT, where, after a step-by-step measurement of a tumor size in three planes, the ratio of the intra- and extraparenchymal parts was found. CKD progression was assessed after 12 months, and GFR was calculated using MDRD formula (Modification of Diet in Renal Disease Study), 2006. GFR less than 60 ml/min was chosen as a preoperative indicator, since it corresponded to chronic renal failure. Logistic regression models were used to assess the association of preoperative characteristics with trifecta and pentafecta. Odds ratios (ORs) and 95% confidence intervals (CIs) for numerical factors were based on the decrease in the predictor variable equivalent to the interquartile range (25th percentile minus 75th percentile). In univariate analysis, Holm's test was used to correct for multiple variables (i.e., p<0.007 was considered significant) [10]. Since we had less than ten indicators per predictor, we used LASSO (Least Absolute Shrinkage and Selection Operator) regression as a method for estimating linear regression model coefficients, complemented by a Bayesian information criterion [11, 12]. To finalize the prognostic model, variables selected using the LASSO method were entered into the logistic regression structure. Model calibration was carried out by assessing the actual and predicted probabilities of the outcome. For actual results, Wilson's method was performed for estimating single proportion CIs. Univariable logistic regression models were used to determine prediction estimates and corresponding 95% CIs. Discrimination ability was assessed using ROC curves. All analyzes were performed using SAS (version 9.4, SAS Institute Inc., Cary, NC) and SAS PROC HPGENSELECT software.

Results. The outcomes of PN in 1114 patients were analyzed. The preoperative data and tumor characteristics are shown in *Table 1*. The trifecta was achieved in 705 (78.0%) cases. The relationship between the trifecta elements and preoperative data is shown in *Table 2*. A tumor size, R.E.N.A.L score, as well as the tumor location have a significant impact on trifecta rate after PN. Tumor size less than 4 cm (OR = 3.17, 95% CI: 1.73 –5.84; p<0.001) and lower R.E.N.A.L. score (OR [6 vs. 9] = 3.37, 95% CI: 1.94–6.27; p<0.001), exophytic growth (OR=2.78, 95% CI: 1.54–5.44; p<0.001) correlates with trifecta rate. However, there were no significant association with other preoperative factors (p⩾0.28). In addition, ROC analysis also showed similar results. In case of tumor size less than 4 cm, AUC was 0.63 (95% CI: 0.58–0.75), while for R.E.N.A.L. score 0.71 (95% CI: 0.63–0.78), and exophytic growth 0.61 (95% CI: 0.56–0.73). However, univariate and multivariate analyses showed no significant differences only for R.E.N.A.L. score. It should be noted that tumor size and location are elements of R.E.N.A.L score, which can explain these results. Considering this, we carried out an additional analysis by dividing R.E.N.A.L. score into three categories (4–6, 7–9 and 10–12), which is graphically displayed in *Fig. 1*. In case R.E.N.A.L. score was from 4 to 6, 95.2% of patients had the trifecta, compared to 85.1% for R.E.N.A.L. score from 7 to 9 and only 64.8% for R.E.N.A.L. score 10–12. AUC for the these R.E.N.A.L. values was 0.71 (95% CI: 0.63–0.78), and 0.71 (95% CI: 0.62–0.78) after calibration by bootstrapping with 1000 resamples. Cumulative GFR at 12 months

Table 1

Preoperative and postoperative characteristics of patients after PN

Number of patients	904
Preoperative patients' factors	
Average age (IQR), years	61 (53. 69)
Men, *n* (%)	523 (57.9)
Average BMI (IQR), kg/m^2	28.7 (25.4. 32,1)
Arterial hypertension, *n* (%)	532 (58.8)
Cardiovascular diseases, *n* (%)	223 (24.7)
GFR less than 60 ml/min, *n* (%)	170 (18.8)
Mean hemoglobin level (IQR), g/dl	13.8 (12.7. 14.7)
Preoperative tumor factors	
Tumor size more than 4 cm, *n* (%)	253 (28.0)
Average R.E.N.A.L. score (IQR)	8 (6.9)
Number of intraparenchymal tumors, *n* (%)	185 (20.5)
Postoperative factors	
Trifecta rate, *n* (%)	705 (78.0)
Pentafecta rate, *n* (%)	180 (28.5)
Pathomorphological features of the tumor	
Clear cell renal cell carcinoma, *n* (%)	505 (55.9)
Papillary renal cell carcinoma, *n* (%)	127 (14.0)
Chromophobic renal cell carcinoma, *n* (%)	53 (5.9)
Other tumors, *n* (%)	45 (5.0)
Oncocytoma, *n* (%)	90 (10.0)
Other benign types, *n* (%)	83 (9.2)

IQR – interquartile range, BMI – body mass index, GFR – glomerular filtration rate, RCC – renal cell carcinoma.

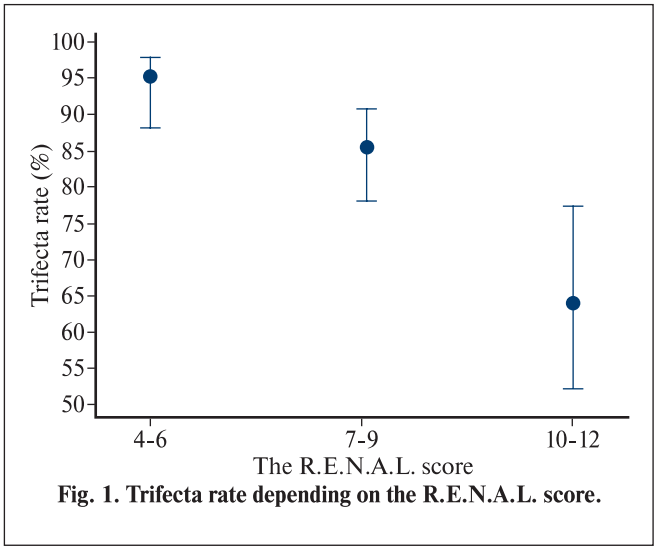

Fig. 1. Trifecta rate depending on the R.E.N.A.L. score.

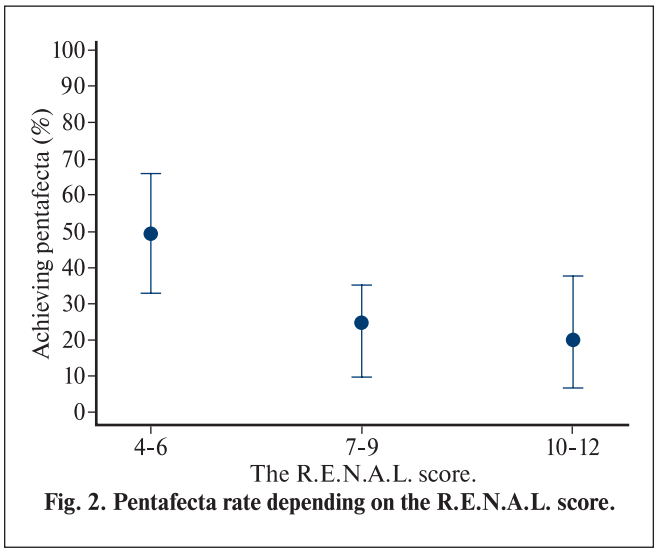

Fig. 2. Pentafecta rate depending on the R.E.N.A.L. score.

after surgery was determined in 632 patients; in 30.1% of patients (n=272) it was not possible for various reasons. Thus, pentafecta was achieved in 180 (28.5%) patients. The relationship between pentafecta elements and preoperative characteristics is shown in Table 3.

As shown in *Table 3*, similarly to the trifecta, tumor size less than 4 cm (OR=2.61, 95% CI: 1.56–5.01; p<0.001), R.E.N.A.L. score less than 6 (OR =2.91 [6 vs 9], 95% CI: 1.61–5.13; p<0.001) and exophytic growth (OR=2.42, 95% CI: 1.49–4 .87; p<0.001) correlate with achieving pentafecta. It should be noted that GFR level of less than 60 ml/min has a significant effect on pentafecta rate (OR = 2.73, 95% CI: 1.62–5.21; p<0.001). The above results were also confirmed by ROC analysis: when assessing tumor size less than 4 cm, AUC was 0.61 (95% CI: 0.56–0.74), compared to 0.69 (95% CI: 0.6–0.7) for R.E.N.A.L. score, 0.58 (95% CI: 0.54–0.71) for exophytic growth, and 0.57 (95% CI: 0.53–0.69) for GFR less than 60 ml/min. On the other hand, when using LASSO regression, only R.E.N.A.L. score and GFR level less than 60 ml/min were predictors of achieving pentafecta, which was also confirmed by univariate and multivariate analyses. Further, as for trifecta, we divided R.E.N.A.L. scores into three groups. With R.E.N.A.L. score from 4 to 6 pentafecta was achieved in 49.3% of patients, compared to 24.1% for scores 7–9 and 19.4% for scores 10–12, which is graphically displayed in *Fig. 2.* After dividing R.E.N.A.L score into subgroups, AUC was slightly lower (0.69; 95% CI: 0.61–0.71).

Discussion. Organ-preserving procedure is the gold standard for treatment of localized kidney cancer. In 2014, the European Association of Urology included PN for surgical treatment of cT2 tumors [13]. Approximately 25% of patients with renal cancer, normal preoperative creatinine levels and a normal contralateral kidney have CKD stage 3 or higher at baseline, and in 16–40% of cases, CKD develop after surgery [14]. Obviously, the functional results of PN will vary depending on both patient's and tumor's characteristics, which dictates the need to study the influence of preoperative factors. Based on more than 1000 PN, we analyzed the influence of preoperative patient-, procedure- and tumor-related factors on the achievement of the trifecta and pentafecta. There are currently a number of systems available for assessing the complexity of renal tumors. In the current study we used one of the most popular R.E.N.A.L. score. Our analysis showed that the tumor size, the R.E.N.A.L score and the tumor location significantly influence on the tri-

Table 2

The influence of preoperative characteristics on trifecta rate after PN (n=904)

Parameter	Univariate analysis of the trifecta rate after PN	
	OR (95% CI)	p-value
Age (53 vs. 69 years old)	1.04 (0.70–1.55)	0.90
Gender (female vs. male)	1.21 (0.65–2.30)	0.54
BMI (25.4 vs. 32.1 kg/m^2)	1.07 (0.75–1.46)	0.73
Arterial hypertension (yes vs. no)	1.28 (0.68–2.34)	0.53
CVD (yes vs. no)	1.45 (0.70–2.78)	0.24
Hemoglobin level (12.7 vs. 14.7 g/dl)	0.85 (0.60–1.20)	0.32
GFR (more or less 60 ml/min)	1.51 (0.73-2.84)	0.20
Tumor size (more or less 4 cm)	3.17 (1.73–5.84)	<0.001
R.E.N.A.L. score (6 vs. 9 points)	3.38 (1.94–6.27)	<0.001
Tumor location (exophytic vs. endophytic)	2.78 (1.54–5.44)	<0.001

BMI – body mass index, CVD – cardiovascular disease, GFR – glomerular filtration rate. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using univariable logistic regression models. After Holm's correction for multiple testing, a p value <0.007 was considered significant.

Table 3

The influence of preoperative characteristics on the frequency of achieving pentafecta after PN (*n*=632)

Parameter	Univariate analysis of the trifecta rate after PN	
	OR (95% CI)	*P*-value
Age (55 vs. 70 years)	1,01 (0,60–1,63)	0,97
Gender (female vs. male)	1,06 (0,52–2,20)	0,91
BMI (25.9 vs. 33.3 kg/m^2)	1,01 (0,64–1,58)	0,98
Arterial hypertension (yes vs. no)	1,84 (0,85–3,75)	0,01
CVD (yes vs. no)	1,80 (0,76–4,82)	0,22
Hemoglobin level (12,8 vs. 14,7 g/dl)	0,95 (0,64–1,44)	0,76
GFR (more or less 60 ml/min)	2,73 (1,62–5,21)	<0,001
Tumor size (more or less 4 cm)	2,61 (1,56–5,01)	< 0,001
R.E.N.A.L. score (6 vs. 9 points)	2,91 (1,65–5,31)	< 0,001
Tumor location (exophytic vs. endophytic)	2,42 (1,49–4,87)	< 0,001

BMI – body mass index, CVD – cardiovascular disease, GFR – glomerular filtration rate. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using univariable logistic regression models. After Holm's correction for multiple testing, a p value <0.007 was considered significant.

fecta and pentafecta rate after PN. Castellucci et al. [15] also analyzed preoperative factors which are associated with achievement of trifecta and pentafecta. They identified age as a predictor of the pentafecta, but no factors were identified that correlated with the trifecta. However, in this study tumor assessment using the R.E.N.A.L. score was not included. In addition, with increasing the R.E.N.A.L. score, there is also an increase in warm ischemia time [16]. Kim et al. [17] also found that the R.E.N.A.L. may predict achieving pentafecta. In addition, they focus on the "L" score, since it has the greatest prognostic value for achieving pentafecta in T1a and T1b tumors. Thus, our analysis demonstrates excellent oncological results of PN regardless a tumor size and good functional results in small kidney tumors. The efficiency of preserving renal function decreases with large tumors and in patients with deterioration in renal function at baseline. Ten years of experience in performing open PN became the basis for the development of novel minimally invasive techniques.

Conclusion. Preoperative R.E.N.A.L. nephrometric score and renal function are the only criteria associated with trifecta and pentafecta for open PN.

REFERENCES

1. *Cozar J.M., Tallada M.* Open partial nephrectomy in renal cancer: a feasible gold standard technique in all hospitals. Adv Urol. 2008;2008:916463. Doi: 10.1155/2008/916463. PMID: 18769498; PMCID: PMC2522334.
2. *Van Poppel H., Joniau S., Goethuys H.* Open partial nephrectomy for complex tumours and >4 cm: Is it still the gold standard technique in the minimally invasive era? Arch Esp Urol. 2013;66(1):129–138. PMID: 23406808.
3. *Derweesh I.H., Staehler M., Uzzo R.G.* A Return to the Days of Radical Nephrectomy as the "Gold Standard" for Localized Renal Cell Carcinoma? Not So Fast. Eur Urol. 2019;75(4):546–547. Doi: 10.1016/j.eururo.2019.01.003. Epub 2019 Jan 14. PMID: 30655089.
5. *Zargar H., Allaf M.E., Bhayani S. et al.* Trifecta and optimal perioperative outcomes of robotic and laparoscopic partial nephrectomy in surgical treatment of small renal masses: a multiinstitutional study. BJU Int. 2015;116:407–414. https://doi.org/10.1111/bju.12933
6. *Kutikov A., Uzzo R.G.* The RENAL nephrometry score: a comprehensive standardized system for quantitating renal tumor size, location and depth. J Urol. 2009;182:844–853. https://doi.org/10.1016/j.juro.2009.05.035
7. *Dindo D., Demartines D., Clavien P.A.* Classifcation of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205–213.
8. *Indarokov T.R., Seregin A.V., Loran O.B., Shustitskiy N.A., Morozov A.D., Yandiev A.M., Bessolova O.V.* Preventive hemostatic suture during open kidney resection as an option to preserve the renal function. Cancer Urology. 2017;13(3):39-45. https://doi.org/10.17650/1726-9776-2017-13-3-39-45. Russian (Индароков Т.Р., Серегин А.В., Лоран О.Б., Шустицкий Н.А., Морозов А.Д., Яндиев А.М., Бессолова О.В. Превентивный гемостатический шов при открытой резекции почки как один из способов сохранения почечной функции. Онкоурология. 2017;13(3):39–45. https://doi.org/10.17650/1726-9776-2017-13-3-39-45).
9. *Seregin A.V., Shustitskiy N.A., Indarokov T.R., Morozov A.D., Bessolova O.V.* Partial nephrectomy using preventive hemostatic suture in renal cell carcinoma patients. Annaly khirurgii (Annals of Surgery, Russian journal). 2016; 21 (4): 235–239). Doi: 10.18821/1560-9502-2016-21-4-235-239. Russian (Серегин А.В., Шустицкий Н.А., Индароков Т.Р., Морозов А.Д., Бессолова О.В. Резекция почки с превентивным швом при почечно-клеточном раке. Анналы хирургии. 2016; 21 (4): 235–239. Doi: 10.18821/1560-9502-2016-21-4-235-239).
10. *Holm S.* A simple sequentially rejective multiple test procedure. Scand J Stat. 1979;6:65–70.
11. *Peduzzi P., Concato J., Kemper E., Holford T.R., Feinstein A.R.* A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol. 1996;49:1373–1379.
12. *Tibshirani R.* Regression shrinkage and selection via the lasso. J R Stat Soc Ser B Stat Methodol. 1996;58:267–288.
13. *Ljungberg B., Bensalah K., Canfeld S., et al.* EAU guidelines on renal cell carcinoma: 2014 update. Eur Urol. 2015;67:913–924. https://doi.org/10.1016/j.eururo.2015.01.005
14. *Lane B.R. et al.* Surgically Induced Chronic Kidney Disease May be Associated with a Lower Risk of Progression and Mortality than Medical Chronic Kidney Disease. Journal of Urology. 2013;5(189):1649–1655.
15. *Castellucci R., Primiceri G., Castellan P., Marchioni M., D'Orta C., Berardinelli F., Neri F., Cindolo L., Schips L.* Trifecta and Pentafecta Rates After Robotic Assisted Partial Nephrectomy: Comparative Study of Patients with Renal Masses <4 and ⩾4 cm. J Laparoendosc Adv Surg Tech A. 2018;28(7):799–803. Doi: 10.1089/lap.2017.0657. Epub 2018 Mar 1. PMID: 29493436.
16. *Mayer W.A., Godoy G., Choi J.M., Goh A.C., Bian S.X., Link R.E.* Higher RENAL nephrometry score is predictive of longer warm ischemia time and collecting system entry during laparoscopic and robotic-assisted partial nephrectomy. Urology. 2012;79:1052–1056. https://doi.org/10.1016/j.urology.2012.01.048
17. *Kim D.K., Kim L.H.C., Raheem A.A. et al.* Comparison of trifecta and

pentafecta outcomes between T1a and T1b renalmasses following robot-assisted partial nephrectomy (RAPN) with minimum 1 year follow up: can RAPN for T1b renal masses be feasible? PloS One.2016;11:e0151738. https://doi.org/10.1371/journal.phone.0151738

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CLINICAL CASE

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LAPAROSCOPIC RIGHT-SIDE PARTIAL NEPHRECTOMY WITH FLUORESCENCE IMAGING IN THE NEAR INFRARED SPECTRUM USING INDOCYANINE GREEN

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A clinical case of the use of fluorescence imaging in the near infrared spectrum with indocyanine green during laparoscopic right-side partial nephrectomy is presented in the article.

K e y w o r d s: *laparoscopic partial nephrectomy, kidney cancer, indocyanine green*

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The incidence of renal cell carcinoma (RCC) has been steadily increasing in recent years. The growth in the incidence is associated with improved diagnostic methods [1], which undoubtedly leads to better survival rates. Over the past two decades, there has been a gradual change in the primary surgical treatment for RCC. According to world literature, radical nephrectomy, previously considered the gold standard in localized T1–2 stage, has been replaced by organ-sparing techniques. Traditionally, partial nephrectomy is performed via open, laparoscopic and robot-assisted approaches. Laparoscopic partial nephrectomy (LRP) is currently the standard of care in many clinics.

Its main disadvantages include difficulties in ensuring reliable intraoperative hemostasis and the need to create kidney ischemia [2–4].

Recently, studies on the use of indocyanine green (ICG) with fluorescence imaging in urological oncology have been increasingly carried out. Intraoperative imaging using ICG near-infrared fluorescence is a safe and effective method for accurately identifying the renal vasculature and determining the zone of bloodless dissection [5].

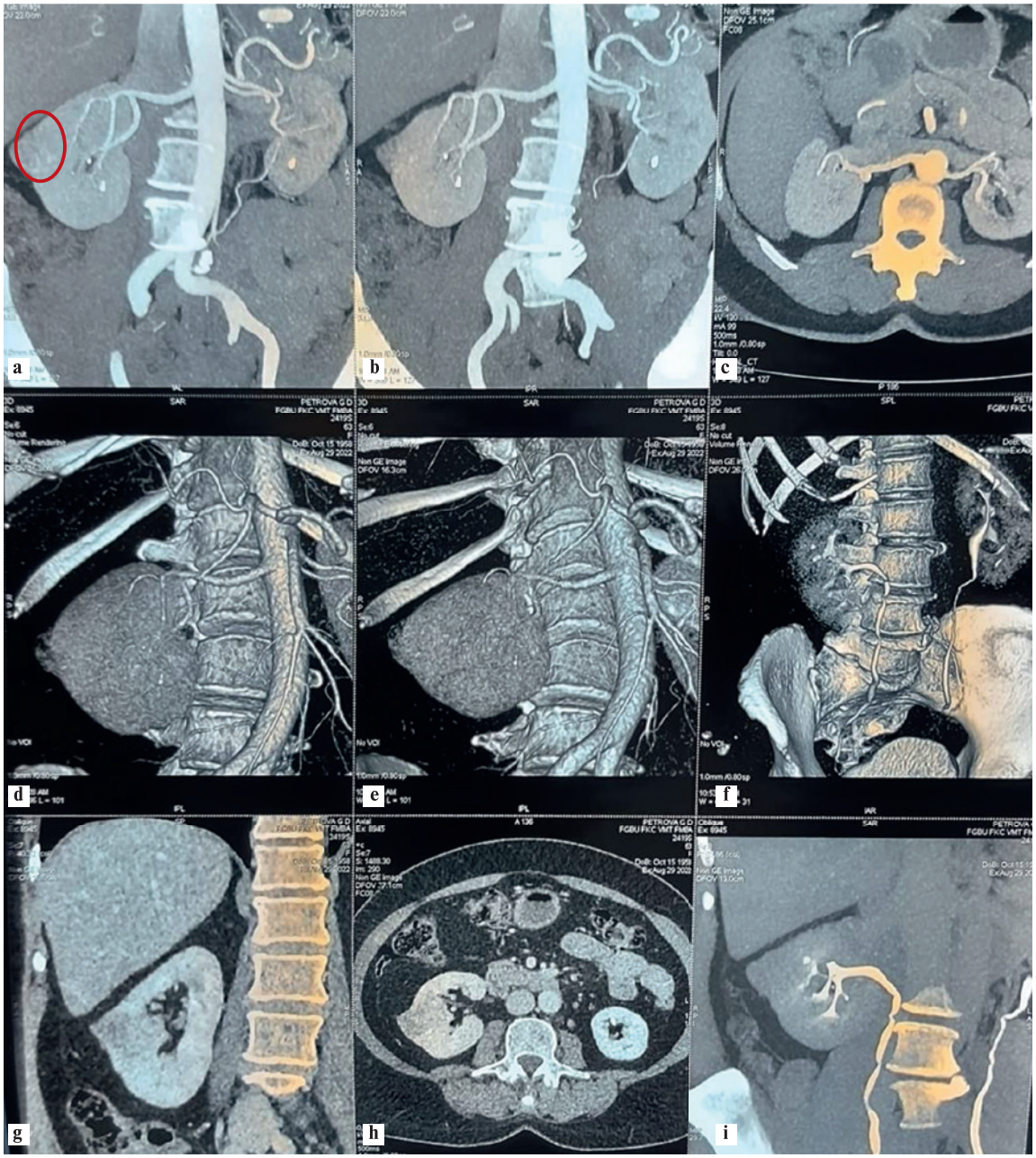
Clinical case

Patient P., 63 years old, in September 2022 had ultrasound examination for urolithiasis. A right kidney tumor was found. The diagnosis was confirmed by multislice computed tomography (CT), according to which in the anterior upper segment of the right kidney there was a lesion of an irregular polycyclic shape with tuberous contours and a maximum size of 33x38x30 mm, with strong contrast enhancement. In both kidneys there were caliceal stones that did not cause any obstruction. On the left side, there were 5- and 6-mm stones in the upper and lower calyces, respectively, while on the right side, 3- and 7-mm stones were located in the lower and the middle calyces, respectively.

Esophagogastroduodenoscopy (EGD) revealed multiple gastric erosions 1–3 mm in diameter, which required preoperative omeprazole 20 mg once daily for 14 days. At colonoscopy, a single simple polyp in the sigmoid colon with size of 0.8 cm was found. MSCT of the chest and Doppler ultrasound of the lower extremity veins revealed no pathological changes.

In October 2022, the patient was admitted to the clinic. On examination: the general condition was satisfactory, with normothermia. The patient was normosthenic, the skin and visible mucous membranes were of normal color and moisture, there was no edema. Available lymph nodes were not increased in size. Blood pressure was 140/90 mmHg, pulse 68 beats/min, rhythmic. Breathing was in normal range. The tongue was moist, the abdomen was soft and painless on palpation. Physiological functions were normal. A woman was in postmenopause. Height was 160 cm, weight 80 kg (BMI 31.25 kg/m^2).

CBC: hemoglobin 131 g/l, hematocrit 38.3 L/L, leukocytes 7.03 10/l, platelets 378 g/l. Biochemical blood test: ALT 31 U/l, AST 23 U/l, glucose 5.65 mmol/l, creatinine 78 μmol/l, urea 6.4 mmol/l, total protein 83 g/l, total bilirubin 9.2 μmol/l. General urinalysis: pH 5.39, specific



a – multiplanar oblique reconstruction in MIP mode, arterial phase, the exophytic part of the tumor is highlighted in red circle.
b – multiplanar oblique reconstruction in MIP mode, arterial phase (another section).
c – multiplanar axial reconstruction in MIP mode, arterial phase.
d – multiplanar oblique reconstruction in VR mode, arterial phase.
e – multiplanar oblique reconstruction in VR mode, arterial phase (another section).
f – multiplanar oblique reconstruction in VR mode, arterial phase.
g – multiplanar oblique reconstruction, venous phase.
h – multiplanar axial reconstruction, venous phase.
i – multiplanar oblique reconstruction in MIP mode, excretory phase.

Fig. 1. 3D CT-angiography

gravity 1.020, single epithelium cells in HPF, single leukocytes in HPF, up to 15–20 erythrocytes in HPF. Urine culture revealed E. coli (5x104) with sensitivity to a wide range of antibacterial drugs.

A follow-up EGD was performed, which revealed a sliding hernia of the 1st degree (n/3 of the esophagus), diffuse superficial gastritis. No pathological changes in the duodenum were detected.

Electrocardiography revealed sinus rhythm, heart rate of 68 beats/min, and electrical axis of the heart in horizontal position. Intraventricular conduction disturbance along the right bundle and moder-

ate changes in the myocardium were also detected.

Cystoscopy showed no inflammatory changes in the bladder neck, tumors or stones; the changes were consistent with chronic cervical cystitis.

After the examination, a following diagnosis was made: tumor of the right kidney of T1aN0M0 RENAL score 9 points.

Concomitant diseases: urolithiasis, chronic cystitis, hypertension of the 2nd degree, 3rd stage, risk 3, chronic gastritis.

According to the multislice CT (*Fig. 1*), the tumor was located in the upper anterior segment. More than 50% of its volume was inside the parenchyma and intimately adjacent to the collecting system. The main renal vessels were represented by one vein and one artery, while the renal artery had an early division. An assessment of the renal artery during CT-angiography suggested the presence of a vessel supplying the tumor and the possibility of performing partial nephrectomy with superselective ischemia.

Method. In the operating room under endotracheal anesthesia, in the left decubitus position of the patient under visual control, a 10-mm trocar was introduced within the umbilicus and a pneumoperitoneum was created. Additionally, two (10 and 5 mm) trocars were put in the right hypochondrium and the right iliac region along the midclavicular line. Inspection of the intestine was unremarkable. There was no free fluid in the abdominal cavity. After mobilizing the kidney from the fat capsule (*Fig. 2*) and isolating the renal pedicle, a vascular clamp was applied to the branch of the renal artery supplying the tumor. The ICG in a dose of 25 mg was diluted in 10 ml of water for injection with a concentration of 2.5 mg/ml, followed by a bolus injection of 5 ml to assess the ischemic zone.

Visualization was performed under illumination in the mode of superimposing near-infrared on white light. Fluorescence of ICG was recorded in the areas, which were supplied by the renal artery; the ischemic segment of the kidney remained unchanged, which indicated that blood flow was absent in the segment with the tumor (*Fig. 3–5*).

A plastic vascular clip was placed on the artery, and a resection of the tumor was performed with minor controlled bleeding. At the end of the tumor resection, the kidney defect was sewed with a continuous suture using a monofilament synthetic thread. A repeated bolus injection of 5 ml of indocyanine green solution was carried out. Under near-infrared light, uniform distribution of the drug was seen, which confirms the preservation of satisfactory blood supply to the kidney. The partial nephrectomy took 140 minutes, the blood loss was 50 ml. The histological report confirmed the presence of renal cell carcinoma and negative surgical margin. Macroscopic description was a kidney fragment of 36x27x23 mm with a surgeon's incision and a bulging nodular lesion of 32x21x27 mm on a variegated section with hemorrhages in the capsule (tumor). Separately, fragments of fatty tis-

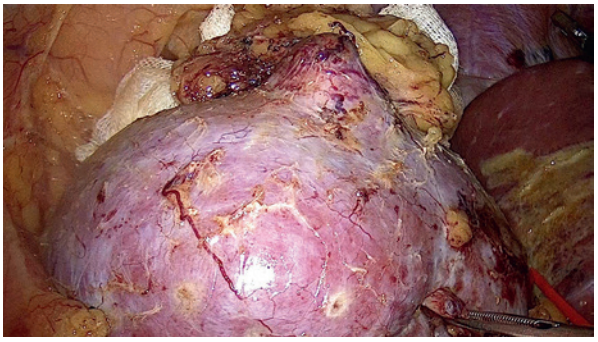


Fig. 2. Localization of the kidney tumor and clamping of the branch of the renal artery supplying the tumor

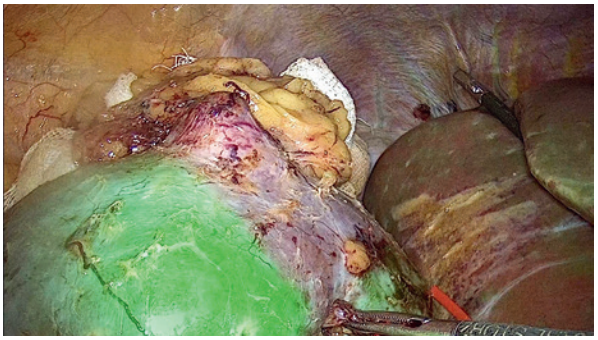


Fig. 3. An image of the kidney with superimposing of near-infrared and white light with fluorescence of the well-vascularized areas in green

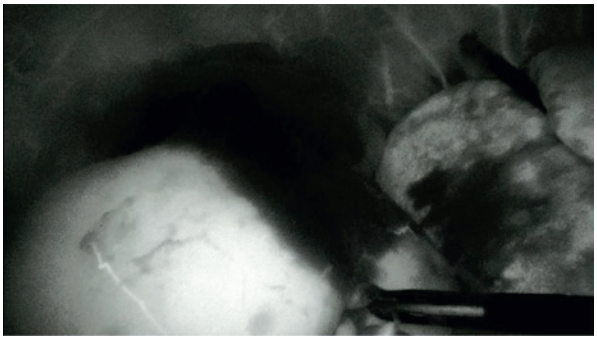


Fig. 4. An image of the kidney in monochromatic mode in the near-infrared spectrum in white light. The ischemic segment of the kidney in the form of a dark triangle can be seen

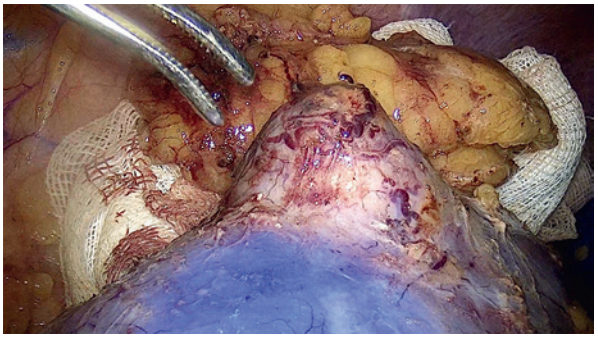


Fig. 5. An image of the kidney with superimposing of near-infrared and white light with fluorescence of the well-vascularized areas in blue. A clear boundary between the well-vascularized renal parenchyma and the ischemic tumor is clearly visualized.

sue with a total size of 84x53x11 mm with focal compactions were taken.

Histopathological study confirmed kidney tumor (clear cell carcinoma, Grade 2) with areas of hemorrhage and edema; along the periphery along its entire length a fibrous pseudocapsule without signs of extracapsular tumor invasion was found. There were focal fresh hemorrhages in the fatty tissue. No additional lesions were identified.

Histopathological diagnosis was right kidney cancer pT1aN0M0. The postoperative period was uneventful. The patient was discharged from the hospital on the 4th day after procedure.

The use of fluorescence imaging in the near-infrared spectrum with indocyanine green contrast allowed intraoperative selective angiography and visualization of the ischemic zone with maximum accuracy, thereby facilitating partial nephrectomy with preserved blood flow in the main renal artery.

ЛИТЕРАТУРА/REFERENCES

1. *Alekseev B.Ya., Kalpinsky A.S., Polyakov V.A., Andrianov A.N.* Laparoscopic resection of the kidney in case of tumor lesion. Oncology. Journal named after P.A. Herzen. 2012;1(1):4–9. Russian (Алексеев Б.Я., Калпинский А.С., Поляковb В.А., Андрианов А.Н. Лапароскопическая резекция почки при опухолевом поражении. Онкология. Журнал им. П.А. Герцена. 2012;1(1):4 9).
2. *Puchkov K.V., Filimonov V.B., Krapivin A.A., Vasin R.V.* Surgical treatment of kidney cancer today: laparoscopic radical nephrectomy and kidney resection. Urology. 2008;1:47–53. Russian (Пучков К.В., Филимонов В.Б., Крапивин А.А., Васин Р.В. Хирургическое лечение рака почки сегодня: лапароскопическая радикальная нефрэктомия и резекция почки. Урология. 2008;1:47–53).
3. *Pavlov A.Yu., Kravtsov I.B.* The functional state of the kidneys and the course of the postoperative period during kidney resection for cancer. General Practitioner's Handbook. 2013;7:64–69. Russian (Павлов А.Ю., Кравцов И.Б. Функциональное состояние почек и течение послеоперационного периода при резекции почки по поводу рака. Справочник врача общей практики. 2013;7:64–69).
4. *Bertolo R., Garisto J., Dagenais J., Agudelo J., Armanyous S.* Cold versus warm ischemia robotaassisted partial nephrectomy: Comparison of functional outcomes in propensity-score matched «at risk» patients. Journal Endourology. 2018;21.
5. *Tobis S., Knopf J., Silvers C., Yao J., Rashid H. Wu G., Golijanin D.* Near infrared fluorescence imaging with robotic assisted laparoscopic partial nephrectomy: initial clinical experience for renal cortical tumors. J Urol. 2011;186(1):47-52. doi: 10.1016/j.juro.2011.02.2701.

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LITERATURE REVIEWS

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ADVERSE EVENTS AFTER DISCONTINUATION OF TESTOSTERONE PREPARATIONSЯ, USED FOR NON-MEDICAL PURPOSES

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The review is devoted to the study of modern aspects of the use of testosterone preparations for non-medical purposes. The search was conducted using Medline, PubMed, and EMBASE databases. Data from a literature search indicate that the use of PT for non-medical purposes is an urgent problem of modern urology, affecting the interests of many specialties, since against the background or after the abolition of unjustified use of testosterone drugs in healthy men, undesirable effects are recorded not only in the urinary tract and reproductive organs, but also other organs and systems.

K e y w o r d s: *testosterone, hypogonadism, testosterone deficiency, testosterone preparations, adverse events*

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Doi: https: //dx.doi.org/10.18565/urology.2023.5.131-135

Introduction. The use of testosterone replacement therapy (TRT) for non-medical purposes is an actively discussed area of modern medicine, which is due to the large number of complications recorded during or after treatment.

Aim. To study the problem of using testosterone (T) preparations for non-medical purposes based on literature review.

Materials and methods. When preparing the literature review, original works published in the PubMed, the scientific electronic library of Russia (eLibrary), SciVerse (ScienceDirect), Scopus, Medline, EMBASE, and websites of professional associations were used. There were no without restrictions on the date of publication. The search was carried out using the following keywords and their combinations: testosterone deficiency, testosterone preparations, adverse events, hypogonadism.

The rapid development of medical science has contributed to the accumulation of a large body of evidence in various fields, which has led to the emergence of narrow specialties in the clinical practice. On the one hand, this process certainly led to the accumulation and improvement of the knowledge in certain areas, and on the other hand, it resulted in the loss of such systematic (comprehensive) view on the patient [1]. One of these problems is the issue of diagnosis, treatment and prevention of T deficiency or hypogonadism, which can occur in men of any age due to various etiological factors [2, 3]. The relevance of the problem of hypogonadism is due to the rapid increase in the number of elderly men in developed countries, but also to the increased exposure of predisposing factors that contribute to a decrease in T level: social stress, urbanization, accelerating pace of life, unhealthy lifestyle, somatic diseases (diabetes mellitus, chronic obstructive pulmonary disease, obesity, arterial hypertension), testosterone-lowering drugs [4, 5]. According to current guidelines, it is recommended to use TRT for men with clinical symptoms and signs of hypogonadism in combination with low T serum level [6–9].

The aim of TRT is to relieve the symptoms of hypogonadism by restoring serum T level to physiological values. The choice of treatment is determined by the form of the disease, risk factors and reproductive plans of the patient. It is necessary to remember about a possible transient decrease in T levels (for example, due to acute diseases or decompensation of chronic disorders), which should be excluded with a thorough clinical examination and repeated measurement of T levels [1].

It is known that T is necessary for the daily functioning of the male body, since it has not only androgenic, but also anabolic effects, regulates the reproductive function through the induction of spermatogenesis and ensuring sexual desire, and also predetermines a number of physiological and metabolic processes. The main biological effect of T is manifested in target tissues, including muscles, seminiferous tubules, seminal vesicles, epididymis, prostate gland, penis, etc. Androgenic properties of T are manifested in the development of the genital organs, the development of secondary sex characteristics, and the formation of sexual desire, orientation and behavior. Congenital low levels of T and androgens disrupt the formation of sexual characteristics, which results in

malformations of the male reproductive and endocrine systems, and also cause a violation of the male stereotype of thinking and behavior [1, 2].

The doses of androgen and its derivatives used in TRT, indications and contraindications, prescription regimens, duration, frequency of follow-up visits and specific physical, laboratory and instrumental examinations are discussed in detail in the protocols or national guidelines and standards [3, 10].

However, in recent years there has been an active use of T preparations for non-medical purposes [11]. The non-medical use of T preparations and its derivatives is widespread among athletes for the purpose of body modification, but the increase in muscle strength occurs without taking into account the recommended dosages and regimens and in most cases leads to significant harm to the health persons, who are mainly active young men of reproductive age [12, 13].

As studies have shown, steroid-induced hypogonadism, or anabolic steroids-induced hypogonadism, becomes one of the common causes in young men, especially those who visit various sports centers and take T drugs for non-medical purpose [14, 15]. Under the influence of T preparations, the production of gonadotropin-releasing hormone by the hypothalamus is reduced, which reduces the production of luteinizing and follicle-stimulating hormones by the pituitary, which in turn triggers a cascade of hormonal dysfunctions. In addition, high T level in the serum lead to its conversion into high levels of estrogen under the influence of aromatase. Also, via a feedback mechanism, inhibin B produced in the testicles influences FSH secretion [16].

In recent decades, the use of T preparations for non-medical purposes has become widely, unreasonably and aggressively used in sports centers, and there are undesirable effects on many organs and systems, including the urinary tract and reproductive organs. Of course, it is difficult to consider this approach as TRT, since the goal is not treatment, but a deliberate increase in T level despite normal level at baseline [17, 18].

Unfortunately, more and more studies are publishing analyzing data on the negative effects of T preparations. Frequent side effects of steroid use or the consequences of their withdrawal include lower urinary tract symptoms, infertility, gynecomastia, sexual disorders, depressive symptoms, psychological dependence, etc. Much less often, which does not make them less important, oncologic diseases of liver, kidneys and reproductive organs are recorded while taking T preparations or anabolic steroids [19].

Stopping steroids after prolonged use can cause a number of sexual disorders, including erectile dysfunction, decreased libido, reduced volition, and impaired ejaculatory function. Due to the fact that most men, after long-term use of T preparations or after their withdrawal, have problems in the sexual sphere or infertility, there are a lot of studies carried out in recent years assessing their negative impact on sexual and reproductive functions. The results have proven that long-term use of T preparations and their analogues inhibits the hypothalamic–pituitary–gonadal axis, which leads to hypogonadotropic hypogonadism, sexual dysfunction and infertility [19, 20].

In addition, the majority of men who have used T preparations for a long time, after their withdrawal, develop “psychological dependence”, which determines the motivation to constantly use exogenous T, despite the adverse consequences [21].

Long-term administration of exogenous T indirectly through hypothalamic–pituitary–gonadal axis, as well as according to negative feedback, promotes hypofunction and atrophy of Leydig cells, which leads to a decrease in the synthesis of endogenous T and testicular hypotrophy. In addition, it is known that the vascular endothelium is a target tissue for T, which results in the active release of NO. The latter, in turn, is a powerful vasodilator and has antiplatelet, anticoagulant, anti-inflammatory and antiproliferative effects [1]. NO is also involved in all processes in cavernous tissue, which ensure erectile function. After discontinuation of T preparations, due to inhibition of the synthesis of endogenous T, hypogonadism develops, which provokes endothelial dysfunction, reduces NO synthesis, which leads to erectile dysfunction. Vascular tone, proliferation of vascular wall elements, thrombus formation also increases, as well as oxidative stress. All this causes ischemia of the cavernous tissue and fibrosis, which further enhances the progression of endothelial and erectile dysfunction.

It should be noted that hypogonadism contributes to the development of both local and systemic endothelial dysfunction, and NO affects the entire body and takes part in various functions of almost all organs [1]. Thus, endothelial dysfunction and decreased NO synthesis may be responsible for many serious complications (thromboembolism, arterial hypertension, coronary artery disease, etc.) [20].

The analysis of epidemiological studies on the use of T preparations for non-medical purposes is difficult, since no studies have been carried out to determine prevalence and patterns in Russia. In this regard, studying the frequency and patterns of non-medical steroid use among men engaged in recreational physical activity is of relevance. In our country, there are pioneering works dedicated to this problem. For example, in the studies of N.P. Likhonosov, A.Yu. Babenko (2019) it was noted that 30.4% of men involved in recreational physical activity used T preparations [22]. A meta-analysis of Brazil studies indicates the prevalence of use of T preparations and their analogues of 2.1 to 31.6%, depending on the region and studied population [23]. The use of T preparations among Iranian bodybuilders ranged from 24.5 to 56.8% [24]. In Saudi Arabia, the prevalence of T preparations use among men's gym users was 31.0% [25]. There are currently no multicenter randomized studies on this issue; however, it is known that almost every fourth gym goer of reproductive age uses T preparations [20].

After T preparations abuse, spontaneous recovery of the pituitary-gonadal system can last from several months to 2 years, while cases of irreversible damage are described, and not only functional, but also anatomical and psychogenic undesirable effects may develop [14]. Men who unreasonably use T preparations and their derivatives, in order to reduce the negative impact of drugs on the pituitary-gonadal system, take them in so-called courses, and between them post-cycle therapy is carried out in order to reduce or relieve adverse effects. However, the efficiency of post-cycle therapy is unknown, as there are no clinical randomized trials have been carried out. Obviously, if irreversible destructive processes have occurred in the organ due to long-term use of T preparations, then the chance of restoration of their function changes would be low [26].

Published data indicate the use of a diverse set of medications in post-cycle therapy that do not have evidence base. In addition, the frequency of use of T preparations for non-medical purposes remains insufficiently studied: most users of this "therapy" often hide this fact, and practitioners need to obtain sufficient specialized knowledge on TRT for non-medical purposes [17, 18, 20].

Thus, the post-cycle therapy used cannot be considered to restore the pituitary-gonadal system or relieve adverse events due to the lack of a comparison group that included men of the same age who also refused to use T preparations but did not take post-cycle therapy. In this regard, the efficiency, doses, nature, duration, indications and contraindications for the post-cycle therapy after taking T preparations for non-medical reasons require further study [17].

Overuse of T preparations to improve body composition and muscle strength remains widespread, despite available data on adverse events. This information is often ignored by men, represented by young persons of reproductive age.

According to the literature, the applied doses of T preparations significantly exceed therapeutic ones (for T, 10 mg daily or 25 mg 2-3 times a week is recommended), and in real practice, for example, in the USA, the average dose of T or its equivalent is 1000 mg per week in 59.6% of examined men [27]. In a study by N.P. Likhonosov and A.Yu. Babenko (2019), it was shown that 32% of men using T preparations received a dosage of 1000 mg per week, while doses above 1000 mg were taken by 23%, and doses above 2000 mg by 2.4% of surveyed athletes. In the latter, the duration of the course was maximum (more than 9 months) and this group had the most severe disturbances of sexual and reproductive functions [22]. It is known that the longer the use and the higher the dose of T preparations, the more pronounced the negative influence on many organs and systems. In addition, long-term administration leads to irreversible sclerotic changes in the testicles, which causes severe disturbances in spermato- and steroidogenesis [20].

To prevent adverse events during or after discontinuation of T preparations for men, a paradigm was developed for the use of androgenic anabolic steroids, which involves their administration in so-called courses followed by stimulating therapy (human chorionic gonadotropin, clomiphene citrate, etc.), the efficiency of which remains unclear. In addition, the timing of spontaneous recovery of the pituitary-gonadal system after the use of androgenic anabolic steroids remains unknown [22].

Unjustified T therapy can be accompanied by various adverse events from the urinary tract and reproductive organs. It is necessary to explain to men the negative effects of T preparations, and also to develop a treatment strategy.

Timely, high-quality diagnosis and effective treatment of T preparations-induced hypogonadism seems to be an underestimated health problem. The guidelines and standards for the diagnosis and treatment of secondary hypogonadism after T preparations abuse by non-professional athletes currently do not exist.

REFERENCES

1. *Kogan M.I., Vorobiev S.V., Khripun I.A., Belousov I.I., Ibishev Kh.S.* Testosterone: From Sexuality to Metabolic Control. Rostov-on-Don: Phoenix; 2017). Russian (Коган М.И., Воробьев С.В., Хрипун И.А., Белоусов И.И., Ибишев Х.С. Тестостерон: от сексуальности к метаболическому контролю. Ростов-на-Дону: Феникс; 2017).
2. *Dedov I.I., Shestakova M.V., Melnichenko G.A., Mazurina N.V., Andree-va E.N., Bondarenko I.Z., Gusova Z.R., Dzgoeva F.K., Eliseev M.S., Ershova E.V., Zhuravleva M.V., Zakharchuk T.A., Isakov V.A., Klepikova M.V., Komshilova K.A., Krysanova V.S., Nedogoda S.V., Novikova A.M., Ostroumova O.D., Pereverzev A.P., Rozhivanov R.V., Romantsova T.I., Ruyatkina L.A., Salasyuk A.S., Sasunova A.N., Smetanina S.A., Starodubo-va A.V., Suplotova L.A., Tkacheva O.N., Troshina E.A., Khamoshina M.B., Chechelnitskay S.M., Shestakova E.A., Sheremet'eva E.V.* Interdisciplinary Clin. Practice Guidelines "Management of obesity and its comorbidities". Obesity and metabolism. 2021;18(1):5–99. Russian (Дедов И.И., Шестакова М.В., Мельниченко Г.А., Мазурина Н.В., Андреева Е.Н., Бондаренко И.З., Гусова З.Р., Дзгоева Ф.Х., Елисеев М.С., Ершова Е.В., Журавлева М.В., Захарчук Т.А., Исаков В.А., Клепикова М.В., Комшилова К.А., Крысанова В.С., Недогода С.В., Новикова А.М., Остроумова О.Д., Переверзев А.П., Роживанов Р.В., Романцова Т.И., Руяткина Л.А., Саласюк А.С., Сасунова А.Н., Сметанина С.А., Стародубова А.В., Суплотова Л.А., Ткачева О.Н., Трошина Е.А., Хамошина М.Б., Чечельницкая С.М., Шестакова Е.А., Шереметьева Е.В. Междисциплинарные клинические рекомендации «Лечение ожирения и коморбидных заболеваний». Ожирение и метаболизм. 2021;18(1):5–99).
3. *Dedov I.I., Mel'nichenko G.A., Shestakova M.V., Rozhivanov R.V., Tereho-va A.L., Zilov A.V., Ladygina D.O., Kurbatov D.G.* Guidelines for the Diagnosis and Treatment of testosterone deficiency (hypogonadism) in male patients with diabetes mellitus. Obesity and metabolism. 2017;14(4):83–92. Russian. (Дедов И.И., Мельниченко Г.А., Шестакова М.В., Роживанов Р.В., Терехова А.Л., Зилов А.В., Ладыгина Д.О., Курбатов Д.Г. Рекомендации по диагностике и лечению дефицита тестостерона (гипогонадизма) у мужчин с сахарным диабетом. Ожирение и метаболизм. 2017;14(4):83–92).
4. Age-related androgen deficiency in men: to treat, not to treat, who to treat? Z.R. Gusova, Kh. S. Ibishev, E.O. Dzantieva, M.I. Kogan. Bulletin of Urology. 2016; 1: 72-85. Russian (Возрастной андрогенный дефицит у мужчин: лечить, не лечить, кому лечить? З. Р. Гусова, Х.С. Ибишев, Е.О. Дзантиева, М.И. Коган. Вестник урологии. 2016;1:72–85.
5. The problem of testosterone deficiency and erectile dysfunction in men (literature review). Kh.S. Ibishev, I.A. Khripun, Z.R. Gusova [etc.]. Urology. 2014;6:104–107. Russian (Проблема дефицита тестостерона и эректильной дисфункции у мужчин (обзор литературы). Х.С. Ибишев, И.А. Хрипун, З.Р. Гусова [и др.]. Урология. 2014;6:104–107.
6. *Trinick T.R., feneley M.R., Welford H., Carruthers M.* International web survey shows high prevalence of symptomatic testosterone deficiency in men. The aging male. 2015;14(1):10–15.
7. *Kogan M.I., Ibishev Kh.S.* Secondary hypogonadism in patients with damage to the urethra. Consilium Medicum. 2007;9(4):50-54. Russian (Коган М.И., Ибишев Х.С. Вторичный гипогонадизм у больных с повреждением мочеиспускательного канала. Consilium Medicum. 2007;9(4):50–54).
8. *Ibishev Kh.S., Kogan M.I., Cherny A.A.* Clinical features of the course of chronic bacterial prostatitis against the background of testosterone deficiency. Vestnik Urologii. 2013;(1):39–45. Russian (Ибишев Х.С., Коган М.И., Черный А.А. Клинические особенности течения хронического бактериального простатита на фоне дефицита тестостерона. Вестник урологии. 2013;(1):39–45).
9. *Gusova Z.R., Vorobiev S.V., Khripun I.A., Dzantieva E.O., Puzyreva V.P., Kogan M.I., Ibishev Kh.S., Cherny A.A., Belousov I.I.* On the role of cytokines in the pathogenesis of metabolic disorders and androgen deficiency in men with obesity and metabolic syndrome. Fundamental Research. 2014;10(6):1227–1233; Russian (Гусова З.Р., Воробьев С.В., Хрипун И.А., Дзантиева Е.О., Пузырева В.П., Коган М.И., Ибишев Х.С., Черный А.А., Белоусов И.И. О роли цитокинов в патогенезе метаболических нарушений и андрогенного дефицита у мужчин с ожирением и

метаболическим синдромом. Фундаментальные исследования. 2014;10(6):1227–1233).
10. *Bhasin S., Brito J.P., Cunningham G.R., et al.* Testosterone therapy inmen with hypogonadism: an Endocrine Society Clinical Practice Guideline. J. Clin. Endocrinol. Metab. 2018;103(5):1715–1744.
11. *Fedorov A.V.* Doping and drugs. Drug control. 2017;2:10–21. Russian (Федоров, А.В. Допинг и наркотики. Наркоконтроль. 2017;2:10–21)
12. *El Osta R., Almont T., Diligent C., et al.* Anabolic steroids abuse and male infertility. Basic. Clin. Androl.2016;26:2.
13. *Lykhonosov M.P., Babenko A.Y.* The medical aspect of using anabolic androgenic steroids in males attending gyms of Saint-Petersburg. Problems of Endocrinology. 2019;65(1):19–30. Russian (Лихоносов Н.П., Бабенко А.Ю. Медицинский аспект использования анаболических андрогенных стероидов у мужчин, посещающих тренажерные залы Санкт-Петербурга. Проблемы эндокринологии. 2019;65(1):19–30.
14. *McBride J.A., Coward R.M.* Recovery of spermatogenesis following testosterone replacement therapy or anabolic-androgenic steroid use. Asian J. Androl. 2016;18(3):373–380.
15. *Park H.J.* Anabolic steroid-induced hypogonadism: a challenge for clinicians. J. Exerc. Rehabil. 2018;14(1):2–3.
16. *Zhu Z.G., Zhao Z.G., Pang Q.Y., et al.* Predictive significance of serum inhibin B on testicular haploid gamete retrieval outcomes in nonobstructive azoospermic men. Asian J. Androl. 2019; 21(2):137–142.
17. *Lykhonosov M.P., Babenko A.Yu.* Prevalence of anabolic androgenic steroid use, its effect on the male pituitary-gonadal axis, and the possibility of reproductive rehabilitation. Problems of Endocrinology 2019;65(2):124–133. Russian. (Лихоносов Н. П., Бабенко А.Ю. Распространенность использования андрогенных анаболических стероидов, их влияние на систему гипофиз-гонады у мужчин и возможности репродуктивной реабилитации. Проблемы эндокринологии 2019; 65(2):124–133).
18. *Likhonosov N.P., Babenko A.Yu., Makaryin V.A., Fedotov Yu.N.* Features of the restoration of the pituitary-gonadal system in men after the use of androgenic anabolic steroids. Endocrinology Problems 2020;66(1): 104–112. Russian (Лихоносов Н.П., Бабенко А.Ю., Макарьин В.А., Федотов Ю.Н. Особенности восстановления системы гипофиз-гонады у мужчин после использования андрогенных анаболических стероидов. Проблемы эндокринологии 2020;66(1):104-112).
19. *Drobnis E.Z., Nangia A.K.* Exogenous androgens and male reproduction. Adv. Exp. Med. Biol. 2017;1034:25–28.
20. *Ibishev Kh.S., Volkova N.I., Gusova Z.R. [et al.]* //Adverse events from the genitourinary organs in men who used testosterone drugs, anabolic steroids for non-medical purposes. Urology. 2022;3:92–97. Russian (Ибишев Х.С., Волкова Н.И., Гусова З.Р. [и др.]. Нежелательные явления со стороны мочеполовых органов у мужчин, использовавших препараты тестостерона, анаболические стероиды в немедицинских целях. Урология. 2022;3:92–97).
21. *Ibishev Kh.S., Sharbabchiev V.A., Palenyi A.I. [et al.]* Symptoms of the lower urinary tract as a consequence of the withdrawal of testosterone drugs that have been used for a long time for non-medical purposes. Journal of Urology. 2022;10(3):5–12. Russian (Ибишев Х.С., Шарбабчиев В.А., Паленый А.И. [и др.] Симптомы нижних мочевых путей как следствие отмены препаратов тестостерона, длительно применявшихся в немедицинских целях. Вестник урологии. 2022;10(3):5–12).
22. *Likhonosov N.P., Babenko A.Yu.* Medical aspect of the use of anabolic androgenic steroids in men visiting gyms in St. Petersburg. Problems of endocrinology. 2019;65(1):19–30. Russian (Лихоносов Н.П., Бабенко А.Ю. Медицинский аспект использования анаболических андрогенных стероидов у мужчин, посещающих тренажерные залы Санкт-Петербурга. Проблемы эндокринологии 2019;65:С.19–30.
23. *Abrahin O.S., Sousa E.C., Santos A.M.* Prevalence of the use of an-abolic-androgenic steroids in Brazil: a systematic eview. Subst. Use Misuse. 2014; 49(9):1156–1162.
24. *Nakhaee Mr., Pakravan F., Nakhaee N.* Prevalence of use of anabolic steroids by bodybuilders using three methods in a city of Iran. Addict Health. 2013;5(3–4):77–82.
25. *Bahri A., Mahfouz M.S., Marran N.M., et al.* Prevalence and awareness of anabolic androgenic steroid use among male body builders in Jazan, Saudi Arabia. Trop. J. Pharm. Res. 2017;16(6):1425–1430.
26. *Tatem A.J., Beilan J., Kovac J.R., Lipshultz L.I.* Management of anabolic steroid-induced infertility: novel strategies for fertility maintenance and recovery. World J. Mens Health. 2020;38(2):141–150.
27. *Parkinson A.B., Evans N.A.* Anabolic androgenic steroids: a survey of 500 users. Med. Sci Sports Exerc. 2006;38(4):644–651.

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