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ЖУРНАЛ ВКЛЮЧЕН В ПЕРЕЧЕНЬ ВАК

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On the left — orthopedic operating room of the Federal Medico-Biological Agency Federal Research Clinical Center, trauma surgeons, Ph.D. A.A. Akhpashev and A.N. Tkalin perform arthroscopy of the knee joint, on the right, thoracic surgeon E.A. Epifantsev operates.

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THE USE OF SODIUM-GLUCOSE COTRANSPORTER TYPE 2 INHIBITORS FOR THE PURPOSE OF TREATING THE CHRONIC CARDIAC FAILURE IN ONCOLOGY PATIENTS RECEIVING CARDIOTOXIC CHEMOTHERAPY: PRELIMINARY RESULTS

A.K. Peresada, D.P. Dundua, A.G. Kedrova, I.N. Oleinikova, A.V. Salimova

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ABSTRACT

BACKGROUND: *Chronic cardiac failure belongs to the most threatening and delayed manifestations of cardiotoxicity in oncology patients receiving the treatment with antitumor medicines. As of today, only two groups of drugs were proven to have significant cardioprotective effects in these categories of patients: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and beta-adrenergic blockers. Recently, the first data were published on the successful use of sodium-glucose cotransporter type 2 inhibitors in patients with chronic cardiac failure, receiving anthracycline therapy.* ***AIM:*** *optimization of cardioprotective therapy in the treatment of chronic cardiac failure in oncology patients receiving cardiotoxic chemotherapy.* ***METHODS:*** *A prospective observational open-label research was carried out with an enrollment of 116 oncology patients with verified chronic cardiac failure, which were receiving cardiotoxic chemotherapy, of which 60 patients of the control group were receiving double cardioprotective therapy (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers) and the 56 patients of the test group were receiving similar therapy with an addition of Dapagliflozin at a dosage of 10 mg once daily in the morning. The controls of the results were conducted in 6 months by means of laboratory and instrumental examinations, as well as by using additional methods of controlling the results.* ***RESULTS:*** *The groups compared did not differ by the combined primary clinical endpoint (the rate of hospitalizations due to cardio-vascular reasons, the refusal to undergo chemotherapy for the reason of chronic cardiac failure progression and the safety of using the drug products: the presence of urinary tract infections and sepsis), but they differed by the surrogate clinical endpoints that included the dynamic trend of the levels of the groups compared did not differ by the combined primary clinical endpoint (the rate of hospitalizations due to cardio-vascular reasons, the refusal to undergo chemotherapy for the reason of chronic cardiac failure progression and the safety of using the drug products: the presence of urinary tract infections and sepsis), but they differed by the surrogate clinical endpoints that included the dynamic trend of the levels of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and the global longitudinal strain (GLS) of the left ventricle, determined within the timeframes established for the research — before the initiation of chemotherapy and in 6 months. The patients that have passed all the control tests (n=47), after the end of the 6 months period, underwent a comparison of the levels of troponin T, left ventricle ejection fraction (LVEF), NT-proBNP and GLS. It was found that the dynamic changes of troponin T levels in both groups did not significantly differ (p=0,260), as well as the LVEF indicator (p=0.340), while the NT-proBNP level was significantly decreasing in the test group — by 7.8% comparing to the control group (p=0.006). Comparable data were obtained for the GLS (the decrease in the test group by 6.5% in relative values) comparing to the control group (p=0.008). In 22/47 (46,8%) patients, chronic cardiac failure was diagnosed before the initiation of chemotherapy, in 25/47 (53,2%), chronic cardiac failure was developing during the antitumor medication therapy. In both groups, a total of 17 (16%) fatal outcomes were registered, none of which was caused by the cardiac failure.* ***CONCLUSION:*** *We suppose that the decrease in the levels of the cardiac failure marker and the less intensive impairment of the left ventricle longitudinal strain with a background of adding sodium-glucose cotransporter type 2 inhibitors to baseline therapy for chronic cardiac failure in oncology patients receiving cardiotoxic chemotherapy, reflects their cardioprotective potential. Thus, the sodium-glucose cotransporter type 2 inhibitor Dapagliflozin slows down the progression of chronic cardiac failure in oncology patients receiving cardiotoxic chemotherapy.*

Keywords: *cardio-oncology; cardiotoxicity; cardioprotection; chronic heart failure; sodium-glucose cotransporter type 2 inhibitors.*

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ПРИМЕНЕНИЕ ИНГИБИТОРОВ НАТРИЙ-ГЛЮКОЗНОГО КОТРАНСПОРТЕРА 2-ГО ТИПА С ЦЕЛЬЮ ЛЕЧЕНИЯ ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ У ОНКОЛОГИЧЕСКИХ БОЛЬНЫХ, ПОЛУЧАЮЩИХ КАРДИОТОКСИЧНУЮ ХИМИОТЕРАПИЮ: ПРЕДВАРИТЕЛЬНЫЕ РЕЗУЛЬТАТЫ

А.К. Пересада, Д.П. Дундуа, А.Г. Кедрова, И.Н. Олейникова, А.В. Салимова

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АННОТАЦИЯ

Обоснование. *Хроническая сердечная недостаточность относится к наиболее грозным и поздним проявлениям кардиотоксичности у онкобольных при лечении противоопухолевыми препаратами. На сегодняшний день лишь две группы препаратов доказали значимые кардиопротективные эффекты у этой категории пациентов: ингибиторы ангиотензинпревращающего фермента/блокаторы рецепторов ангиотензина и бета-адреноблокаторы. Недавно появились первые данные об успешном применении ингибиторов натрий-глюкозного котранспортера 2-го типа у пациентов с хронической сердечной недостаточностью, которые находятся на терапии антрациклинами.* ***Цель исследования*** *— оценить эффективность дапаглифлозина в комплексной кардиопротективной терапии хронической сердечной недостаточности у онкологических больных, получающих кардиотоксичную химиотерапию.* ***Методы.*** *Проспективное наблюдательное открытое исследование, включившее 116 онкологических пациентов с верифицированной хронической сердечной недостаточностью, которые получали кардиотоксичную химиотерапию, из них 60 пациентов контрольной группы получали двойную кардиопротективную терапию (ингибиторы ангиотензинпревращающего фермента/блокаторы рецепторов ангиотензина, 56 пациентов группы исследования — аналогичную терапию с добавлением дапаглифлозина в дозе 10 мг 1 раз утром. Контроль результатов проводился через 6 месяцев с помощью лабораторных и инструментальных методов исследования, а также дополнительных методов контроля.* ***Результаты.*** *Группы сравнения не различались по комбинированной первичной клинической точке (частота госпитализации по сердечно-сосудистым причинам, отказ от химиотерапии по причине прогрессирования хронической сердечной недостаточности, безопасность применения препарата: наличие инфекции мочеполовых путей и сепсиса), но различались по суррогатным клиническим точкам, динамике уровней мозгового предсердного натрийуретического пептида (NT-proBNP) и продольной деформации миокарда левого желудочка (GLS), определяемых в регламентированные исследованием сроки — перед началом химиотерапии и через 6 месяцев. Пациентам, прошедшим все контрольные исследования (n=47), по истечении 6 месяцев проведено сравнение уровней тропонина T, фракции выброса левого желудочка (ФВ ЛЖ), NT-proBNP и GLS. Отмечено, что динамика тропонина в обеих группах значимо не отличалась (p=0,260), также как и показатель ФВ ЛЖ (p=0,340), а уровень NT-proBNP значимо снижался в группе исследования на 7,8% в сравнении с контрольной группой (p=0,006). Сопоставимые данные были получены и по GLS (снижение в группе исследования на 6,5% в относительных значениях) по сравнению с контрольной группой (p=0,008). У 22/47 (46,8%) пациентов была хроническая сердечная недостаточность до начала проведения химиотерапии, у 25/47 (53,2%) хроническая сердечная недостаточность возникла в процессе противоопухолевой лекарственной терапии. В обеих группах зарегистрировано 17 (16%) летальных исходов, из них ни одного по причине сердечной недостаточности.* ***Заключение.*** *Мы полагаем, что снижение маркера сердечной недостаточности и менее выраженное нарушение продольной деформации левого желудочка на фоне добавления ингибитора натрий-глюкозного котранспортера 2-го типа дапаглифлозина к базисной терапии хронической сердечной недостаточности у онкологических больных, получающих кардиотоксическую химиотерапию, отражает их кардио-*

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протективный потенциал. Таким образом, добавление к терапии ингибитора натрий-глюкозного котранспортера 2-го типа может замедлять прогрессирование хронической сердечной недостаточности у онкологических больных, получающих кардиотоксическую химиотерапию.

Ключевые слова: *кардиоонкология; кардиотоксичность; кардиопротекция; хроническая сердечная недостаточность; ингибиторы натрий-глюкозного котранспортера 2-го типа.*

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BACKGROUND

Chemotherapy is successfully used for the treatment of malignant neoplasms, at the same time, a number of medicines induce toxic effects in the cardiac muscle, resulting in the death of cardiomyocytes, decreased contractility and cardiac rhythm disorders, which leads to developing various diseases of the cardiovascular system [1].

Chronic heart failure belongs to the most threatful and delayed manifestations of cardiotoxicity in the treatment of antitumor medicines. Chronic heart failure, in case of its development or progression, not only significantly affects the quality of life of the patient, even in cases of successful treatment of malignant neoplasms, but also deteriorates the expected lifetime of the patient [2], and, in a number of cases, compels to interrupt the chemotherapy cycle or to slow it down significantly.

At the present moment, in cancer patients receiving cardiotoxic chemotherapy, only two classes of agents have proven their efficiency in the treatment and prevention of chronic cardiac failure — inhibitors of angiotensin-converting enzyme/angiotensin receptor blockers and beta-adrenergic blockers [3] or their combinations [4]. Gradually, the data is being accumulated on the successful use of the combination of neprilysin receptor inhibitor and of the angiotensin receptor blocker (Sacubitril/Valsartan) in cancer patients with chronic cardiac failure [5, 6]. First data were also obtained on the successful use of inhibitors of sodium-glucose cotransporter type 2 in cancer patients with diabetes mellitus receiving therapy with anthracyclines [7].

Research aim — optimization of the cardioprotective therapy in the treatment of chronic cardiac failure in cancer patients, receiving cardiotoxic chemotherapy.

METHODS

Research design

A prospective observational open-label research was conducted, involving 60 cancer patients with verified chronic cardiac failure, which were receiving cardiotoxic chemotherapy and double cardioprotective therapy: Bisoprolol at a dosage of 1.25 mg once daily in the morning and Perindopril at a dosage of 2.5 mg once daily in the morning (Control group, the dosages were adjusted, if necessary, depending on the blood pressure and heart rate values), along with 56 cancer patients, which were receiving similar therapy with an addition of Dapagliflozin at a dosage of 10 mg once daily in the morning (test group). The controls of the obtained results were arranged after 6 months due to the fact that the patients had a high comorbidity background, and the majority of patients had stage IV of the oncology disease and, as a result, they had a small life expectancy. During the course of the research, 3 patients were excluded. Failure to timely undergo control check-ups (established by the research protocol) was reported for 9 patients. In the control group, after a 6 months period, 24 patients have completely passed all the research controls, while in the test group the number was 23 patients. The patients were distributed using block randomization at a ratio of 1:1. Statins were not included into the therapy scheme due to the absence of proven evidences of their efficiency to the moment of enrollment into the research.

The research design is provided in Fig. 1.

Conformity criteria

Inclusion criteria: consent obtained from the patient for the participation in the research; patients aged from 18 to 85 years; any stage of the oncological disease; presence of chronic cardiac failure class I–IV according

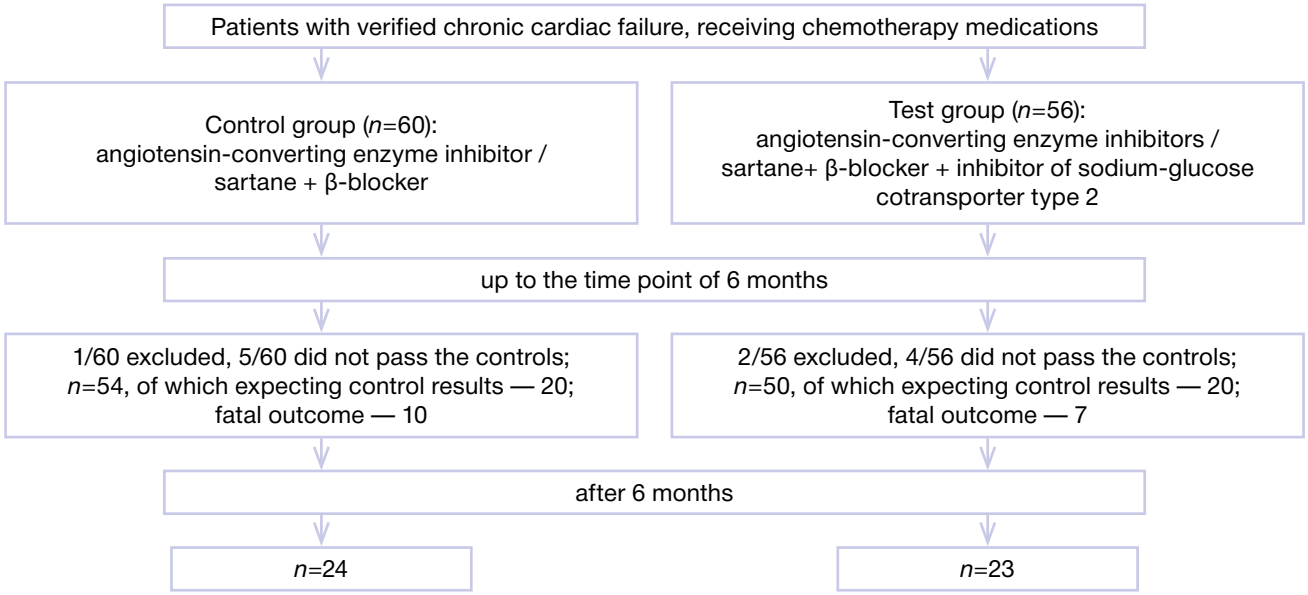

Fig. 1. Study design.

to the classification issued by the New York Heart Association (NYHA), which was defined as an elevation of the levels of N-terminal fragment of cerebral natriuretic peptide (N-terminal prohormone of brain natriuretic peptide, NT-proBNP) >300 pg/ml in the absence of atrial fibrillations or >900 pg/ml in case of having atrial fibrillations in the individuals aged under 75 years old, for the patients older than 75 years — >450 pg/ml, as well as the presence of clinical-instrumental data, which includes the analysis of the functional status of the patient, echocardiography data and clinical signs (including shortness of breath, the noncardiac origin of which has been ruled out); estimated glomerular filtration rate calculated using the CKD-EPI formula — >30 ml/1.73 m^2 per minute; blood pressure above the levels of 100/60 mm. Hg.; patients with diabetes mellitus type 2 and or without diabetes. It should be noted that, during the initial stage of the research, there were no indications for prescribing Dapagliflozin in patients with chronic cardiac failure without diabetes mellitus and the patients that had no diabetes mellitus were included already during the on-going research. The patients were enlisted into the research during the first chemotherapy cycle or during further chemotherapy cycles upon the verification of chronic cardiac failure already during the course of therapy.

Exclusion criteria: refusal of the patient to participate in the research; patients aged less than 18 years and more than 85 years; absence of chronic class I–IV cardiac failure acc. to NYHA classification; acute heart failure at the decompensation stage, requiring the intravenous administration of diuretics, vasodilating agents, inotropic agents or mechanical support of circulation within the 1st hospitalization week; acute myocardial infarction, major cardiac surgeries, as well as transitory ischemic attack or stroke episode during the last 3 months; glomerular filtration rate (calculated using the CKD-EPI formula) values of <30 ml/1.73 m^2 per minute; arterial hypotension (blood pressure below the levels of 100/60 mm. Hg.); acute infectious diseases; autoimmune diseases.

Research facilities

The treatment and follow-up procedures were carried out within the premises of the Federal State Budgetary Institution "Federal Scientific and Clinical Center for Specialized Types of Medical Care and Medical Technologies" of the Federal Medical-Biological Agency of Russia (FSBI FSCC of the FMBA).

The patients were selected from two departments — the Oncology Department No. 1 and the Department of Antitumor Medication Therapy.

The procedures of controlling the compliance (passing all the control points) were carried out at the Federal State Budgetary Institution FSCC of the FMBA and remotely within the medical institutions at the place of residence.

Research duration

The recruitment of patients was conducted during the time period from December 2021 until December

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2023 (inclusive). The data provided includes the patients with a status description compiled to the date of 01.08.2023.

Medical procedure description

After receiving an informed consent, the patients were enlisted to participate in the research and underwent long-term follow-up procedures. The whole spectrum or required tests was divided into the laboratory and the instrumental ones. As the primary documentation, the medical records of the patients were analyzed: initial examination, examinations by dedicated specialists, laboratory and instrumental findings. Then followed the additional examination within the framework of the claimed protocol of collecting all the necessary data.

Laboratory tests. All the patients (before the initiation of chemotherapy) had their blood samples collected for performing the following laboratory tests: clinical hematology panel, blood biochemistry panel, coagulation panel, determination of the levels of troponin T and NT-proBNP in blood plasma, the last one was the clinical urinalysis. The NT-proBNP levels were determined before the initiation of chemotherapy and after 6 months. The troponin T blood tests were carried out before each chemotherapy cycle.

Instrumental examinations. All the patients underwent two-dimensional echocardiography with an estimation of the left ventricle ejection fraction using the Simpson's method and with the obligatory measurement of the global longitudinal strain of the myocardium (GLS) using the General Electric Vivid 7 equipment. These parameters were also tracked before the initiation of chemotherapy and after 6 months. The routine measurements in all the patients included the electrocardiogram readings with using 12 leads before each chemotherapy cycle. Besides, for the purpose of evaluating the treatment efficiency and for the objectivization of symptoms, at the end of the 6 months period, all the patients had filled in the modified Kansas City Cardiomyopathy Questionnaire (KCCQ), which allows for objectifying the presence of symptoms of chronic cardiac failure, its severity and dynamic changes during the whole follow-up period. All the patients have also underwent a Six Minute Walk Test for the purpose of defining the functional class of chronic cardiac failure.

Research outcomes

During the course of the research, the following primary (combined) endpoint was evaluated: hospitalization due to cardio-vascular reasons, cessation of chemotherapy for the reason of progressive chronic cardiac failure, safety of using the therapeutic agent: the presence of urinary tract infection or sepsis. Secondary endpoint: total clinical index, which is defined as the functional status of the patient and the sum of factors, determining the quality of life and social restraint. The surrogate endpoints (evaluation of dynamic changes in the levels of NT-proBNP, troponin T, left ventricle ejection fraction and GLS) were measured within the timeframes established for the research — before the initiation of chemotherapy and after 6 months.

Ethical review

The procedures were carried out within the framework of the research named "The use of sodium-glucose cotransporter type 2 inhibitors for the purpose of treating the chronic cardiac failure in oncology patients receiving cardiotoxic chemotherapy", approved by the local Ethics Committee of the Federal State Budgetary Institution FSCC of the FMBA, which was established and which is acting in accordance with the Declaration of Helsinki of the World Medical Association (WMA), with the ICH GCP and with the Law of the Russian Federation on Circulation of Medicines (protocol No. 5, issued on 14.06.2022).

Statistical analysis

The procedures of collecting the data for statistical analysis were carried out manually by systematizing them in the Excel table with further processing them using the SPSS Software. Quantitative variables were presented as a median with adding the interquartile range (Me [Q1; Q3]). The sample size was not analyzed, for the research included only the patients that met the inclusion criteria. The obtained differences were considered statistically significant at the p level of <0.05 (95% confidence).

RESULTS

Research sample (participants)

A total of 104 patients participated in the research, of which 63 (61%) were females and 41 (39%) were males (table 1). The mean age was 68 years. More than 14 various locations of the oncological diseases were presented: 8 (7.69%) patients had several locations of the oncological process; lung cancer was diagnosed in 12 (11.5%) patients, mammary gland cancer — in 14 (13.4%), gastric cancer — in 11 (10.2%), colorectal cancer — in 18 (17.3%), ovarian cancer — in 12 (11.5%),

Table 1

Characteristics of the studied patient groups

Parameter	Control group *n*=54 (%)	Test group *n*=50 (%)
Gender: • male • female	 20 (34.07) 34 (62.96)	 21 (42) 29 (58)
Age, years, Me [Q1; Q3]	66 [43–84]	72 [48–84]
Location of the oncological process: • mammary gland • stomach • lungs • colorectal cancer • ovaries • pancreatic gland • other locations	 9 (16.67) 6 (11.11) 5 (9.26) 8 (14.81) 8 (14.81) 1 (1.85) 21 (38.89)	 5 (10) 5 (10) 8 (16) 10 (10) 4 (8) 4 (8) 18 (36)
Monochemotherapy	9 (16.67)	7 (12.96)
Combined therapy: • fluoropyrimidines • taxanes and platinum-based drugs • anthracyclines • other schemes	45 (83.33) 18 (33.33) 12 (22.22) 4 (7.41) 18 (33.33)	43 (86) 22 (44) 7 (14) 5 (10) 16 (32)
Stages of oncological diseases: • I • II • III • IV	 5 (9.26) 6 (11.11) 15 (27.78) 29 (53.7)	 3 (6) 8 (16) 16 (32) 27 (54)
Lethal outcomes	10 (18.52)	7 (14)
Hypotension	2 (3.7)	1 (2)

pancreatic cancer — in 5 (4.8%). Other malignant tumors were found in 39 (37.5%) cases. Combined chemotherapy was prescribed to 88 (85%) patients. Monochemotherapy was used in 16 (15%) patients. Combined chemotherapy with fluoropyrimidines was used in 40 patients (38.4%), taxanes and platinum-based drugs — 19 (18.2%), anthracyclines — 9 (8.6%), other schemes were used in 34 (32.6%) cases. A total of 56 (53%) patients were diagnosed with stage IV of the oncological diseases, another 31 (29.8%) had stage III, while 14 (13.4%) and 8 (7.6%) had stages II and I, respectively. The registered number of fatal outcomes was 17 (16%), however, fatal outcomes due to cardiac failure were not reported in any of the two groups.

The patients had a complicated comorbidity background, which has increased their total cardiovascular risk (table 2): arterial hypertension was reported in 77 (74%) patients, atrial fibrillation — in 11 (11.5%), ischemic heart disease — in 32 (31%), diabetes mellitus — in 26 (25%), increased body mass index or obesity — in 16 (15%).

The patients that have passed all the control examinations (*n*=47), after 6 months from the initiation of the research, underwent a comparison of the levels of troponin T, NT-proBNP, GLS and the left ventricle ejection fraction. The patients were distributed based on the inclusion criteria with using block randomization at a ratio of 1:1. Eventually, 24 patients were selected

Table 2

Data on the distribution of comorbid nosologies by study groups

Nosology	Control group *n*=54 (%)	Test group *n*=50 (%)
Arterial hypertension	37 (68.52)	40 (82)
Atrial fibrillations	4 (7.41)	7 (14)
Ischemic heart disease	17 (31.48)	15 (30)
Diabetes mellitus type 2	8 (14.81)	18 (36)
Body mass index, or obesity	7 (12.96)	9 (18)

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to represent the control group and 23 were enrolled into the test group. As a result, it was found, that the dynamic changes of troponin T levels in both groups did not significantly differ (p=0.26), while the levels of NT-proBNP had significantly decreased in the test group — by 7.8% comparing to the control group (p=0.006). Comparable data were also found for the GLS levels (a decrease in the test group by 6.5% comparing to the control group; p=0.008). The values of the left ventricle ejection fraction, upon dynamic assessment, practically did not change (p=0.340).

A total of 22 (46.8%) patients had chronic heart failure before the initiation of chemotherapy, while 25 (53.2%) had the disorder developing during the course of antitumor medication therapy.

Main research outcomes

At the end of the 6 months period, all the patients with chronic cardiac failure had filled in the modified Kansas City Cardiomyopathy Questionnaire.

In the control group, 10 (41.67%) patients had the total clinical index value (calculated with taking into consideration the functional status and the sum of factors, determining the quality of life and social restraint) of 50–69%, which corresponds to moderate quality of life and the presence of moderate restraint regarding the physical aspects of life; 13 (54%) patients had a total clinical index of 70–89% (good quality of life, some restrictions regarding the physical activity or other aspects of life), while only in 1 (4.17%) patient this index was 30–49% (low quality of life, serious restraint of physical functions and other aspects of life). In the test group, 8 (34.78%) patients had a total clinical index of 50–69%, 14 (60.87%) patients had the same index at the level of 70–89%, while 1 (4.35%) patient had a total clinical index of 30–49%. As a result, it was found, that the dynamic changes of the total clinical index values in both groups did not differ (p=0.343).

Two cases of hospitalization were registered as related to the cardio-vascular reasons (one in each group): paroxysm of atrial fibrillations and acute myocardial infarction. Death caused by sepsis caused by developing pneumonia was reported for 5 patients (3 in the control group and 2 in the test group). No cases of urinary tract infections and refusal to undergo chemotherapy for the reason of progressing chronic cardiac failure were registered. No significant statistical differences were reported regarding the combined primary endpoint (p=0.317).

In the control group, 10 (41.67%) patients died comparing to 7 patients (30.43%) in the test group. The details of the fatal outcomes are the following: 5 patients had succumbed due to sepsis caused by developing pneumonia; 6 patients have passed away due to the progression of the oncological process, 1 patient has deceased after an episode of COVID-19 infection, while in 5 patients the cause of death remained unknown. The statistics of fatal outcomes shows that a little less than 1/5 of the total number of patients, which is 17 (16%) patients, have deceased before the end of 6 months period. Six (5.7%) patients had a fatal outcome resulting from the progression of the main disease. This indicates the small life expectancy in oncology patients. It should also be noted that no significant role of cardiovascular system disorders was found in the thanatogenesis. Fatal outcomes caused by cardiac failure were not observed in any of the two groups.

Undesirable phenomena

When analyzing the data for both groups during the whole follow-up period, a total of 3 hypotension episodes with a background of taking basic cardioprotective therapy were reported. One of the patients was taking the research medication (Dapagliflozin), which, according to the Instructions for use and according to the results of the latest multi-center randomized clinical researches, is practically not capable of affecting the blood pressure levels (a decrease by a maximum of 3 mm. Hg. was noted) [8]. There were no cases of significant hypoglycemia, requiring a consultation by the Endocrinologist, as well as no cases of urogenital infections, requiring a consultation by the Urologist.

DISCUSSION

The possibility of cardioprotection in cancer patients, receiving cardiotoxic chemotherapy, has been studied for quite a long time. Sufficient data were obtained for the effects caused by various groups of antitumor agents in terms of the cardio-vascular system, resulting in the development of cardiac failure, atrial fibrillations, arterial thromboses, acute coronary syndrome along with the spasms of the vessels and venous thromboembolism [9, 10]. There are also successful results obtained for large samples within the framework of secondary prevention of chronic cardiac failure, for example, combination of angiotensin-converting enzyme inhibitors and beta-adrenergic blockers [11]. The main parameter defining the contractile function of the heart is considered the left ventricle ejection fraction [12], however, the decrease in the said parameter is an

indicator of already existing myocardial dysfunctions, which is why it is important not to let it develop. The research of cardiotoxicity markers has a major importance in preventing myocardial dysfunctions [1].

A comparison was carried out for the onset of the outcomes by the combined primary endpoint (the rate of hospitalizations caused by cardio-vascular reasons, refusals to continue chemotherapy due to the progression of chronic cardiac failure, infections of the urinary tracts and sepsis). The infections of the urinary tracts were defined as subfebrile fever (>37°C), leukocytosis found in the clinical hematology panel (WBC count >11.0×10^9/l) and proteinuria (>0.5 g/day). The results happened to be comparable in both groups and did not statistically differ. This is probably related to the sample size and to the short duration of following up the patients.

According to our data, when analyzing the troponin T levels, a positive trend was found in the test drug group, however, the result was statistically insignificant. Troponin T is the earliest marker of myocardial damage in response to various effects, hence, it cannot be considered as strictly specific for the processes of developing chronic cardiac failure induced by antitumor therapy.

When comparing the dynamic changes in the levels of the left ventricle ejection fraction, no significant and strong inter-relation was detected, which is probably affected by the time factor and the high number of patients with intact left ventricle ejection fraction, included in the research.

Upon the evaluation of the NT-proBNP levels, a clear significant positive dynamic trend was found in a group of patients taking Dapagliflozin. Taking into consideration the specificity of NT-proBNP in terms of diagnostics and further progression of chronic cardiac failure, the prognostic and clinical significance can be supposed for the intake of the said medicinal product for the purpose of treating the chronic cardiac failure at the early stage (within the timeframe of up to 6 months).

The analysis of the GLS levels show the presence of clear significant positive dynamic trend in a group of patients taking Dapagliflozin. The trend is similar to the one observed for the natriuretic propeptides, which, probably, indicates the commonness of the pathomorphological processes taking place in the myocardium under the effects of chemotherapy, also indicting the changes in the cardiac muscle in response to the given effects.

The high significance factor for cancer patients with chronic cardiac failure is the physical activity. If the Six Minute Walk Test defines only the functional class of cardiac failure, which did not significantly change under the effects of chemotherapy, the results of using the Kansas City Cardiomyopathy Questionnaire have demonstrated an insignificant positive tendency in patients taking the study drug, however, the difference was statistically insignificant. This is probably related to the fact of the research including predominantly patients with intact ejection fraction of the left ventricle (93%). Similar results were demonstrated in a complementary research [13]. Nevertheless, even the small positive dynamic trend in such a comorbid cohort of patients, the functional activity of which can be restrained by the effects of chemotherapeutic agents or by complications developing upon the progression of the main disease, gives ground for proposing the improvement of the motor activity and the increase in the quality of the patients' life.

The important fact was the relatively favorable safety profile of Dapagliflozin. Oftentimes cancer patients receive strong immunosuppressive therapy, which increases the risk of developing inflammatory and infectious diseases. No substantial adverse effects of taking the test drug were observed to the present moment.

Data on the primary, the secondary and the surrogate endpoints is described in Table 3.

We suppose that the observed positive trends occur under the influence of taking Dapagliflozin and can indicate its role in the prevention and treatment of chronic cardiac failure.

Thus, according to our research, no differences were observed in terms of the primary endpoint between the research groups, which is related to small sample size and does not allow for judging on the effects of sodium-glucose cotransporter type 2 inhibitors in terms of clinical outcomes in cancer patients, receiving cardiotoxic chemotherapy. Along with this, the NT-proBNP and GLS levels had significantly decreased with a background of study drug therapy, which can indicate its protective role in the prevention of cardiac failure. The preliminary data raises the hopes, though, evidently, the sample is rather small, which is why larger scale research works are necessary along with further monitoring the patients, including the participation of the multidisciplinary team of specialists.

Research limitations

The research limitations include the design (prospective observational open-label) and the research facilities (in a single medical center, though

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Table 3

Data on primary, secondary and surrogate endpoints

Parameter	Control group *n*=54	Test group *n*=50	*p*
Primary endpoint, *n* (%)			
Combined (death caused by cardio-vascular diseases, refusal to undergo chemotherapy, presence of urinary system infections or sepsis)	4 (6.67%)	3 (5.36%)	0.317
Secondary endpoint, Me [Q1; Q3]			
Total clinical index (%)	65.22 [37–83]	66.46 [34–86]	0.343
Surrogate endpoints, Me [Q1; Q3]			
Troponin T	20.14 [3.37–48.80]	18.67 [3.35–59.81]	0.260
Brain (atrial) natriuretic peptide (NT-proBNP)	608 [56–9345]	511 [60–3163]	0.006
Left ventricle ejection fraction	56.2 [51–60]	55.9 [48–63]	0.340
Global longitudinal strain of the myocardium (GLS)	-17.6 [-22.6; -16.3]	-18.8 [-22.8; -14.3]	0.008

the grouping was done using the random sample method). We did not analyze the outcomes separately in patients with diabetes mellitus or without diabetes, for the reason that, during the initial stage, there were no indications for prescribing Dapagliflozin in patients with chronic cardiac failure without diabetes mellitus, and the patients without diabetes mellitus were enrolled into the research already at the stage of its execution after registering the corresponding indications.

CONCLUSION

The addition of the sodium-glucose cotransporter type 2 inhibitor Dapagliflozin to basic therapy for chronic cardiac failure in cancer patients, receiving chemotherapy, did not statistically affect the rate of hospitalization caused by cardio-vascular reasons, the rates of refusing to undergo chemotherapy due to the progression of the chronic cardiac failure or the rates of developing urinary tract infections and sepsis. At the same time, the addition of Dapagliflozin to baseline therapy for chronic cardiac failure in cancer patients, receiving cardiotoxic chemotherapy, resulted in a significant decrease in the NT-proBNP levels and to a less prominent decrease of the longitudinal strain of the left ventricle myocardium.

We suppose that the decrease in the levels of the cardiac failure marker and the less intensive impairment of the longitudinal strain of the left ventricle with a background of adding sodium-glucose cotransporter type 2 inhibitor to baseline therapy for chronic cardiac failure in cancer patients, receiving cardiotoxic chemotherapy, reflects the cardioprotective potential of the study drug and it can slow down the progression of chronic cardiac failure.

ADDITIONAL INFORMATION

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TANNERELLA FORSYTHIA AS ONE OF SEVERITY DEGREE PREDICTORS FOR CHRONIC GENERALIZED PERIODONTITIS

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ABSTRACT

BACKGROUND: *Chronic generalized periodontitis takes the second place by the occurrence rate worldwide among the diseases of the maxillofacial area. High significance of preventing and early diagnostics for chronic generalized periodontitis is defined by the early tooth loss, by the decrease in chewing efficiency and by the development of chronic infection foci. It is known that the main etiology factor of chronic periodontitis is the microbial one, including the representative of the oral cavity microbiota — Tannerella forsythia, which is a Gram-negative, anaerobic bacterium.* ***AIM:*** *To verify the presence of T. forsythia in cases of chronic generalized periodontitis depending on the disease severity.* ***METHODS:*** *The research included 126 patients with chronic generalized periodontitis of various severity degree, for which, an analysis of the content of periodontal recess was carried out. In the control group, consisting of individuals with no periodontal tissue abnormalities (n=39), the content of gingival sulcus was analyzed. The samples were examined using the method of polymerase chain reaction following the real time mode by means of employing the DT-96 detection thermocycler (DNA-Tekhnologia NPO) and the «ParadontoScreen» test kit.* ***RESULTS:*** *The findings included a high direct correlation between the rate of detecting T. forsythia and the severity degree of the course of chronic periodontitis (the correlation coefficient value was found to be 0.997; p <0.05). A strong direct relation (0.948; p <0.05) was demonstrated between the concentration of T. forsythia genomic equivalent and the severity degree of chronic periodontitis.* ***CONCLUSION:*** *The conducted research has shown that the concentration of T. forsythia is a predictor for severity degree of chronic periodontitis.*

Keywords: *chronic periodontitis; Tannerella forsythia; parodontal pathogens; periodontal recess; microorganism.*

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BACKGROUND

Chronic generalized periodontitis takes the second place worldwide by the occurrence rate among the diseases of the maxillofacial area. Based on the research carried out in 2016 (Global Burden of Disease Study), it was found that the severe diseases of periodontal tissues take the 11th place worldwide. So, the incidence of chronic periodontitis by population cohorts, generally, varies from 36% in the countries of the Western Europe to 80–100% in the developing countries. In recent years, a growth of incidence was reported up to 30% among the individuals aged 19–25 and up to 60% — among the ones aged 25–30 [1–5].

The high significance of the problem of chronic generalized periodontitis occurrence in the modern society is defined by the early loss of teeth, by the decrease in chewing efficiency and by the development of chronic infection foci. As of today, one of the most topical issues in periodontology is the development and improvement of the methods of early diagnostics and treatment for periodontal diseases [6–9].

The clinical signs of chronic generalized periodontitis are characterized by hemorrhages in the gingival mucosa; by the presence of solid and soft dental deposit, by loosening of teeth and by the presence of periodontal recess; by loss of alveolar process bone tissue height.

Three disease stages are known — mild, moderate and severe. The mild degree of severity is characterized by the presence of swelling, cyanotic and bleeding mucosa of the gingival margin, 1st degree loosening of teeth and by the presence of a periodontal recess

TANNERELLA FORSYTHIA КАК ОДИН ИЗ ПРЕДИКТОРОВ СТЕПЕНИ ТЯЖЕСТИ ХРОНИЧЕСКОГО ГЕНЕРАЛИЗОВАННОГО ПАРОДОНТИТА

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АННОТАЦИЯ

Обоснование. *Хронический генерализованный пародонтит занимает второе место по распространённости среди заболеваний челюстно-лицевой области в мире. Высокая значимость профилактики и ранней диагностики хронического генерализованного пародонтита определяется ранней потерей зубов, снижением жевательной эффективности, формированием хронических очагов инфекции. Известно, что основным фактором этиологии хронического пародонтита является микробный, а одним из представителей микрофлоры ротовой полости — Tannerella forsythia, представляющая собой грамотрицательную анаэробную бактерию.* ***Цель исследования*** *— верифицировать носительство T. forsythia при хроническом генерализованном пародонтите в зависимости от степени тяжести заболевания.* ***Методы.*** *В исследовании приняли участие 126 пациентов с хроническим генерализованным пародонтитом различной степени тяжести, которым проводили анализ содержимого из пародонтального кармана. В группе контроля, состоявшей из лиц без патологии тканей пародонта (n=39), изучали содержимое десневой борозды. Образцы исследовали методом полимеразной цепной реакции в режиме реального времени на амплификаторе ДТ-96 (НПО ДНК-Технология) набором «ПародонтоСкрин».* ***Результаты.*** *Обнаружена высокая прямая корреляция между встречаемостью T. forsythia и степенью тяжести течения хронического парадонтита (значение коэффициента корреляции составило 0,997; p <0,05). Выявлена прямая сильная связь (0,948; p <0,05) между концентрацией геномного эквивалента T. forsythia и степенью тяжести хронического пародонтита.* ***Заключение.*** *Проведённое исследование показало, что концентрация T. forsythia является предиктором степени тяжести хронического пародонтита.*

Ключевые слова: *хронический пародонтит; Tannerella forsythia; пародонтопатогены; пародонтальный карман; микроорганизм.*

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up to 4 mm deep. The radiology images in cases of mild disease show dilation of periodontal fissure, loss of integrity in the cortical plate, resorption of the alveolar bone walls by 1/3 of the dental root length. In cases of moderate severity of chronic generalized periodontitis, the findings include an increase in the depth of periodontal recess up to 6 mm, pathological loosening of teeth (2nd degree) and exposition of the dental roots. The orthopantomograms from the patients with 2nd degree show resorption of alveolar bone walls, reaching up to 1/2 of the length of the dental root and showing signs of destruction in the cortical plate. The severe chronic generalized periodontitis is characterized by an increase in the pathological loosening of teeth (up to degree II or III), by dislocation of teeth, by the presence of periodontal recesses with a depth of more than 6 mm and with the presence of purulent exudate, by significant traumatic occlusion and exposition of the roots. Upon radiology examination, the findings include resorption of alveolar bone walls to a distance of more than 1/2 of the dental root length with the presence of pathological bone pockets.

The detection of pathological loosening of teeth is based on the classification that is the most used in clinical practice — the one from the D.A. Entin (1954): 1st degree — tooth dislocation only in the vestibulooral direction; 2nd degree — tooth dislocation in the vestibulooral and medio-distal directions;

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3rd degree — tooth dislocation in the vestibulooral, medio-distal and vertical directions [6–8].

It is known that the main etiology factor for chronic periodontitis is the microbial one, with one representative of oral cavity microbiota being the *Tannerella forsythia*, which is a Gram-negative anaerobic bacterium. This microorganism, described by the scientist Ann Tanner, was later called *Bacteroides forsythus* and it is currently classified as a member of *Tanerella* genus. There are data indicating that *T. forsythia* does not ferment sugar and, for implementing its active vital activities, it has trypsin- and cysteine-like proteases, encoded by the *PrtH*, allowing the bacteria to exhibit cytopathic effects. The PrtH protease decreases the cellular adhesion of periodontal tissues and stimulates the processes of inflammation, accompanied by the secretion of interleukin 8 (IL-8). At the initial stages of research activities, it was found that PrtH phenotype *T. forsythia* is a forsythia exfoliation factor, it takes part in cell fragmentation and disintegration of gingival mucosa and, thus, it can act as a pathogenic factor of developing periodontosis [10–13].

As for adaptation mechanisms, *T. forsythia* has an enzyme called karyolysine, capable of cleaving fibrinogen and hemoglobin along with inactivating the complement system, and an antimicrobial peptide LL-37, promoting chronic inflammation by means of producing tumor necrosis factor (tumor necrosis factor, TNF) in macrophages. For protection purposes, the bacteria have a specific protein Serpin (Miropin), being a pathogenicity factor, which suppresses serine proteases found in neutrophils. At the same time, the surface of the bacteria is covered in BspA proteins, interacting with extracellular fibronectin and fibrinogen, which allows the bacteria to firmly attach to gingival tissues and reproduce there. The lipoproteins located at the bacterial surface also play an important role of in the growth of the bacteria, inducing apoptosis in fibroblasts of the host's gingival mucosa. For productive vital processes, *T. forsythia* has enzymes (glucosidases), cleaving oligosaccharides and proteoglycans of host cells: exo-α-sialidase, α-D-glucosidase and N-acetyl-β-D-glucosaminidase. It was found that, in the presence of glucose, the microorganism accumulates a lot of methylglyoxal products that are toxic for host cells [11, 12].

Considering the above, it can be concluded that *T. forsythia* has multiple molecular factors, each of which can participate in the pathogenesis of chronic periodontitis. Thus, monitoring of *T. forsythia* gains special significance in diagnostics and determining further treatment tactics, as well as in predicting the disease [12, 14, 15].

Research aim — to verify *T. forsythia* presence in cases of chronic generalized periodontitis depending on the severity diseases.

METHODS

Research design

Within the premises of the Clinical Hospital of the Federal State Budgetary Educational Institution of Higher Education " Chita City State Medical Academy" of the Ministry of Health of the Russian Federation, an observational single-center selective controlled non-randomized research work was carried out.

Conformity criteria

Inclusion criteria: patients suffering from chronic generalized periodontitis and aged from 44 to 60 years, not receiving antibacterial therapy for 6 months before the research activities.

Exclusion criteria: patients with chronic generalized periodontitis aged under 44 years and older than 60 years, receiving antibacterial therapy; patients suffering from primary or secondary immune deficiency, autoimmune diseases, diabetes mellitus or malignant neoplasms.

Research facilities

The examination was carried out within the premises of the Clinical Hospital of the Federal State Budgetary Educational Institution of Higher Education "Chita City State Medical Academy" of the Ministry of Health of the Russian Federation (Chita) during the time period from 2021 until 2023.

Medical procedure description

The patients in all the research groups underwent sampling of the periodontal recess content, while the patients from the control group had their gingival sulcus content sampled. All the samples were examined using the method of polymerase chain reaction (PCR) with real-time detection using the DT-96 detecting thermocycler ("NPO DNK-Tekhnologia" LLC) and the "ParodontoScreen" test kit. This procedure does not require special preoperational preparation or the use of local anesthetics.

Research outcomes

Main outcome of the research: a "surrogate" final point was assessed (genomic equivalent of microbial burden).

Subgroup analysis

The disease severity criterion was used to designate subgroups according to the classification of chronic generalized periodontitis.

Ethical review

The research was approved at the meeting of the local Ethics Committee of the Federal State Budgetary Educational Institution of Higher Education "Chita City State Medical Academy" (extract from the Minutes No. 112 dd. 23.04.2021).

Statistical analysis

Statistical processing of the obtained results was carried out using the "SPSS Statistics 10" software v. 10 (StatSoft Inc., USA) with following the statistical analysis principles, accepted for research activities in biology and medicine. The results were presented as means with standard deviations. For the purpose of assessing the correlation and determining the strength and direction of the correlation relationship between two factors, Spearman's test was used, while the Student's test with Bonferroni adjustment was applied when comparing the research groups to the clinical control group [16].

RESULTS

Research sample (participants)

The number of examined patients with chronic generalized periodontitis was 126. The patients were divided into three groups comparable by age and gender, depending on the disease severity: mild degree — group 1 (n=39); moderate degree of severity — group 2 (n=42); severe degree — group 3 (n=45), along with a separate control group (n=39), which included individuals without abnormalities in the periodontal tissues. The degree of periodontitis severity was set based on such criteria as the depth of the periodontal recess, pathological loosening of teeth and the degree of bone tissue resorption in the alveolar processes.

Primary findings

It was found that the occurrence rate of *T. forsythia* in patients with chronic generalized periodontitis was significantly increasing along with an increase in disease severity (table 1), with the correlation coefficient value being 0.997 (p <0.05), which indicates the direct and strong relationship between the detection of the said microorganism and the severity degree of disease.

In patients with mild degree chronic generalized periodontitis (Group 1), the orthopantomogram was showing a dilation of the periodontal fissure, loss of integrity in the cortical plate, resorption of alveolar bone walls by 1/3–1/4 of the length of dental root (Fig. 1), with this being said, the mean value of genomic equivalent per 1 ml of biological sample (GE) for *T. forsythia* was 5.0±1.03, which is 1.5 times more than the values in the control group (p=0.012) (Fig. 2).

The clinical signs and objective examination data in Group 2 allowed for defining the depth of periodontal recesses as reaching 6 mm, along with 2nd degree pathological loosening of teeth and exposing the dental roots. The orthopantomogram in patients from this subgroup shows a resorption of alveolar bone walls down to 1/2 of the length of dental root and destruction of the cortical plate (Fig. 3), with the mean microorganism concentration in Group 2 being increased up to 5.7±0.80 GE, which is 1.7 times higher than the same parameter in the control group (p <0.001).

During the analysis of the obtained data, the highest concentration of *T. forsythia* was found in patients from Group 3 — 6.6±1.87 GE, which is 1.3 times higher comparing to the values in Group 1 (p <0.001), 1.16 times higher comparing to Group 2 and 2 times higher comparing to the values in the control group. In patients from Group 3, the clinical signs and visual examination results have revealed a degree

Table 1

The incidence of *Tannerella forsythia*

Occurrence	Study groups, *n* (%)			
	Control (*n*=39)	1 (*n*=39)	2 (*n*=42)	3 (*n*=45)
Positives	16 (41)	21*, 2* (54)	36[3]* (86)	40[4]* (89)
Negatives	23 (59)	18 (46)	6 (14)	5 (11)

Note. p-level: * <0.001 in groups 1 and 2; [2]* <0.001 in groups 1 and 3; [3]* <0.001 in groups 2 and control; [4]* <0.001 in groups 3 and control.

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2–3 pathological loosening of teeth, dislocation of teeth, as well as the presence of periodontal recesses with a depth exceeding 6 mm together with the presence of purulent exudate, significant traumatic occlusion and exposed roots. Upon radiology examination, this category of patients shows resorption of alveolar bone walls exceeding 1/2 of the length of dental roots along with the presence of pathological bone pockets (Fig. 4).

Based on the results of the conducted research, a direct strong relationship was found (0.948; p <0.05) between the concentration (genomic equivalent) of *T. forsythia* and the severity degree of chronic periodontitis. When analyzing the sensitivity and specificity of *T. forsythia* genomic equivalent in patients from the research groups, it was found that the maximal sensitivity value is 78.4% [confidence interval 73.79–83.01] with the specificity being equal

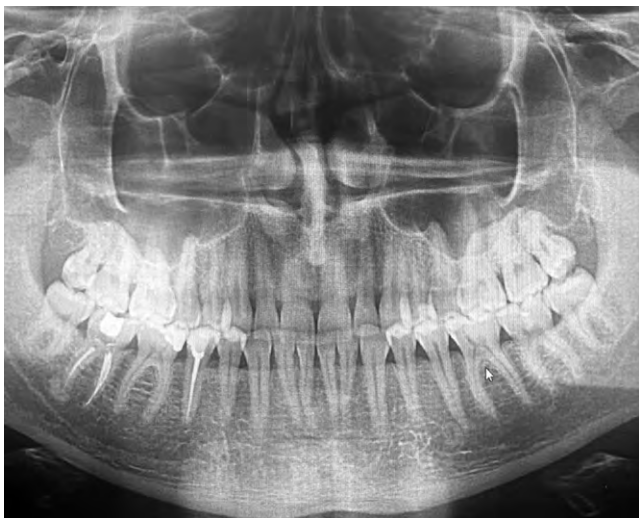

Fig. 1. Orthopantomogram — patient K. aged 44 years old: chronic generalized periodontitis of mild severity degree.

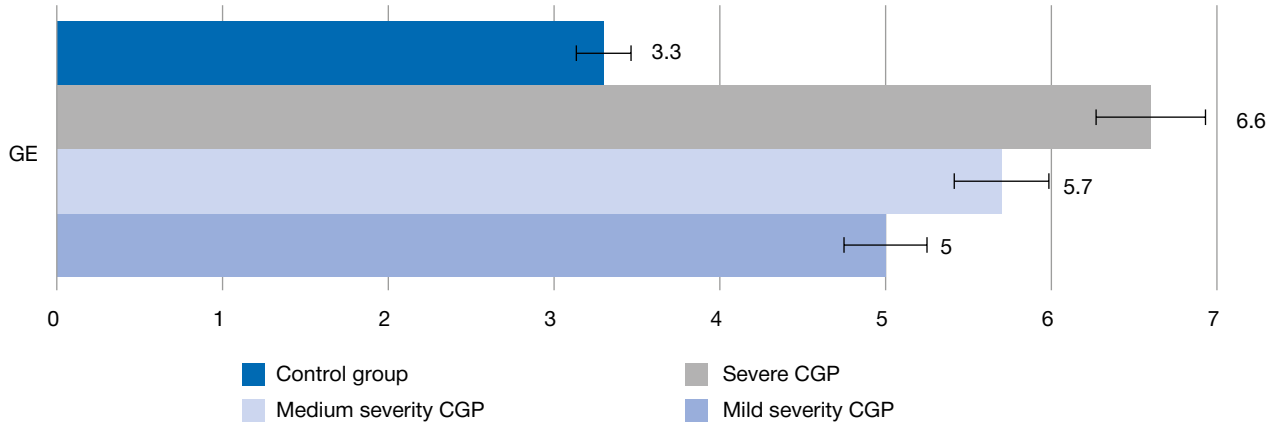

Fig. 2. Mean values of *Tannerella forsythia* concentration. GE — genomic equivalent; CGP — chronic generalized periodontitis.

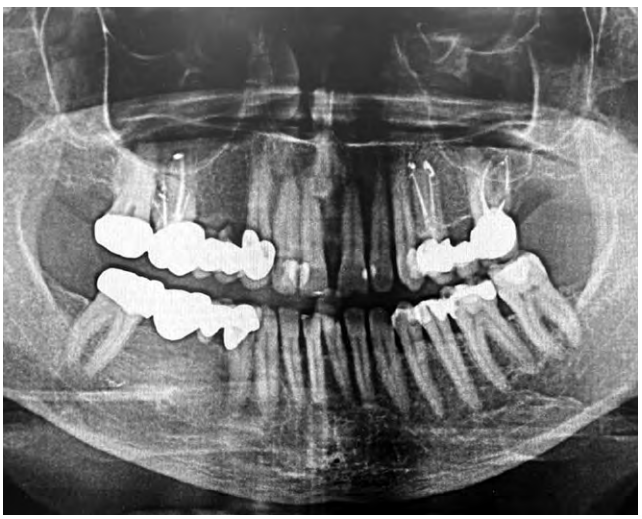

Fig. 3. Orthopantomogram — patient N., aged 49 years: chronic generalized periodontitis of moderate severity degree.

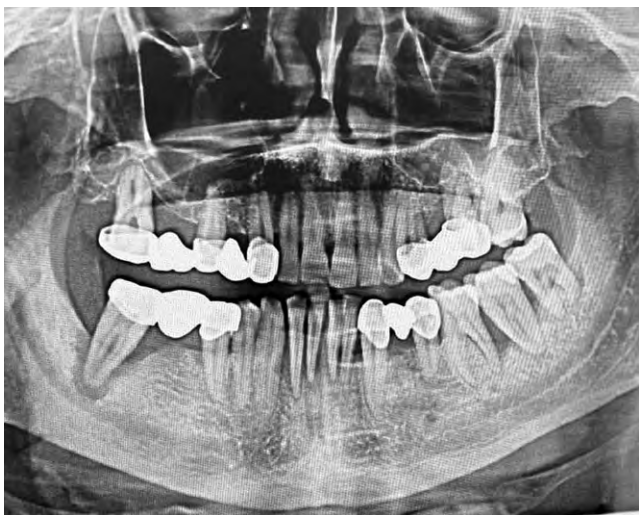

Fig. 4. Orthopantomogram — patient G., aged 56 years old: severe chronic generalized periodontitis.

to 62.1% [confidence interval 59.76–64.44] for the detection of this bacteria in a group with severe disease degree (Fig. 5).

DISCUSSION

Chronic periodontitis is a complex, multifactorial and not yet completely studied disease. The main role in the development of periodontitis is given to the periodontal pathogenic microbiota. At the same time, the highest pathogenicity is shown for the so-called red (periodontal) complex that includes *T. forsythia*, *Porphyromonas gingivalis* and *Treponema denticola*. This being said, in her scientific articles, L.S. Sazanskaya [17] has shown a definite role of *T. forsythia* and other periodontal pathogens in the development and progression of periodontitis in cases of gastroesophageal reflux disease. E.V. Markelova et al. [18] have found the presence of *T. forsythia* at the etiologically significant concentration in cases of severe chronic periodontitis. Besides, the recent scientific data show that this microorganism (due to having its pathogenicity factors) causes inflammatory and destructive changes.

The research work we have performed demonstrates that, with the increase of periodontitis severity degree, an increase is found in the genomic equivalent for the said bacteria, which indicates the growth of bacterial burden. The research work results indicate the necessity for combined specific antibacterial therapy in cases of chronic generalized periodontitis for the purpose of preventing disease progression.

CONCLUSION

A direct correlation relationship was found between the increase in the genomic equivalent and the increase of the degree of destructive changes in the periodontal tissues. The obtained results confirm that *T. forsythia* at the etiologically significant concentration is the predictor of severity degree for chronic periodontitis. The diagnostics of *T. forsythia* concentration shall allow (combined with classic examination methods) for predicting the risk of developing periodontitis in healthy individuals, and in cases of its presence — for practically unerringly defining the degree of severity for the disease, which shall provide a possibility of prescribing the corresponding combined treatment.

Such a significant correlation interrelationship between the presence of *T. forsythia* and the severity degree of periodontitis allows for drawing up a conclusion that the protocol of therapeutic procedures for this disease shall include antibacterial medications with effective bactericidal and bacteriostatic effects. The use of antibacterial therapy in the treatment of chronic periodontitis shall increase its quality.

ADDITIONAL INFORMATION

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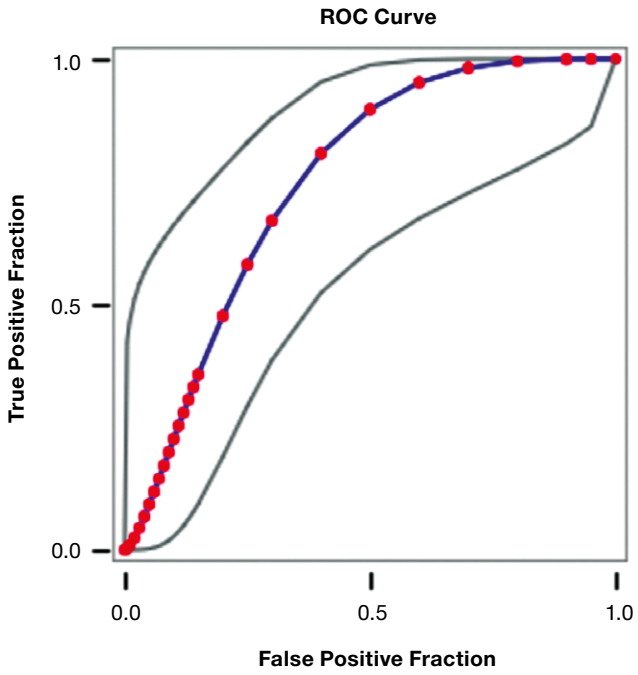

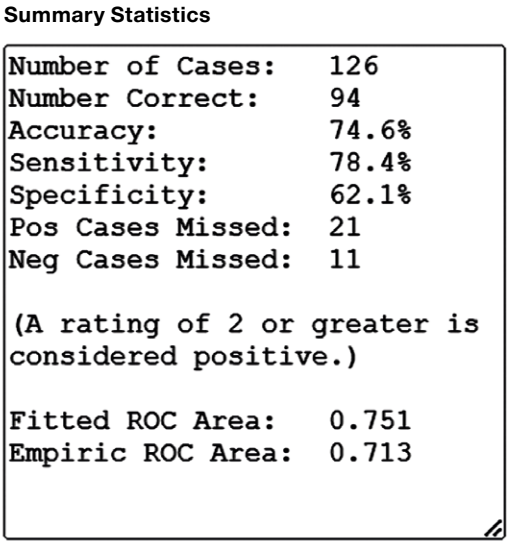

Fig. 5. Sensitivity and specificity of *Tannerella forsythia*.

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Competing interests. The authors declare that they have no competing interests.

Authors' contribution. *N.B. Yashnova* — search and analytical work, processing and discussion of research results, writing the manuscript; *A.A. Dutova* — laboratory testing of biological samples taken from the patients; *Yu.I. Pinelis* — editing; *A.A. Yashnov* — discussion of the results of the research, editing. The authors made a substantial contribution to the conception of the research work, acquisition, analysis and interpretation of data from the research work, drafting and revising the article, as well as final approval of the version to be published and the authors agree to be accountable for all aspects of the research work.

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COMMENTS TO THE ARTICLE SUBMITTED BY A.A. KOVALEV ET AL. "THE INTRALUMINAL ADMINISTRATION OF INDOCYANINE GREEN AS A METHOD OF INTRAOPERATIVE DIAGNOSTICS OF MACHINE SUTURE INCOMPETENCE IN EXPERIMENTAL CASES OF LONGITUDINAL GASTRIC RESECTION"

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ABSTRACT

The editorial policy of the "Clinical Practice" journal is supposed to be oriented to Applied Clinical Researches, the results of which practicing physicians could use in their routine work. The main objective of creating the journal was informing the physicians on the novel approaches in the diagnostics and treatment of various diseases, as well as rehabilitation and restoration of the quality of life. For this reason, the editorial board had often refused to publish the articles from the authors of well-planned and performed animal research works, even despite the fact that the clinical specialty certificate 3.1.9 "Surgery" supposes the experimental development of new methods.

In this specific case, the decision was made to publish the article.

Bariatric surgery in Russia is only passing its development phase. Despite the fact that such surgeries are indicated to a significant part of the population, their yearly number remains very small. A considerable role in this is contributed by mass media, which are regularly publishing the cases of complications resulting from the obesity-related surgeries and the consequent judicial proceedings.

Safety issues take the central place in bariatrics, for surgical aggression is applied to a healthy organ for the reason of the general disease, not causing a direct threat to life.

Longitudinal gastric resection (sleeve gastrectomy) is the most popular bariatric surgery type in Russia. According to data from the National Bariatric Surgery Register, this type of procedure represents 56% of all the primary surgeries. Machine suture incompetence is a rare but the most threatening complication of such a surgery, associated with high mortality rates. In Russia, from 2013 until 2022, a total of 70 cases were reported for suture line disruption, which corresponds to 0.4%, with that being said, three such patients died within the first week after surgery. Due to the high pressure inside the created gastric tube, the treatment of these complications is long-term and requires substantial financial costs. The methods for intraoperative diagnostics of problematic areas of the machine suture line, which require additional suture reinforcement, are deemed necessary. Traditionally, many surgeons use the so-called "bubble-test", which can detect only large defects and which shows low informational capability. With all of these, two large researches were published recently, which have confirmed the concerns of some investigators about the fact that rapid inflation of air into the nasogastral tube can damage the tissue and can increase the risk of incompetence. In a systematic review and meta-analysis by Ma L., et al. (2024.), involving 469 588 patients, in case of performing the intraoperative diagnostics, the risk was 0.38%, while in absence of such — 0.31% (p=0.000) [1]. When analyzing the database of the American Society for Metabolic and Bariatric Surgery (MBSAQIP) within a time period of 2015–2019, based on the evaluation of data from the research works including 283 520 patients, the risk of incompetence during the intraoperative diagnostics was 1.1 (95%CI 1.0–1.4) [2]. Based on these research works, it is possible to recommend the surgeons to avoid the routine use of the "bubble test". But the alternative option is required. Data on the use of Indocyanine green are still sparse. The research performed by A.A. Kovalev et al., must serve as a basis for more frequent use of this method, especially in complex situations. The editorial board of our journal shall eagerly await for the team of authors to present the results of the clinical approbation of the said method.

Keywords: *bariatric surgery; gastroplasty, leak; indocyanine green; ICG.*

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THE INTRALUMINAL ADMINISTRATION OF INDOCYANINE GREEN AS A METHOD OF INTRAOPERATIVE DIAGNOSTICS OF MACHINE SUTURE INCOMPETENCE IN EXPERIMENTAL CASES OF LONGITUDINAL GASTRIC RESECTION

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ABSTRACT

BACKGROUND: *Bariatric surgery represents an actively developing surgery field. With this, thanks to using modern automated methods of dissecting and suturing the tissues, a significant decrease is observed in the number of postoperative complications. At the same time, the problem of surgical suture incompetence remains topical even at the present times. The traditional methods of intraoperative diagnostics of incompetence are the provocative tests: the methylene blue test and the air leak test. One of the promising methods for intraoperative control during surgery is the use of fluorescent visualization in the near infrared range using the indocyanine green (ICG).* ***AIM:*** *Evaluate the informativity of intraoperative diagnostics of machine suture incompetence during the longitudinal gastric resection using fluorescent visualization with indocyanine green (ICG) by using the pig model to imitate various reasons of incompetence and to control surgical complications using morphological tests.* ***METHODS:*** *The research was carried out with using 20 pigs, each of which underwent the longitudinal gastric resection. The animals were distributed into the following experimental groups: the control group with performing standard longitudinal gastric resection (n=4) and the tests groups with longitudinal gastric resection and modeling of two variants of mechanical reasons of incompetence (n=12), as well as the local ischemia group (n=4). Intraoperationally, the gastric lumen was filled with a solution containing methylene blue and indocyanine green, after which, an evaluation was performed of the developed staining or Indocyanine green fluorescence visualization. Besides, in the ischemia group, ICG was administered intravenously. On Day 7 after surgery, samples were taken for histological examination.* ***RESULTS:*** *In 10 out of 11 experiments with the mechanical factor of modeling used to stimulate the machine suture incompetence, ICG visualization was found, with the ingress of methylene blue found in two cases out of 11, respectively. In 90% of the cases, the transudation of ICG corresponded to significant signs of inflammation, with the ingress of methylene blue being found only in 20% of the cases.* ***CONCLUSION:*** *The method of intraluminal administration of Indocyanine green in "mechanical" models of machine suture incompetence upon longitudinal gastric resection is more informative comparing to the introduction of methylene blue. Data from fluorescent ICG-angiography completely correspond to the location of ischemia modeling area.*

Keywords: *bariatric surgery; gastroplasty; leak; indocyanine green; ICG.*

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BACKGROUND

Bariatric surgery represents an actively developing field of surgery aimed for the treatment of obesity and its concomitant metabolic disorders. The number of bariatric procedures performed increases with every passing year [1, 2]. In Russia, for the last three years, their number has increased 2.7-fold, while in the year of 2023, a total of 8955 such surgeries were carried out. With this, thanks to using modern automated methods of dissecting and suturing the tissues, a significant decrease is observed in the number of postoperative complications. At the same time, surgical suture incompetence (staple line leak) is still considered a culprit of severe postoperative complications. In recent years, within the structure of the bariatric surgeries, the most wide-spread is the laparoscopic longitudinal

ВНУТРИПРОСВЕТНОЕ ВВЕДЕНИЕ ИНДОЦИАНИНА ЗЕЛЁНОГО КАК МЕТОД ИНТРАОПЕРАЦИОННОЙ ДИАГНОСТИКИ НЕСОСТОЯТЕЛЬНОСТИ АППАРАТНОГО ШВА ПРИ ПРОДОЛЬНОЙ РЕЗЕКЦИИ ЖЕЛУДКА В ЭКСПЕРИМЕНТЕ

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АННОТАЦИЯ

Обоснование. *Бариатрическая хирургия представляет собой активно развивающийся раздел хирургии. Благодаря использованию современных аппаратных способов разъединения и сшивания тканей существенно снизилось количество послеоперационных осложнений, в то же время проблема несостоятельности хирургического шва остаётся актуальной и в настоящее время. Традиционными методами интраоперационной диагностики несостоятельности аппаратного шва являются провокационные пробы: пробы с метиленовым синим и воздухом. Одним из перспективных методов интраоперационного контроля в хирургии является применение флуоресцентной визуализации в ближнем инфракрасном диапазоне с помощью индоцианина зелёного.* ***Цель исследования*** *— оценка информативности интраоперационной диагностики несостоятельности аппаратного шва при продольной резекции желудка с использованием флуоресцентной визуализации с индоцианином зелёным.* ***Методы.*** *Исследование проведено на 20 животных (свиньи), каждому из которых выполнена продольная резекция желудка. Животные были разделены на экспериментальные группы: контрольная группа с выполнением стандартной продольной резекции желудка (n=4); опытные группы с выполнением продольной резекции желудка и моделированием двух вариантов механических причин несостоятельности хирургического шва (n=12), группа локальной ишемии (n=4). Интраоперационно в просвет желудка вводился раствор с метиленовым синим и индоцианином зелёным, после чего производилась оценка появления красителя и визуализация флуоресценции индоцианина зелёного. Кроме того, в группе ишемии индоцианин зелёный вводился внутривенно. На 7-е сутки после операции проводилось гистологическое исследование операционного материала.* ***Результаты.*** *В 10 из 11 экспериментов с механическим фактором моделирования несостоятельности аппаратного шва отмечалась визуализация индоцианина зелёного, при этом поступление метиленового синего было отмечено в 2 случаях из 11. В 90% случаев просачивание индоцианина зелёного соответствовало значимым признакам воспаления, при этом поступление метиленового синего отмечено только в 20% случаев.* ***Заключение.*** *Методика внутрипросветного введения индоцианина зелёного в «механических» моделях несостоятельности аппаратного шва при продольной резекции желудка более информативна по сравнению с введением метиленового синего.*

Ключевые слова: *бариатрическая хирургия; продольная резекция желудка; несостоятельность шва; индоцианин зелёный; ИЦЗ.*

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gastric resection (LLGR, sleeve gastrectomy) [3]. With this, according to data from numerous research works, after the LLGR, a total rate of 0.5% to 7% of suture incompetence is reported [4–6].

Currently, the most common cause of developing suture incompetence, according to the discussions, is the insufficiency of regional circulation, as well as non-conformity of the staple line height to the thickness of the tissues being connected [7–9].

The conventional methods of intraoperative diagnostics for incompetence of anastomoses and machine suture lines include the provocative tests, indicating the loss of hermeticity in the latter, specifically, the methylene blue test and the bubble test. The advantages of these methods are simplicity and accessibility. However, the diagnostic value of the latter remains disputable and the number of authors call it into question [10, 11]. The main downside is limited sensitivity, which, upon minimal damage, is the cause of false-negative results. A number of research works have found a correlation between using such provocation tests and the increase of the risk of suture incompetence [11–13].

One of the promising methods for intra-operative control in surgery is the use of fluorescent visualization in the near infrared range using Indocyanine green (ICG) [14].

The first data became available with the application of the ICG-visualization method in the bariatric surgery [15–17]. Such methods are being used both for the detection of ischemic areas by means of intravenous administration of the staining agent and for the control of suture hermeticity by means of its administering into the operated stomach. In the research work by Ortega C.B. et al., the application of ICG-angiography was indicated for the detection of individual specific features of auxiliary blood supply of the gastroesophageal junction during the laparoscopic longitudinal gastric resection, which can aid in the assessment of the viability of the tissues being combined [18].

Another interesting research is the one conducted by Kalmar C.L. et al., in which ICG, for the first time in clinical practice, was used not during angiography as a contrasting agent, but during the provocative test with intraluminal administration of the latter during LGR and stomach shunting (SS) [19]. With the administration of ICG to 59 patients, the obtained findings include a single true positive and a single false-positive result, and sensitivity and specificity of the method were 100 and 98.28%, respectively. However, this research describes only one case of suture incompetence, the origin of which is unclear. Besides, this research was conducted without comparing to other methods. Such comparison was performed in the research work by Hagen et al. during the course of robot-assisted stomach shunting. It was shown that the use of the methods of intraluminal administration of the combined solution containing ICG (5 mg) and methylene blue (2 mg) shows greater sensitivity of ICG methods comparing to the classic bubble test and the methylene blue test. Four patients out of 95 patients had positive ICG test result, in which additional suture line reinforcement was applied [20]. The limited informativity of these research works is due to the type of clinical research, in which there is no possibility to unequivocally state the prime cause of developing incompetence. This circumstance can be overcome in the experimental settings, allowing for simulating the defects of applying the surgical suture, which, in turn, allows for defining what consequences it may result in.

Research aim: an evaluation of the intraoperative diagnostics of machine suture incompetence when performing the LGR surgery using fluorescent visualization with Indocyanine green (ICG) by using the pig-based modeling of various reasons of incompetence and by controlling surgical complications with the aid of morphological tests.

METHODS

Research design

The experiments included 20 pigs (Sus scrofa domesticus) of the Landrace breed weighing 40–45 kg (obtained from the breeding station of the “Pulkovskiy” Agricultural Holding) in accordance with the protocol, approved by the Institutional Animal Care and Use Committee of the Federal State Budgetary Institution “Almazov NMRC”, under the Ministry of Health of the Russian Federation. The animals were distributed into the following experimental groups: the control group with standard LGR (n=4), the test groups receiving LGR with the modeling of two variants of mechanical reasons for incompetence (n=12), as well as the local ischemia group (n=4). Intraoperationally, the stomach lumen was filled with the solution containing methylene blue and indocyanine green, after which an evaluation followed of the ingress of the staining agent along with the visualization of the indocyanine green fluorescence. Besides, in the ischemia group, ICG was administered intravenously. On Day 7 after surgery, or in case of developing signs of peritonitis, laparotomy was used with the visual evaluation of the operated zone, taking samples of material for histological examination.

Research facilities

This research work was carried out within the premises of the Pre-Clinical Translational Research Center of the Federal State Budgetary Institution "Almazov NMRC", under the Ministry of Health of the Russian Federation. The experimental animals (pigs) were provided by the breeding station of the "Pulkovskiy" Agricultural Holding.

Research duration

The experiment for each separate animal was completed on Day 7 after surgery or in case of developing signs of peritonitis. The research activities were carried out from July 2018 until May 2019.

Medical procedure description

The animals were not deprived in terms of feeding and hydration. Within 12 hours before surgery, the animals were consuming only water.

Surgical interventions were carried out under endotracheal anesthesia (isofluorane at a concentration of 1–5%). After the upper midline laparotomy, longitudinal gastric resection was performed according to the standard method [21]. The mobilization of the greater gastric curvature was done using the ultrasound scalpel (Johnson & Johnson). The gastric resection itself with the formation (from the remaining part of the stomach) of the so-called "sleeve" was performed using the Echelon FLEX 45 (Johnson & Johnson) suturing apparatus. The control group was sutured with the use of green Echelon cartridges with an open staple height of 4.1 mm (closed — 2.0 mm). As for the staples with lesser height, white cartridges were used with the height of the open staple of 2.6 mm, the closed staples were 1.0 mm high.

After finishing the resection stage with the formation of the "gastric tube", further closing was done in the outflow segment of the stomach, while the gastric lumen was filled (using the nasogastral tube) with 50 ml of the combined solution, containing physiological saline, Indocyanine green (Roth, China) at a concentration of 0.02 mg/ml and methylene blue (SamaraMedprom, Russia) at a concentration of 0.04 mg/ml. The evaluation of the machine suture zone was done directly after the administration of the solution, first using the visible light, then at the infrared spectrum using the IMAGE1 STM laparoscopic video-system and the D-LIGHT P SCB light source (KARL STORZ, Germany) with an illumination within the wavelength interval of 750–810 nm. The test was considered positive in case of registering the fluorescence in the area of the staple line [22].

The animals in the group of local ischemia modeling underwent intravenous injection of ICG at a dosage of 0.1–0.3 mg/kg, with performing the visual evaluation of the evenness of the fluorescence in the resected stomach. In the settings of impaired blood supply, impaired or absent staining was expected in the area of artificially created ischemia.

Surgical interventions were completed with layered suturing of the wound.

The experiment was completed on Day 7 after the surgery or in case of developing signs of peritonitis. Under endotracheal anesthesia, repeated laparotomy was carried out with the visual evaluation of the machine suture zone, after which the stomach was completely removed for histological examination. The sacrification of experimental animals was done by intravenous administration of KCl solution with the euthanasia control parameter being the stable ECG isoline.

Research outcomes

Main research outcome. The parameter characterizing the main outcome of the research, was the case of suture incompetence. During the course of the longitudinal gastric resection, the onset of incompetence was registered by the ingress of methylene blue, by ICG fluorescence during the tests. (Fig. 1). Upon the repeated laparotomy, the case of machine suture incompetence was registered upon detecting the macroscopic changes expressed as abscesses and peritonitis (table 1, 2).

Additional research outcomes. The evaluation of histological parameters was carried out semi-quantitatively with grading by points from 0 to 3, where 0 is the absence of the manifestation, 1 is its mild intensity, 2 is the moderate intensity and 3 is the strong intensity.

The following pathological changes were registered: necroses, the degree and the content of cellular infiltration, the presence of colonies of microorganisms, fibrin deposits at the serous membrane with signs of inflammation, the intensity of fibrosis and granulation tissue, as well as the presence of hemorrhages, foreign body gigantic multinuclear cells and glandular epithelium with inflammatory atypia. Outside the area of the machine suture (staple line), various background changes were evaluated within the gastric wall: presence of ulcers, hyperplastic growth of surface epithelium and others.

For the purpose of quantitative and statistical evaluation of the histological signs of machine suture

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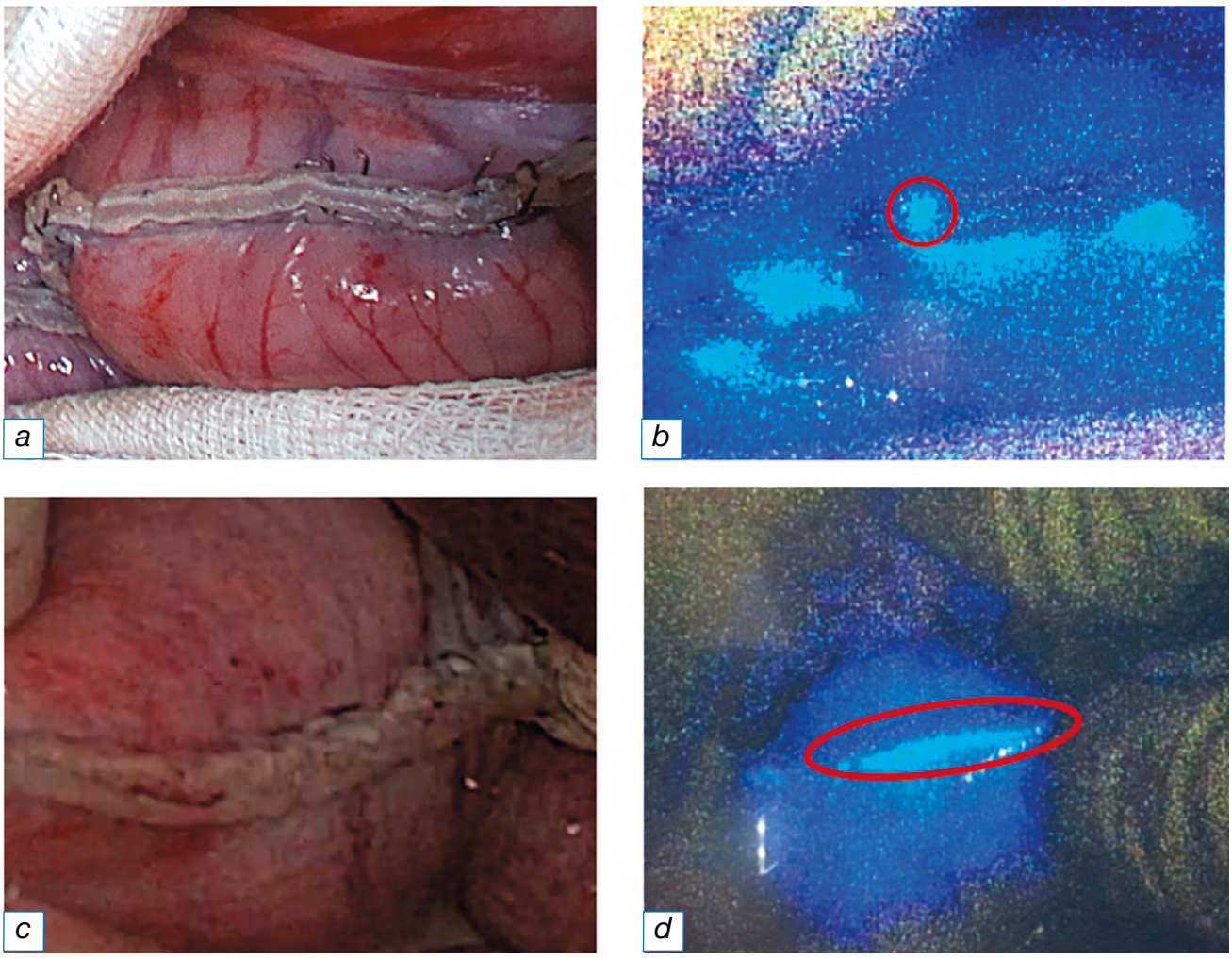

Fig. 1. *a, b* — ICG leakage between the stitched walls of the stomach distal to the hardware suture line when simulating incompetence by unbending the hardware suture staples. *c, d* — "Point leakage" of ICG along the inner row of the staple seam when simulating failure by using cassettes with a lower staple height.

incompetence, an integrative parameter was used, which was developed specifically for the aims of this research. Histological parameters were selected which characterize the severity and the degree of intensity of the inflammatory infiltration, as well as signs of local deterioration of the reparative process — necrosis and fibrin deposits in the area of the suture. The integrative parameter was compiled using the sum of the points for these parameters and has a maximum of 12 points, which is the sum of maximal points for each of the four evaluated parameters. The grades were corresponding to the following points: 0–3 points — absence of clear manifestations, 4–5 points — mild intensity, 6–7 points — moderate intensity, 8–12 points — strong intensity.

Subgroup analysis

The animals after the longitudinal resection were randomly distributed in the following research groups:

1) longitudinal gastric resection (LGR) without the pathological process modeling (n=4) (control group);
2) modeling of the mechanical origin of incompetence by means of unbending three rows of staples of the machine suture at a distance of 1 cm right after applying the last one (n=6);
3) modeling of the mechanical origin of incompetence using suturing equipment cartridges with lesser staple height comparing to the thickness of sutured tissues (n=6);
4) modeling of local ischemia by an application of U-shaped sutures onto the anterior gastric wall at the machine suture zone with the formation of square-shaped ischemia zone with an area of 1.0–1.5 cm^2 (n=4).

Methods for registration of outcomes

The evaluation of research outcomes was performed by means of intraoperative diagnostics of

Table 1

Histological indicators of the inflammatory process in the hardware suture area. Integrative summary indicator

Groups	S.№	MC	ICG	Acute inflammation, points	Intensity of inflammatory infiltration, points	Necrosis, points	Fibrin (with neutrophils) on the serous membrane, points	Integrative parameter, points
Control	1	No	No	1	1	1	0	3
	2	No	No	0	1	0	0	1
	3	No	No	1	1	0	0	2
	4	No	No	1	1	0	0	2
Unbent staples	5	No	Yes	3	2	3	0	8
	6	Yes	Yes	3	3	2	3	11
	7	No	Yes	1	3	2	0	6
	8	No	Yes	2	2	2	0	6
	9	No	Yes	2	2	0	0	4
Staple height	10	No	Yes	2	2	2	2	8
	11	No	Yes	2	3	2	3	10
	12	No	Yes	2	2	3	0	7
	13	No	No	3	3	3	3	12
	14	No	Yes	3	3	2	0	8
	15	Yes	Yes	2	2	2	0	6
Ischemia*	16	No	No*	1	2	1	0	4
	17	No	No*	1	2	2	0	5
	18	No	No*	2	2	3	0	7
	19	No	No*	1	1	1	0	3

Note. * in the group of modeling the ischemic cause of failure, there was no leakage of ICG between the connected walls of the stomach, but a filling defect in the ischemic zone was detected.

Table 2

Analysis of the indicator "Severity of inflammatory infiltration" depending on the Group

Parameter	Category	Group, *n* (%)				*p*
		Control	Unbent staples	Staple height	Ischemia	
Severity of inflammatory infiltration	mild	4 (100.0)	0 (0.0)	0 (0.0)	1 (25.0)	0.005* $p_{\text{Control — staple height}} = 0.040$
	moderate	0 (0.0)	4 (80.0)	3 (50.0)	3 (75.0)	
	strong	0 (0.0)	1 (20.0)	3 (50.0)	0 (0.0)	

Note. * — differences in indicators are statistically significant (p <0.05). Method used: Pearson's chi-squared test.

incompetence, by macroscopic visualization during repeated laparotomy and by morphological examination of the histological material.

In order to detect the morphological changes, two 5–7 mm thick sections were cut from the tissues in the machine suture zone where the pathological process was modeled.

The histological slides were prepared and examined using the standard method of hematoxylin-eosin staining and the Mallory staining. A combined pathomorphological analysis was carried out with the evaluation of the acute inflammation, including its intensity and cell composition, the dystrophic changes in the parenchymal and stromal cells and the impaired circulation.

Ethical review

The research protocol PZ_22_3_SoninDL_V3 was approved by the Institutional Animal Care and Use Committee (IACUC) of the Federal State Budgetary

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Institution "Almazov NMRC", under the Ministry of Health of the Russian Federation and by the Ethics Committee of the Federal State Budgetary Institution "Almazov NMRC", under the Ministry of Health of the Russian Federation

Statistical analysis

Statistical analysis was done using the StatTech v. 3.1.10 software (developed by the "Stattech" LLC, Russia). The categorical variables of semi-quantitative histological examination were described with adding the absolute values and percentages. The comparison of percentages during the analysis of multifield contingency tables was performed using the Pearson's chi-squared test.

RESULTS

Research sample (participants)

The research sample included the animals (20 Landrace breed pigs weighing 40–45 kg) undergoing surgical intervention — longitudinal gastric resection (LGR). After the LGR, the animals were randomly distributed into the experimental groups with modeling various origins of machine suture incompetence and the control group. Intraoperationally, the procedures included the methylene blue and ICG tests with the visual evaluation of the result. On Day 7 after the surgical intervention or in case of developing signs of peritonitis, repeated laparotomy and gastrectomy were carried out. Further procedures included the histological evaluation of the stomach material.

Main research outcomes

In the control group, as the combined solution (ICG and methylene blue) was introduced, even fluorescence was observed in the walls of the operated stomach, except for the tissues, located distally from the staple line (machine suture).

In the group of modeling the machine suture incompetence by unbending the staples, one case of fatal outcome was reported during the application of the anesthesia. During the course of the experiment, after suturing by means of using the suturing machine, the ICG fluorescence between the joined stomach walls was found in all five cases (Fig. 1), with the ingress of methylene blue being found only in one of five tests. Upon the repeated laparotomy, two confirmed cases of machine suture incompetence were registered, which were represented by macroscopic changes expressed as abscesses and peritonitis (table 1). In other cases, adhesion process was found with various degree of intensity. It is worth noting that, with this type of modeling the machine suture incompetence, the detection of the staining solution was found (both the methylene blue and the ICG) between the sutured gastric walls distally from the machine suture line.

In six animals within the group of modeling of machine suture incompetence using the suturing machine with lesser height staples, the ingress of methylene blue was observed in one case, while the ICG fluorescence was found in five cases. Upon the repeated laparotomy, suture incompetence was observed in two cases, represented as macroscopic signs of abscesses and peritonitis (see table 1). In other cases, an adhesion process was found with various degree of intensity. Unlike the previous group, ICG fluorescence was observed not between the joined tissues, distally from the machine suture line, but as a specific "dotted transudation" along the proximal row of staples, which may indicate the mechanical damage (crushing) of the stomach walls upon suturing (see Fig. 1). With this, one of the incompetence cases was reported in an animal in which intraoperationally there was no visualization of the methylene blue or of the ICG (table 2).

In the group of local ischemia modeling, in several seconds after an intravenous administration of the ICG, just like in the control group, evenly intensive staining was observed in the walls of the operated stomach, except for the margins of the gastric walls, located distally from the machine stitch line and except for the local ischemia modeling zone, matching with the latter by the shape and the dimensions. Upon the repeated laparotomy, the zone of ischemia modeling shows a more significant (comparing to the control) adhesion process with no macroscopic signs of incompetence.

Additional research outcomes

Upon histological examination, all the samples, both in the control and in the test groups, were showing signs of inflammatory and reparative processes, related to the mechanical damage of gastric walls, with various degree of intensity.

In the control group, the inflammatory processes in the majority of cases were represented by subacute mild- and moderately-expressed inflammation with the predominance of lymphocytes, plasmacytes and histiocytes. In single cases, the admixture of granulocytes and eosinophils was observed. Local tissue necrosis was found in 1 sample. No cases of massive purulent inflammation, fibrin deposits on the serous membrane or adhesions with the organs

of the abdominal cavity were reported. The degree of developing the granulation tissue and forming the mature collagen fibers indicate the on-going reparative process in the area of the machine suture.

In all the cases of modeling the mechanical origin of suture incompetence, inflammatory infiltration was observed with various degree of intensity, in the majority of cases with the predominance of neutrophils (often combined with the necroses of tissues in the area of the suture line and with signs of peritonitis), in part of the cases with the predominance of lymphocytes. Besides, oftentimes the infiltrate was showing the presence of eosinophilic admixture (in some cases significant) and of foreign body gigantic multinucleated cells. Along the peripheral areas of the infiltrate, in the majority of cases the findings included a plethoric granulation tissue and signs of fibrosis (the Mallory staining), which was more significant in case of lymphocytic (not neutrophilic) predominance in the inflammatory infiltrate. The maturity of collagen fibers indicates the on-going reparative process within the zone of the machine suture, however, the pronounced fibrosis in part of the cases resulted in the development of adhesions with the small intestine, liver and spleen. Besides, in a number of cases, the suture line zone was showing the presence of gastric epithelium with signs of inflammatory atypia.

The local ischemia group is characterized by local necrosis of various degree of intensity with pronounced inflammatory infiltration with the predominance of granulocytes. This zone had signs of slowed reparative process, however, in the remote areas, the visualized findings included the developed granulation tissue with inflammatory infiltration of various degree of intensity and collagen fibers of various degree of maturity.

In this research, it is not possible to isolate any specific morphological parameter, which could be applicable as a morphological analogue for incompetence of the surgical suture. However, upon the point-based evaluation of the histological changes, we could count the sum of mean points and compare the results obtained between groups. The parameters that are significant for the evaluation, which were included into the integrative parameter, are the following: acute inflammation, degree of inflammatory infiltration, necrosis and fibrin deposits on the serous membrane.

The results of semi-quantitative evaluation are provided in tables 1–3, while the images illustrating the characteristic histological changes are provided in Fig. 2.

Upon the analysis of the histological material after mechanical modeling of suture incompetence, the following data were obtained. In the “unbent staples” group, 40% were showing an acute inflammatory reaction, predominantly of moderate degree of intensity (80%), while in the “staple height” group, 33% were showing acute inflammatory reaction of moderate or strong degree of intensity (by 50%) (statistically significant differences, $p \leq 0.05$; table 3). The mean integrative parameter in the groups with modeling the incompetence was higher than in the control group and in the ischemia group (statistically significant differences, $p \leq 0.05$; table 3). With this, the integrative parameter of inflammatory changes in the “staple height” group was higher than in the “unbent staples” group (statistically significant differences, $p \leq 0.05$; tables 2, 3).

Upon the morphological examination of all the cases, in which ICG transudation was registered during the experiment, the following data were obtained: in 90% of the cases, significant signs of inflammation were observed, which indirectly indicates the histological equivalents of incompetence. In the opposite case, when the ICG transudation was not registered, in 80%, the histological response was showing signs of mild intensity inflammatory changes (statistically significant differences, $p \leq 0.05$; table 4).

The results of evaluating the ICG transudation, unlike the methylene blue, correlate with the data from the histological analysis.

Undesirable phenomena

A fatal outcome was reported in one animal after the application of general anesthesia.

Table 3

Analysis of the “Integrative indicator” indicator depending on the Group

Parameter	Category	Group, *n* (%)				*p*
		Control	Unbent staples	Staple height	Ischemia	
Sum of points	normal	4 (100.0)	1 (20.0)	0 (0.0)	1 (25.0)	0.015*
	mild	0 (0.0)	2 (40.0)	0 (0.0)	2 (50.0)	
	moderate	0 (0.0)	0 (0.0)	2 (33.3)	1 (25.0)	
	strong	0 (0.0)	2 (40.0)	4 (66.7)	0 (0.0)	

Note. * — differences in indicators are statistically significant ($p < 0.05$). Method used: Pearson’s chi-squared test.

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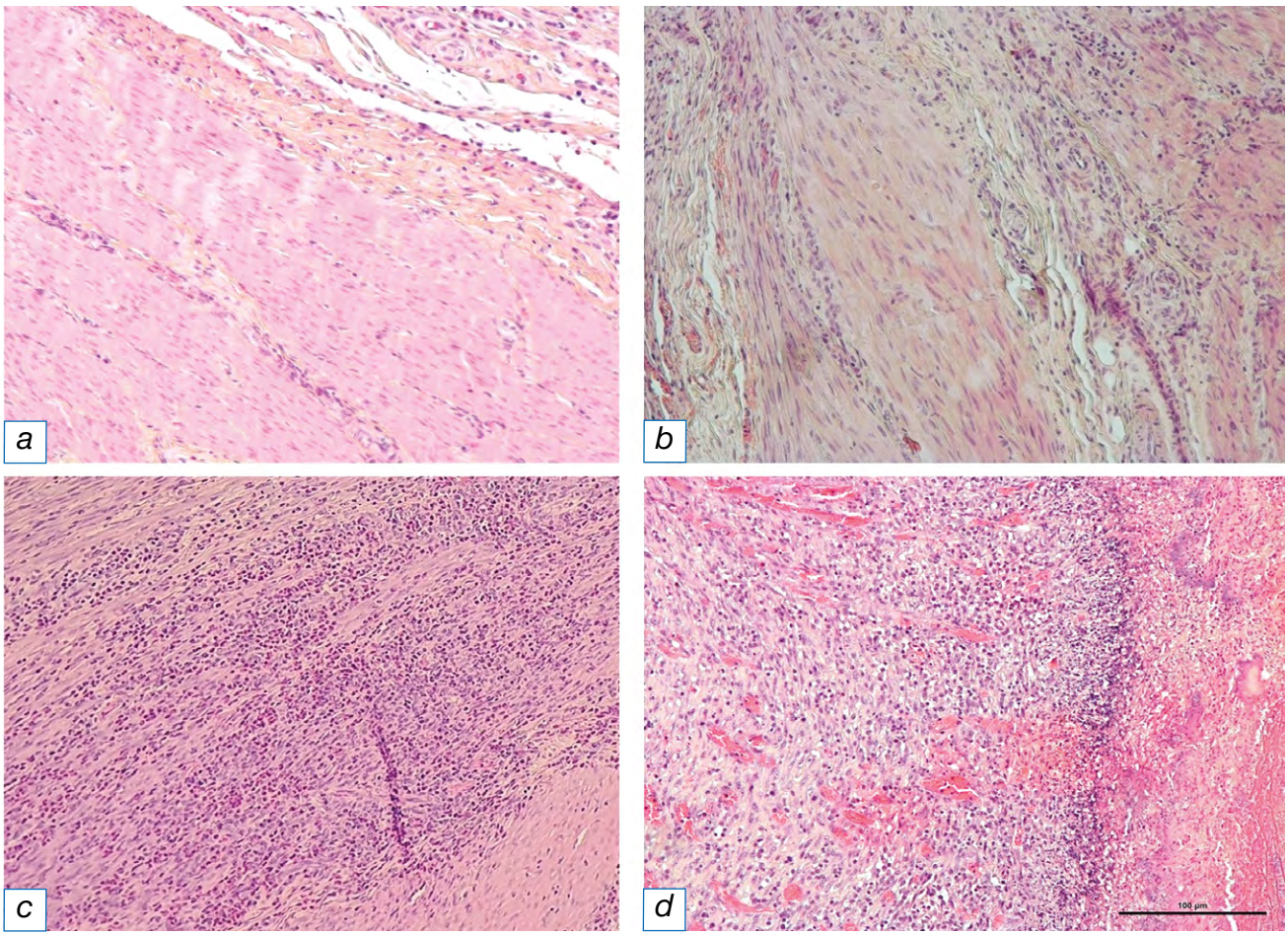

Fig. 2. Representative photographs of the features of inflammatory infiltration in the hardware suture area in samples of different groups. *a* — "control", the formation of dense layers of collagen fibers between muscle bundles in the damage zone, weak inflammatory infiltration is represented by single lymphocytes. *b* — "ischemia", locally areas of necrosis with strong inflammatory infiltration. *c* — "removal of staples", acute inflammation, severe inflammatory infiltration, predominantly neutrophilic and eosinophilic. *d* — "height of staples", acute plethora of granulation tissue, severe inflammatory infiltration, fibrin on the surface. Hematoxylin-eosin staining, magnification 100×.

Table 4

Analysis of the indicator "Integrative indicator — gradation of points" depending on the Group

Parameter	Category	MB, *n* (%)		ICG, *n* (%)	
		Yes	No	Yes	No
Integrative indicator — gradation of points	none	0 (0.0)	4 (30.8)	0 (0.0)	4 (80.0)
	mild	0 (0.0)	1 (7.7)	1 (10.0)	0 (0.0)
	moderate	1 (50.0)	3 (23.1)	4 (40.0)	0 (0.0)
	strong	1 (50.0)	5 (38.5)	5 (50.0)	1 (20.0)
p		0.730		0.010*	

Note. * — differences in indicators are statistically significant ($p < 0.05$). Method used: Pearson's chi-squared test.

DISCUSSION

The incompetence of the anastomosis after bariatric surgeries still remains one of the most serious complications, resulting in an increase in the morbidity and in costs required for restoring the health of the patients. Currently, the rate of developing the major adverse events within 30 days after surgery, depending on its type, is within a range from 2.5% to 5.0%. The most common location of incompetence is the angle of His, both for the ischemic and for the mechanical factors. The conventional methods of suture control, due to their insufficient sensitivity, do not allow for

timely detection of the developing problems and this is why the fundamental task is searching for new approaches for solving these problems. One of them can be the use of ICG test and the visualization of its fluorescence in the near infrared range [23, 24]. The higher sensitivity of ICG fluorescence comparing to the methylene blue test was demonstrated during the recently conducted clinical trial [20]. However, such research works do not allow for determining in which way the defects of creating a suture line can lead to one or another complication.

This research is aimed at the experimental evaluation of the informativity of the intraoperative diagnostics of machine suture incompetence using the visualization of the fluorescence of administered ICG in the settings of modeling various reasons of machine suture incompetence when performing the longitudinal gastric resection and with comparing the method to the methylene blue test.

In clinical practice, the machine suture incompetence is generally understood as the presence of a defect associated with a characteristic set of symptoms and with the development of local pathological changes and with further systemic inflammatory reaction, detectable upon the instrumental tests or during the revision surgery. In the aspect of morphological changes, it is necessary to note the presence of generic differences between humans and animals in terms of the pathological processes in the abdominal cavity [25–27].

Thus, in the research by Henne-Bruns D, when applying only four sutures with a single knot when forming an anastomosis in rats, out of 24 animals, only 3 had the development of peritonitis, while in 30 days the anastomoses were covered in granulation tissue, but the adhesion process was more pronounced than in cases of creating a complete anastomosis [25]. According to the opinion from number of authors, one of the reasons of the complexity of modeling the suture incompetence is using young and healthy animals for the experiment, as well as the species-related physiological features of healing the wounds. When modeling the incompetence of the large intestine anastomosis, a fast fibrin deposition was found and, as a result, adhesions were developing, which prevented the development of peritonitis or intra-abdominal abscesses, which is not characteristic for humans [26, 27].

Thus, in the experimental settings, only the combined histological analysis of the processes taking place in the damage zone with the estimation of the activity and intensity of inflammation, of the presence of fibrin on the surface of serous membranes, of the spreading of necrosis and fibrosis within the tissues, of the presence of adhesions and signs of peritonitis — all of these allow for evaluating the surgical suture incompetence.

The experiments conducted in pigs have allowed for reproducing the possible mistakes of forming the staple line. The estimation of the findings in light of ICG — fluorescence, as well as in light of the morphological analysis of the material obtained in 7 days, allow for defining what consequences may be resulting from these mistakes.

The comprehensive assessment of the mechanisms of modeling the mechanical origin of pathological changes in the area of the joined tissues, along with the fluorescence images allowing for real time mode identification of the developing impairment with further correlating the intensity of morphological changes — all of these allow for intraoperative predicting the possibility of developing surgical suture incompetence.

A series of experiments with modeling local ischemia have confirmed the possibilities provided by fluorescent ICG-angiography in terms of visualizing the problematic foci of perfusion, which were completely matching the location of ischemia modeling area and the inflammatory changes of various degree of intensity [28–30].

Upon summarizing the data obtained in the groups of modeling the mechanical origin for incompetence with intraluminal administration of the staining agents, intensive inflammatory changes (integrative parameter ≥6 points) were found in 10 cases out of 11. With this, the positive ICG test was reported in 9 cases, while when using methylene blue, only 2 cases were positive, which demonstrates higher informativity of the methods employing the intraluminal administration of ICG in "mechanical" models of machine suture incompetence comparing to the administration of methylene blue.

In the present research, the shapes were defined for ICG fluorescence depending on the incompetence model, namely: transudation between the sutured gastric walls distally from the machine suture line when modeling the incompetence by unbending the staples and "dotted transudation" along the internal staple line when modeling the incompetence by using the cartridges with lesser staple height.

The obtained data, most probably, can allow for intraoperationally supposing not only the presence of machine suture incompetence risk, but also for defining the probable cause of the latter.

In the majority of cases, the information required for making a decision can be obtained upon the

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intraluminal administration of ICG, including the area in the proximal third of the staple line, where the higher rate (up to 85%) of incompetence cases was described [24]. Besides, it is known that 24–28% of bariatric patients undergo repeated interventions, having higher risks of developing the incompetence, which defines the topicality of using ICG for the evaluation of specific features and of the adequacy of blood supply, as well as for defining the hermeticity of joined tissues [17, 24].

Research limitations

This research was exploratory, due to which, within the framework of this research, there was no analysis of the sensitivity and of the specificity of the methods tested.

CONCLUSION

Using the ICG fluorescent staining agent allows for determining the changes in the staple line, which are invisible when employing the visible light, which potentially can lead to the development of the machine suture incompetence during the course of the longitudinal gastric resection. The method of ICG visualization demonstrates significantly higher sensitivity comparing to the diagnostics methods employing the methylene blue.

The methods of fluorescent ICG visualization with intravenous and intraluminal administration of the said fluorophore, shall not be considered as the competing methods, for they augment each other, covering the whole spectrum of the causes of developing the machine suture incompetence — from the impaired blood supply to mechanical factors. Within this context, further clinical and experimental research are deemed topical for the purpose of developing the standardized protocols of implementing these methods.

These methods may be useful upon revision interventions, in cases of intraoperative technical difficulties, occurring at the centers with small number of annually performed surgeries, as well as at the training phase, allowing for timely detection of already existing or potential defects of the machine suture, by this minimizing the risks of incompetence development.

ADDITIONAL INFORMATION

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Competing interests. The authors declare that they have no competing interests.

Authors’ contribution. *A.A. Kovalev*, *O.V. Korniushin* — planning and conducting experiments, preparing for publication; *G.V. Papayan* — conducting experiments, scientific guidance; *V.V. Maslei* — conducting experiments; *A.E. Neimark* — scientific guidance, preparation for publication; *I.A. Zelinskaya* — processing the results; *Ya.G. Toropova*, *A.V. Starzhevskaya* — preparation for publication; *N.Yu. Semenova* — histological studies and their evaluation, preparation for publication; *V.A. Zinserling* — evaluation of histological data, preparation for publication; *I.N. Danilov* — scientific guidance. The authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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THE FIRST EXPERIENCE OF THORACOSCOPIC THYMECTOMY FROM A UNIFIED SUBXIPHOID ACCESS

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ABSTRACT

BACKGROUND: *Thoracoscopic thymectomy performed with using the lateral intercostal access in cases of non-invasive thymic tumors is the commonly used technique. Most frequently, the three-port and the single-port techniques are used. As the experience was accumulating, it became evident that the intercostal access has a number of disadvantages, such as unsatisfactory visualization of the nerve on the opposite side and of the cervical portion of the thymus, along with a probably of developing chronic pain syndrome. One of the possible solutions for this issue can include the use of sub-xyphoid access.* ***AIM:*** *An evaluation of direct results obtained when using the unified sub-xyphoid access during thoracoscopic thymectomy in patients with non-invasive epithelial thymic tumors.* ***METHODS:*** *An experience was analyzed that was gained after the treatment of 14 patients undergoing thoracoscopic thymectomy using the unified sub-xyphoid access for non-invasive epithelial tumors of the thymus. The age of the patients ranged from 24 to 70 years (median — 42 years); 9 of them were females (64.3%) and 5 were males (35.7%). In all the patients, at the moment of surgical treatment, stage I disease was diagnosed. The minimal dimension of the excised thymoma in this research was 15 mm with the maximal dimension being 65 mm, the median value was 38 mm.* ***RESULTS:*** *Two surgeries (14.3%) were accompanied with technical difficulties due to the presence of an adhesion process after a previous episode of pulmonary inflammation, which resulted in more significant intraoperative blood loss, which was 200 ml. The surgery duration varied from 60 to 180 minutes with the median of 82.5 minutes. In the majority of cases (97.6%), the pain syndrome level did not exceed 4 points of the visual analogue scale for pain. During the postoperative period, a single surgical complication was reported — the development of the retrosternal hematoma; no fatal outcomes were reported.* ***CONCLUSION:*** *The thoracoscopic thymectomy from the unified sub-xyphoid access is a justified option for cases of non-invasive epithelial thymic tumors. This method allows for performing the surgery in full range, not violating the oncology principles. It was proven that, for tumors measuring up to 65 mm, this method does not result in an increase in surgery duration or an increase in the rates of intraoperative complications.*

Keywords: *thymoma; epithelial tumors; thoracoscopic thymectomy; thymectomy from subxyphoid access.*

For citation:

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BACKGROUND

At the present moment, the use of minimally invasive technologies is the gold standard in thymic surgery. According to various research works [1–10], thoracoscopic thymectomy is characterized by better direct and remote results comparing to classic open-access methods (sternotomy and thoracotomy). With the accumulation of the experience, it became evident that intercostal access has a number of disadvantages, the main of which are the unsatisfactory visualization of the opposite phrenic nerve and of the cervical portion of thymus, as well as the possibility of developing the chronic pain syndrome [4, 11–14]. One of the possible solutions for this issue may include the use of sub-xyphoid access [11, 14]. For the first time this method was used in 1999 by the group of Japanese surgeons headed by T. Kido [15] for the case of thymus disease, and, at the present moment, it is one of the alternative options for gaining access to the tumors located in the anterior mediastinum.

Research aim — to evaluate the direct results of using the sub-xyphoid access in patients with non-invasive epithelial tumors of the thymus.

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ПЕРВЫЙ ОПЫТ ТОРАКОСКОПИЧЕСКОЙ ТИМЭКТОМИИ ИЗ ЕДИНОГО СУБКСИФОИДАЛЬНОГО ДОСТУПА

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АННОТАЦИЯ

Обоснование. *Торакоскопическая тимэктомия из бокового межрёберного доступа при неинвазивных опухолях тимуса является общепринятой методикой. Чаще всего используется трёхпортовая и однопортовая техника. По мере накопления опыта стало очевидно, что межрёберный доступ имеет ряд недостатков, таких как неудовлетворительная визуализация противоположного нерва и шейной порции тимуса, возможность формирования хронического болевого синдрома. Одним из возможных решений данного вопроса может быть использование субксифоидального доступа.* ***Цель исследования*** *— оценка непосредственных результатов использования единого субксифоидального доступа при торакоскопической тимэктомии у больных с неинвазивными эпителиальными опухолями тимуса.* ***Методы.*** *Проанализирован опыт лечения 14 пациентов, перенёсших торакоскопическую тимэктомию из единого субксифоидального доступа при неинвазивных эпителиальных опухолях тимуса. Возраст больных составил от 24 до 70 лет (медиана 42 года); женщин было 9 (64,3%), мужчин — 5 (35,7%). У всех пациентов на момент проведения оперативного лечения выявлена I стадия заболевания. Минимальный размер удалённой тимомы в исследовании составил 15 мм, максимальный — 65 мм, медиана 38 мм.* ***Результаты.*** *Две операции (14,3%) были сопряжены с техническими сложностями ввиду наличия спаечного процесса после ранее перенесённого воспаления лёгких, что обусловило более выраженную интраоперационную кровопотерю, которая составила 200 мл. Продолжительность операций варьировала от 60 до 180 минут, медиана 82,5 минуты. В большинстве случаев (97,6%) уровень болевого синдрома не превышал 4 баллов по визуальной аналоговой шкале боли. В послеоперационном периоде наблюдали одно хирургическое осложнение — формирование ретростернальной гематомы; летальных исходов не было.* ***Заключение.*** *Торакоскопическая тимэктомия из единого субксифоидального доступа является обоснованным вариантом при неинвазивных эпителиальных опухолях тимуса. Данный способ позволяет выполнить операцию в полном объёме, не нарушая при этом онкологических принципов. Доказано, что при опухолях размером до 65 мм данная методика не приводит к увеличению продолжительности операции и увеличению интраоперационных осложнений.*

Ключевые слова: *тимома; эпителиальные опухоли тимуса; торакоскопическая тимэктомия; тимэктомия из субксифоидального доступа.*

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METHODS

Research Design

The research is designed as a single-center retrospective and exploratory one.

Conformity Criteria

Inclusion criteria: age from 18 to 80 years old; verified stage I and II epithelial tumor of the thymus; absence of myasthenia.

Exclusion criteria: stage III and IV epithelial tumor of the thymus; past episodes of operated chest cavity organs.

Research Facilities

All the procedures were carried out within the premises of the Federal State Budgetary Institution “Federal Scientific and Clinical Center for Specialized Types of Medical Care and Medical Technologies”

of the Federal Medical-Biological Agency of Russia (FSBI FSCC of the FMBA of Russia, Moscow).

Research Duration

The analysis was carried out using the direct results of thoracoscopic thymectomy, performed using the unified sub-xyphoid access for cases of non-invasive epithelial tumors of the thymus at the Surgery Department No. 1 of the FSBI FSCC of the FMBA of Russia during the time period from January 2021 until March 2024.

Medical Procedure Description

The patients were operated using the unified sub-xyphoid access in cases of epithelial thymic tumors. The indications taken into account when using the unified sub-xyphoid access included the presence of the tumor in the anterior mediastinum with the tumor stage I or II, absence of previous surgeries in the organs of the chest cavity, as well as the absence of myasthenia. All the patients underwent the standard pre-operational examination, the extent of which is stated by the national clinical recommendations. All the surgeries were conducted under general anesthesia using the single lumen pulmonary ventilation without using the carboxythorax.

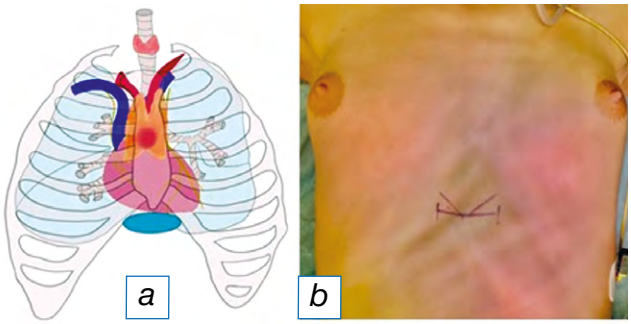

Fig. 1. Access diagram for thoracoscopic thymectomy from a uniportal subxiphoid approach (*a*); preoperative marking of a uniportal subxiphoid approach (*b*).

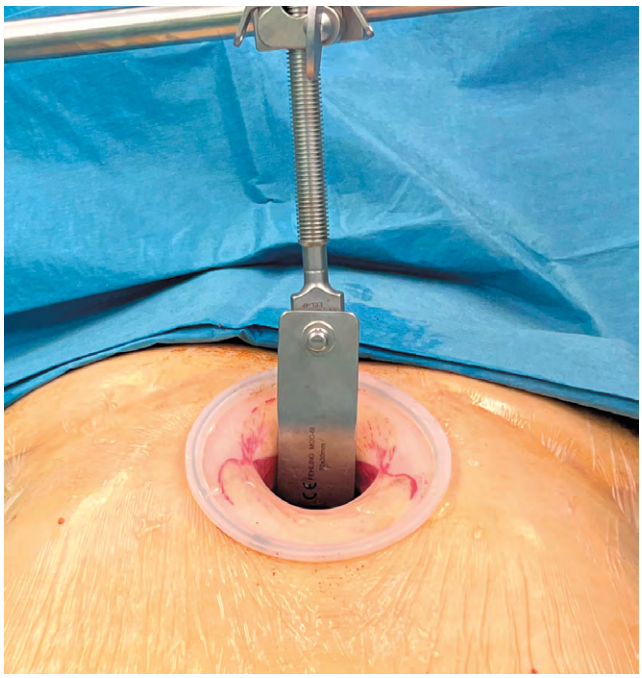

Fig. 2. View of an installed sternal retractor with a wound protector.

Surgery technique. The patient was positioned on the operating table at the supine position with the abduction of the lower limbs. The operating surgeon was positioned between the legs of the patient with the assisting surgeon standing on the right side from the patient. Each patient had a peripheral venous access provided. Further procedures included a transverse incision with a length of 4 cm, 2 cm below the xyphoid process (Fig. 1). In a number of cases, the incision could be enlarged up to 6 cm for the evacuation of the surgery sample with the tumor dimensions being more than 6 cm. Taking into consideration that, in our research, the maximal tumor size was 65 mm, no extending of the access was carried out.

For the purpose of comfortable positioning the sternal retractor and creating the exposed area to operate, it is possible to resect the xyphoid process. In our research, the xyphoid process was removed in 2 cases for the reason of an asthenic body constitution of the patients.

Upon the formation of the sub-xyphoid access, blunt separation was performed in terms of the tissues behind the sternum for the purpose of creating a space for wound protector and for positioning the sternal hook (Fig. 2) for providing additional retrosternal space (Useful model patent No. 225786 dd. 06.05.2024 “Sternal retractor for sub-xyphoid access” [16]. This useful model differs from the analogous devices by the presence of a videocamera slot at its working part, which provides better view in the settings of the limited spaces).

Further procedures included opening both pleural cavities with searching the main anatomic reference points — the phrenic nerves, the sup. vena cava and the brachiocephalic vein (Fig. 3). The positioning of the instruments was done in the following way: camera — middle of the port, ultrasonic scalpel — right half of the wound, forceps — left half of the wound.

The dissection of tissues was performed along both phrenic nerves (Fig. 4), after which followed the isolation of the brachiocephalic vein with the processing of the thymic vein (Fig. 5). The vessels with a diameter more than 5 mm were preferably processed using the clips. The important step of surgery was the isolation of the

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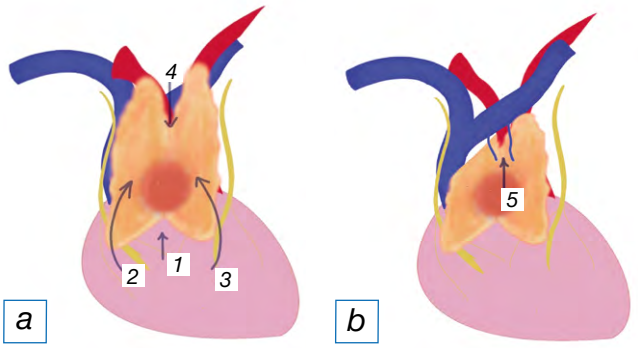

Fig. 3. Thoracoscopic thymectomy from a uniportal subxiphoid approach. Operation diagram (*а, б*). *1* — separation of thymus tissue from the pericardium; *2* — separation of thymus tissue along the right phrenic nerve; *3* — separation of thymus tissue along the left phrenic nerve; *4* — separation of the cervical portion of the thymus; *5* — ligation of thymic veins.

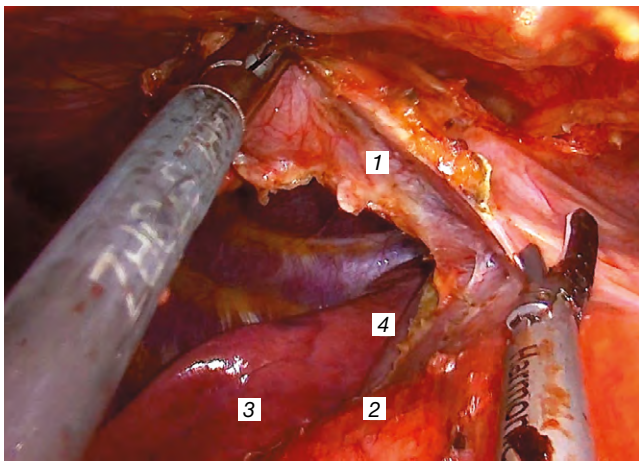

Fig. 4. Thoracoscopic thymectomy from a uniportal subxiphoid approach. Stage of pericardial separation. *1* — thymic tissue; *2* — pericardium; *3* — right lung; *4* — superior vena cava.

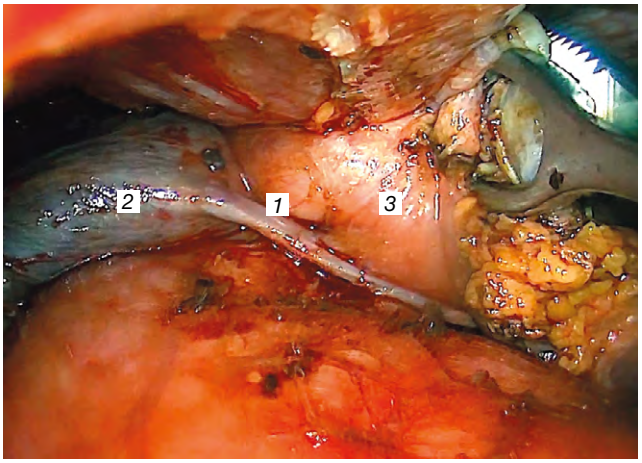

Fig. 5. Thoracoscopic thymectomy from a uniportal subxiphoid approach. Dissection of the brachiocephalic and thymic veins. *1* — thymic vein; *2* — brachiocephalic vein; *3* — cervical part of the right lobe of the thymus.

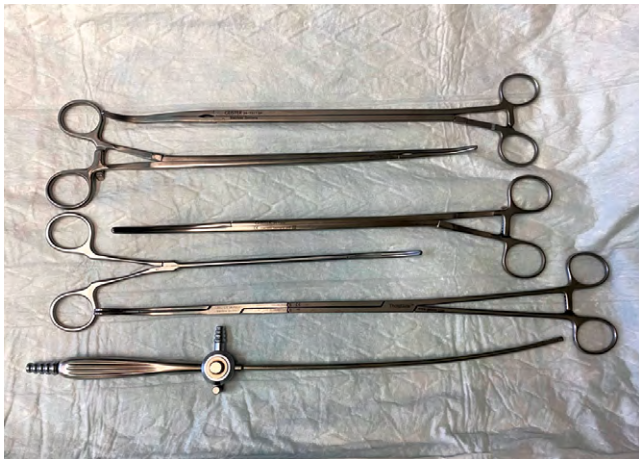

Fig. 6. Instrument set for minimally invasive thoracoscopy (Scanlan Int., ThoraGate Geister Medizintechnik GMBH, Germany).

cervical portion of thymus. The objective of the surgical intervention was to remove the whole thymic tissue, including the tumor.

During the surgery, an instrument was used that was specifically developed for minimally invasive thoracoscopy (Fig. 6). The dissection of tissues was done using the ultrasound scalpel (Harmonic Ethicon). The surgical intervention was completed by the installation of the single-lumen draining tube with the diameter of 20 Fr into the aperture of the left half of the chest cavity, which was passed through the surgical wound (Fig. 7, 8).

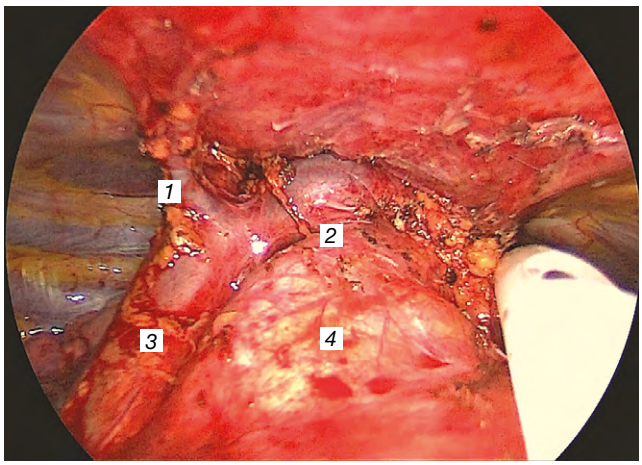

Fig. 7. Thoracoscopic thymectomy from a uniportal subxiphoid approach. The final view of the operation. *1* — internal mammary vein; *2* — brachiocephalic vein; *3* — superior vena cava; *4* — pericardium.

Ethical review

The research procedures were approved by the local ethics committee of the FSBI FSCC of the FMBA of Russia (protocol No. 5 dd. 19.12.2019).

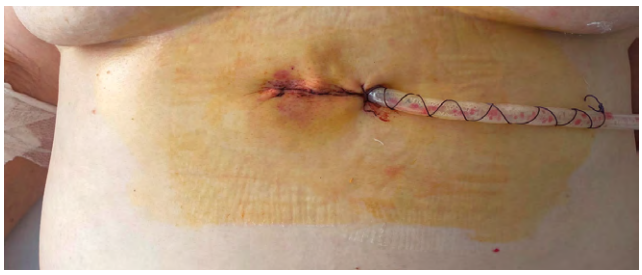

Fig. 8. Thoracoscopic thymectomy from a uniportal subxiphoid approach. Appearance of the wound on the first postoperative day.

Statistical analysis

The preliminary estimation of the sample was not performed due to the low occurrence of the studied disease and due to the research design (retrospective, descriptive).

The research data underwent statistical processing by using the methods of descriptive statistics. The accumulation, correction and systematization of the baseline information was performed using the Microsoft Office Excel 2016 tables. The statistical analysis was carried out using the STATISTICA 26 software (developed by StatSoft Inc., USA). In case of describing the quantitative parameters, the obtained data were combined into variation series, in which the calculations of mean arithmetic values (M) and standard deviations (SD) were performed along with the median and the interquartile range Me [Q1; Q3]. The nominal variables were described with stating the absolute values and percentages (*n*, %).

RESULTS

Research sample (participants)

A total of 14 patients were operated using the unified sub-xyphoid access for epithelial tumors of the thymus. The age of the patients varied from 24 to 70 years with the median of 42 years old. Nine patients were females (64.3%) with 5 being males (35.7%). In all the patients, at the moment of the surgical treatment, stage I disease was diagnosed. Table 1 represents the total characteristics of the distribution of patients depending on the process stage, the tumor dimensions and the presence of concomitant diseases. The morphological types of tumors, found in the patients undergoing thymectomy from the unified sub-xyphoid access, are provided in table 2.

Main research outcomes

The analysis was performed using the direct results of thymectomy carried out using the unified sub-xyphoid access (table 3). The minimal dimension

Table 1

Distribution of patients depending on the stage of the disease and concomitant pathology

Parameter	Single subxiphoidal access *n*=14
Age, years (Me [Q1; Q3])	42.0 [39.5; 51.75]
Gender, *n* (%)	Men's — 5 (35.7) Women's — 9 (64.3)
Associated diseases, *n* (%)	11 (78.6)
Hypertensive disease, *n* (%)	8 (57.1)
Chronic obstructive pulmonary disease, *n* (%)	1 (7.1)
Thyroid cancer, *n* (%)	1 (7.1)
History of pneumonia, *n* (%)	7 (50)
Disease stage (TNM classification), *n* (%)	T1aN0M0 — 14 (100)

Table 2

Distribution of patients according to gender and morphological type of tumor, *n* (%)

Morphological type of tumour	Men	Women	Total
AB	3 (50)	3 (50)	6 (42.9)
B1	1 (20)	4 (80)	5 (35.7)
B2	1 (33.3)	2 (66.77)	3 (21.4)
Total	5 (35.7)	9 (64.3)	14 (100)

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Table 3

Analysis of immediate results of thoracoscopic thymectomy from a uniportal subxiphoid approach

Parameter	Single-port access *n*=14
Duration of surgery, minutes (Me [Q1; Q3])	75 [70; 87.5]
Volume of blood loss, ml (Me [Q1; Q3])	50.0 [7.5; 50]
Tumour size, mm (Me [Q1; Q3])	38 [35; 48.5]
Intraoperative adhesions, frequency of development, *n* (%)	2 (14.3)
Frequency of retrosternal haematoma development in the postoperative period, *n* (%)	1 (7.1)
Duration of drainage, days (Me [Q1; Q3])	1.0 [1.0; 1.0]
Postoperative bed days, days (Me [Q1; Q3])	3.0 [3.0; 3.0]

of the resected thymoma in the research was 15 mm with the maximal being 65 mm (median 38 mm). Two surgeries (14.3%) were accompanied by technical difficulties due to the presence of an adhesion process after a previous episode of pulmonary inflammation, which resulted in more significant intraoperative blood loss of 200 ml in both cases.

The surgery duration varied from 60 to 180 minutes with the median of 82.5 minutes. In 5 patients, the duration of surgical treatment was more than 100 minutes.

The time period of pleural cavity draining in 11 patients was 24 hours and in 3 patients it lasted for two days.

The research procedures also included an evaluation of the pain syndrome intensity in 2 hours after the conducted surgical treatment, during the first 24 hours after the surgery and after the drainage tube removal. In the majority of cases (97.6%), the pain syndrome intensity did not exceed 4 points of the visual analogue scale for pain (VAS). A single episode (1 patient (7.1%)) was reported of developing the pain syndrome score of 5 VAS points.

It is worth noting that, for the purpose of pain relieving, narcotic analgesics were not used. The patients after the thoracoscopic thymectomy from the unified sub-xyphoid access were staying at the In-Patient Department for the time period of 3–4 days with the median of 3 days.

DISCUSSION

Currently, thoracoscopic thymectomy is the gold standard in the treatment of non-invasive epithelial tumors of the thymus. One of the possible accesses is the sub-xyphoid one, which is characterized by the absence of dissecting the intercostal nerves and by the possibility of performing surgery without using separate intubation [11, 12, 17–19]. This method allows for fully performing the revision of the anterior mediastinum, of the aortic window zone and, if necessary, for performing the dissection of the mediastinal lymph nodes on both sides.

For the first time, the data on the advantages of using the sub-xyphoid access for cases of pathological neoplasms in the anterior mediastinum, as it was mentioned previously, were obtained in 1999. A group of Japanese surgeons headed by T. Kido, has presented their experience of creating the sub-xyphoid access using the sternal lifting retractors in cases of anterior mediastinum tumors [15].

In 2012, T. Suda et al. [20] have published the data on the possibility of using the unified sub-xyphoid access for diseases of thymus. Currently, a certain experience was accumulated, demonstrating the efficiency of this approach in cases of thymic neoplasms. With this being said, the meta-analysis conducted in 2024 by J. Wang et al. [21] has identified significant differences found for the unified sub-xyphoid access with thoracoscopic three-port method in terms of the pleural cavity draining time and in terms of the pain syndrome level.

As of today, various modifications were proposed for the sub-xyphoid access, which differ between each other mainly by the number of ports installed and by the method of creating the additional operative space. The followers of the multi-port sub-xyphoid thymectomy install additional 5 mm ports in the intercostal spaces or in the subcostal space. By their opinion, taking into consideration the fact that the intercostal space has an average length of 10 mm, while the installation of the 5 mm port is not resulting in the damage of the intercostal nerve, the additional ports provide a more comfortable course of the

surgical intervention [22–25]. With this modification, the sub-xyphoid access is actually used as a port for locating the camera and as the route for surgical material extraction.

As opposed to the multi-port technique, as a logical extension of the single-port thoracoscopic surgeries, there is a modification of the unified sub-xyphoid access. With this access, all the instruments and the video-camera are being introduced through a single port having the size of up to 4 cm. The followers of this modification of the surgical access consider that such an approach may provide better cosmetic effect and may minimize the risk of developing chronic pain syndrome [26–28]. The only relative disadvantage of this method is the necessity of using special instruments with parallel transfer and with the presence of anatomic fold; also, for using this modification, an experience is required in performing the single-port thoracoscopy surgeries, which may elevate the learning curve. For the purpose of increasing the operational space, two different methods are being used: the application of the carboxythorax or the use of various systems to elevate the sternum. There are no significant differences between these methods, and, mainly, their use is dictated only by the Surgeon's preferences.

Our choice of using the unified sub-xyphoid access is dictated by the commitment to lesser intraoperative trauma and, as a result, to lesser number of bed days. The results provided by us, are only preliminary and, in fact, they reflect the learning curve upon the implementation of the new method into the routine practice. We have not observed any significant complications, while the duration of the surgical intervention itself and the further stay at the In-Patient Department were similar with those described in the foreign and domestic literature. All of these indicates the safety of the sub-xyphoid access and allows for continuing further use of this method. With the accumulation of the sufficient quantity of material, it shall become possible to arrange a more comprehensive comparative evaluation of the benefits and disadvantages of the studied surgical access.

Undesirable phenomena

An episode of post-operative complication has developed in 1 (7.1%) patient. This complication, although being only of surgical origin (retrosternal hematoma), did not require further active interventions. No therapeutic complications were observed.

No postoperative fatal outcomes were observed during the research.

CONCLUSION

Performing the thoracoscopic thymectomy from the unified sub-xyphoid access is a justified variant for cases of non-invasive epithelial tumors of the thymus. This method allows for performing the surgery in full range, not violating the oncology principles. It was proven that using the unified sub-xyphoid access for tumors sized up to 65 mm does not result in an increase in surgery duration or an increase in the number of intraoperative complications. The benefits of this method include lesser injury of the chest cavity, absence of the necessity for separate intubation, better visualization of the opposite phrenic nerve. However, taking into consideration the necessity of using specialized instruments and the longer learning curve, the method of unified sub-xyphoid access has not gained wide spreading.

The data obtained by us allow for recommending the use of thymectomy via the unified sub-xyphoid access for cases of non-invasive thymic tumors in the settings of specialized departments.

ADDITIONAL INFORMATION

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Authors' contribution. *E.A. Epifantsev* — performing surgical operations on patients general concept, processing and discussion of research results, manuscript writing; *V.Yu. Gritsun* — performing surgical operations on patients, search and analytical work; *Yu.A. Khabarov* — performing surgical operations on patients, search and analytical work; *Yu.V. Ivanov* — general concept, management of patient treatment and discussion of study results, manuscript editing. The authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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PATENT FORAMEN OVALE AND MIGRAINE IN ISCHEMIC STROKE PATIENTS: INCIDENCE, PATHOGENETIC INTERRELATION AND THE EFFECTS OF ENDOVASCULAR CLOSURE

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ABSTRACT

BACKGROUND: *Migraine is a chronic neurovascular disease with high incidence rate and medical-social significance. Despite more than half a century of studying the disease, the pathogenesis of migraine is not yet completely clear. The results of separate research works demonstrate the inter-relation of migraine with the presence of patent foramen ovale and circulation shunting from the right side to the left one.* ***AIM:*** *Detailing the incidence rates and the clinical characteristics of migraine, as well as the effects of endovascular installation of the occluding device into the patent foramen ovale in terms of migraine course in a cohort of patients that had an ischemic stroke episode according to the mechanism of paradoxical embolism due to having a functionally significant patent foramen ovale.* ***METHODS:*** *The examined population included 97 patients aged from 18 to 50 years old (mean age 32.29±2.19 years; 70.8% females), undergoing examination procedures at the Research Center of Neurology from January 2018 until October 2023. All the patients previously had an ischemic stroke that had involved the mechanism of paradoxical embolism, associated with the presence of patent foramen ovale and high functional significance shunting. All the patients underwent an assessment of their conditions associated with the presence of a patent foramen ovale — migraine with or without aura, other procedures included the detailing of headache characteristics and of the effects of migraine on social adaptation. The endovascular intervention was performed in 61 patients. Dynamic follow-up data were obtained for 36 patients, of which 24 migraine patients had an assessment of headache characteristics before and after the foramen ovale closure.* ***RESULTS:*** *Within the cohort of patients with patent foramen ovale accompanied with functionally significant shunting and with a previous episode of ischemic stroke, the incidence of migraine was 39.2% (no aura — 21 patients or 55%; with aura — 17, or 45%), while the proportions of women and men being 1.9:1. The rate of headache attacks was 4 [1; 7] days per month. In 6 months after the installation of the foramen ovale occluder, migraine patients were showing a significant decrease in the rate of headache onsets from 4 [2; 24] to 2 [1; 5] days a month (p=0.009); a decrease was reported for pain intensity from 7 [7; 9] to 3 [3; 7] points of the visual analogue scale for pain (p=0.0001) along with a decrease in the degree of migraine affecting the patients' everyday activity from 20 [6; 89] to 17 [2; 26] points (p=0.019) of the MIDAS questionnaire.* ***CONCLUSION:*** *The present research has confirmed the high incidence found in a cohort of patients with patent foramen ovale. Installation of the occluder resulted in a decrease in the rate and intensity of headache along with a decrease of migraine affecting the social adaptation. The research limitations were a small number of patients and the absence of data on the residual shunting circulation.*

Keywords: *patent foramen ovale; migraine; migraine with aura; ischemic stroke; paradoxical embolism; right-left shunt; patent foramen ovale closure.*

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ОТКРЫТОЕ ОВАЛЬНОЕ ОКНО И МИГРЕНЬ У ПАЦИЕНТОВ, ПЕРЕНЁСШИХ ИШЕМИЧЕСКИЙ ИНСУЛЬТ: РАСПРОСТРАНЁННОСТЬ, ПАТОГЕНЕТИЧЕСКАЯ ВЗАИМОСВЯЗЬ, ВЛИЯНИЕ ЭНДОВАСКУЛЯРНОГО ЗАКРЫТИЯ

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АННОТАЦИЯ

Обоснование. *Мигрень — хроническое нейрососудистое заболевание с высокой распространённостью и медико-социальной значимостью. Несмотря на более чем полувековую историю изучения заболевания, патогенез мигрени до конца не раскрыт. Результаты отдельных исследований демонстрируют взаимосвязь мигрени с наличием открытого овального окна и шунтирующего кровотока справа налево.* ***Цель исследования*** *— уточнение распространённости и клинических характеристик мигрени, а также влияния эндоваскулярной установки окклюдера открытого овального окна на течение мигрени в когорте пациентов, перенёсших ишемический инсульт по механизму парадоксальной эмболии вследствие функционально значимого открытого овального окна.* ***Методы.*** *Обследовано 97 пациентов в возрасте от 18 до 50 лет (средний возраст 32,29±2,19 года; 70,8% женщин), проходивших обследование в Научном центре неврологии с января 2018 по октябрь 2023 года. Все пациенты перенесли ишемический инсульт по механизму парадоксальной эмболии, ассоциированный с наличием открытого овального окна и шунтом высокой функциональной значимости. Всем пациентам проводилась оценка состояний, ассоциированных с наличием открытого овального окна — мигрени с аурой и без ауры, уточнялись характеристики головной боли и влияние мигрени на социальную адаптацию. Эндоваскулярное вмешательство проведено 61 пациенту. Получены данные динамического обследования 36 пациентов, из них у 24 пациентов с мигренью были оценены характеристики головной боли до и после закрытия овального окна.* ***Результаты.*** *Среди когорты пациентов с открытым овальным окном с функционально значимым шунтом, перенёсших ишемический инсульт, распространённость мигрени составила 39,2% (без ауры — у 21 человека, или 55%; с аурой — у 17, или 45%), соотношение женщин и мужчин 1,9:1. Частота приступов головной боли составила 4 [1; 7] дня в месяц. Через 6 месяцев после установки окклюдера овального окна у пациентов с мигренью выявлено достоверное снижение частоты приступов головной боли с 4 [2; 24] до 2 [1; 5] дней в месяц (p=0,009); сокращение интенсивности боли с 7 [7; 9] до 3 [3; 7] баллов по визуальной аналоговой шкале оценки боли (p=0,0001); уменьшение степени влияния мигрени на повседневную активность пациентов с 20 [6; 89] до 17 [2; 26] баллов (p=0,019) согласно опроснику MIDAS.* ***Заключение.*** *Настоящее исследование подтвердило высокую распространённость мигрени в когорте пациентов с открытым овальным окном. Установка окклюдера привела к уменьшению частоты и интенсивности головной боли, уменьшению влияния мигрени на социальную адаптацию. Ограничением исследования стали небольшое число пациентов и отсутствие данных по остаточному шунтирующему кровотоку.*

Ключевые слова: *открытое овальное окно; мигрень; мигрень с аурой; ишемический инсульт; парадоксальная эмболия; право-левый шунт; установка окклюдера овального окна.*

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BACKGROUND

Migraine is a widespread neurological disease (found in 12–15% of the population), the pathogenesis of which is not completely clear [1, 2]. During the last decades, the factors are being studied that predispose the development of cephalgia, one of which is the presence of a patent foramen ovale.

Patent foramen ovale is the form of intracardial communication, anatomically representing an opening, located in the central part of the interatrial septum. Patent foramen ovale is a rudiment form of normal embryonic circulation, which normally should close during the first year of life in a child, however, it remains unclosed in 1/4 of the population [3]. The morphological variability is found both in the dimensions and in the shape of the oval foramen — from a simple opening covered by a valve to a long corrugated passage. The structure of the patent foramen ovale defines the degree of shunting circulation passing through the opening, which may vary from small to significant. The diagnostics of the patent foramen ovale is being carried out using the transthoracic and transesophageal echocardiography. For the purpose of verifying the degree of shunting circulation, a micro-bubble test with intravenous administration of the contrasting agent is used (most frequently — an aerated physiological saline), allowing for quantitative assessment of the shunting degree by means of calculating the number of signals from the micro-bubbles. The most widespread and informative method used to perform the micro-bubble test is the transcranial Doppler sonography with the registration of embolic air signals in the middle cerebral arteries [4, 5].

The relation between the patent foramen ovale and migraine was first described by S.M. Del et al. [6] in 1998. The authors have found that the rate of patent foramen ovale presence in migraine patients was significantly higher comparing to healthy individuals. Later on, a number of research works have confirmed that the occurrence rate of migraine among the individuals with patent foramen ovale is 2–3 times higher than in the general population [7–10], correlating with the degree of shunting circulation [11]. Besides the possible interrelation with the onset of migraine attacks, patent foramen ovale plays a role in the development of stroke by employing the paradoxical embolism mechanism. In younger patients with cryptogenic ischemic stroke and migraine with aura, the occurrence rate of having a patent foramen ovale reaches up to 93% [12, 13].

The mechanism of the effects of right-to-left shunting circulation on the onset of migraine attack is not yet completely clear. According to one of the hypotheses, 5-hydroxytryptamine (5-HT, or serotonin) contained in platelets, has one of the leading roles in the development of migraine. Normally, practically all the serotonin present in venous blood is being removed by decomposition in lungs. In case of the presence of a patent foramen ovale, it is supposed that the passage of platelets through the narrow opening of the foramen ovale promotes hyperaggregation of platelets with the secretion of serotonin and other vasoactive mediators into peripheral blood. High 5-HT concentrations induce vasoconstriction of meningeal arteries with developing aura symptoms, while lesser 5-HT concentration promotes vasodilation due to synergetic effects with nitrogen oxide (NO) and prostaglandins, stimulating the pain receptors of pial arteries, which leads to the development of the headache phase [14]. Alternative hypothesis considers the migraine attack predictor being the decrease in blood oxygen saturation due to right-to-left shunting. A research by T. Takano et al. [15] has shown that cortical spreading depression is associated with severe hypoxia, while the elevation of partial oxygen pressure (pO_2) shortens its duration. According to the third hypothesis, the development of spreading depolarization is related to microembolism of the cortical arteries. Animal studies conducted by M.A. Moskowitz et al. [16] at the laboratory of Harvard University, have demonstrated that air and platelet aggregates, injected to 28 mice directly into the carotid arteries, initiate cortical spreading depression. Upon the injection of air microemboli (with the diameter of <10 μm), polystyrene microspheres (10 μm) and cholesterol particles (<70 μm), the microembolism has induced the development of cortical spreading depression in 16 (57%) animals. Some mice had ischemic changes detected in the cortical neurons with no focal changes upon neurovisualization. Smaller emboli (with the diameter of <10 μm) have induced rapid and transient episodes of cortical spreading depression, related to significant decreases of cortical perfusion. Larger emboli (<70 μm) had higher probability of inducing microinfarctions, however, the latter were not detected upon cerebral visualization, though being verified upon histological examination. The authors draw up a conclusion that the majority of emboli are too small and they rapidly undergo spontaneous lysis, by this causing the onset of depolarization events with no developing clinically significant ischemia. In contrast, larger emboli, resistant to lysis, can become the culprit of cortical microinfarctions [17].

Endovascular closure of the patent foramen ovale using the special devices (occluders) is the main treatment method for functionally significant cases of foramen ovale. In 1992, the first transcutaneous closure of the patent foramen ovale was performed in a patient with ischemic stroke occurring via the mechanism of paradoxical embolism [18]. In 2000, P.T. Wilmshurst et al. [19] have first reported the benefits of patent foramen ovale closure in migraine patients. To the present moment, a significant number of observation research works were carried out in real clinical practice [20–24] along with several large randomized controlled research works, in particular, MIST (Migraine Intervention With STARFlex Technology), PRIMA (PRIMA PFO Migraine Trial) and PREMIUM (Prospective, Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects With Migraine and PFO Using the AMPLATZER PFO Occluder to Medical Management) [20–22], which have demonstrated controversial results with regard to the effects of foramen ovale closure in the course of migraine.

In Russia, endovascular installation of occluders for closing the foramen ovale for the purpose of secondary prevention of paradoxical embolism-related ischemic stroke has been performed since 2018, however, there was no evaluation performed on the incidence of migraine among the patent foramen ovale patients and on the effects of foramen ovale occluder installation on the course of cephalgia until the present moment.

Research aim — detailing the incidence rates and clinical characteristics of migraine, as well as the effects of endovascular installation of the patent foramen ovale occluder on the migraine course in a cohort of patients that had an episode of ischemic stroke caused by the mechanism of paradoxical embolism due to functionally significant patent foramen ovale.

METHODS

Research design

A prospective non-randomized open-label research was carried out to assess the effects of patent foramen ovale occluder installation on migraine course within the Russian cohort of patients.

Conformity criteria

Inclusion criteria: group I — patients after an episode of ischemic stroke caused by the mechanism of paradoxical embolism; group II — patients with a past episode of ischemic stroke resulted by paradoxical embolism and after the procedure of patent foramen ovale closure with a past history of migraine.

Non-inclusion criteria: patients having a concurrent cause of developing a stroke; other neurological or mental disease; concomitant severe somatic disturbances; past history of hemiplegic migraine or cluster headache; preventive treatment of migraine (tablets or injectables) within 3 months prior to the inclusion into the research program.

Exclusion criteria: less than 80% of headache diary keeping compliance; refusal from repeated visiting the neurologist after the installation of patent foramen ovale occluder.

Research facilities

The research included 97 patients aged from 18 to 50 years old (39 females and 56 males, mean age: 32.29±2.19 years old), undergoing examination procedures at the Federal State Budgetary Scientific Institution "Research Center of Neurology" from January 2018 until October 2023. All the patients had an episode of ischemic stroke caused by paradoxical embolism, associated with the presence of patent foramen ovale with moderate and severe interatrial shunting circulation.

Medical procedure description

The degree of shunting circulation from the right side to the left one was evaluated using transcranial Doppler sonography with the administration of the contrasting agent — agitated mixture of 9 mm 0.9% physiological saline and 1 ml of air. The shunting degree was calculated using the number of registered microembolic signals: no shunting — 0 microembolic signals; insignificant — from 1 to 20 microembolic signals; moderate — more 20 microembolic signals with no "curtain effect"; severe — a "curtain" of microembolic signals, where a single signal cannot be recognized within the circulation spectrum [7].

The evaluation of the interrelation of the stroke episode in the past with the detected patent foramen ovale was carried out using the paradoxical embolism risk score (Risk of Paradoxal Embolizm, RoPE). The mean RoPE scale value in the group was 8.3±1.09 points, which confirms the high (84%) probability of an interrelation between the ischemic stroke and the presence of patent foramen ovale [23].

All the patients have underwent an assessment of their conditions, associated with the presence of the patent foramen ovale, in the settings of having migraines with aura (MA) and without aura (MnA). The migraine diagnosis was set in accordance with the International headache classification, beta-version (3rd edition,

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2018, IHC 3 beta) [24]. In case of having migraine, the patients were included into research group 1: ischemic stroke + patent foramen ovale + migraine (group I, IS+PFO+Migraine). The algorithm used for selecting the patients is provided in Fig. 1.

After the confirmation of paradoxical embolism, all the patients had been given the recommendations of installing the patent foramen ovale occluder for the purpose of secondary prevention of strokes. Endovascular interventions were performed in 61 patients. After the occluder installation, the patients had a 6 months period of taking double antiplatelet therapy (Acetylsalicylic acid + Clopidogrel), then, according to the European recommendations from the Endovascular surgery society on managing the patent foramen ovale patients (2019) — only acetylsalicylic acid at a dosage of 75–100 mg/day [25]. Six months after the foramen ovale closure, repeated patient's visit was scheduled for evaluating the somatic and neurological status.

As of the moment of drafting the article, the data were obtained from dynamic follow-up of 36 ischemic stroke patients with patent foramen ovale occluder installed, of which 24 patient had migraine, which were included in to the second research group: ischemic stroke + patent foramen ovale + occluder + migraine (group II, IS+PFO+Occluder+Migraine), where the cephalgia characteristics were assessed before and after the endovascular closure of the foramen ovale.

Methods for registration of outcomes

The patients in the main research groups were filling in a standard questionnaire including the demographic data, the clinical features of migraine course (duration of disease, attack rate during the last month, attack intensity according to visual analogue scale), the information on the presence of vascular risk factors (arterial hypertension, diabetes mellitus, smoking and intake of oral contraceptive pills) and the presence of past or chronic diseases.

The rates and clinical characteristics of migraine attacks were assessed using the paper or digital version of headache diary, which the patient had to fill in for 3 months before the installation of the patent foramen ovale occluder and for 3 months after the

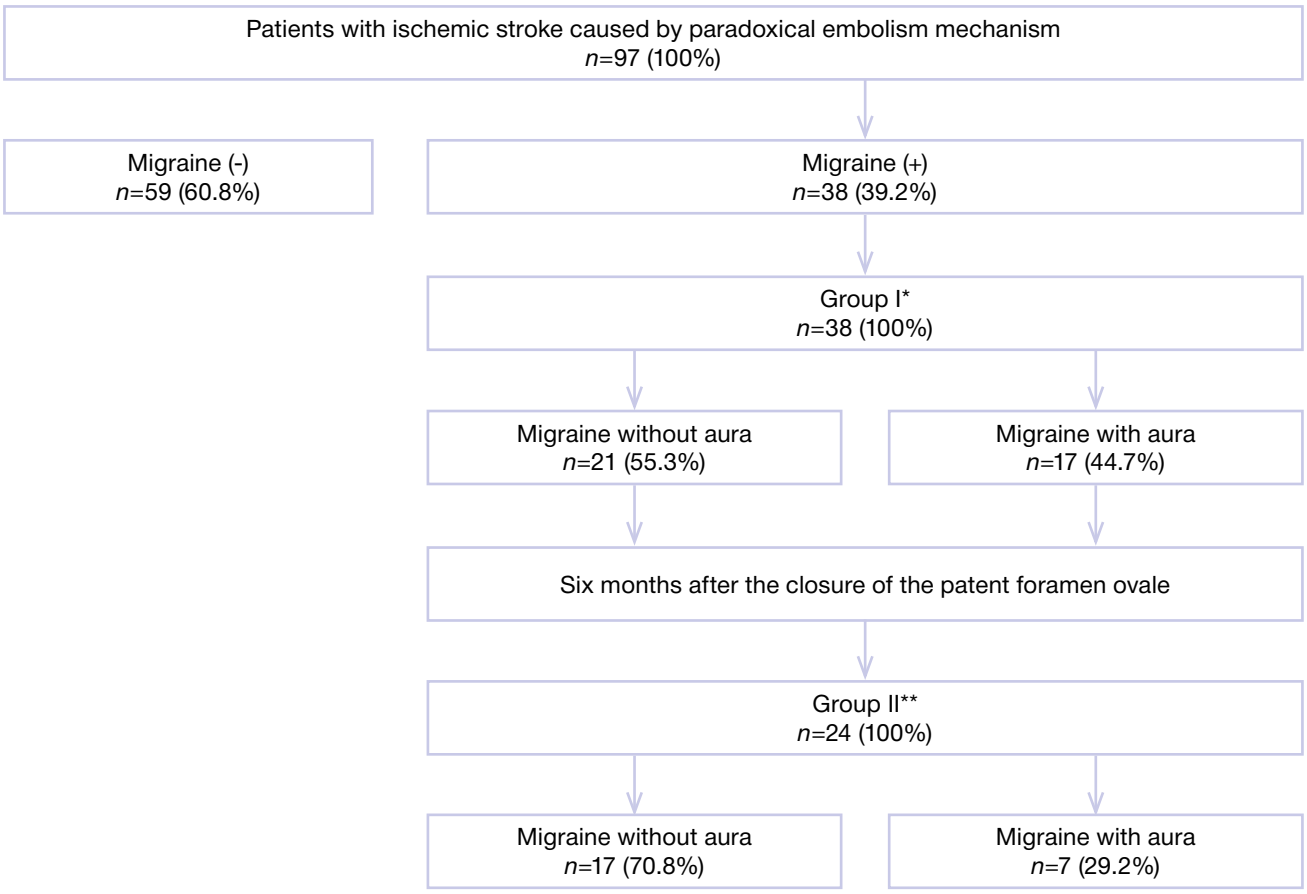

Fig. 1. Flowchart of the algorithm used for distributing patients into research groups.
Note. * Group I — ischemic stroke + patent foramen ovale + migraine. ** Group II — ischemic stroke + patent foramen ovale + occluder + migraine.

foramen ovale closure. The dairy had to be filled in on a daily basis and had to show at least 80% of dairy filling compliance.

For the purpose of assessing the quality of life and the effects of migraine on everyday activity and working capacity, all the patients had to fill in (twice — before and in 6 months after the occluder installation) the MIDAS questionnaire (Migraine Disability Assessment). According to the questionnaire, the total number of points ranging from 0 to 5 corresponded to low pain intensity, absence or minimal decrease of everyday activity; 6–10 points — moderate/severe pain, insignificant limitation of everyday activity; 11–20 points — severe pain, significant restriction of everyday activity; from 20 points and higher — severe pain, significant restriction of everyday activity [26].

Research outcomes

The research endpoint included changes in headache intensity, in the number of headache days and in the level of social de-adaptation in a patient in 6 months after the installation of patent foramen ovale occluder.

Ethical review

The research was approved by the local ethics committee of the Federal State Budgetary Scientific Institution "Research Center of Neurology" (minutes of the meeting No. 1-4/22 dd. 19.01.2022). Each patient had signed a voluntary informed consent for participating in the research activities.

Statistical analysis

The procedures of statistical analysis were carried out using the IBM SPSS Statistics 23.0 application software package. The main descriptive statistics for categorical and ordinal variables included the rate and the percentage (*n*, %), while for normal distribution of quantitative variables — the mean values and standard deviation (M±SD), as for the data, the distribution of which did not meet normality criteria — the median and quartiles 1–3 (Me [Q25%; Q75%]). The comparative analysis of two independent groups by quantitative variable was carried out using the Mann-Whitney test. The null hypothesis was rejected in case of $p < 0.05$.

RESULTS

Research sample (participants)

Among 97 patients with ischemic stroke caused by paradoxical embolism, 38 (39.2%) were diagnosed with migraine, of which 21 (55.3%) had MnA and 17 (44.7%) had MA; the ratio of women and men was 1.9:1. The frequency of headache days per month was 4 [1; 7], which corresponds to criteria for infrequent episodic migraine. The main characteristics of headache corresponded to the average population values (table 1).

Group II (IS+PFO+Occluder+Migraine) consisted of 24 patients having migraine with or without aura. Further analysis did not include an assessment of dynamic changes in migraine characteristics after the installation of patent foramen ovale occluder within the MA and MnA groups due to insufficient statistical power of the research group (table 2).

Primary findings

Based on the results of analyzing the dependent samples (before and after the installation of occluder), a significant decrease was found in the frequency of migraine attacks — from 4 [2; 24] to 2 [1; 5] days

Table 1

Clinical characteristics of migraine in patients from group I (IS+PFO+Migraine)

Characteristics	Migraine patients *n*=38 (100%)	Migraine with no aura *n*=21 (55.3%)	Migraine with aura *n*=17 (44.7%)
Mean age, years (M±SD)	35.76±1.41	33.67±1.93	38.50±1.90
Age of headache onset, years (Me [Q25%; Q75%])	20.06±1.78	21.72±2.43	18.07±2.61
Headache history, years (Me [Q25%; Q75%])	16.12±1.85	13.17±2.38	19.67±2.70
Women, *n* (%)	25 (66)	13 (62)	12 (71)
Men, *n* (%)	13 (34)	8 (38)	5 (29)
Hereditary history, *n* (%)	22 (57)	13 (62)	9 (53)
Frequency — migraine days per month (Me [Q25%; Q75%])	4 [1; 7]	4 [1; 5]	4 [1; 12]
Headache intensity (VAS), points (Me [Q25%; Q75%])	6 [5; 7]	6 [6; 7]	6 [5; 6]
MIDAS, points (Me [Q25%; Q75%])	20 [5; 49]	25 [5; 49]	18 [6; 39]

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Table 2

Demographical and Clinical characteristics in patients from Group II (IS+PFO+Occluder+Migraine) before the installation of patent foramen ovale occluder

Characteristics *n*=24		Parameter
Women, *n* (%)		17 (71)
Age, years (Me [Q25%; Q75%])		36 [30; 43]
Migraine with aura, *n* (%)		7 (29)
Number of headache days a month (Me [Q25%; Q75%])		4 [2; 24]
Pain intensity (VAS), points (Me [Q25%; Q75%])		7 [7; 9]
De-adaptation degree (MIDAS) (Me [Q25%; Q75%])		20 [6; 89]
Characteristics of the interatrial septum, *n* (%)	normal	14 (59)
	hypermobility	2 (8)
	aneurism	8 (33)
Shunting degree according to data from transcranial Doppler sonography, *n* (%)	insignificant	-
	moderate/severe	24 (100)

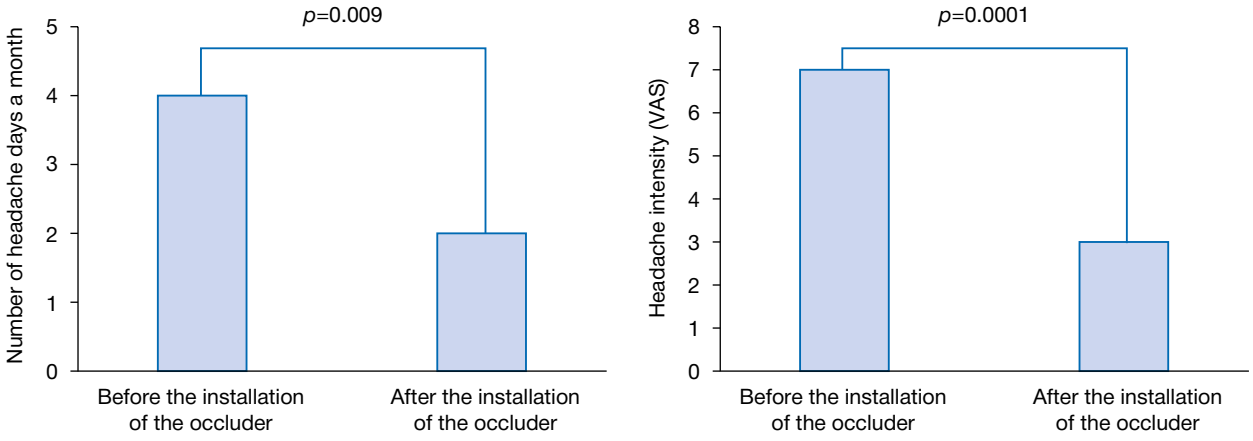

Fig. 2. Dynamic changes in the frequency and intensity of headache before and after the installation of PFO occluder.

a month (p=0.009) along with a decrease in the headache intensity from 7 [7; 9] to 3 [3; 7] points of VAS (p=0.0001) (Fig. 2). A statistically significant decrease was found in the degree of migraine affecting patient's everyday activity — from 20 [6; 89] to 17 [2; 26] points (p=0.019), according to MIDAS questionnaire (Fig. 3).

DISCUSSION

Despite the significant number of conducted researches studying the interrelation of migraine with the presence of patent foramen ovale and its endovascular closure, to the present moment, there is no univocal opinion regarding the commonness of the pathogenesis in the said conditions. Taking into consideration the wide spreading of both nosologies, there is a probability for both diseases (comorbidities) existing in a single person.

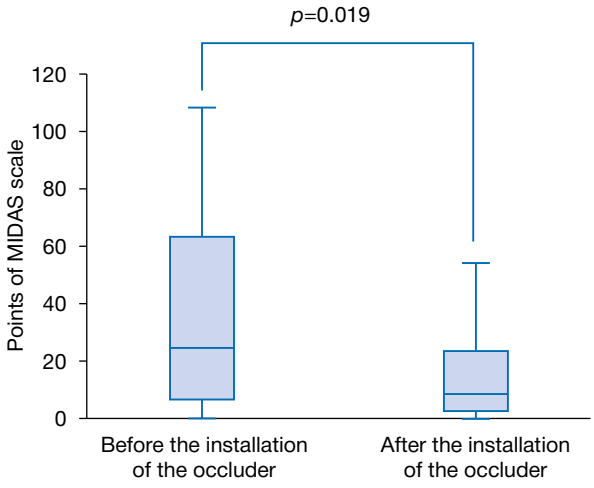

Fig. 3. Dynamic changes in the levels of social de-adaptation of migraine patients before and after the installation of PFO occluder.

Our research works has confirmed the thesis on the high incidence of migraine in patent foramen ovale patients: approximately 40% of research participants were suffering from cephalgia, which corresponds to the data from P.T. Wilmshurst [11], according to which, the incidence of migraine in cases of patent with patent foramen ovale with moderate shunting was 25%, while in cases of significant shunting — up to 53%.

The incidence for MA and MnA patients in our sample was 45% and 55%, respectively, while the patent foramen ovale, according to literature data, was associated predominantly with classic migraine (the occurrence rate for migraine with aura among the patients with patent foramen ovale is within the range of 46–88%) [27, 28].

The conducted research had a women to men ratio of 1.9/1, while the specific feature of migraine is the prevalence in female population with the ratio of women and men during the peak incidence period (30–45 years) being 3 – 4/1 [29].

When assessing the clinical characteristic of cephalgia, no specific features of the disease course were found, which complies with the results of SAM (Shunt-Associated Migraine) prospective multi-center observational research with the participation including 460 patients, the objective of which was to reveal the difference in the clinical signs of migraine depending on the presence of right-to-left shunting circulation. The differences in disease symptoms among the patients with patent foramen ovale (58%) and without one (42%) were also not detected. The authors came to the conclusion that the right-to-left shunt, apparently, plays a role in the initiation of migraine attacks, however, not affecting its clinical characteristics [30].

Data from real clinical practice indicate the presence of positive effects caused by foramen ovale occluder installation on the course of migraine, by this confirming the commonness of pathogenesis. From the beginning of 2000, more than ten observational research works were conducted, successfully demonstrating a decrease in the severity and in the duration of headache attacks along with the number of medicines used to alleviate migraine attacks, as well as an improvement in the quality of life according to data from HIT-6 and MIDAS scales in patients undergoing an installation of patent foramen ovale occluder [31–35]. So, the data from randomized controlled research are not so unambiguous. The objective of MIST [20], PRIMA [21] and PREMIUM [22] research works was an assessment of the effects caused by endovascular installation of the patent foramen ovale occluder on the course of migraine. Though none of the research activities had reached its primary endpoints (elimination of migraine in 6 months during the MIST research; decreasing the monthly rate of migraine attacks in 9–12 months during the PRIMA research; decreasing the migraine attacks >50% within 1 year during the PREMIUM research), upon achieving the secondary endpoints, a benefit was demonstrated for the patent foramen ovale closure, especially in patients having migraine with aura.

Our research has shown positive dynamic changes in cephalgia parameters in 6 months after the installation of patent foramen ovale occluder, namely: a statistically significant shortening of frequency (in days) and a decrease in the intensity of headache; a decrease in the degree of migraine affecting the patient's everyday activity. The obtained results confirm the method's efficiency, just like the previously conducted observational researches. Insufficient level of evidence found in the results of randomized controlled researches, may be related to specific features of selecting the patients with drug-resistant migraine, which often resists any correction, including also the drug-free modalities. Our cohort, like in other research works employing the settings of real clinical practice, had a prevalence of patients with initially low rate of headache days, corresponding to episodic migraine.

After an installation of the occluder, all the patients were receiving double antiplatelet therapy with acetylsalicylic acid and clopidogrel, thus, besides the elimination of shunting, the prescribed therapy was directed to decreasing the aggregation properties of platelets. Taking into consideration the hyper-aggregation theory of migraine pathogenesis [14], the literature contains a discussion on what is causing the efficiency of endovascular treatment for patent foramen ovale — the fact of eliminating the shunt itself, the drug-induced decrease in platelet aggregation during the post-surgery period or the synergy of both methods. That being said, the CANOA research (Clopidogrel for the prevention of new migraine after transcatheter closure of the interatrial septal defect) has shown that, among the patients with a past episode of transcatheter closure of interatrial septal defect using the Amplatzer apparatus, the combination of acetylsalicylic acid and clopidogrel taken for 3 months after the procedure, as compared to acetylsalicylic acid monotherapy, resulted in lesser number of migraine attacks within 3 months [36]. The retrospective research by R.J. Sommer et al. [37] has shown that successful inhibition of platelet thienopyridine P2Y12-receptors improves the course

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of migraine in patients with patent foramen ovale and is considered a prognostic marker of the efficiency of endovascular patent foramen ovale closure for the prevention of migraine. Investigators propose using the sensitivity to thienopyridine antiaggregants when selecting migraine patients for further research works on the closure of patent foramen ovale.

In January 2021, the European recommendations were issued on managing the patients with patent foramen ovale and migraine [38], containing regulations on the endovascular treatment of functionally significant patent foramen ovale in case of diagnostic procedures being performed among the patient with transient ischemic attacks or ischemic stroke caused by paradoxical embolism and with concomitant migraine, as well as on the procedures of occluder installation as a "salvage therapy" in patients with refractory migraine and the significant decrease in the quality of life. Taking into consideration the literature data mentioned above, as well as the proprietary clinical experience within the framework of the conducted research, the conclusions drawn up by the colleagues appear justified and rational.

Research limitations

The limitations of the present research were a small patient sample and insufficient duration of migraine course dynamic assessment after the occluder installation.

When assessing the research results, the data on the presence of residual shunting circulation were not registered. The research by E. Ben-Assa et al. [8] has shown the significance of residual shunting for the dynamic course of migraine. The absence of shunting from the right side to the left was associated with a decrease in migraine burden by more than 50% (OR4.60; 95%CI 1.30–16.10; p=0.017). Besides, the main research population included patients after an ischemic stroke, which is why the obtained results cannot be projected to the general cohort of patients with migraine and patent foramen ovale.

CONCLUSION

Further research on the effects of endovascular closure of the patent foramen ovale on the course of migraine shall take into account the sensitivity to thienopyridine antiaggregants with evaluating the dynamic course of the disease during a time period of not less than 12 months after the installation of occluder with a background of initiating and canceling the double antiaggregant therapy. The important aspect is also an evaluation of the procedure safety and efficiency (complete closure of the right-to-left shunt or preserving residual shunting) for the treatment of such a patient cohort.

ADDITIONAL INFORMATION

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Competing interests. The authors declare that they have no competing interests.

Authors' contribution. *A.V. Belopasova* — concept development, literature analysis, patient selection and examination, data analysis and interpretation, manuscript writing, data collection; *A.O. Chechetkin* — examination of patients, data collection, analysis and interpretation of the data obtained, manuscript writing; *V.D. Merezhko* — literature analysis, data analysis and interpretation, manuscript writing. The authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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REPEATED ARTHROSCOPY OF THE ANKLE JOINT AFTER DISTRACTION ARTHROPLASTY, A CASE SERIES

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ABSTRACT

BACKGROUND: *Distraction arthroplasty of the ankle joint is the treatment method used for the cases of terminal osteoarthritis of the ankle joint that allows for delaying the arthrodesis or the total endoprosthesis replacement. The therapeutic effect is being achieved due to the separation of the articular surfaces (arthrodiastasis) with using the Ilizarov frame (or other devices for external fixation) for a period of 8–12 weeks. Only one research was described with the patients undergoing repeated arthroscopy of the ankle joint after the distraction arthroplasty in a combination with microfracturing of the cartilage defects, or repeated arthroscopy at the moment of removing the external fixation device (after 3 months).* ***AIM:*** *To study the changes in the articular surfaces according to the Outerbridge before and after the distraction arthroplasty of the ankle joint using the repeated arthroscopy of the ankle joint.* ***METHODS:*** *A total of 17 distraction arthroplasty surgical interventions of the ankle joint were performed (7 [41.2%] females and 10 [58.8%] males; the mean age of the patients was 48.5±13.57 years). Repeated arthroscopy of the ankle joint due to the recurrence of anterior impingement-syndrome after the distraction arthroplasty of the ankle joint within up to 12 months from the moment of removing the Ilizarov frame was carried out in 4 patients. For the evaluation of the treatment results, the Foot and Ankle Ability Measure (FAAM) scales were used, with an evaluation of pain, functions, deformity and the alignment of the foot and of the ankle joint (AOFAS Ankle-hindfoot scale), with subjective evaluation of pain (VAS); the status of the cartilage tissue in the ankle joint was evaluated using the modified Outerbridge scale.* ***RESULTS:*** *In all the patients, a statistically significant improvement of the functional result was found in 12 months from the moment of surgery when using the FAAM (p=0.0006) and AOFAS Ankle-hindfoot scales, as well as after removing the Ilizarov frame in 1, 3 and 6 months. The pain intensity according to the VAS scale has decreased from 6.17±1.32 cm before surgery to 2 cm (1.4; 2.1) (p=0.00002) in 12 months. The arthroscopic findings upon the repeated interventions demonstrate the development of the massive arthrofibrosis with its further degradation to the end of 6 months, also showing the restoration of the cartilage defects from Outerbridge grade IV to grade II–III.* ***CONCLUSION:*** *Upon the repeated arthroscopy, including the one performed at the end of 12 months after the distraction arthroplasty of the ankle joint, signs of regeneration were observed in the cartilage tissue defects with further defect coverage with a cartilage-like tissue, which, probably, determines the analgesic effect of the distraction arthroplasty of the ankle joint.*

Keywords: *distraction arthroplasty; ankle; Ilizarov frame; osteoarthritis.*

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BACKGROUND

Distraction arthroplasty of the ankle joint is the treatment method used for the cases of terminal osteoarthritis of the ankle joint, the method that allows for delaying the arthrodesis procedure (complete immobilization of the joint by means of fusing the adjacently located bones) or the total endoprosthesis replacement. The therapeutic effect is being achieved due to the dissociation of the articular surfaces (arthrodiastasis) by means of using the Ilizarov frame (or other devices intended for external fixation) for the period of 8–12 weeks [1]. For the purpose of the effective use of the method, it is necessary to create the arthrodiastasis of 5–6 mm [2]. The mobile (articulating) and the fixated arrangements of the Ilizarov frame are used, with the proven benefit of the articulating

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СЕРИЯ СЛУЧАЕВ ПОВТОРНОЙ АРТРОСКОПИИ ГОЛЕНОСТОПНОГО СУСТАВА ПОСЛЕ ДИСТРАКЦИОННОЙ АРТРОПЛАСТИКИ

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АННОТАЦИЯ

Обоснование. *Дистракционная артропластика голеностопного сустава — метод лечения терминального остеоартрита голеностопного сустава, позволяющий отсрочить артродезирование или тотальное эндопротезирование. Лечебный эффект достигается за счёт разобщения суставных поверхностей (артродиастаза) с помощью аппарата Илизарова (или других аппаратов внешней фиксации) на срок 8–12 недель. Описано всего одно исследование пациентов с повторной артроскопией голеностопного сустава после дистракционной артропластики в комбинации с микрофрактурированием дефектов хряща, повторной артроскопией на момент демонтажа аппарата наружной фиксации (через 3 месяца).* ***Цель исследования*** *— изучить изменения суставных поверхностей по классификации Outerbridge до и после дистракционной артропластики голеностопного сустава с помощью повторной артроскопии голеностопного сустава.* ***Методы.*** *Всего выполнено 17 оперативных вмешательств по дистракционной артропластике голеностопного сустава (7 [41,2%] женщин и 10 [58,8%] мужчин; средний возраст пациентов 48,5±13,57 года). Повторная артроскопия голеностопного сустава в связи с рецидивом переднего импиджмент-синдрома после дистракционной артропластики голеностопного сустава в срок до 12 месяцев с момента демонтажа аппарата Илизарова выполнена 4 пациентам. Для оценки результатов лечения использовали шкалы функционального ограничения стопы и голеностопного сустава (FAAM), оценки боли, функции, деформации и выравнивания стопы и голеностопного сустава (AOFAS Ankle-hindfoot scale), субъективной оценки боли (ВАШ); состояние хряща голеностопного сустава оценивали с помощью модифицированной шкалы Outerbridge.* ***Результаты.*** *У всех пациентов отмечено статистически значимое улучшение функционального результата через 12 месяцев с момента операции по шкалам FAAM (p=0,0006) и AOFAS Ankle-hindfoot scale, а также после демонтажа аппарата Илизарова через 1, 3 и 6 месяцев. Интенсивность боли по шкале ВАШ снизилась с 6,17±1,32 см до операции до 2 см (1,4; 2,1) (p=0,00002) через 12 месяцев. Артроскопическая картина при повторных вмешательствах демонстрирует развитие массивного артрофиброза с его последующей деградацией к 6 месяцам, а также восстановлением дефектов хряща с IV степени по Outerbridge до II–III степени.* ***Заключение.*** *При повторной артроскопии, в том числе спустя 12 месяцев после дистракционной артропластики голеностопного сустава, отмечаются признаки регенерации хрящевых дефектов с покрытием их хрящеподобной тканью, что, вероятно, и обусловливает анальгетический эффект дистракционной артропластики голеностопного сустава.*

Ключевые слова: *дистракционная артропластика; голеностопный сустав; аппарат Илизарова; остеоартрит.*

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arrangement. The method of distraction arthroplasty of the ankle joint allows for delaying the radical intervention (arthrodesis or endoprosthesis replacement) in 80% of the cases by up to 5 years after surgery [3].

The epidemiological data show the values of 9–15% of the ankle joint osteoarthritis cases in the general population, while among the causes of chronic inflammation, it has a share of about 70–78% [4].

The mechanism of distraction arthroplasty of the ankle joint is insufficiently studied. Several hypotheses exist that explain the efficiency of the method. When dissociating the joint, the cascade of events occurs: mechanical unloading of the joint, improvement of blood supply, creating an excessive negative pressure within the joint cavity, increase in the number of mesenchymal cells, activation of catabolism and anabolism, resorption of subchondral sclerosis and a decrease in the density of the bone tissue [5, 6].

The only research with studying the repeated arthroscopy of the ankle joint after the distraction arthroplasty is the research by Y. Ikuta et al. [7], in which the authors have studied a combination of the distraction arthroplasty of the ankle joint with microfracturing of the cartilage defects.

Research aim — an evaluation of the changes in the articular surfaces in accordance with the Outerbridge classification before and after the distraction arthroplasty of the ankle joint using repeated arthroscopy, as well as the evaluation of the efficiency of the distraction arthroplasty of the ankle joint.

METHODS

Research design

Prospective non-randomized open-label multicenter research.

The main method of the research was the analysis of the arthroscopy images of the articular cartilage in the ankle joint. Repeated arthroscopy after the distraction arthroplasty of the ankle joint was carried out in patients with the recurrence of the anterior impingement-syndrome (subacromial syndrome) within the period from the removal of the Ilizarov frame up to 12 months. The evaluation also included the clinical results of conducted treatment based on the evaluation systems (see "Methods for registration of outcomes").

Conformity criteria

Inclusion criteria: stage III post-traumatic osteoarthritis of the ankle joint; patient's age from 18 to 65 years old; absence of infectious process in the joint; preserved motion amplitude in the ankle joint — not less than 15 degrees.

Exclusion criteria: violations of the postoperative regimen; violation of control check-up schedule by more than 10 days.

Research facilities

The examination was carried out within the facilities of the State Budgetary Healthcare Institution "Municipal Clinical Hospital No. 13" under the Healthcare Department of the City of Moscow, within the facilities of the State Budgetary Healthcare Institution "V.M. Buyanov Municipal Clinical Hospital" under the Healthcare Department of the City of Moscow, and within the premises of the State Budgetary Healthcare Institution of the Moscow Oblast "Zhukovskiy Oblast Clinical Hospital" during the period from 2022 until 2023.

Medical procedure description

The diagnosis of the anterior impingement-syndrome was set based on the presence of pain syndrome in the anterior segment of the ankle joint upon the passive forced plantar flexion (plantar flexing of the foot) and dorsiflexion (dorsal flexing of the foot), also being confirmed by radiation diagnostics methods (magnetic resonance tomography or radiography).

All the patients were initially undergoing arthroscopy of the ankle joint with further installation of the Ilizarov frame using the articulating arrangement, consisting of a single ring and the U-shaped semi-circle for the foot. The joint movements were initiated during the first 24 hours after surgery: the patients were using dosed walking with crutches. In general, the arthrodiastasis was reaching up to 5.5 mm and lasted for up to 8 weeks.

Methods for registration of outcomes

For the evaluation of the treatment results, the Visual Analogue Scale for pain (VAS) was used along with the FAAM (Foot and Ankle Ability Measure) scale, as well as the clinical scale for the evaluation of pain, functions, deformity and foot/ankle alignment from the AOFAS (American Orthopaedic Foot and Ankle Society Ankle-Hindfoot Scale) before treatment and after de-installing the Ilizarov frame in 1, 3, 6 and 12 months. The evaluation of the cartilage defects on the arthroscopy images was carried out using the modified Outerbridge classification.

Ethical review

The conduction of the research was approved by the local Ethics Committee of the Medical Institute of the Federal State Autonomous Educational Institution for Higher Education "Patrice Lumumba Peoples' Friendship University of Russia", protocol No. 10, dd. September 22, 2022.

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All the patients have signed the voluntary informed consent form.

Statistical analysis

The statistical processing of data was carried out using the SciPy 1.12.0 and NumRu 1.24.2 statistical libraries for Python 3.9.10 (Python Software Foundation, Delware, USA). For each of the continuous variables, the mean (M) and the standard deviation (SD) were provided, or the median (Me) with the upper (25%) and the lower quartiles (75%) depending on the type of distribution. The hypothesis on the normal distribution was verified using the Shapiro-Wilk test. The significance of differences was tested using the Student t-test for dependent samples with normal distribution, for the non-normal distribution — using the non-parametric Wilcoxon T-test and the calculation of the significance level (p). The differences were considered statistically significant if the p value was <0.05.

RESULTS

Research sample (participants)

A total of 17 distraction arthroplasty of the ankle joint surgical interventions in combination with the arthroscopy of the anterior segment of the ankle joint were carried out in the patients with post-traumatic stage III osteoarthritis of the ankle joint. The mean age of the patients was 48.5±13.6 y.o.a., with the number of women being 7 (41.2%) and men — 10 (58.8%).

The control radiography was performed after de-installing the Ilizarov frame in 6 and 12 months. In 10 patients, the findings included the anterior impingement-syndrome due to the presence of osteophytes, 4 patients had an impaired lateral ligamentous complex, 2 were diagnosed with damaged medial ligamentous complex, with 1 patient having a local bone-cartilage defect of the of the talus bone. Repeated arthroscopy of the ankle joint was carried out for 4 patients with the anterior impingement-syndrome: 1 — at the moment of de-installing the Ilizarov frame, 1 — in 6 months, 2 — in 12 months. The characteristics of the patients with repeated arthroscopy of the ankle joint are provided in table 1. The indication for conducting the repeated arthroscopy of the ankle joint was the recurrence of the symptoms of the anterior impingement-syndrome.

Main research outcomes

In all the patients, there was a statistically significant change in the functional results to Month 12 from the moment of surgery according to the FAAM and AOFAS scales, except for patient No. 2, in which the functional decrease was found when applying these scales after 12 months (Fig. 1).

Table 1

Characteristics of patients with second-look arthroscopy

Patient	Gender	Age, years	Body mass index, kg/m²	Osteoarthritis type	Time, months
1	M	65	27.4	Symmetrical	0
2	M.	57	35.5	Talus bone collapse	12
3	F.	44	30.9	Symmetrical	6
4	M.	44	26.5	Asymmetrical	12

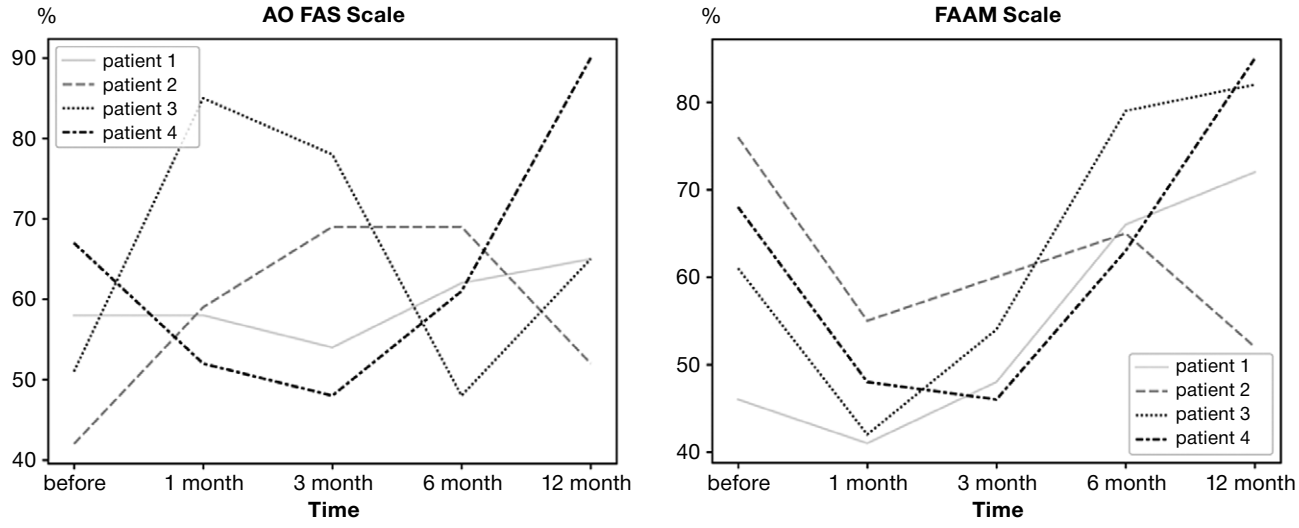

Fig. 1. Functional outcomes of patient measuring scales after ankle distraction arthroplasty.

The pain syndrome had statistically significantly decreased in all the patients to the end of 12 months when using the VAS scale (p=0.00002), with the mean values from 6.17±1.32 cm before surgery to 2 cm (1.4; 2.1) in 12 months (Fig. 2).

Patient No. 1 before the distraction arthroplasty of the ankle joint had a total absence of cartilage tissue (grade IV according to the Outerbridge scale) (Fig. 3). At the moment of de-installing the Ilizarov frame, repeated arthroscopy was carried out, revealing the presence of abundantly vascularized soft connective tissue, which was completely filling the ankle joint cavity. The arthroscopic signs of arthrofibrosis are provided in Fig. 4.

Patient No. 2 had a significant collapse of the talus bone with incorrectly consolidated subtalar arthrodesis and a varus deformity of the lower limb axis, which are prognostically unfavorable in the treatment when using the distraction arthroplasty of the ankle joint. Before surgical treatment, there were visible grade IV foci of cartilage defects (Outerbridge) (Fig. 5). In 12 months after the distraction arthroplasty of the ankle joint, due to the recurrence of the anterior impingement-syndrome and repeated formation of osteophytes in the anterior segment, repeated arthroscopy was done. The visualized findings included the coverage of the defect areas with the cartilage-like tissue, showing the grade II–III of the Outerbridge classification (Fig. 6). Similar findings were observed in patients No. 3 and No. 4.

Patient No. 3 previously had signs of arthrofibrosis, which were not detected in 6 months from the moment

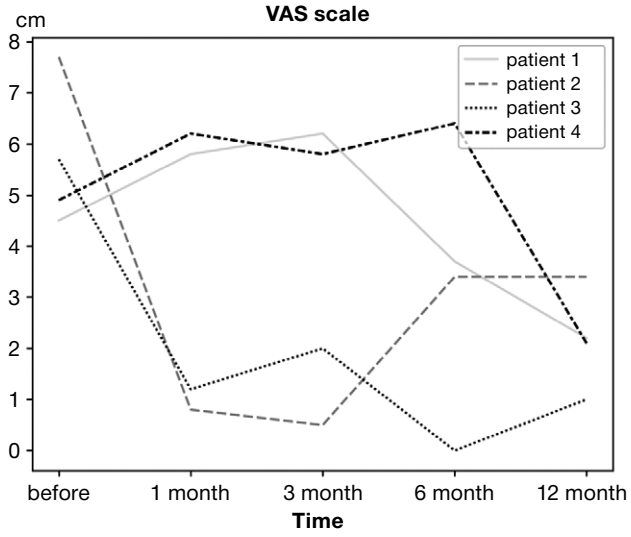

Fig. 2. Visual Analogue Scale outcomes after ankle distraction arthroplasty.

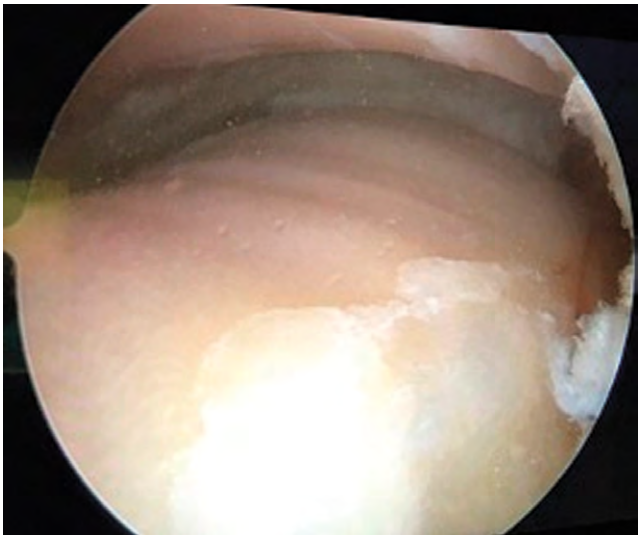

Fig. 3. Total absence of cartilage tissue of the talus of patient No. 1 before ankle distraction arthroplasty.

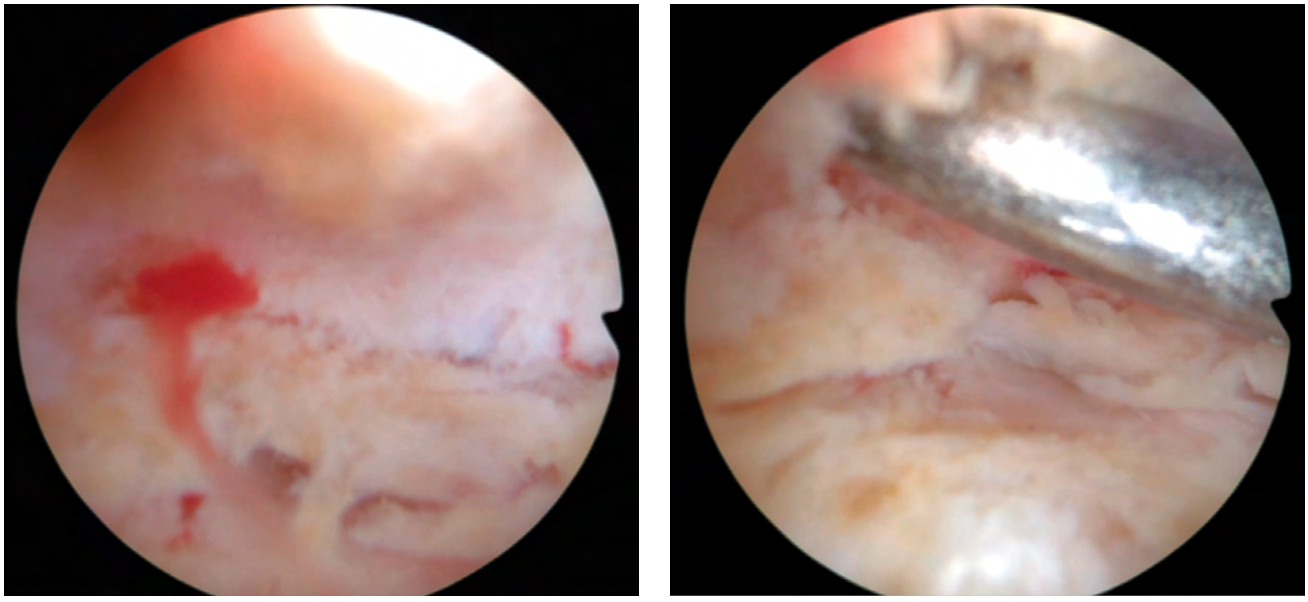

Fig. 4. Arthroscopic image of total arthrofibrosis of patient No. 1 at the time of removing the Ilizarov frame.

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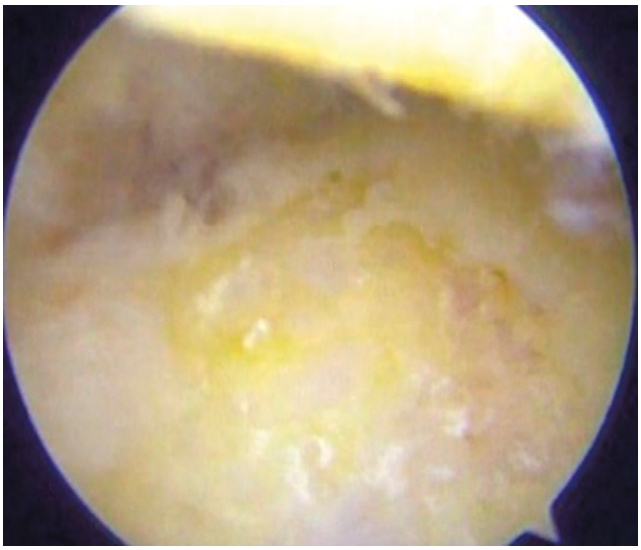

Fig. 5. Patient's No. 2 talus before ankle distraction arthroplasty with areas of grade IV cartilage defects by Outerbridge.

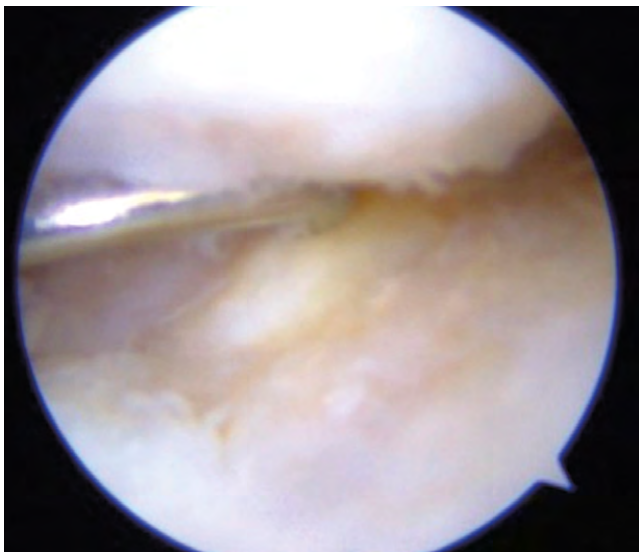

Рис. 6. Patient's No. 2 talus 12 months after ankle distraction arthroplasty with signs of regeneration of cartilage tissue.

of the distraction arthroplasty of the ankle joint. The articular fissure is not filled with the connective tissue, which allows for judging on its complete degradation to the end of 6 months of follow-up.

Undesirable phenomena

The undesirable phenomena included the inflammation in the area of the wires passing through the calcaneal bone, developing in 6 weeks after the installation of the Ilizarov frame (in 2 patients). After the conservative treatment, positive effect was reported.

DISCUSSION

The research works on the distraction arthroplasty of the ankle joint are few, and when searching the literature, we did not find any original research works on the fundamental principles and scientific justification of the efficiency of arthrodiastasis. No research works were published previously on the repeated arthroscopy of the ankle joint after the distraction arthroplasty of the ankle joint with the middle-term follow-up. There is a research of the effects of the distraction arthroplasty of the ankle joint in the cartilage tissue: based on the results of magnetic resonance tomography, during the postoperative period, an enlargement was observed in the cartilage, reaching up to 0.5 mm comparing to data from the examination before surgery [8].

As of today, 8 studies were published on the effects of arthrodiastasis on the structure of the cartilage tissue in the animals, which show an increase of the metabolic activity and restoration of II type collagen in the cartilage matrix, as well as an increase in the number of reparative signaling molecules, corresponding to the ones found in humans [9–16].

The research by F. Inori et al. [14] proves the capabilities of distraction arthrogenesis. The distraction of the fragment of the condyle of the femoral bone after osteotomy was performed during the experiments in rabbits (the fragment includes the cartilage and the subchondral bone). Histological results indicate the possibility of forming the new cartilage and subchondral bone when using the distraction. This serves as an evidence of the possible growth of cartilage tissue *in vivo*.

Research limitations

The research limitation is the absence of histological analysis of the developed regenerate, which could confirm our opinion on the restoration of the cartilage tissue. Taking into consideration the small total area of the cartilage in the talus bone, as well as the initially present terminal degree osteoarthritis, for the purpose of preserving the maximal area of the cartilage, the decision made was to refuse from performing histological evaluation for the well-being of the patient. The understanding of the mechanism of action of the distraction arthroplasty of the ankle joint is a complex issue open for discussion. For the purpose of defining the clinical efficiency and studying the mechanism of action of the distraction arthroplasty of the ankle joint, further research works are required with more prolonged follow-up period.

CONCLUSION

Based on the data obtained during the repeated arthroscopy, during the arthrodiastasis, the articular fissure is being filled with fibrous vascularised tissue, which gradually degrades and which is completely absent in 6 months. There were signs of regeneration in the cartilage defects with further covering with the cartilage-like connective tissue, due to which, probably, an analgesic effect develops after the distraction arthroplasty of the ankle joint.

The research results confirm the efficiency of the distraction arthroplasty of the ankle joint.

ADDITIONAL INFORMATION

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THE METHODS OF PERFECTING THE SURFACE OF TITANIUM ALLOY-BASED ENDOPROSTHESES USED IN PEDIATRIC ONCOLOGY

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ABSTRACT
The rehabilitation of pediatric patients with oncology diseases localized in the maxillofacial area is a complex and long-term process. Most frequently, the resection area involves the maxilla or the mandible, which, in turn, impairs the functioning of the whole dentofacial system. The restoration of the integrity of the facial structures is the key task in the treatment of such patients. One of the main materials used for reconstructing the jaws is the titanium alloy. However, despite its beneficial properties and characteristics, there is a high risk of inflammation, encapsulation or failure of the endoprosthesis. The aim of the research was to analyze the data available up to date on the methods of perfecting the surfaces of titanium endoprostheses based on the published research works. After analyzing the articles devoted to the modification of the surface of titanium constructions used for endoprosthetics, for the period from 2008 until 2022 (n=41), we came to a conclusion that the modification of the surface of titanium endoprostheses results in an increase in its osteointegration, which decreases the risks of failure for the constructions.

Keywords: *titanium alloy; endoprosthesis; pediatric oncology; rehabilitation; jaw resection; plasma-electrolytic oxidation.*

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INTRODUCTION

Every year the number of oncological diseases worldwide grows. According to our data, at the Federal State Budgetary Institution “Dmitry Rogachev National Medical Research Center Of Pediatric Hematology, Oncology and Immunology” of the Ministry of Health of the Russian Federation (Dmitry Rogachev NMRC PHOI), for the time period of 2017–2022, a total of 118 patients aged from 3 to 18 years were admitted with various neoplasms of the maxillofacial area, of which malignant neoplasms were found in 49% and benign neoplasms were detected in 51%, with the tumor process located in the maxilla reported in 66% of the cases and in the mandible — in 34%.

Generally, the surgical treatment in cases of oncology diseases located at the maxillofacial area is accompanied by not only the functional impairment (respiration, chewing, swallowing, speaking), but it also results in significant esthetic problems [1]. The excision of the tumor focus together with growth center can cause the incomplete development of the jaws and severe secondary deformation.

The growth and development of the upper and the lower jaws, as well as the facial skeleton in general, in the opinion of a number of authors, depend on the correct anatomic ratio between them [2]. During the childhood and the adolescent age, when the development of the facial skeleton is not complete, the most important is to restore the integrity of the jaws and to stimulate growth in the remaining bone fragments. Early maxillofacial rehabilitation, when conducted timely, helps decreasing the extent of secondary deformation related to polyvisceral resections [3]. This is why early restoration of the defect after the excision of the tumor focus is an important aspect in reconstructive surgery.

There are multiple materials used for the restoration of the integrity of jaws: natural (auto-, allo- and xenotransplants) and synthetic (hydroxyapatite, tricalcium phosphate, chirulen, metals alloys etc.), mixtures of synthetic materials with the organic ones are also being used. The main objective of searching new artificial materials is to avoid using autobone transplants in pediatric maxillofacial surgery in order to preserve the donor area and to prevent complications. On top of that, the significant downside of autotransplants is the absence of growth potential in the bone tissue flap, while the individually adjusted construction made of artificial materials, for example

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МЕТОДЫ УСОВЕРШЕНСТВОВАНИЯ ПОВЕРХНОСТИ ЭНДОПРОТЕЗОВ НА ОСНОВЕ ТИТАНОВЫХ СПЛАВОВ, ПРИМЕНЯЕМЫХ В ДЕТСКОЙ ОНКОПЕДИАТРИИ

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АННОТАЦИЯ

Реабилитация пациентов детского возраста с онкопатологией, локализованной в челюстно-лицевой области, — сложный и длительный процесс. Чаще всего резекция затрагивает верхнюю или нижнюю челюсть, что в свою очередь нарушает функционирование всей зубочелюстной системы. Восстановление целостности лицевых структур является ключевой задачей при лечении таких пациентов. Одним из основных материалов для реконструкции челюсти является сплав титана. Однако, несмотря на его положительные свойства и характеристики, велик риск воспаления, инкапсуляции и отторжения эндопротеза. Целью исследования был анализ существующих на сегодняшний день данных по методикам усовершенствования поверхности титановых эндопротезов на основании опубликованных работ. Проанализировав статьи по модификации поверхности конструкций из титана, применяемых для эндопротезирования, за период с 2008 по 2022 год (n=41), мы пришли к выводу, что модификация поверхности титановых эндопротезов ведёт к повышению их остеоинтеграции, что снижает риски отторжения конструкций.

Ключевые слова: *сплав титана; эндопротез; детская онкология; реабилитация; резекция челюсти; плазменно-электролитическое оксидирование.*

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"growing" endoprostheses, would not prevent the growth of the facial skeleton in a child or undergo eventual atrophy [4, 5].

Within the facilities of the Dmitry Rogachev NMRC PHOI, the individually adjusted titanium constructions are being used for replenishing the jaw defects. With this, in case of failure in the vascularised bone flap, repeated restoration of the defect is carried out using the titanium prosthesis.

We have performed an analysis of 41 articles describing the modifications of the surface of titanium constructions used for endo-prosthetics, for the period from 2008 to 2022.

TI-6AL-4V ALLOW

The main alloy that is used for endoprostheses is Ti-6Al-4V. Its benefit is that it can be used in 3D-printers for creating any shape of endoprostheses.

The orthopedic implants must be biocompatible, must have proper mechanical properties, corrosion and wear resistance, also providing the osteointegration capabilities for their safe and effective usage [6].

Titanium is an extremely reactive material. Due to oxidation when interacting with water or air, it maintains its main characteristics and resistance to the effects of the environment. The oxidation film determines the biocompatibility of titanium. Due to the presence of negatively charged oxygen, there occurs the fixation of the bone morphogenetic proteins (BMP), of blood proteins and free calcium, promoting to the formation of the bone tissue matrix. Ti-6Al-4V alloy has high mechanical resistance with its torsional-axial characteristics being similar to the ones of the normal bone [7]. However, despite all the beneficial properties and characteristics of this metal, titanium endoprosthesis is a foreign body in the organism of the patient, which, in turn, can result in acute or chronic inflammation, fibrous encapsulation and developing granulation tissue. In order to solve this problem, the biomimetic approach is being used: changes are made in the structure and in the content of the implant surface, making it more compatible with the human tissue. This allows for achieving the biochemical and biomechanical compatibility and stimulates the osteointegration of the endoprosthesis into the bone tissue [8].

PLASMA ELECTROLYTIC OXIDATION

The promising methods of creating inorganic layers on the surface of implant include the techniques of electrochemical anodising, from which, a method of plasma electrolytic oxidation (PEO) can be highlighted, that forms (on the surface of titanium and its alloys) a conversion oxidation layer, showing high degree of adhesion [9]. The PEO mechanism includes the effect of microdischarges, multiple times penetrating and melting the oxidation layer, which results in the formation of a well-developed porous surface [10]. Such an approach allows for getting the surfaces with a unique morphology, which provides smooth modification of the modulus of elasticity from the metallic implant to the bone, increasing the mechanical compatibility. When treating the metal surface in a medium containing calcium and phosphorus, it becomes possible to obtain a surface, containing bioactive inorganic crystalline phases — hydroxyapatite, tricalcium phosphate, tetracalcium phosphate and perovskite [11]. The highly fractal structure of the PEO coating allows for applying various functional organic components, acting as a sub-layer, increasing the adhesion, and as a carrier for organic substances. For the purpose of forming a porous superficial layer with calcium phosphate compound on the surface, as an electrolyte component, calcium-containing salts are being used with a Ca/P ratio similar to the one found within the human bone tissue [12, 13].

BIOLOGICALLY ACTIVE COATINGS BASED ON RGD

Together with the PEO, for the purpose of improving the implant osteointegration, biologically active substances can be used that are based on the RGD tripeptide (arginine-glycine-aspartic acid), which is the ligand of integrins — one the major proteins of the intercellular matrix. The introduction of phosphonate groups increases the adhesion of the molecules to the surface, but the smooth metallic surface can not provide long-term retention of the biomolecules [14].

The Ti alloy, the PEO coating and the RGD pore filler can provide the necessary mechanical, physical and chemical properties of the implant [15]. In the research conducted by E.V. Parfenova et al. [15], it was shown that the combination of PEO coating and RGD-modified bisphosphonic acid applied to the nano-Ti, results in an increase in the number of proliferating cells by 45% comparing to the non-coated nano-Ti and by 66% comparing to coarse-grain Ti. It should be mentioned that this research included the use of cell lines of human pulmonary fibroblasts, the mesenchymal stem cells of human adipose tissue and the human osteosarcoma cells, which are very resistant to toxic effects, which can not precisely reflect the interaction of the normal bone tissue cells with the said materials.

The *in vitro* researches have demonstrated that the bioactivity of the molecules depends on the structure of the anchor and the linker. For example, RGD derivatives with short bisphosphonate anchors and a linker consisting of bone morphogenetic proteins (BMPS), as well as the molecules with the linker containing a cyclohexyl fragment, increase the cell proliferation at the PEO-modified titanium [10]. Upon the analysis of literature data, no pathological effects were found that are related to the interaction with the RGD.

ANTIBACTERIAL COATINGS

The use of endoprostheses oftentimes results in complications, resulting in their instability. The most common reason of implant failure and loss of surrounding tissues is the infection, caused by forming biofilms on its surface, upon the development of which, almost in half of the cases (51%), extraction of the endoprosthesis may be required [16].

The ingress of infection depends on multiple factors: the microorganism species, the status of the immune response in a patient, the procedure and the technique employed during the surgical intervention, the construction of the implant and the antibacterial prophylaxis used.

It was proven that, even in case of scheduled surgery, the sterility of the operating room decreases within the first several hours of surgery [17, 18], while in the majority of cases the quite low bacterial burden, ultimately present during the surgery, can be generally overcome by the immunological protection system and by systemic antibiotic prophylaxis [19]. However, some patients after the surgical intervention may develop an infection, especially those with concomitant diseases, elevating the risk of infection by a factor of 20 comparing to the population of relatively healthy patients [20]. In the same way, it was shown that the most complex surgical procedures and methods are more dangerous in terms of septic complications [21].

The characteristics of the implant, for example, its dimensions, shape, material and intended application, also play an important role [22]. In order to decrease the rate of developing infections related to the implantation, local antibacterial prophylaxis can be used, for example, the bone cement saturated with antibiotics [23].

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With this background in mind, the methods were proposed of creating a surface of the biomaterials, capable of preventing the bacterial infection by means of using the surface biofunctionalization based on constructing the chimeric peptides with antibiotics.

The efficiency of TiBP1-GGG-AMP and TiBP2-GGG-AMP bifunctional peptides was evaluated both in the solution and on the solid surface of the titanium base in terms of counteracting *Streptococcus mutans*, *Staphylococcus epidermidis* and *Escherichia coli*. It was found that the surfaces modified using chimeric peptides, significantly decrease the bacterial adhesion to all three bacteria comparing to clear titanium. The research results show that surface modification by means of constructed biomolecules consisting of antimicrobial and titanium-bindings peptide domains represents a promising approach for preventing the bacterial infection development on the surfaces of the implants [24].

Another attractive approach for the prevention and treatment of implantation-related infections is coating the endoprostheses with vancomycin. The antibiotic coating was releasing 82.7% of the total vancomycin contained within the coating, as shown by *in vitro* research. A biphasic type of antibiotic release was demonstrated with an initial burst in day 1, followed by slow and controlled release lasting 28 days. No cytotoxicity of the vancomycin-containing coating was observed during the *in vitro* research. Titanium implants, coated with vancomycin, were active in the treatment of implantation-associated infections, as shown by *in vivo* research [25]. However, microbial resistance should be taken into consideration, as well as allergic reactions in susceptive individuals. In such cases, in a context of individually adjusted medicine, the optimal variant can include coating the titanium endoprosthesis with a matrix, into which, an antimicrobial agent should be introduced directly before surgery. In order to solve this problem, in recent years, the research works were carried out on modifying the surfaces of implanted materials, in particular, coating it with carbon nanotubes [26]. However, data exist indicating the risk of toxicity related to its size, surface charge, chemical composition, reactivity, chemical and crystalline structure, shape, solubility and agglomeration degree. Moreover, nanomaterials may cause oxidative stress and may impair the phagocytosis inside the cells, decreasing the viability of cells and suppressing their growth [27].

The alternative to using antibiotics may include the use of zinc (Zn). It is well known that zinc is an important microelement for humans, capable of performing various functions in the bone tissue, such as the participation in the DNA synthesis, the activity of enzymes, the metabolism of nucleic acids, the biomineralization and the hormonal activity, with all these being said, zinc exhibits excellent antibacterial properties [28]. The inclusion of zinc into bioglass and bioceramics within the Ca-P and Ca-Si systems for improving their mechanical properties and the interactions of cells with the materials is deemed quite promising [29–32]. A research by H. Zhang et al. [33] has shown that the TiO_2 coating, containing zinc and obtained by means of using the PEO method, exhibits antibacterial effects on *Staphylococcus aureus and Escherichia coli*. Zinc was evenly distributed along the surface, not affecting the microstructure, the roughness, the phase composition or the chemical state of the TiO_2 coating. High efficiency was demonstrated for TiO_2 coatings containing zinc in terms of inhibiting the bacteria, due to slow release of zinc ions. In turn, a research by M. Shimabukuro [34] has shown that the antibacterial effect of zinc on the surface of the implant manifests itself after 28 days of incubation in the physiological saline solution. These specific results can help controlling the antibacterial effects at the surface of the implant in the long-term perspective.

The porous and nanostructurized TiO_2 coatings with an addition of zinc show excellent antibacterial activity and the capability to stimulate osteogenic differentiation, which gives ground for considering them the promising materials for reconstructive maxillofacial surgeries. At the same time, the effects of zinc on the tumor cells is insufficiently studied, also, the incorrectly adjusted zinc dosage can be cytotoxic [35]. This method requires further research activities, especially when used in patients with oncology diseases.

BONE MORPHOGENIC PROTEINS

Another promising approach for increasing the osteoinductivity of bone implants and for increasing the connective tissue regeneration is creating biocomposite materials containing growth factors. Bone morphogenetic proteins (BMP) are considered the most important factors for bone and cartilage regeneration. They affect the cell membrane, regulating the growth, differentiation and apoptosis of various cell types, including osteoblasts, chondroblasts, neural and epithelial cells. BMP can be found in the extracellular connective tissue matrix, containing osteoprogenitor and mesenchymal cells. For the fixation of proteins on the surface of the implant, synthetic, biological,

mineral or biocomposite polymers are being used as a "carrier". The main role of the BMP "carrier" after the implantation is keeping these osteoinductors at the area of their biological effects within a long-term and clinically justified period of time. Long-term release of small quantities or initial burst of significant quantities of BMP extremely negatively affects the regeneration processes [36].

In a research by Z. Liu et al. [37], microspheres were developed that contain the endothelium growth factors and the bone morphogenetic protein 2, with further applying them to the porous titanium alloy manufactured by 3D-printing. The microspheres were encapsulated into the gelatin coating and used for creating a composite frame, which has shown good results when tested in rabbits. The system provides sequential release of growth factors, promoting to the osteogenic differentiation and osteointegration.

Despite the positive results of scientific-clinical research works on studying the bone morphogenetic proteins, a number of questions within this issue remains unsolved. The main of them are the selection of an effective technology for obtaining the BMP; the selection of an adequate biodegradable carrier for the BMP; finding the variants of BMP chemical fixation on the biodegradable carrier; determining the clinically effective dosage of BMP depending on the etiology, the location and the severity of the pathological process; finding the ways of decreasing the commercial cost of BMP. The experimental and clinical researches of BMP are currently being carried out practically in all the countries of the world. The participation of large number of leading foreign scientific-research centers, as well as the addition of significant material and financial resources gives hope of further effective solving these problems and of successful application of the said osteoinductor in practical medicine [38]. However, it is worth noting the impossibility of using BMP in cases of cancer diseases: data exist showing that BMP is highly expressed in various cases of cancer and promotes the proliferation, migration, metastatic spreading and invasiveness of various types of cancer cells [39, 40].

CONCLUSION

After analyzing the domestic and foreign literature data, a conclusion can be drawn up that one of the promising directions is the development of bone-tissue engineering, which allows for studying the use of bioactive materials with antiinflammatory and regenerative properties. However, this is a long process, requiring larger numbers of cost-intensive scientific research with developing complex technological protocols. It will take plenty of time until such materials become accessible in Pediatric oncology. With all of these, the factors of utmost importance shall include the availability of such technologies and the possibility of their implementation in the medical institutions.

In the modern era, using reconstructive materials made of titanium alloys, including their use in children with oncology diseases, have already shown good results. The modification of the surface of titanium reconstructive materials for the purpose of increasing the osteoinductive, osteoconductive and antimicrobial properties shall allow for decreasing the number of repeated surgeries, for decreasing the risks of developing infections and implant failures, as well as for preventing the development of secondary deformations and, hence, for improving the quality of life of the pediatric patient.

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SURVIVAL RATE OF CORNEAL ENDOTHELIAL CELLS AFTER CATARACT SURGERY WITH A BACKGROUND OF GLAUCOMA

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ABSTRACT

Glaucoma is one of the main causes of irreversible blindness worldwide. Up to 76% of the glaucoma cases are accompanied with complicated cataract. The issue of cataract treatment in glaucoma patients is a difficult task for any surgeon, for the surgical procedure itself can result in a number of complications. One of them is the loss of endothelial cells in the cornea. A decrease in the endothelial cell density in such patients occurs due to long-term use of various hypotensive drops, due to variations of intraocular pressure, as well as due to the surgical interventions themselves. Up to 16.9% of cataract removal cases with a background of glaucoma are accompanied by pronounced post-operative corneal swelling, which leads to an increased risk of losing corneal endothelial cells. The perspective branch of surgical treatment for cataract and glaucoma is the development of a unified algorithm taking into account the individual characteristics of the patient, such as the eye lens clouding, the glaucoma stage, the intraocular pressure, the past surgeries, the hypotensive therapy and the density of corneal endothelial cells.

Keywords: *open-angle glaucoma; cataract; surgical treatment of cataracts; endothelial cells.*

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BACKGROUND

Glaucoma in Russia, as well as worldwide, is one of the main reasons of incurable blindness and vision-related disability [1]. According to data from the Ministry of Health of the Russian Federation, the number of glaucoma patients in Russia is more than 1.3 mln people. During the 6 years period (2013–2019), the number of glaucoma cases in the country has increased by 10.7% (from 823.8 to 911.7 per 100 thous. of population) [2]. Y.C. Tham et al. [3] are predicting that, by the year of 2040, the number of glaucoma patients worldwide shall reach up to 111.8 mln people.

Glaucoma is a chronic eye disorder, which can be considered as a multifactorial neurodegenerative disease. Glaucoma is characterized by progressive optic neuropathy, pathological changes affecting the fields of view, by death of ganglionic cells in the retina, as well as by the loss of corneal endothelial cells [4]. Absence of complaints in patients, primary diagnostic problems, gradual and progressive visual deterioration, resulting in a decrease in working capacity and disability along with significant expenses both for individual patients and for the whole society — all of these allows for considering glaucoma as being also a social-economical disease [5].

The percentage of primary open-angle glaucoma is up to 72.3–96.1% of all the glaucoma forms [5]. The incidence of glaucoma combined with cataract varies over a wide range — from 14.6 to 76% [6–10], however, in case of pseudoexfoliative syndrome, the number of such cases increases up to 85% [7, 9, 11–14]. In glaucoma patients, a significantly elevated risk of developing complicated cataract is shown, for both conditions are involution-dependent diseases [11, 15, 16]. In persons aged over 55 years old with the diagnosis of glaucoma and cataract, the probability of developing such a combination is 3 times higher than in persons from the same age group with no ocular diseases [17–20].

GLAUCOMA AS A MULTIFACTORIAL NEURODEGENERATIVE DISEASE

In the development of primary open-angle glaucoma, two mechanisms are involved: the first one affects the anterior segment of the eye, in particular, the structure of the anterior angle, increasing the intraocular pressure,

ВЫЖИВАЕМОСТЬ ЭНДОТЕЛИАЛЬНЫХ КЛЕТОК РОГОВИЦЫ ПОСЛЕ ХИРУРГИИ КАТАРАКТЫ НА ФОНЕ ГЛАУКОМЫ

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АННОТАЦИЯ

Глаукома во всём мире является одной из основных причин необратимой слепоты. До 76% случаев глаукома встречается в сочетании с осложнённой катарактой. Проблема лечения катаракты у пациентов с глаукомой является сложной задачей для любого хирурга, поскольку операция может привести к ряду осложнений. Одним из них является потеря эндотелиальных клеток роговицы. Снижение плотности эндотелиальных клеток у таких пациентов происходит из-за длительного использования гипотензивных капель различных групп, колебания внутриглазного давления, а также в результате хирургических вмешательств. До 16,9% случаев удаления катаракты на фоне глаукомы сопровождается более выраженным послеоперационным отёком роговицы, что приводит к увеличению риска потери эндотелиальных клеток роговицы. Перспективным направлением хирургического лечения катаракты и глаукомы является разработка единого алгоритма, учитывающего индивидуальные характеристики пациента, такие как помутнение хрусталика, стадия глаукомы, внутриглазное давление, хирургический анамнез, гипотензивная терапия, плотность эндотелиальных клеток роговицы.

Ключевые слова: *открытоугольная глаукома; катаракта; хирургическое лечение катаракты; эндотелиальные клетки.*

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while the other occurs in the posterior segment of the eye, resulting in the development of glaucoma-related optic neuropathy [5].

Ophthalmologists suppose that the progression of cataract in glaucoma is being affected by various factors, which may include the close location of the eye lens, the ligaments, the ciliary body and the eye's draining system, which form the posterior and the anterior ocular chambers. Besides, a certain role belongs to impaired hydrodynamics, blood microcirculation and dystrophic/immunological changes in the ocular tissues [21, 22]. Variations of intraocular pressure, changes in the content of the aqueous humour in the chamber and the associated metabolic changes within the eye structures additionally promote cataract progression, negatively affecting the course of glaucoma and, ultimately, resulting in permanent loss of visual functions [11].

Currently, the attention of the majority of ophthalmologists is attracted by the loss of corneal endothelial cells associated with glaucoma. The dystrophy of the endothelial layer in the cornea can be also caused by long-term use of glaucoma eye drops, by variations of intraocular pressure and by surgical interventions [23]. As for practical application, the majority of physicians are concerned about the levels of intraocular pressure, for it is the most controllable parameter, which can be effectively modified using medicinal and surgical correction. T. Olsen [24] in 1980 has first reported a mean cell density decrease by 23.1% in case of acute glaucoma comparing to the unaffected eye.

Investigators Y.C. Ko et al. [25] in 2007 have found that the loss of corneal endothelial cells after phacoemulsification surgery is associated with shorter anterior-posterior axis and with the elevation of intraocular pressure within the first 24 hours after surgery, which results in the loss of corneal endothelial cells in 14.5% of the cases. In order to

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minimize the damage in corneal endothelial cells, it is of utmost importance to avoid sudden increases of intraocular pressure at the early post-surgery period and to exercise special caution when operating the eyes with the anterior-posterior axis being shorter than 22.6 mm.

Already in the year of 1997, M. Gagnon et al. [26] suggested a hypothesis that the mechanism of damaging the corneal endothelium, just like the damage of the optic nerve, depends on pressure. Glaucoma patients had significantly lower numbers of corneal endothelial cells (2.154±419 cells/mm^2) comparing to the control group with no glaucoma (2.560±360 cells/mm^2). The authors have demonstrated that the density of corneal endothelial cells is inversely proportional to the mean intraocular pressure. In patients receiving 3–4 glaucoma medications, the number of cells was lower comparing to those undergoing the treatment that employed only 1-2 medications. The number of cells was significantly lower both for primary closed-angle and for primary open-angle glaucoma.

In 2011, the research work by S. Ranno et al. [27] has evaluated the effects of glaucoma eye drops (β-blockers or prostaglandin analogues) on the corneal endothelium. Initially, in glaucoma patients, the density of corneal endothelial cells was 3187±312 cells/mm^2, however, after two years of using hypotensive drops, the cell density has decreased to 2925±313 cells/mm^2, including a decrease in the number of nerve fibers in the cornea along with a decrease in the reflectivity of the sub-basal plexus.

S.A. Kandarakis et al. in their descriptive review came to the conclusion that it is preferable to avoid the intake of β-adrenergic blockers Betaxolol and Carteolol at high dosages [28, 29], while patients with Fuchs endothelial dystrophy shall prefer rho-kinase inhibitors [30]. Rho-kinase stimulates the progression of cellular cycle, increasing cell migration, increasing the barrier and pumping functions, also preventing mesenchymal transformation of corneal endothelial cells in patients with Fuchs endothelial dystrophy [31, 32].

Some investigators suggested that the changes in the endothelial cell density were not related to high intraocular pressure [33, 34]. So, Japanese researchers [35] have found that, in patients with primary open-angle glaucoma, a significant decrease was found in the density of corneal endothelial cells, which was not reported in cases of glaucoma with normal pressure. The authors have explained this as being caused by a decrease in the effects of elevated intraocular pressure. Belorussian investigators P.N. Marchenko and Yu.I. Rozhko [36] have reported a decrease in the density of corneal endothelial cells comparing to the control group of the same age at all the stages of glaucoma, with the statistically significant differences being found at stages II–IV. In 2012 L.A. Deyev et al. [37] have found a direct correlation between the changes in corneal structure and the disease stage. Besides, in 2022 D. Kang et al. [38] have published the results of a research work on the inter-relation between the corneal endothelium parameters and the severity of primary glaucoma. The number of corneal endothelial cells has decreased along with the increase of severity, for in patients with early glaucoma, the density of endothelial cells was 2284 cells/mm^2, in case of moderate severity disease — 2261 cells/mm^2, while the severe disease cases were showing the values of 2086 cells/mm^2 and the difference was statistically significant.

A growing number of surgeons prefer combined interventions performed in one step [39–45]. This approach is attractive, for it allows for simultaneously normalizing the intraocular pressure and improving the vision acuity. At the same time, there are analysis data on the density of corneal endothelial cells in patients with cataract combined with glaucoma. According to the opinion from a number of authors, comparing to single-step combined treatment including the glaucoma surgery and cataract phacoemulsification, two-stage surgery significantly decreases the number of endothelial cells [46–49].

There are research works showing the results of combined surgery for glaucoma using drainages and cataract phacoemulsification [50–53], with the loss of endothelial cell density being more than 30% within 5 years was reported in 27.2% of the patients. In patients undergoing cataract removal and implantation of the CyPass Micro-Stent (Alcon, USA), an epithelial-endothelial dystrophy was found, that was caused by the damage of corneal endothelium. This condition has occurred as a result of the effects caused by the intraocular end of the draining tube, which resulted in cessation of its production [54]. In the research work by E.H. Fang et al. [55], limited reliable evidences were obtained showing that glaucoma surgery associated with the use of long-term implants results in a greater loss of endothelial cell density comparing to cases without using prosthetic appliances.

In patients with glaucoma combined with cataract, the decrease in endothelial cell density results in an increased inflammatory reaction after cataract phacoemulsification [56, 57], which imposes a risk

of corneal swelling and descemetitis of various severity degree. According to data from a number of research works, 16.9% of the patients after cataract extraction had corneal swelling [58, 59]. It is important to note that postoperative swelling is significantly less frequently found in patients with uncomplicated senile cataract (2.7% of the cases). At the same time, mature eye lens clouding was found in 19.3% of all the study patients [13].

T. Dada et al. [60] have arranged a research work on phacoemulsification in patients, focusing on factors which may impair surgical intervention. These factors include a narrow pupil caused by various conditions, such as posterior synechias, atrophy of iris, pseudoexfoliative syndrome, the use of miotics and past history of acute glaucoma onsets. In such cases, additional measure are necessary, in particular, iris retractors or pupil expansion [61]. The cataract removal surgery in glaucoma patients along with such precipitating factors represents a higher risk of damaging the endothelial cells. The research works show that from 17.8 to 51.6% of such surgeries end with intra- or post-operative complications [62].

The acute onset of closed-angle glaucoma plays one of the key roles in changing the number of corneal endothelial cells. M. Chen et al. [63] have found that the density of corneal endothelial cells was inversely related to the duration of an acute onset, but it was not related to demographic and biometric characteristics. The loss of endothelial cell density up to 2271 cells/mm^2 was reported in patients with a past medical history of acute glaucoma onset comparing to paired eyes, where the cell density was 2458 cells/mm^2. In patients with diagnosed closed-angle glaucoma with no history of onsets, the density of endothelial cells was 2559±45 cells/mm^2. The central thickness of cornea and the curvature radius of cornea were not related to earlier acute onset of closed-angle glaucoma. The postoperative corneal swelling was found in 22.85% of the closed-angle glaucoma cases [63].

In 2021, the data were published on the factors affecting the corneal endothelium after selective laser-assisted trabeculoplasty in cases of primary open-angle and closed-angle glaucoma. Based on the research results, the main factors of losing the endothelial cell density after selective laser trabeculoplasty are the age, the initial number of endothelial cells and the shallow anterior chamber for closed-angle glaucoma. It is worth noting that corneal endothelium in cases of primary open-angle glaucoma was recovering within one month, while in closed-angle glaucoma its damage was persisting for the whole follow-up period. The importance of the research is that it confirms that the obtained data should be taken into account when selecting the algorithm of glaucoma treatment, especially in case of alternative therapy (eye lens/cataract extraction) for closed-angle glaucoma [64].

The main risk factor for losing the endothelial cell density is more long-term phacoemulsification time. High phacoemulsification energy and high vacuum positively correlate with nuclear density, which defines for the surgeon the correct selection of the viscoelastic gel (solution) and the surgery technique. In 2023, I.A. Loskutov et al. [65] have developed a scale for optimal combining the content of the viscoelastic gel depending on the number of corneal endothelial cells in patients with various stages of cataract. The scale is based on matching various types of viscoelastic gels, which have their own characteristics, specific features, benefits and drawbacks that can significantly affect the surgery results and facilitate the work of the surgeon. With correctly selected viscoelastic gel, the decrease in the number of corneal endothelial cells during the postoperative period is less than 3% regardless of the stage of cataract.

CONCLUSION

The progression of primary open-angle glaucoma negatively affects the structure of cornea and aggravates the age-related conditions, especially in persons aged 55 and older. These factors shall be taken into account when monitoring the patient status and selecting the treatment strategy.

The combination of glaucoma and cataract represents a wide-spread and topical issue in ophthalmology. The development of a unified algorithm of managing the patients with cataract and glaucoma is a promising direction of surgical treatment. Such an approach requires an individual treatment plan taking into account various factors, including the degree of eye lens clouding, the glaucoma stage, the levels of intraocular pressure, the past surgeries, the glaucoma therapy and the density of corneal endothelial cells.

The absence of effective protection method for corneal endothelial cells is a serious problem in developed countries, which results in a significant decrease in the quality of life for the patients. Developing an algorithm of managing the patients with cataract and with a background of glaucoma is the most important task for modern ophthalmology, solving which can improve not only the quality of life for the patients, but also the whole economical aspect worldwide.

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LIQUID BIOPSY OF GLIOMAS WITH DETECTION OF EXTRACELLULAR TUMOR NUCLEIC ACIDS

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ABSTRACT

Gliomas are the reason of fatal outcomes in an overwhelming number of patients with oncology diseases located in the central nervous system. The diagnostics of such neoplasms requires using stereotaxic biopsy, which cannot be performed in a certain percentage of the patients. Besides, this disease is characterized by high recurrence rates, despite the advances in developing resection and chemotherapy — based technologies. The early detection of oncological diseases located in the central nervous system and the differential diagnostics of tumor pseudo progression, not affecting the survival of the patient, represents a challenge for modern Medicine. Liquid biopsy is a minimally invasive diagnostic method based on the analysis of tumor derivatives (such as extracellular tumor DNA and RNA), contained within the biological fluids of the organism. For the purpose of defining the presence of the tumor component, the tests are used to detect the so-called hot-spot mutations and the patterns of epigenetic regulation, found in specific types of tumors. The technology can be used for detecting tumor recurrences and for the differential diagnostics of space-occupying mass lesions in patients, in which stereotaxic biopsy is contraindicated. The review contains a discussion on modern advances of fluid biopsy based on the analysis of the extracellular tumor DNA and RNA levels in blood plasma and in the cerebrospinal fluid of glioma patients.

Keywords: *circulating tumor DNA; microRNA; liquid biopsy; glioma; central nervous system; central nervous system malignancies; screening.*

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BACKGROUND

Despite the fact that gliomas represent only 18–19% of all the brain neoplasms, they are the cause of fatal outcomes in an overwhelming number of patients with oncology diseases affecting the central nervous system. Its most widespread type is glioblastoma, in which the 5-year survival rate does not exceed 7% [1]. Low-grade gliomas are characterized by the relative 5-year survival of more than 80%, however, the majority of them ultimately show a tendency to further malignization [2]. At the present moment, the first stage of treating the brain tumors, the recommendations include performing the maximal possible resection of the neoplasm. Sadly, but the infiltrating growth type of gliomas prevents its total resection. Moreover, due to the severity of the patient status and due to the risk of possible complications, the total resection of such tumors can be switched to partial resection or the resection itself can be cancelled, which decreases the efficiency of the conducted treatment even more [3].

In order to increase the survival rate of the patients, adjuvant therapy is being used, however, despite its use, within a year and a half after setting the diagnosis, in about 70% of the glioblastoma patients and in 20% of low-grade glioma patients, the development of recurrences is observed, requiring repeated surgical intervention [3–5]. For the purpose of their timely detection, every 3–6 months the patients undergo examinations using the method of magnetic resonance imaging (MRI) [3]. The changes in the brain tissues, such as radiation-induced necrosis, swelling or decreased contrasting, caused by the therapy, in 36% of the glioblastoma cases lead to the findings similar to the manifestations of tumor recurrence — pseudoprogression [6]. Despite the fact that the median of progression-free survival for low-grade gliomas is approximately 5 years, in 20% of the cases they are also characterized by the presence of pseudoprogression [7]. This event, apparently, does not affect the overall survival of the patients and requires using separate therapy. The use of specific anti-relapse therapy at this stage, on the contrary, can worsen the patient status [3, 6, 7]. When using classical MRI modes (T1-weighed MRI with contrast enhancement and T2-FLAIR), it is not always possible to determine the presence of true progression of the tumor, which results in untimely

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ЖИДКОСТНАЯ БИОПСИЯ ГЛИОМ С ВЫЯВЛЕНИЕМ ВНЕКЛЕТОЧНЫХ ОПУХОЛЕВЫХ НУКЛЕИНОВЫХ КИСЛОТ

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АННОТАЦИЯ

Глиомы являются причиной гибели подавляющего числа больных с онкологическими заболеваниями центральной нервной системы. Диагностика таких новообразований требует использования стереотаксической биопсии, которая может быть проведена далеко не у всех пациентов. Кроме того, данное заболевание характеризуется высокой частотой рецидивов, несмотря на успехи в развитии резекционных и химиотерапевтических технологий. Раннее выявление онкологического заболевания центральной нервной системы и дифференциальная диагностика с псевдопрогрессией опухоли, не влияющей на выживаемость пациента, представляет актуальную задачу для современной медицины. Жидкостная биопсия является малоинвазивным методом диагностики, основанным на анализе опухолевых дериватов (таких как внеклеточная опухолевая ДНК и РНК), находящихся в биологических жидкостях организма. Для определения опухолевого компонента используют анализ так называемых hot-spot мутаций и паттернов эпигенетической регуляции, присущих определённому типу опухоли. Технология может быть использована для выявления рецидивов опухоли и дифференциальной диагностики объёмных образований у пациентов, которым противопоказана стереотаксическая биопсия. В обзоре обсуждаются современные достижения жидкостной биопсии на основе анализа внеклеточной опухолевой ДНК и РНК в плазме крови и спинномозговой жидкости пациентов с глиомами.

Ключевые слова: *циркулирующая опухолевая ДНК; микроРНК; жидкостная биопсия; глиомы; центральная нервная система; злокачественные новообразования ЦНС; скрининг.*

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use of therapy and a decrease in the survival rate. In both cases, clinicians receive corrupted data on the prognosis and on the efficiency of conducted therapy.

At the present moment, there is a development going on in the field of perfusion and radio-isotopic methods of diagnostics, allowing for more precise defining the tumor status, however, their wide spreading is still pending [6].

Due to the fact that the histopathological examination of surgical material still remains the main method for the differential diagnostics of space-occupying neoplasms in the brain, the absence of surgical intervention encumbers not only the process of fighting the disease, but also setting the correct diagnosis [3]. In such cases, the decisive diagnostic procedure is the stereotaxic biopsy of the neoplasm [6]. Despite this method demonstrating high sensitivity and specificity, it is characterized by relatively high rate of complications (up to 17%), as well as by high requirements in terms of the qualification of the medical staff and of the visualization equipment quality [8]. For this same reason, the stereotaxic biopsy, probably, can not be used for routine regular detection of recurrences. Moreover, such factors as the involvement of the brain stem, the presence of serious concomitant diseases in the patient or progressive worsening in the neurological status, may ultimately become the reason for avoiding such a manipulation [9]. Due to the fact that MRI signs of some non-oncological diseases may match to those of gliomas (and vice versa), the absence of precise diagnosis shall impose a risk of using incorrect therapy and shortening the life expectancy of the patient [10, 11].

For the purpose of increasing the survival rate and the quality of life in the patients, it is necessary to develop new methods for diagnosing gliomas. Currently, the potential of fluid biopsy is being actively studied — the method for analyzing the cellular and molecular tumor derivatives within various biological fluids of the organism. Special attention in this field is paid to the analysis of extracellular tumor DNA and RNA, the levels of which are informative regarding the volume and the mutation burden of the investigated tumor [12, 13].

The aim of this review is to summarize the data from the research works evaluating the diagnostic and prognostic potential of fluid biopsy of glioblastoma based on the analysis of the extracellular tumor DNA and RNA.

GENETIC CHARACTERISTICS OF GLIOMAS (DNA AND RNA OF THE TUMOR TISSUE)

Initially, the analysis of molecular markers as an important component of diagnosing gliomas was recommended in the classification of the central nervous system tumors, issued by the World Health Organization (WHO) in 2016. According to this classification, the key mutations of gliomas, associated with better survival of the patients, are the mutations in genes *IDH1*, *IDH2*, *TP53*, the deletion of *ATRX* gene and the co-deletion of 1p/19q. In the later classification issued in 2021, as well as in the Clinical recommendations from the European Association of Neuro-Oncology and from the Korean Association of Oncology, a relation was reported for the mutations in genes *CIC* and *FUBP1* with better survival of patients, while the mutations of *TERT* (*pTERT*) promoter, of the *NOTCH1* and *EGFR* genes, the deletion of *CDKN2A/B*, as well as the alteration of the number of chromosomes 7/10 — with worse survival. These mutations are most commonly found in cases of gliomas and they have the most influence on the clinical signs. Their presence is considered a justification for referring gliomas to one of three main histotypes, defined by the WHO classification issued in 2021 [3]. At the same time, the mutation of genes *VEGF*, *ARF*, *PTEN*, *NF1*, *RTK/ RIS* and others were not used for typological classification of gliomas, but they also can be found in a significant part of glioma patients, being the negative prognostic markers [14]. The list of commonly found molecular changes having a prognostic value, is provided in table 1.

The characteristics of glioma, besides the genetic changes, are also affected by alterations in the epigenetic regulation of the cells. In glioblastoma cells, generally, hypermethylation is shown for chromosomes 1, 2, 3 and 17 with hypomethylation of chromosomes 11, 16, 19 and 20. Most commonly, the hypermethylated gene promoters include *pLRRC4*, *pANKDD1A*, *pGAD1*,

Table 1

List of mutations that have the greatest impact on the prognosis of patients with adult type diffuse glioma

Molecular alterations	Positive prognosis	Negative prognosis
Nucleotide substitutions	*IDH1*$^{R132H, R132C}$, *IDH2*^{R172*} *CIC*$^{R1124W, R1110W, R1111W}$ etc. *FUBP1*$^{X83\_splice, I443Rfs*47, X314\_splice}$ etc. *ATRX*$^{R1426*, R907*}$ etc.	*pTERT*$^{C228T, C250T}$ *VEGF* *p14*^{ARF}/*p16*^{INK4A} *EGFR*$^{G598V, A289V}$ etc. *TP53*$^{R273C, R175H, R248Q}$ etc. *PTEN*$^{R130*, R233*, R335*, R173H}$ etc. MUC16$^{T11587M, T11535M, T4653K}$ etc. *PIK3R1*$^{G376R, N564D, X583\_splice}$ etc. *NF1*$^{F1247Ifs*18, R2450*, C167Qfs*10}$ etc. *PIK3CA*$^{H1047R, R88Q, G118D}$ etc. *RB1*$^{S318Nfs*13, R552*, X445\_splice}$ etc. *PDGFRA*$^{E229K, N468S, V309F}$ etc. *RTK/RIS* *NOTCH1*$^{F357del, A465T, D338del}$ etc.
Deletion of genome areas	Deletion of *ATRX* Co-deletion of 1p/19q	Loss of chromosome 10 Deletion of *CDKN2A/B* Deletion of *MTAP*
Duplication and amplification of genome areas	-	Duplication and amplification of 7th chromosome Amplification *MDM2/MDM4* Amplification *EGFR* Amplification *MYC*
Methylation etc.	Hypermethylation of *pMGMT*, *CDKN2A*, *RASSF1A* Microsatellite instability	Hypermethylation *pPARP-1*, *pSHP-1*, *pDAPK-1 и pTIMP-3*
Increase in the number of extracellular tumor RNA	*miRNA-1-3p*, *26a-1-3p*, *487b-3p*, *342-3p* etc. cRNA *CM21D*, *circPTK2*, *circSERPINE2* etc. lnRNA *CASC2*, *MEG3*, *PDCD4-AS1*, *GSCAR*, *SPRY4-IT1* etc.	*miRNA-454-3p*, *21*, *17-5p*, *125b*, *221*, *128*, *342-3p* etc. кRNA *circSKA3*, *CircXPO1*, *circENTPD7* etc. lnRNA *HOTAIRM1*, *STEAP3-AS1*, *CASC2c*, *HOXA11-AS*, *ASLNC22381*, *ASLNC20819*, *CRNDE* etc.

Note. p — gene promoter; RNA — ribonucleic acid; miRNA — micro ribonucleic acid; cRNA — circular ribonucleic acid; lnRNA — long non-coding ribonucleic acid.

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pSIX3, *pSST*, *pPHOX2B*, *pPCDHA8*, *pHIST1H3E* and *pPCDHA13*, while the hypomethylated ones include *pF10*, *pPOTEH*, *pCPEB1*, *pLMO3*, *pELFN2* and *pPRDM16* [14]. One of the most studied markers is the hypermethylation of *MGMT* (*pMGMT*) promoter, which occurs in more than half of glioma cases and which is associated with better survival [3]. Additionally, data is available on more than 160 genes, the expression of which in glioma cells is decreased under the effects of hypermethylation in their promoters [15]. At the same time, there is a point of view stating that the features of glioma course are affected not by methylation of individual genes, but by the change in the epigenetic regulation pattern of the whole cell genome in general. For example, there is a well known interrelation between the G-CIMP glioma methylation profile and the presence of *IDH1/IDH2* mutations, associated with better survival among the patients [14].

The epigenetic regulation of gene expression includes not only the changes in the methylation of their promoters, but also the interaction with a broad set of non-coding RNA. Among them, the most studied is the microRNA, consisting of 20–22 nucleotides. In glioma cases, modified expression is found in more than 300 microRNA, the most prominent representatives of which are the *microRNA-21*, *221*, *222*, *26-a*, *10-b* and *182*, the hyperexpression of which is often observed in glioma tissues, as well as *microRNA-181a*, *181b* and *181c*, *34a*, the expression of which in gliomas is reduced [14]. Minor RNA also include the circular RNA, of which the role is the regulation of microRNA and matrix RNA activity, which results in changes in the expression of the key genes, such as *PAQR3*, *MKP1*, *GLUT1* etc. In glioma tissues, more than 400 abnormally expressed circular RNA were found [16]. The characteristics of the tumor are also affected by long-chain non-coding RNA, consisting of more than 200 nucleotides. The most comprehensively described are the *ASLNC22381*, *ASLNC20819*, *CRNDE* and *HOTAIRM1* long-chain non-coding RNA, which become significantly activated in glioblastoma tissues (the high levels of which, in turn, are considered as a negative prognostic sign), as well as *CASC2*, *PDCD4-AS1*, *GSCAR*, *MEG3* and others, which prevent the development of tumors and the levels of which are decreased in gliomas comparing to normal tissues [14, 17].

EXTRACELLULAR TUMOR DNA

The extracellular tumor DNA is a component of the total extracellular DNA, which, generally, consists of DNA fragments with a length of 80–200 base pairs, which corresponds to about one volution of the nucleosome. Its main source is believed to be the dead cells, as well as the cells that actively produce the extracellular DNA. Besides the immune system cells, releasing extracellular DNA during the NETosis, such sources include the tumor cells, apparently, using these molecules as intercellular messengers [18]. In physiological conditions, the blood concentration of extracellular DNA does not exceed 40 ng/ml, however, in cases of cancer processes, it can increase by a factor of tens [19]. The increase of DNA concentration is associated not only with the secretion by tumor cells or their necrosis, but also with the death of cells surrounding the tumor caused by the Warburg effect [20].

Upon the analysis of the extracellular tumor DNA, information can be obtained on the mutation pattern and on the changes of the epigenetic regulation pattern in the tumor cells. These may be important for non-invasive diagnostics of neoplasms. It is worth noting that extracellular tumor DNA have a half-life period of less than 1.5 hours, which also allows for using them for dynamic monitoring of the treatment efficiency [18].

Genetic changes of the extracellular tumor DNA

Most commonly, the fluid biopsy of gliomas reveals mutations in the *pTERT* (~65%), *TP53* (40–60%), *H3F3A* (~50%), *IDH1* (30%), *CDKN2A/B* (25%), *NF1* (~24%), *EGFR* (20–25%), *ATRX* (10–20%), *MET* (~18%), *APC* (~15%), *PDGFRA* (10–14%) and *FAT1* (<10%) genes (table 2, 3) [12–52]. Reports were also provided on

Table 2

Studies on the analysis of cell-free tumor DNA and RNA in the diagnosis of adult type diffuse glioma

Research	Research sample	Substrate (tested volume); Test method (marker tested)	Analysis outcome, %		
			Se	Sp	AUC
Analysis of mutations in the extracellular tumor DNA					
[21]	57, glioma	CSF (3 ml) + serum (3 ml) + tissue (n/d); NGS (Panel of 68 genes)	91.9	-	-
[22]	85, glioma (46 cases of brain glioblastoma — BGB); 7, control	Serum (3.5 ml) + CSF (3.5 ml); NGS (Panel of 410 genes)	49.4	-	-

Table 2

Continued

Research	Research sample	Substrate (tested volume); Test method (marker tested)	Analysis outcome, %		
			Se	Sp	AUC
[26]	34, glioma	CSF (1–3 ml); ddPCR (*IDH1*, *pTERT*, *H3F3A*)	87	-	-
[27]	42, glioma *TERT-mut*; 9, glioma *TERT-wt*; 23, control	Serum (1 ml); ddPCR (*pTERT*)	52.38	90.91	-
[28]	45, glioma	Serum (1 ml) + tissue (n/d); RtPCR (*IDH1*)	11.54	-	-
[32]	395, BGB	Serum (n/d) + tissue (n/d); NGS (*pTERT*)	75	-	-
[34]	4, recurrence of BGB; 111, glioma; 111, control	CSF (10 µl) + tissue (n/d); NGS (panel of 68 genes)	-	-	94.4
The analysis of changes in the methylation patterns of extracellular tumor DNA					
[35]	149, glioma	Serum (1.2–9.3 ml); bisulfite conversion + NGS (panel of 100 epigenetic variants)	100	97.78	-
[36]	17, glioma	Serum (3 ml) + tissue (n/d); bisulfite conversion + PCR in the agarose gel (*pMGMT*, *pRASSF1A*, *p15INK4B*, *p14ARF*)	70.58	-	-
[38]	20, astrocytoma; 20, oligodendroglioma; 10, control	Serum (1 ml) + tissue (n/d); bisulfite conversion + PCR in the agarose gel (*pCDKN2A*)	75	-	-
[39]	41, astrocytoma; 29, oligodendroglioma	Blood (5 ml) + serum (200 µl) + tissue (n/d); bisulfite conversion + RtPCR (*pPTEN*, *pMGMT*); RtPCR (loss of heterozygosity in 10q, 19q, 1p)	Astrocytoma 59%; oligodendroglioma 58%	Astrocytoma 100%; oligodendroglioma 94%	-
[40]	89, glioma	CSF (4–5 ml) + tissue (n/d) + serum (n/d); bisulfite conversion + PCR + chromatography (*pMGMT*)	65	100	-
Analysis of the extracellular tumor RNA levels					
[12]	7, BGB; 4, glioma stage II	Serum (200 µl); ddPCR (*miRNA-320e*, *223*, *23a*, *21*)	100	97.8	98
[43]	111, BGB; 84, control (non-oncological diseases)	CSF (1 ml); RtPCR (*miRNA-21*, *218*, *193b*, *331*, *374a*, *548c*, *520f*, *27b*, *130b*)	80	67	75
[44]	30, glioma stage II–IV; 10, adenoma of the hypophysis; 10, meningioma; 10, control	Serum (400 µl); RtPCR (*miRNA-21*, *128*, *342-3p*)	90	100	93
[47]	23, BGB; 5, glioma stage III; 10, control	Serum (n/d); ddPCR (*circHIPK3*, *circSMARCA5*)	-	-	90.1
[48]	25, BGB; 20, control	Serum (n/d); RtPCR (*miRNA-17-5-p*, *125b*, *221*)	96	95	98.8
[49]	30, EGFRvIII positive; 10, EGFR wild type; 14, control	Serum (2 ml) + tissue (n/d); ddPCR of tissues and serum, RtPCR of tissue samples (*mRNA-EGFRvIII*, *mRNA-EGFR wild type*)	72.77	97.67	-

Note. Se — sensitivity; Sp — specificity; AUC — area under the ROC curve; BGB — brain glioblastoma; CSF — cerebrospinal fluid; NGS — next generation sequencing; RtPCR — real-time PCR; ddPCR — digital droplet PCR; RNA — ribonucleic acid; miRNA — micro ribonucleic acid; cRNA — circular ribonucleic acid; lnRNA — long noncoding ribonucleic acid; *p* — gene promoter; n/d — data is not available.

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Table 3

Studies on the relationship between cell-free tumor DNA and RNA in the prognosis of adult type diffuse glioma

Research	Research sample	Substrate (test sample); Test method (investigated marker)	Analysis outcome	
			Positive prognosis	Negative prognosis
Analysis of mutations in the extracellular tumor DNA				
[13]	370, glioma (222 BGB)	Serum (n/d); NGS (panel of >54 genes)	-	*TP53* ↑ *NF1* ↑ *EGFR* ↑ *PIK3CA* ↑
[19]	122, BGB; 55, adenocarcinoma; 130, control	Serum (n/d); fluorimetry (ecDNA)	-	*ecDNA* ↑
[23]	30, glioma (TISF); 14, glioma (CSF)	TISF (n/d) + CSF (n/d) + serum (n/d); NGS (panel of 68 genes)	-	etDNA ↑
[24]	42, BGB; 42, control	Serum (1 ml); RtPCR (ecDNA)	-	etDNA ↑
[25]	240, glioma; 25, control	Serum (n/d) + tissue (n/d); RtPCR (*IDH1*)	*IDH1* ↑	-
[28]	45, glioma	Serum (1 ml) + tissue (n/d); RtPCR (*IDH1*)	*IDH1* ↑	-
[29]	49, BGB	Serum (1–5 ml); ddPCR (*pTERT*)	The marker level is not a prognostic sign	
[31]	60, BGB	Serum (n/d) + CSF (n/d) + tissue (n/d); ddPCR (*pTERT*)	-	*pTERT* ↑
[32]	395, BGB	Serum (n/d) + tissue (n/d); NGS (*pTERT*)	-	*pTERT* ↑
Analysis of changes in the methylation patterns of extracellular tumor DNA				
[25]	240, glioma; 25, control	Serum (n/d) + tissue (n/d); bisulfite conversion + RtPCR (*pPARP-1*, *pSHP-1*, *pDAPK-1*, *pTIMP-3*, *pMGMT*)	*pMGMT* ↑	*pPARP* ↑ *pSHP* ↑ *pTIMP* ↑
[33]	124, glioma; 58, control	Serum (n/d); bisulfite conversion + Sanger sequencing (Alu, *pMGMT*, *pRASSF1A*, *pCDKN2A*)	-	Alu ↑ *pMGMT* ↑
[35]	149, glioma	Serum (1.2–9.3 ml); bisulfite conversion + NGS (Panel of 100 epigenetic signs)	-	High level of the tumor methylation scale
[34]	4, recurrence BGB; 111, glioma; 111, control	CSF (10 μl) + tissue (n/d); NGS (Panel of 68 genes)	*pFLRT2* ↑ *pETV1* ↑ *pNTRK3* ↑ *pC1orf226* ↑	*NKD1* ↑ *GNB5* ↑ *COMMD1* ↑ *CHI3L2* ↑
[37]	66, glioma; 20, control	CSF (n/d) + serum (n/d) + tissue (n/d); Immunoprecipitation of methylated DNA + RtPCR (*pMGMT*, *pTIMP-3*, *pP16INK4a*, *pTHBS1*)	-	*pMGMT* ↑ *pTIMP-3* ↑ *pP16INK4a* ↑ *pTHBS1* ↑
[40]	89, glioma	CSF (4–5 ml) + tissue (n/d) + serum (n/d); bisulfite conversion + PCR + chromatography (*pMGMT*)	-	*pMGMT* ↑

Table 3

Continued

Research	Research sample	Substrate (test sample); Test method (investigated marker)	Analysis outcome	
			Positive prognosis	Negative prognosis
[41]	58, glioma	Serum (n/d) + tissue (3–5 samples with a thickness 10 μm); bisulfite conversion + RtPCR (*pMGMT*)	*pMGMT* ↑	-
Analysis of the extracellular tumor RNA levels				
[12]	7, BGB; 4, glioma stage II	Serum (200 μl); ddPCR (*miRNA-320e*, *223*, *23a*, *21*)	-	*miRNA-320e* ↑ *miRNA-223* ↑ *miRNA-21* ↑
[43]	111, BGB; 84, control (non-oncological diseases)	CSF (1 ml); RtPCR (*miRNA-21*, *218*, *193b*, *331*, *374a*, *548c*, *520f*, *27b*, *130b*)	-	*miRNA-21* ↑
[44]	30, glioma stage II–IV; 10, adenoma of the hypophysis; 10, meningioma; 10, control	Serum (400 μl); RtPCR (*miRNA-21*, *128*, *342-3p*)	*miRNA-128* ↑ *miRNA-342-3p* ↑	*miRNA-21* ↑
[45]	15, BGB; 4, low grade glioma; 7, control	Serum (n/d); RtPCR (panel of 84 mRNA)	-	*mRNA-GZMB* *mRNA-HLA-A*
[46]	25, glioma; 25, control	Serum (n/d) + tissue (n/d); RtPCR (*circMMP1*, *miRNA-433*, *HMGB3*)	-	*circMMP1* ↑ *miRNA-433* ↑ *HMGB3* ↑
[47]	23, BGB; 5, glioma stage III; 10, control	Serum (n/d); ddPCR (*circHIPK3*, *circSMARCA5*)	-	*circSMARCA5* ↓ *circHIPK3* ↓
[48]	25, BGB; 20, control	Serum (n/d); RtPCR (*miRNA-17-5-p*, *125b*, *221*)	-	*miRNA-17-5-p* ↑ *miRNA-125b* ↑ *miRNA-221* ↑
[49]	30, EGFRvIII positive; 10, EGFR wild type; 14, control	Serum (2 ml) + tissue (n/d); ddPCR from the tissues and serum, RtPCR from the tissues (*mRNA-EGFRvIII*, *mRNA-EGFR wild type*)	-	*mRNA-EGFRvIII* ↑
[50]	50, astrocytoma; 60, control	Serum (100 μl); RtPCR (*9 miRNA*)	-	*miRNA-19a-3p* ↑ *miRNA-106a-5p* ↑ *miRNA-181b-5p* ↑
[51]	15, glioma (8 IDH-wt and 7 IDH-mut); 15, control	Serum (200 μl); ddPCR (*10 miRNA*)	-	*miRNA-1-3p* ↓ *miRNA-26a-1-3p* ↓ *miRNA-487b-3p* ↓
[52]	106, BGB	Serum (n/d); RtPCR (*miRNA-222-3p*, *20a-5p*, *106a-5p*, *182*, *145-5p*)	*miRNA*-182 ↑ *miRNA*-145-5p ↑	*miRNA*-222-3p ↑ *miRNA*-20a-5p ↑ *miRNA*-106a-5p ↑

Note. BGB — brain glioblastoma; CSF — cerebrospinal fluid; NGS — next generation sequencing; RtPCR — real-time PCR; ddPCR — digital droplet PCR; DNA — desoxyribonucleic acid; RNA — ribonucleic acid; mRNA — messenger RNA; miRNA — micro RNA; cRNA — circular RNA; lnRNA — long noncoding RNA; *p* — gene promoter; n/d — data is not available; ↑ or ↓ — identification of elevated or decreased level of marker in groups of patients in comparison with control groups.

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the elevation of the total extracellular DNA levels in glioma patients being 1.3–30 -fold higher comparing to the individuals in the control group [19, 24]. At the same time, in healthy volunteers, no mutation-related changes were observed in plasma and in the cerebrospinal fluid, which was expected [22, 25]. The sensitivity of droplet digital polymerase chain reaction (PCR) when searching for extracellular tumor DNA in the cerebrospinal fluid when diagnosing gliomas reaches up to 87%, with a specificity of 100%. The use of next generation sequencing (NGS) allows for increasing the sensitivity up to 91.9% [21, 26, 27]. However, testing the serum samples for extracellular tumor DNA using digital droplet PCR is characterized by the sensitivity of only 52.38% [27]. The sensitivity of PCR performed in the real time mode when searching for extracellular tumor DNA in the serum samples, is only 11.54% [28]. The results of determining the diagnostic efficiency of fluid biopsy are provided in table 2.

The level of mutation burden is related to the tumor tissue volume, decreasing after the tumor resection or after chemotherapy with an increase during the recurrence [27, 29], however, no correlation was observed between the extracellular DNA levels in plasma and the radiologically determined tumor volume [24]. In cases of recurrence, the number of observed alterations in the mutated genes or in the signaling pathways associated with them, can increase up to 3 times then the levels in the primary tumor [22, 23]. Probably, the increase of genetic variability of the tumor is due to the effect of post-therapeutic evolution, in which, under the effects of therapy, there occurs the selection of subclones having a dysregulated reparative system responsible for being more prone to mutagenesis, which, in turn, can explain their resistance to therapy. This phenomenon can be observed in about 78% of gliomas, representing worse prognosis and the risk of developing remote recurrences. As it was found by G. Liu et al. [30], after the conducted therapy and further tumor recurrence, the tumors show significantly more aggressive mutational phenotype.

The patients with high-grade gliomas are characterized by the presence of higher levels of extracellular tumor DNA [13]. Respectively, higher levels of extracellular tumor DNA (>15 ng/ml) are associated with lesser progression-free survival (p <0.0001, Spearman's rank correlation coefficient ρ=-0.844) and lesser total survival rate of the patients (the overall survival in patients with low levels of extracellular tumor DNA is about 2 times higher than in patients with high levels of extracellular tumor DNA) [19, 22–24]. However, in some cases such an interrelation was not observed [29]. The variety of mutations, apparently, does not correlate with the progression-free survival [23], but it is closely related to worse total survival rates (median of overall survival — 15.4 months [95% CI 11.6–19.2] in a group showing low variability of mutations compared to the values of 8.3 [95% CI 2.3–14.4] in a group with high variability of mutations) [31]. Despite this fact, the presence of *IDH1* mutations in patients is the positive prognostic sign (at an average, the patients with mutant *IDH* have at least 3 months higher overall survival) [25, 28]. The *pTERT* gene mutation is a negative prognostic factor (median of overall survival — 13.8 months for patients with mutated *pTERT* comparing to 37.6 for wild type *pTERT*; p <0.0022), while the patients with *EGFR* amplification show 2 times lesser overall survival comparing to patients not having such alterations [32]. Table 3 shows the results of studying the prognostic efficiency of fluid biopsy.

Epigenetic alterations of the extracellular tumor DNA

When evaluating the epigenetic changes, most commonly by means of real-time PCR and digital droplet PCR, the alterations of Alu-repeats methylation are being studied, as well as the alterations of the *MGMT*, *RASSF1A*, *pPARP-1*, *pSHP-1*, *pDAPK-1*, *CDKN2A* and *TIMP-3* gene promoters (see table 2, 3). M. Gong et al. [33] have used Sanger sequencing for the evaluation of the methylation of Alu-repeats, as well as for *pMGMT*, *pRASSF1A* and *pCDKN2A*. L. Dai et al. [34] have studied the methylation of extracellular tumor DNA from the cerebrospinal fluid using NGS with further use of the UCSC RefSeq data bases to determine the differentially methylated genome areas in glioma patients and in healthy individuals. These areas were then analyzed to search the most differentially expressed genes and for compiling the diagnostic and prognostic models. T. Sabedot et al. [35] have proposed the use of NGS to investigate the methylation of extracellular tumor DNA in serums and glioma tissues. After bisulfite conversion and performing the sequencing procedures using the Illumina Human EPIC set for serum and Illumina Human 450K (HM450K) set for tumor tissues, the authors have isolated 476 genome sites, differentially methylated in glioma patients and in healthy individuals. Using this information, a scale was compiled for evaluating the DNA methylation, which could allow for differentiating the samples obtained from glioma patients (the scale

value that is close to 100%) and from healthy individuals (close to 0%). An increase of the scale value in each patient means that, in his plasma, extracellular tumor DNA was found, methylated in a similar manner to the set of 476 sites used for creating the scale. As a result of evaluating the data from the test cohort, after using the machine learning, the threshold level for the scale intended for the differentiation of individuals with gliomas and without them, was set as being equal to 49%.

The methylation of Alu-repeats is significantly lower in glioblastoma patients (46–47%) comparing to the control group (approximately 60%) [33], with the mean level of *MGMT*, *CDKN2A* and *RASSF1A* methylation, on the contrary, being significantly higher in glioma patients, than in healthy individuals [33, 36, 37]. The occurrence rate of *p16* hypermethylation varies among the patient cohorts with gliomas of different histological types: in 9/20 patients with astrocytomas and only in 1/20 patients with oligodendrogliomas (p <0.05) [38]. L. Dai et al. [34] have stated that *pFLRT2*, *pETV1*, *pNTRK3* and *pC1orf226* are hypomethylated in tumor cells, while the *pNKD1*, *pGNB5*, *pCOMMD1* and *pCHI3L2* are hypermethylated.

T. Sabedot et al. [35] have found a decrease of the genome methylation scale value after successful therapy. During the primary diagnostics, the median scale value among the patients was 78.41%, in cases of remission or pseudoprogression, the scale value had decreased below 49%, while in cases of recurrences it was increasing (for the first recurrence, the median was 61.1%, for the second — 56.1%). It is also probable that, during the abovementioned post-therapeutic tumor evolution, the tumor mass was accumulating cell subclones, the methylation DNA in which differed from the initial set of 476 sites, due to which, the scale value during the recurrence did not return to previous values. Nevertheless, for all the glioma recurrence patients, the scale value exceeded 49%, which allowed for clearly differentiating them from the patients with pseudo-recurrence. The sensitivity of the test was 100%, the specificity was 97.78% [35].

The sensitivity of differentiating glioma patients from the healthy volunteers for the *pMGMT*, *pRASSF1A*, *p15INK4B*, *p14ARF*, *pPTEN*, *pCDKN2A* methylation test using the PCR method was 58–75% with the specificity of 94–100% (see table 2). The diagnostic model by L. Dai et al. [34] has allowed for differentiating the patients and healthy volunteers with an AUC 94.4%.

The patients with high methylation levels of Alu, *NKD1*, *GNB5*, *COMMD1*, *CHI3L2* and *pMGMT* have greater overall survival than the patients with low methylation level (the mean survival after setting the diagnosis is approximately 23 months in patients with pronounced methylation of Alu comparing to 11 months in patients with no methylation; p <0.05) [34, 41], at the same time, high methylation levels of *pPARP-1*, *pSHP-1*, *pFLRT2*, *pETV1*, *pNTRK3*, *pC1orf226*, *pP16INK4a*, *pTHBS1 and pTIMP-3* for serum extracellular tumor DNA are associated with lesser survival [25, 34, 37]. Besides, the methylation degree of *pPARP-1*, *pSHP-1* and *pTIMP-3* promoters in tumor samples and in the serum is, to a significant extent, related to the malignancy grade of glioma (the mean methylation levels for the stated genes is 0.18–0.30 in patients with grade I gliomas and up to 0.4–0.6 in patients with malignancy grade IV gliomas) [25]. In the research by L. Dai et al. [34], the high level of *pNKD1*, *pGNB5*, *pCOMMD1* and *pCHI3L2* methylation is associated with negative prognosis, and the high level of *pFLRT2*, *pETV1*, *pNTRK3* and *pC1orf226* methylation is a positive prognostic sign. It is worth noting that, at the present moment, the test of *pMGMT* methylation is already being used for predicting the course of the disease, though the test substrate is limited to using only the tumor tissue [3]. The analysis of methylation for other markers, as of today, is not being widely used in practice. The results of studying the prognostic efficiency of fluid biopsy with testing the methylation of extracellular tumor DNA are summarized in table 3.

EXTRACELLULAR TUMOR RNA

The research works show that both the tumor and the normal cells release high quantities of RNA into the environment, with its release taking place not only from the dying cells, but also by means of secretory mechanisms, such as exosome-mediated transfer of signals by live cells. The concentration of the total extracellular RNA in blood plasma samples from oncology patients has an average level of 7.9 ng/ml, which is comparable to the release of this substance in healthy individuals [42]. At the same time, the concentration of separate RNA in patients may differ from those in healthy individuals by a factor of tens [43, 44]. The analysis of them allows for judging not only on the presence of a neoplasm, but also on its characteristics.

The majority of the research works devoted to the analysis of extracellular tumor RNA, evaluates the levels of microRNA, among which the most attention is paid to *microRNA-21* and *221* (see table 2, 3). Some studies evaluate the levels of circular RNA *circHIPK3*

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and *circSMARCA5*, long-chain non-coding RNA — *HOTAIR*, *SOX21-AS1* and *STEAP3-AS1*, as well as levels of expressed matrix RNA [45–47]. *MicroRNA-21*, *218, 198b* and other, as well as long-chain non-coding RNA *HOTAIR*, *SOX21-AS1* and *STEAP3-AS1* are significantly (100–10000 -fold; p <0.05) increased in glioblastoma patients comparing to the control group [43, 44]. *MicroRNA-17-5p*, *125b*, *21*, *221* and *222*, as well as *circMMP1*, were found to be elevated in glioma patients comparing to the control by a factor of 2–10 (p <0.05) [46, 48], however, the levels of *microRNA-128* and *342-3p*, as well as the *circSMARCA5* and *circHIPK3* circular RNA, on the contrary, were found to be lower in glioma patients than in healthy individuals, 2–10 -fold (p <0.05) [44, 47]. Based on the results of the analysis of circulating matrix RNA, glioma patients are characterized by overexpression of *BCL2L1*, *GZMB*, *HLA-A*, *IRF1*, *MYD88*, *TLR2* and *TP53* genes, while the *BCL2*, *CCR2*, *CXCL9*, *CXCR3*, *GBP1*, *HIF1A* and *IL23A* genes are insufficiently expressed (with a 2–10 -fold difference; p <0.05) [45].

The sensitivity of differentiating glioma patients and healthy individuals using the Real time PCR by the presence of such RNA as *microRNA-10b*, *17-5p*, *125b* and *221*, is 30–96% with the specificity reaching up to 95% (see table 2).

The levels of detectable *microRNA-21*, *128*, *342-3p* and some others decrease after resection or chemotherapy, though increasing during the recurrences [43, 44, 49], with the elevation of *microRNA-320e* levels being associated with higher progression risk than the tumor volume according to data from MRI [12].

The levels of detectable *microRNA-21*, *17-5p*, *125b* and *221* are higher in glioma patients with higher malignancy degree and with more aggressive histological type (2–10 times higher in high malignancy degree gliomas comparing to low-grade gliomas; p <0.05), while the levels of *microRNA-128 and 342-3p* decrease 2–3 -fold with higher tumor grade (see table 3) [44, 48]. High expression levels of *microRNA-17-5p*, *125b* etc., as well as of the *HOTAIR* and *STEAP3-AS1* long-chain non-coding RNA is associated with worse total survival rate and progression-free survival [48, 50], while the high expression of *microRNA-1-3p*, *26a-1-3p*, *487b-3p* and *342-3p* is a positive prognostic factor [44, 51, 52]. The plasma levels of *microRNA-1-3p*, *26a-1-3p* and *487b-3p* are decreased in patients with wild type IDH, which is associated with lower survival among these patients (odds ratio, OR, 0.24; 95% CI 0.12–0.47; p <0.05) [51].

DISCUSSION

The capability of fluid biopsy to qualitatively and quantitatively determine the levels of markers in various biological fluids allows for not only diagnosing the presence of glioma, but also for differentiating the true tumor recurrence from the pseudorecurrence. Besides, fluid biopsy demonstrates the capability to define the malignancy degree of the tumor and to predict the survival of the patients after conducted therapy (see table 3). The optimal markers for this instrument are the extracellular tumor nucleic acids, such as DNA and RNA, with the most significant genetic and epigenetic alterations, such as mutations in genes *TERT*, *TP53*, *H3F3A*, *IDH1*, *CDKN2A/B* etc., aberrant methylation patterns of *MGMT*, *RASSF1A*, *pPARP-1*, *pSHP-1*, *pDAPK-1*, *CDKN2A* and *TIMP-3*, as well as *microRNA-21* and *microRNA-221*, detectable in the cerebrospinal fluid using digital droplet PCR. With the introduction of NGS into wide clinical practice, most probably, spreading of the analysis of large gene panels could be observed, capable of precisely diagnosing oncological diseases when testing the serum samples. However, this list will probably be expanded during further studies of fluid biopsy.

The highest diagnostic potential in the diagnostics of gliomas, probably, belongs to testing the cerebrospinal fluid for markers using NGS and digital droplet PCR, which are characterized by high (up to 90–100%) sensitivity and specificity [12, 21, 26, 34]. On the other hand, testing the serum for markers using the abovementioned methods or testing the cerebrospinal fluid with using Real time PCR shows significantly lesser values (up to 50–75% and up to 90%, respectively) [22, 27, 39]. To a great extent, this is due to the ability of the blood-brain barrier to hamper the penetration of marker substances into blood from the cerebrospinal fluid and to prevent its detection in serum [40]. Probably, for the reason that the extracellular tumor RNA has lesser size, its capabilities of passing through the blood-brain barrier is significantly higher comparing to the extracellular tumor DNA. Thus, detecting the given marker in serum using Real time PCR shows the sensitivity and specificity of up to 90–100%, unlike the testing for extracellular tumor DNA [44, 48]. Besides, low sensitivity and specificity of detection can be resulting from the features of the testing methods themselves. As it is known, Real time PCR has a lower resistance to PCR inhibitors comparing to digital droplet PCR, along with the limitations when operating in the range of low concentrations of nucleic acids (characteristic for plasma extracellular tumor DNA of gliomas), which can

negatively affect the testing results [53]. NGS allows for simultaneously testing multiple genomic loci, detecting the exact sequence alterations, which may determine its higher sensitivity and specificity [54]. Thus, for example, in the research by T. Sabedot et al. [35], testing the extracellular tumor DNA for methylation in serum samples using NGS had a sensitivity of 100% with a 97.78% specificity, which is significantly higher comparing to Real time PCR in similar settings.

Thus, fluid biopsy shows a significant diagnostic and prognostic potential. Despite this, it is characterized by a number of limitations (one of the main being the absence of validated approaches to testing the marker substances), preventing its routine application. For example, in the majority of the research works, DNA isolation is performed out of 1–4 ml of the substrate, while the RNA — from 100–400 µl (see table 2, 3), with the reagent kits used by the authors, which allow for processing up to 5 ml and 900 µl of biological fluids, respectively, without losing the extraction efficiency [55, 56]. As a result, there is a potential loss of 20–90% of nucleic acids present, which may negatively affect the test outcome. Moreover, in most part of the research works, the volume of the test material is not disclosed, which hampers even more the evaluation of the efficiency of the proposed approach to fluid biopsy. This problem can be solved by arranging the large scale multicenter research, which could allow for univocal defining the set of markers and the approach to testing them, which could be optimal for routine clinical application of fluid biopsy. Besides, the analysis of the epigenetic regulation of gliomas is encumbered by using bisulfite conversion, which may lead to the degradation of 50–90% of nucleic acids, resulting in a decrease in the sensitivity of this method. Apparently, the most part of the fragments after the conversion represent up to 80–90 base pairs, which sometimes affects the capabilities of analyzing them [57]. Probably, in order to detect the genome methylation aberrations, it could be practical to use methylation-sensitive restrictases, which, to a lesser degree, may result in the non-specific degradation of DNA [58]. However, the limitation of this approach is that, by no means all the perspective DNA foci, intended for testing and showing an altered methylation pattern, carry the restriction sites matching the currently available enzymes [59].

The promising methods of DNA methylation analysis include also the enzymatic conversion. This procedure, just like the bisulfite conversion, transforms the non-methylated cytosine into uracil, however, not resulting in massive degradation of the genetic material, which increases the test sensitivity and makes it possible to analyze also the damaged DNA, for example, obtained from the paraffin-embedded sample slices. The benefits of enzymatic conversion can also include the capability of operating with low levels of DNA content (ranging from 100 pg), which is oftentimes observed in liquid biopsy substrates. Due to its novelty, this technology has still not gained wide spreading, however, in future, probably, more and more research groups shall prefer this method, rather than bisulfite conversion [60].

CONCLUSION

The present review has estimated the role of fluid biopsy with sampling plasma and cerebrospinal fluid containing extracellular tumor nucleic acids in glioma patients. This promising method has demonstrated its efficiency in the diagnostics and predicting the course of this disease, however, it requires further development. Upon its implementation in clinical practice, the medical community may gain access to wide possibilities in the diagnostics, treatment efficiency control and therapy selection in cases of oncological diseases.

ADDITIONAL INFORMATION

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KERATOCONUS: CURRENT DIAGNOSTIC APPROACH

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ABSTRACT

Keratoconus is an ectatic corneal disease, resulting in loss of visual functions in young population. Diagnosis of the disease at a moderate stage with a typical progressive clinical course is not particularly difficult; however, the diagnosis verification in a few cases is rather troublesome. This literature review systematizes modern conceptions to the keratoconus diagnosis, outlines current approaches to patients examining and diagnostics results assessing. The clinical manifestations (complaints, anamnesis data, visometry and autorefractokeratometry results) at the early stages of keratoconus with its non-progressive course are similar to ordinary myopia and regular myopic astigmatism; as a result, it is quite difficult to suspect the disease in such cases. With progressive keratoconus course, as corneal protrusion develops, the disease acquires features specific for gradual irregular corneal myopic astigmatism growth. Currently valuable pathognomonic slit-lamp signs of keratoconus are Fleischer's ring, stromal Vogt's striae and focal thinning of the cornea in the ectasia apex. Nowadays the gold standard of keratoconus diagnosis and screening is comprehensive examination of the cornea by means of modern computer optical scanning (Scheimpflug camera in particular) keratoanalyzers, combining keratoscopy (Placido's disc) and keratotomography. The keratoanalyzers original software generates maps and calculates irregularity indices of the cornea shape (keratotopography), refractive power (keratometry) and thickness (keratopachimetry), as well as values the probability and stage of corneal protrusion. Such diagnostic platforms provide differential diagnosis and verification of keratoconus at the earliest signs of the topographic stage of the disease; to date, there are no effective methods, that can reliably confirm or exclude ultrastructural changes at the pretopographic stage of keratoconus.

Keywords: *Fleischer ring; corneal topography; slit lamp examination; classification; subclinical keratoconus.*

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INTRODUCTION

Keratoconus is a non-inflammatory ectatic disease of the cornea, having a degenerative-dystrophic origin and being associated with destructive changes in the corneal tissues. The disease manifests as progressive thinning and bulging (protrusion, ectasia) of the central part of the cornea, as a result of which, it gains a cone shape, which clinically manifests as a progressive irregular corneal myopic astigmatism with a decrease in the maximal (best) corrected (with using the corrective lenses) vision acuity (BCVA). The keratoconus is commonly believed as being a bilateral disease, due to which, in cases of detecting the signs of keratoconus in one eye, the other eye (in the absence of visible pathological changes in it) is considered a subclinical form (stage) of keratoectasia [1–5].

The diagnostics of keratoconus in its progressed stage and with typical clinical signs is not very difficult in the practice of an ophthalmologist. However, at the initial stages of the disease and in case of its non-progressive course, the process of verifying the diagnosis can be quite difficult. During the several decades of active research on the methods for diagnostics, treatment and correction of keratoconus, the terminology and the classification of this disease have undergone a number of significant evolutionary changes, while the criteria for managing the patients have been multiple times revised depending on the clinical tasks and the possibilities of practical medicine.

DIAGNOSTICS OF KERATOCONUS

The diagnostics of keratoconus is based on the disease history data, on the presence of some specific complaints, on detecting certain biomicroscopic symptoms and on the results of the visualization methods used to define the shape of the cornea (keratotopography), its refractive power (keratometry)

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СОВРЕМЕННЫЕ ПОДХОДЫ К ДИАГНОСТИКЕ КЕРАТОКОНУСА

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АННОТАЦИЯ

Кератоконус — эктатическое заболевание роговицы, наблюдаемое у лиц молодого и трудоспособного возраста, приводящее к утрате зрительных функций. Диагностика этого заболевания на развитой стадии и при типичном прогрессирующем клиническом течении не представляет особых затруднений, однако в ряде случаев верификация диагноза сопряжена с некоторыми сложностями. В обзоре систематизированы современные представления о диагностике кератоконуса, последовательно изложены актуальные подходы к обследованию пациентов и интерпретации результатов исследования. Клиническая картина (жалобы, данные анамнеза, результаты визометрии и авторефрактокератометрии) на начальных этапах развития кератоконуса и при не прогрессирующем его течении идентична ординарной миопии и регулярному миопическому астигматизму, вследствие чего заподозрить наличие заболевания достаточно сложно. При прогрессирующем кератоконусе по мере развития кератэктазии клиническая картина приобретает специфические для этого заболевания особенности, представляющие собой, по сути, прогредиентные проявления иррегулярного роговичного миопического астигматизма. К актуальным патогномоничным биомикроскопическим симптомам кератоконуса можно отнести пигментное кольцо Флейшера, стромальные стрии-полосы Фогта и фокальное истончение роговицы в области вершины экстазии. Золотым стандартом диагностики и скрининга кератоконуса в настоящее время считается комплексное исследование роговицы при помощи современных компьютерных оптических кератоанализаторов сканирующего типа (в том числе типа ротационной Шаймпфлюг-камеры), сочетающих в себе кератоскопию (диск Пласидо) и кератотомографию. Оригинальное программное обеспечение кератоанализаторов моделирует карты и рассчитывает индексы иррегулярности формы (кератотопография), преломляющей силы (кератометрия) и толщины (кератопахиметрия) роговицы, а также оценивает вероятность и стадию кератэктазии. Такие диагностические платформы позволяют проводить дифференциальную диагностику и верифицировать кератоконус при самых ранних проявлениях кератотопографической стадии заболевания, при этом эффективных методик, позволяющих достоверно подтвердить или исключить ультраструктурные изменения на прекератотопографической стадии кератоконуса, на сегодняшний день не существует.

Ключевые слова: *кольцо Флейшера; кератотопография; биомикроскопия; классификация; субклинический кератоконус.*

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and thickness (keratopachymetry). At the initial stages of keratoconus, one cannot always suspect the development of keratoectasia. As the disease progresses, more and more clear manifestations of specific symptoms and complaints, characteristic for keratoconus, can be observed. In case of non-progressive keratoconus, the patients can spend a long time under medical supervision by ophthalmologists with the diagnosis of myopia or myopic astigmatism. Due to wide spreading of modern high-tech computed corneal analyzers and of the keratorefractive surgical interventions performed for the purpose of correcting the ametropies, a considerable growth is observed in the rate of detecting keratoconus in the population of relatively healthy individuals.

The keratoconus patients can present with both non-specific and sufficiently specific complaints, in particular, complaints of progressive decreased vision acuity, often changing spectacles or contact lenses used for vision correction, difficulties when adjusting the optical correction (or impossibility of such adjustment), as well as unclear, blurred or clouded vision; complaints of visual deterioration (decreased clarity, presence of halo, glares, optic radiation, backlights and other optical light effects) in the twilight settings (with the pupil being dilated at twilight); complaints of variability

in the visometry results from one examination to another; monocular polyopia (diplopia, multi-image); photophobia; irritation of eyes expressed as dry eye symptoms or asthenopic signs [1, 3–10].

At the initial stages of keratoconus development, the complaints in the patients are, generally, identical to the ones in patients with myopia or regular myopic astigmatism, due to which suspecting the development of keratoconus is quite difficult.

When collecting the disease history data, attention should be paid to such characteristic features of the disease progression as the development of an acquired corneal myopic astigmatism or index myopia (due to progressive increase of the curvature and of the refractive capacity of the cornea) at the adult age (at the postpubertal period); progressing increase of the corneal myopic astigmatism or index myopia [1, 3–10].

The visometry results in patients with initial stages of keratoconus development are generally identical to those found in cases of ordinary refraction anomalies, such as myopia or regular myopic astigmatism. As the keratoconus progresses and as irregular corneal myopic astigmatism develops along with clinically significant corneal deformation, the following characteristic features appear:

- decreased BCVA when using spectacle lenses testing (incapability of achieving the retinal vision acuity);
- increased visometry results (BCVA elevates up to achieving the retinal vision acuity) in the settings of diaphragmation;
- increased visometry results (BCVA elevates up to achieving the retinal vision acuity) when using the testing with hard gas-permeable contact lens;
- "fluctuating" (from one examination to another, during the same ophthalmologist's appointment or when adjusting the spectacles) degree and axis of corneal astigmatism;
- the patient is trying to find a comfortable position for the head and eyes when viewing the optotypes [1, 3–10].

The refractometry results, as the disease progresses, become more typical for keratoconus with unstable refraction (after several consecutive measurements, or from one examination to another) and abnormally high astigmatism degree [1, 3–10].

The keratometry (ophthalmometry) parameters at the beginning of keratoconus development do not exceed the mean statistical reference ranges. As the disease progresses, the corneal curvature gradually increases: the curvature radius of the cornea and the keratometry parameters exceed the normal reference ranges. During the course of keratometry in keratoconus patients, the following characteristic signs of the disease can be noted:

- irregular (incorrect) corneal astigmatism;
- dislocation (dislocation and deformation) of marker reflexes (distortion-curving of the mires or asymmetry in four mutually perpendicular points); Fig. 1;
- abnormally high degree of refractive power of the cornea or corneal astigmatism [1,3–10].

Biomicroophthalmoscopy allows for visualizing the specific signs of keratoconus, generally, in cases of advanced stages of the disease. Biomicroscopic symptoms of keratoconus can be found when examining under various angles with various light intensity: when using direct focal illumination, indirect illumination (in the dark field) and reflected light, as well as when optical section illumination is used. In patients with initial stages of keratoconus, the examination with using the slit-lamp commonly does not allow for verifying the diagnosis. The specific biomicroscopic markers of keratoconus are the following:

- pigment ring (Fleischer's) — a sub-epithelial deposit of pigmented compound of chalcophylic metals (copper, zinc and iron), situated at the base of the ectasia, visualized as a closed ring or (more often) an arch (semicircle) in the lower segment of the cornea (Fig. 2, *a*);
- stromal striae (Vogt's) — the apical vertical stripes in the corneal stroma, developing due to the over-extension of stroma (see Fig. 2, *b*), most probably, represent cracks and folds in the posterior stroma of cornea and the folds of the Descemet's membrane in the apical area of the protrusion; they disappear upon compression applied to the cornea;
- "fading star" symptom, or "fireworks" — rarefaction of corneal stroma at the zone of the developing ectasia, visualized as the inhomogeneity in the cornea or grayish opalescence (see Fig. 2, *c*); arising from the impairment of the collagen plate architectonics in the anterior corneal stroma;
- focal thinning of the cornea at the apex of ectasia (apical protrusion) at the central or paracentral zone of the cornea;
- prominent lenticular stromal nerves of the cornea (see Fig. 2, *d*);
- turbidity and scars in the cornea at the apex of the protrusion, located at the level of the corneal epithelium, sub-epithelially and in the corneal stroma; arising as a result of swelling and fibrotic processes (cicatrization) in the corneal tissues due

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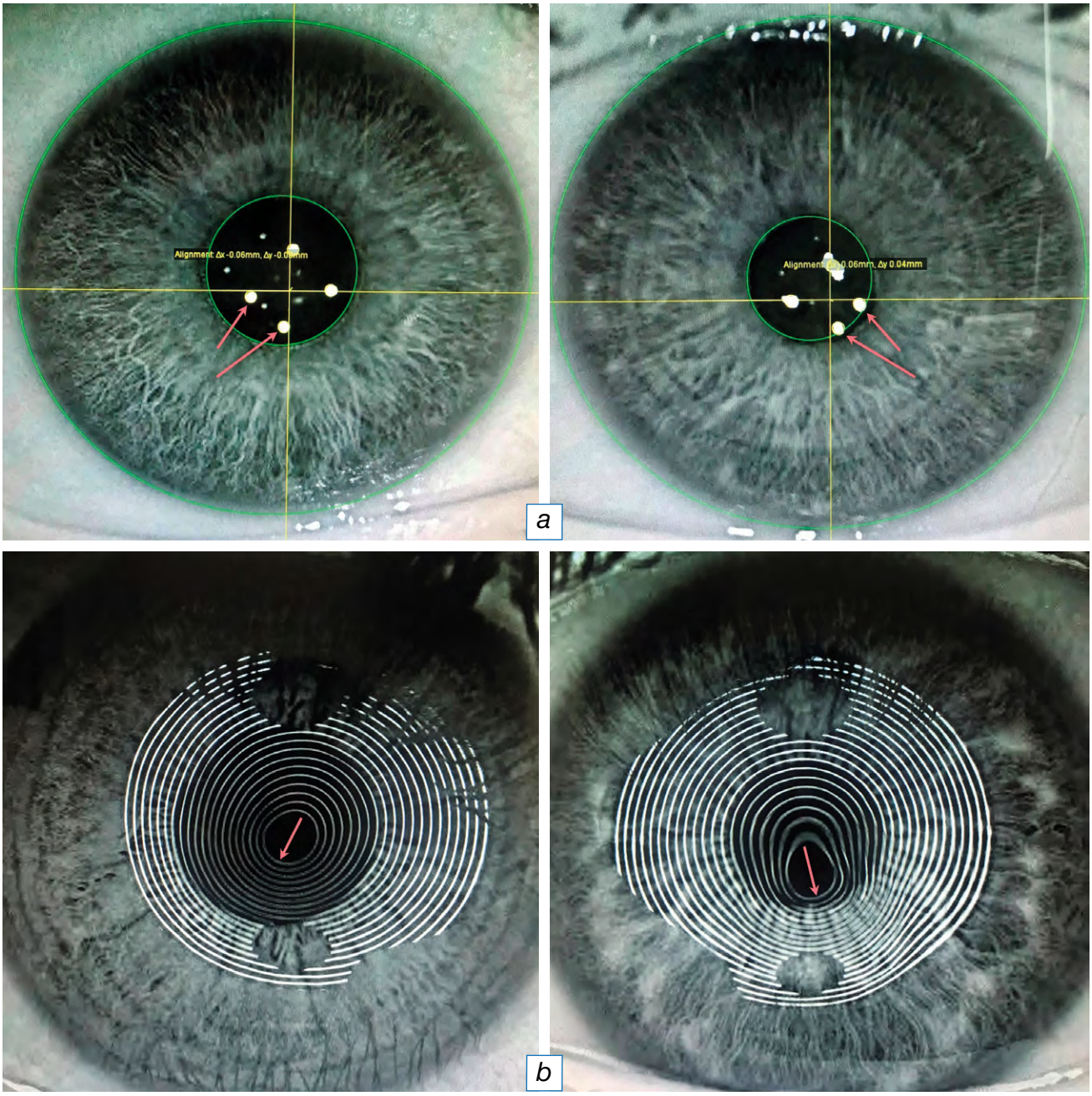

Fig. 1. Cornea anterior surface reflexes in keratoconus: *a* — autorefractokeratometry four dot marks displacement (red arrows indicate spot light reflexes shift adjacent to ectasia apex); *b* — Placido disk mires-rings distortion (red arrows indicate concentric light reflexes convergence adjacent to ectasia apex).

to rough abnormalities in the architectonics of the over-extended stroma, “cracks” (ruptures) in the Descemet’s membrane (with stromal swelling and corneal hydrops) and as a results of using the hard gas-permeable contact lens [1, 3–12].

Among the specific symptoms of keratoconus that have practically lost their clinical-diagnostic significance due to the high level of ophthalmology equipment development, the following are worth noting:

- Munson symptom — V-shaped profile of the lower eyelid margin when the patient is looking downwards;
- Rizzuti symptom — when illuminating with focused light in the frontal plane of the eyeball from the temporal side, a light reflex can be observed in the sclera from the nasal side as a result of pathological deflection of light towards the base of the cornea as a prism caused by impaired optical properties of the cornea;
- “scissor” symptom upon sciascopy, or “shadow whirling”, or “folding shadow” — a specific counter motion of the reflected stripes — reflexes and shadows, resulting from the development of an irregular astigmatism;

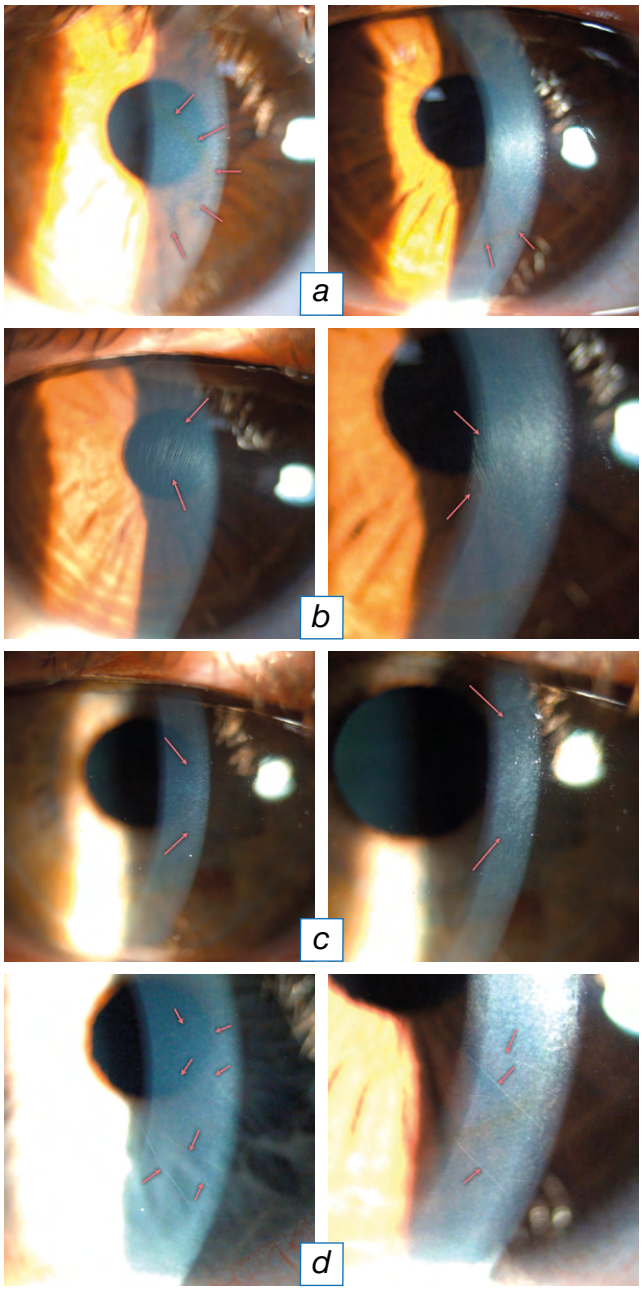

Fig. 2. Slit-lamp imaging of keratoconic cornea (red arrows point keratoconus signs): *a* — Fleischer ring; *b* — Vogt's striae; *c* — fading star or firework symptom; *d* — stromal nerves.

- "oil drop" symptom, or "oil drop/petroleum drop", or Charleaux's symptom, — revealing (upon using direct light) a contour (the base of the cone-shaped deformity — the protrusions) showing a yellowish-orange tint with a background of a red fundal reflex [1, 3–12].

As of today, the gold standard for the diagnostics of keratoconus is the combined examination of the cornea using modern computed keratoanalyzers — diagnostic platforms that allow for visualizing the structure and evaluating the functions of the cornea. The combined computed examination includes keratoscopy and keratotomography with using the original software, which (based on the obtained data) models the shape charts/maps (keratotopography/leveling maps), the refractive power (keratometry maps) and the thickness (keratopachymetry maps) of the cornea, also calculating (in an automatic mode) the shape irregularity indexes, the refractive power (curvature) and the thickness of the cornea along with the probability of keratoectasia presence and the stage of the keratoconus. As a result, a single diagnostic platform (computed optical analyzer of the anterior segment of the eye) allows for performing a complex examination of the cornea, generally, combining such diagnostic methods, as keratoscopy, keratotomography, keratotopography, keratometry and keratopachymetry [1–5, 12–18].

Keratoscopy (videokeratoscopy, photokeratoscopy, keratography) is a method used for examining the anterior surface of the cornea, based on the evaluation and the analysis of corneal ability to reflect (as a reflex) the so-called Placido keratometry disc — a pattern of concentric alternating black and white mire rings of the same width. The basis of the method is the effect of reflecting the rings from the corneal surface: at the high curvature areas (central optical zone), the rings become thinner and closer, while at the area of lesser curvature (periphery of the cornea) the rings expand. In case of keratoconus, the method allows for visualizing the distortion (changes in the shape and width) of the rings — its dislocation, deformation and curving of its contours. In the area of the cornea steeping (the apex of the protrusion), the rings become thinner with their contours converging, the rings group and concentrate downward. At the area of the corneal flattening, the rings expand and rarefy (see Fig. 1, *b*) [1–5, 12–18].

Keratotomography is an optical scanning of the cornea (including the use of the rotational Scheimpflug-camera), based on the results of which, the software built into the computed keratoanalyzer creates a series of optical slices of the cornea. Further digital analysis of the data obtained during keratoscopy and keratotomography is performed by means of analytical software integrated into the equipment for plotting the visualization charts, exercising the following examinations functions:

- keratotopography (elevation/keratotopography maps of the shapes of the anterior and posterior surfaces of the cornea);
- keratometry (curvature /refractive power maps of the anterior and posterior surfaces of the cornea);
- keratopachymetry (corneal thickness maps) [1–5, 12–18].

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In case of keratoconus, the keratotopography (elevation) maps allow for visualizing the forward prominence of the anterior and/or posterior surface of the cornea (protrusion, ectasia) as an area of local elevation (prominence, bulging) of the cornea in relation to the "ideal" sphere (elliptical), directed generally downwards and outwards (temporally) from the optical center (Fig. 3) [1–5, 12–18].

In case of keratoconus, the keratometry maps (corneal refractive power and curvature maps) show typical patterns (Fig. 4) expressed as local steeping area in the cornea (round-shaped pattern, oval-shaped pattern or symmetrical bowtie pattern), directed generally downward and outward (temporally) from the optical center, also expressed as an asymmetrical astigmatism with downward steeping (asymmetrical bowtie or curved bowtie with rounded axes) [1–5, 12–18].

When examining the keratoconus cases using the keratopachymetry maps (corneal thickness maps), the minimum corneal thickness can be defined for keratoconus with the dislocation of the thinnest point of the cornea, generally, downward and outward (temporally) from the optical center (Fig. 5) [1–5, 12–18].

Additionally, the tomography-assisted evaluation of the corneal epithelium allows for visualizing its local thinning at the area of the cone apex and its thickening in the area of the cone base, as a result of which, the corneal epithelium thickness profile gains a ring-shaped (doughnut) pattern. Such an effect in case of keratoectasia develops due to the ability of the corneal epithelium to compensate the irregularity of the anterior corneal surface in cases of its deformation [1–4, 6, 12, 19, 20].

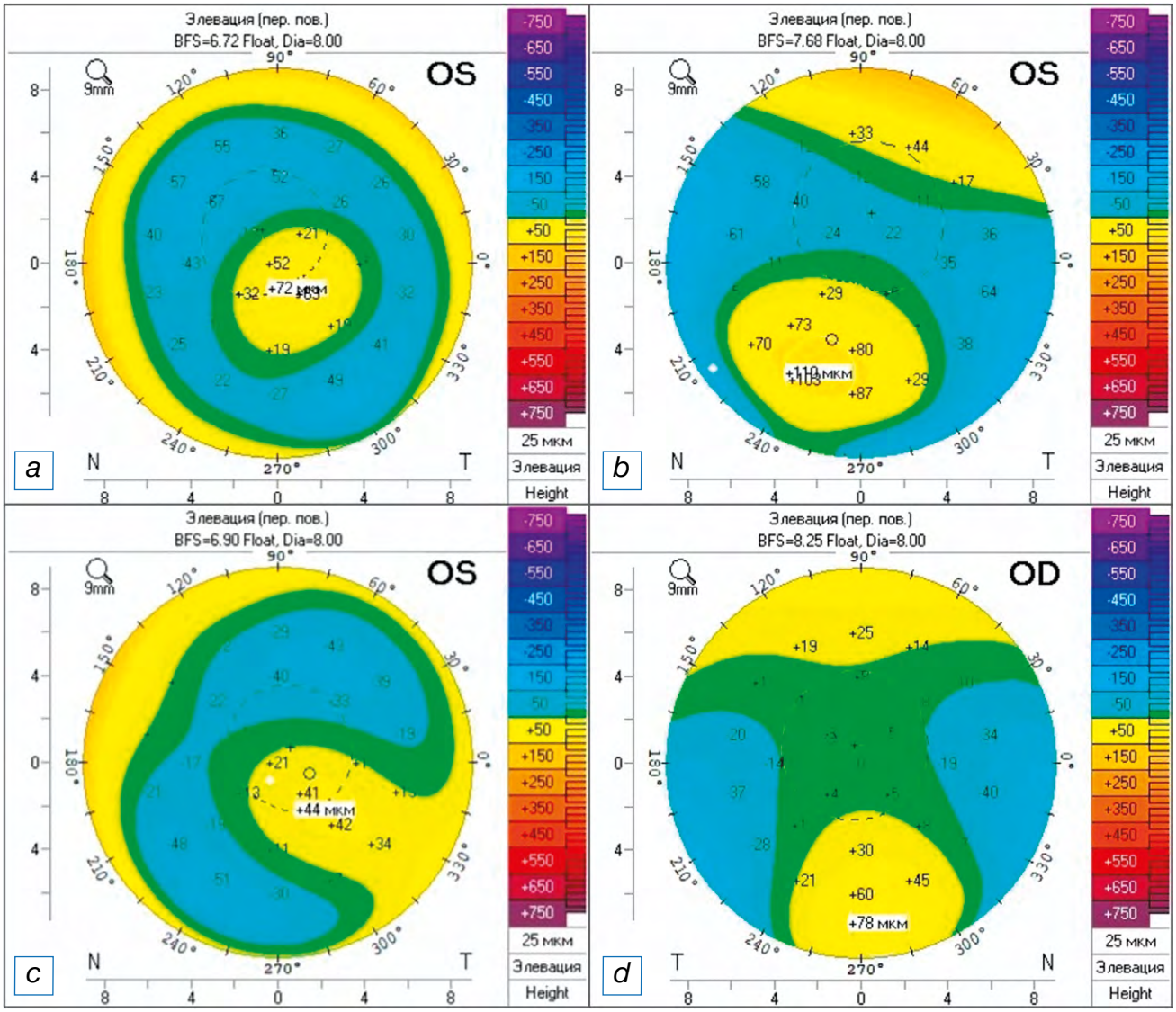

Fig. 3. Cornea anterior surface elevation maps in keratoconus: the local elevation of the cornea anterior surface relatively to the «best-fit sphere» is indicated in yellow with the numerical value (microns) of the protrusion level.

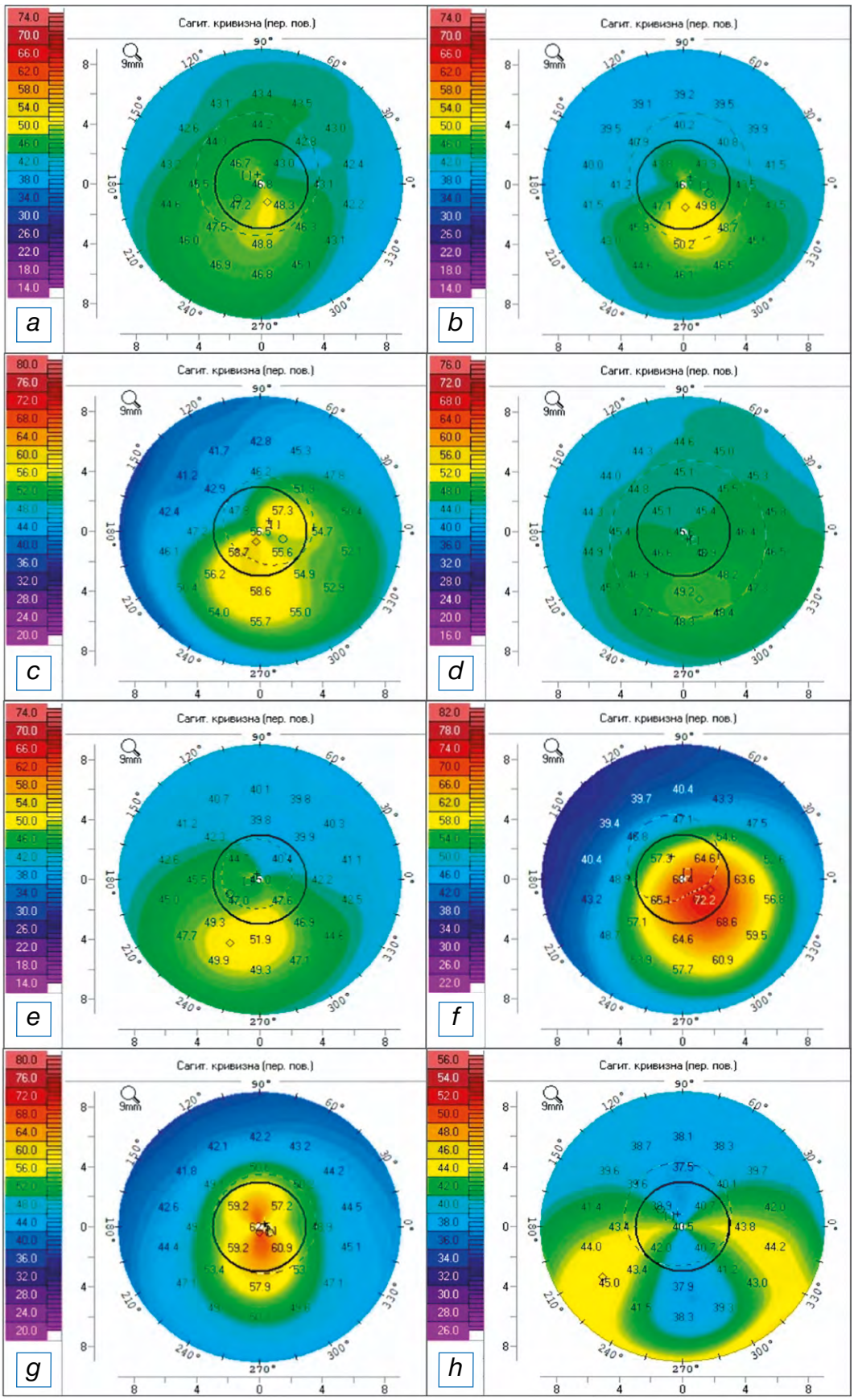

Fig. 4. Cornea anterior surface keratometry maps in keratoconus. The numerical values of the cornea refractive power (diopters) at each point of the map are indicated. Typical keratoconus patterns: *a, b* — asymmetric «bow-tie» with inferior steepening; *c* — «bow-tie» with screwed axes; *d–f* — local inferior steepening; *g* — «baby bow-tie»; *h* — «crab claw», or «kissing birds».

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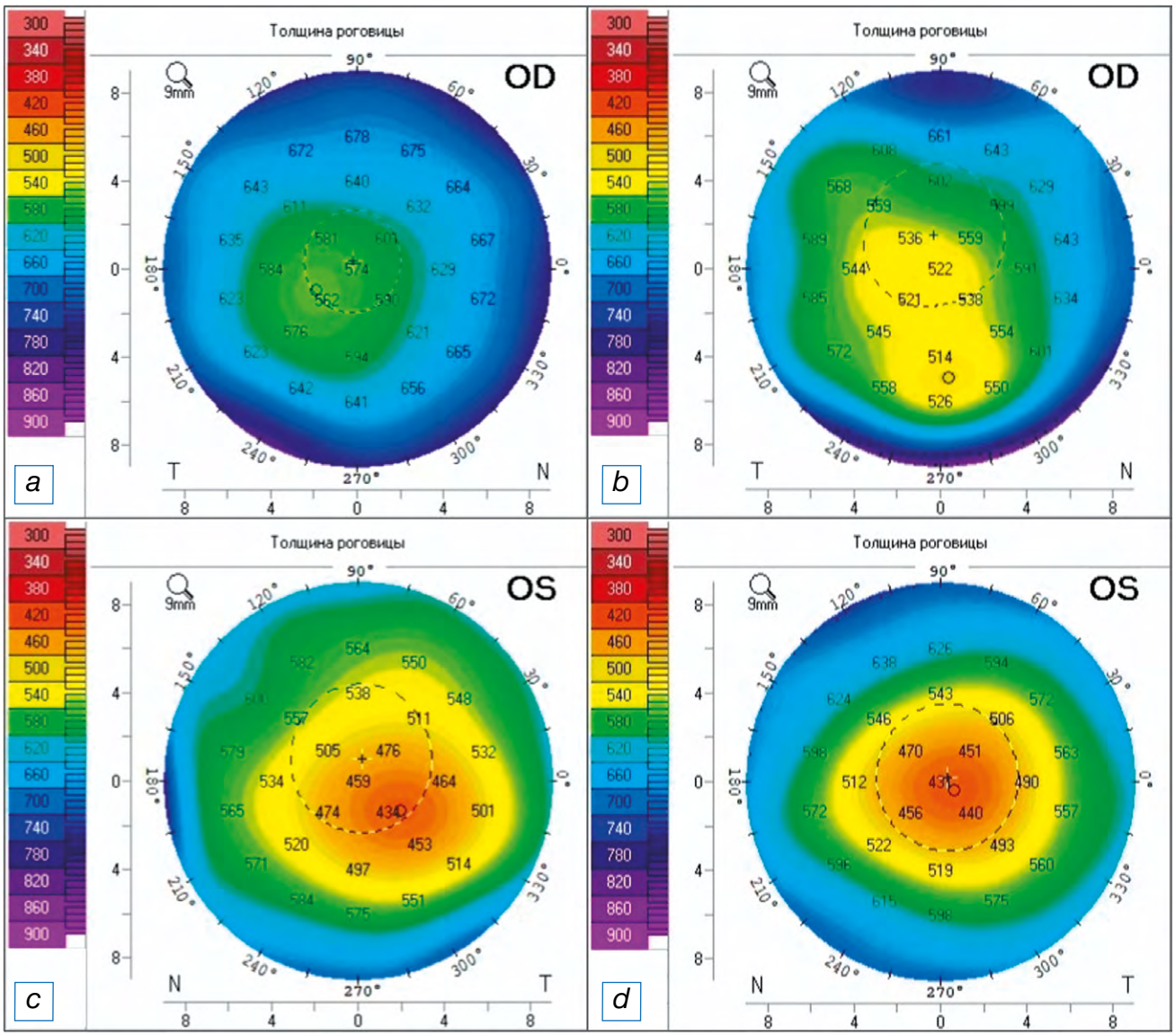

Fig. 5. Cornea pachymetry maps in keratoconus: *a–c* — inferiorly displaced thinnest point; *c, d* — significant decrease in minimal cornea thickness.

Optical coherent tomography of the anterior segment of the eyeball (cornea) allows for evaluating the transparency (absorbance) of the cornea (densitometry), visualizing the corneal layers (keratotomography), measuring the cornea thickness (keratopachymetry) and analyzing the shape of its surface (keratotopography). Optical coherent tomography devices can have the same functions and analytical options as the ones employed in computed optical keratoanalyzers, the fundamental differences include only the technical features of the hardware [1–4, 12, 21].

The necessity for precise verification of keratoconus at the earliest stages of its development is gaining special topicality in ophthalmology practice when drawing up a conclusion on the possibility of performing the surgical (laser) correction of refraction abnormalities. When performing such an examination, special attention should be paid to examining the cornea by using the slit-lamp in order to reveal the specific biomicroscopic signs of keratoconus (for example, Fleischer's ring — even in the absence of keratotopography manifestations). With the aid of modern computed keratoanalyzers, the screening procedures are carried out among the patients that are considered candidates to undergo excimer-laser vision correction, in order to reveal the most initial changes of the shape and the most minimal abnormalities in the curvature of the anterior and posterior surface of the cornea. For the same reason, the research scientists have made attempts to reveal signs of degenerative-dystrophic processes in the corneal tissues at

the stage of keratoconus-related ultrastructural changes (before the development of significant keratotopography signs of keratoectasia) by means of using several additional special diagnostic methods: the analysis of biomechanical properties of the cornea, the corneal confocal microscopy, the corneal specular microscopy of the cornea, the ultrasound examination of corneal epithelium thickness profile, the aberrometry of the eyeball optical system, etc. However, in the absence of keratotopography manifestations of the keratoconus, the abovementioned specific methods used for additional examination have no fundamental independent value in the diagnostics of this disease. They are not sufficiently sensitive and specific, due to which they have not gained any wide spreading in the clinical ophthalmology practice [13, 16–32].

CLASSIFICATION OF KERATOCONUS

The results of conducted diagnostic research allow for not only verifying the diagnosis, but also detailing the type and the stage of the disease. The first classifications of keratoconus in the absence of high-tech methods for evaluating the corneal status were based predominantly on the clinical signs of the disease. The staging of the pathological process was carried out with taking into consideration the vision acuity, the biomicroscopic findings and the refractive power of the cornea according to data from basic keratometry. As of today, a number of authorial clinical classifications for keratoconus have been proposed, allowing for staging the pathological process depending on a number of criteria and application objective: classifications developed by M. Amsler (1951/1961, translated by T.D. Abugova in 1998), by Z.D. Titarenko (1982), by Yu.B. Slonimskiy (1992), by J.H. Krumeich (1998), by M. Amsler and J.H. Krumeich (1998), by M. Hom and A.S. Bruce (2006), by T.D. Abugova (2010), by the Global Keratoconus Foundation (2014), by M.M. Belin “ABCD” (2020) etc. Modern classifications are based predominantly on the results of the computed (keratotopography) keratometry and keratopachymetry with subdividing the keratoconus into four gradual stages in accordance with the severity degree of the pathological process (with some terminological differences): I — initial stage (early, mild); II — progressed (medium, moderate); III — advanced (severe, advanced); IV — terminal (severe) [7, 12, 33–35].

It is worth noting that in practice it is often not possible to determine the keratoconus stage discretely, for even within a single classification, according to the criteria proposed, the clinical signs of the disease math for the adjacent stages (for example, I–II or II–III). Currently, in clinical work, a possibility came up of using the classifications based on the data from computed optical keratoanalyzers: the staging of keratoconus is being performed automatically with using the diagnostic platform software based on the indexes of irregularity in the shape, the curvature and the thickness of the cornea.

Oftentimes, the categorization by the keratoconus stages in the patients is lacking applied significance for the reason of the presence of individual features of the clinical signs in each individual patient and due to subjective manifestations, due to a variety of treatment and correction options in the clinical centers along with the development of personalized approaches in medicine. For the purpose of defining the tactics to be used when managing the patient, the fundamental value belongs to the clinical course of the disease: progressive keratoconus or stable one (non-progressive). The criteria, defining the extent of therapeutic procedures, are the status of the cornea (thickness, curvature and transparency) and the shape of the protrusion. In accordance with shape defined for the keratoconus-related ectasia, it can be classified as nipple-shaped (or local, having a diameter of up to 5 mm), oval-shaped (5–6 mm in diameter) and round-shaped (ball-shaped, having a diameter of more than 6 mm). In terms of the base area (spreading of ectasia), the keratoconus can be classified as dome-shaped (vast, extended, with broad spreading base) or bell-shaped (local, with a localized base). Taking into account the location of the protrusion apex, the keratoconus can be classified into the lower, the upper and the central ones [1–4, 12].

As for the clinical manifestations, the keratoconus can be clinically manifesting, or clinically expressed (manifesting form, manifesting keratoconus) or subclinical [1–4, 12]. Regarding the term “subclinical keratoconus”, the medical community shows some degree of uncertainty. In general, the literature contains a number of terms, semantically proposing the presence of keratoectasia cases with non-typical symptoms or challenging in terms of verifying the diagnosis (the cases of keratoconus, when the disease has no typical clinical manifestations). The first variant is lacking clear manifesting clinical signs of keratoconus: the ametropy does not progress, the visual functions remain stable for many years, while the parameters of the corneal astigmatism, definable upon using the routine methods of standard

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ophthalmology examination (autorefractokeratometry and visometry with maximal spectacle correction), show no clear signs of irregularity. Oftentimes such patients are being specifically managed by ophthalmologists with the diagnosis of "myopic astigmatism"; due to the fact that the suspected keratoconus in such situations does not develop, the keratotopography examinations are not performed in such patients. The second variant includes the keratoconus at the earliest stages of the disease development, when it is difficult to suspect and verify the diagnosis: the specific biomicroscopic signs are not always visualized and not always one can find the characteristic keratotopography signs, while the ultra- and microstructural degenerative-dystrophic changes in the corneal tissues cannot to be found using accessible methods and they are not to be considered as the principal specific and pathognomonic signs of keratoconus. In such cases (most commonly), the patients with no definitive diagnosis or with the diagnosis of "suspected keratoconus" shall be left under follow-up for monitoring purposes and for the evaluation of dynamic changes in the pathological process. For the designation of both variants, the scientific literature and clinical practice employ a number of terms and definitions: "subclinical keratoconus", "pre-clinical", "latent", "delayed", "non-manifesting", "initial", "early", "topographic", "abortive", "hibernating", "subtle", "aborted", "unfulfilled", "uncompleted", "forme fruste", "suspected keratoconus", but in various contexts and with various semantic meanings [14, 31].

Taking into consideration the advances in diagnostic equipment and practically ubiquitous use of computed corneal analyzers, as of today, it is possible to accentuate two keratoconus stages according to keratotopography findings:

- pre-(kerato)topography stage (the stage of ultrastructural changes, while the keratotopography manifestations are still absent);
- keratotopography stage (the stage of ectatic changes, keratotopographically manifesting stage) [31].

DIFFERENTIAL DIAGNOSTICS

Currently, the term "keratoconus" is used to define the initial, or true keratoconus as an independent idiopathic disease of the cornea, as a type of primary keratoectasia. Regarding the secondary corneal protrusion (post-traumatic, post-inflammatory or post-surgical/post-operative or iatrogenic), it is more correct to use the term "secondary keratoectasia" [1–4, 33–39].

Upon examining the keratoconus patients, the differential diagnostic shall be carried out keeping in mind both the primary (idiopathic) and the secondary keratoectasias (developing due to the traumatic lesions in the cornea, due to past episodes of inflammatory diseases, surgical interventions or some independent types of corneal dystrophias). The primary ones include the pellucid marginal degeneration (transparent marginal dystrophy), the keratoglobus and the congenital posterior keratoconus; the secondary ones include the post-surgical (post-keratorefractive, iatrogenic) keratoectasia (secondary keratoconus); the Terrien's marginal degeneration; the Mooren's ulcer and other independent (including the idiopathic, autoimmune, rheumatoid and allergic) marginal impairments of the cornea; the senile furrow degeneration; the deformation of the cornea due to long-term wearing contact lenses [1, 3, 4 12, 40–43]. Besides, the differential diagnostics requires the clarification of such terms as «acute keratoconus» and «posterior keratoconus».

Acute keratoconus, or corneal hydrops (hydropsy) — is a status associated with stromal edema, acutely developing as a result of a rupture in the Descemet's membrane; it can occur both as an emergency acute complication of the keratoconus at its terminal stage or as an independent disease due to other causes [1, 3, 4, 17, 44].

Posterior keratoconus is a term that can be used both in terms of the independent congenital corneal status (with multiple concomitant development abnormalities of the eyeball and of the organism in general) and in terms of the clinical cases, in which signs of keratoectasia are observed only in the posterior surface of the cornea (generally, based on the results of combined examination of the cornea using computed optical keratoanalyzers) [1, 3, 4, 12].

CONCLUSION

Currently, the gold standard in the diagnostics of keratoconus is a combined examination of the cornea using modern computed optical keratoanalyzers, the role of which has significantly increased due to the necessity for timely and maximally early verification of this disease, which is caused by wider spreading of keratorefractive surgeries. Besides, the maximally early diagnostics of keratoconus at the initial stages of its development allows for arranging timely treatment, directed to ceasing the keratoectasia progression, to the stabilization of the pathological process and to preserving the visual functions among young patients of employable age at a sufficiently high level. The wide use of computed optical keratoanalyzers in clinical practice has resulted in a growth in the rates of

detecting the keratoconus at its early stages, as well as the case of keratoconus with no signs of progression — the subclinical forms of keratoectasia. Nevertheless, it should be kept in mind that the routinely employed ophthalmology methods allow for (in a number of cases) clearly verifying the keratoconus, including its earliest stages, preceding the keratotopography manifestations.

ADDITIONAL INFORMATION

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VENOUS THROMBOSES AND THROMBOEMBOLISM IN ONCOLOGY PATIENTS

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ABSTRACT

Deep vein thrombosis and pulmonary artery thromboembolism are the most commonly occurring cardio-vascular complications of oncological diseases, which may develop at any stage of the oncological process. These life-threatening complications take the leading positions within the structure of mortality among cancer patients, giving place only to the oncology disease itself. It is important to note that the patients with cancer-associated thromboses are the most difficult group of patients, in which the development of thromboses and thromboembolisms may not only delay the vitally important treatment of the main disease, but also to completely cease the treatment due to the lack of possibility for its adequate performing. This is an important social and economic task, taking into consideration the costs for the healthcare system required to treat the disease itself and its concomitant complications. Thus, there is a criticality factor of not only the treatment itself, but also of the prevention of oncology-associated thromboses and thromboembolisms. Currently, due to the wide spreading of the said complications, the therapy and the prevention of them undergo significant changes. The traditionally used warfarin is being switched to low molecular weight heparin. At the present moment, oral anticoagulants are used more and more often. The analysis of special scientific literature has allowed for evaluating the novel principles of treatment in cases of oncology-associated thromboses and thromboembolisms depending on the location of the process, on its stage, on the severity of the patient status, as well as to define the risk factors of oncology-associated thromboses, the practicability and possible methods of its prevention in various groups of patients.

Keywords: *deep vein thrombosis; pulmonary embolism; cancer-associated thrombosis.*

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BACKGROUND

Deep vein thrombosis and pulmonary artery thromboembolism are the most frequent cardio-vascular complications of oncological diseases, which may occur at any stage of tumor development [1, 2]. Thromboses, both venous and arterial, as well as the embolisms related to them, represent the second major cause of mortality among the oncology patients right after the complications related to cancer diseases. Venous thromboembolisms may precede the oncology disease or may occur at any stage of cancer development or even at the stage of its successful treatment [2, 3].

Thromboembolism affects the course of the oncology disease, compelling to pause or delay the vitally important anti-tumor therapy [4, 5]. The rate of venous thromboembolisms in oncology patients is 4–7-fold higher than in healthy individuals [6]. The improvement of the survival rate in oncology patients results in an increase in the rates of venous thromboembolisms, first of all, due to the extension of the survival among the oncology patients, secondly, due to the wide use of central venous catheters/ports and the increased rates of thromboses caused by them.

It is also important to note that the diagnostics of oncology-associated thromboses has become widely accessible [7]. In general, patients with oncology-associated thrombosis represent a more severe group of cancer patients: the morbidity levels among them are significantly higher comparing to the individuals of the same age and gender without oncology diseases [8]. About 15% of the patients with oncology diseases develop venous thromboembolisms and, on the contrary, 20% of non-induced venous thromboembolisms may be the first signs of malignant neoplasms [9]. Arterial thromboses and ischemic heart disease also occur more often among the oncology

ВЕНОЗНЫЕ ТРОМБОЗЫ И ТРОМБОЭМБОЛИИ У ОНКОЛОГИЧЕСКИХ БОЛЬНЫХ

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АННОТАЦИЯ

Тромбоз глубоких вен и тромбоэмболия лёгочной артерии — наиболее часто встречающиеся сердечно-сосудистые осложнения онкологического заболевания, которые могут возникать на любой стадии онкологического процесса. Эти жизнеугрожающие осложнения занимают лидирующие позиции в структуре смертности у онкобольных, уступая место только самому онкозаболеванию. Необходимо заметить, что пациенты с онкоассоциированными тромбозами — это наиболее тяжёлая группа больных, у которых возникновение тромбозов и тромбоэмболий может не только отсрочить жизненно важное лечение основного заболевания, но и полностью исключить его ввиду невозможности проведения адекватной терапии. Это важная социальная и экономическая задача, учитывая затраты здравоохранения на лечение самого заболевания и сопутствующих осложнений. Таким образом, остро стоит вопрос не только самого лечения, но и профилактики онкоассоциированных тромбозов и тромбоэмболий. В настоящее время в связи с распространением данных осложнений лечение и профилактика претерпевают большие изменения. Традиционно использовался варфарин, на смену которому пришёл низкомолекулярный гепарин. На данный момент всё чаще используются пероральные антикоагулянты. Анализ специальной научной литературы позволил оценить новые принципы лечения онкоассоциированных тромбозов и тромбоэмболий в зависимости от локализации процесса, его стадии, тяжести состояния пациента, а также определить факторы риска онкоассоциированных тромбозов, целесообразность и возможные методы их профилактики в разных группах пациентов.

Ключевые слова: *тромбоз глубоких вен; тромбоэмболия лёгочной артерии; онкоассоциированные тромбозы.*

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patients comparing to the groups of individuals comparable by age but with no cancer diseases [10]. Venous thromboembolism in case of cancer is not limited to the deep vein thrombosis and pulmonary artery thromboembolism. There are also the so-called atypical thromboses in the veins of the upper limbs and of the visceral organs [11].

PREVENTION AND TREATMENT OF ONCOLOGY-ASSOCIATED VENOUS THROMBOSES: NEW TREATMENT SCHEMES, APPROACHES AND STRATEGIES

New trends in the treatment of oncology-associated thromboses

Anticoagulant therapy, primarily with low molecular weight heparins, was and still remains the basics of therapy for venous thromboembolisms. However, in recent years, a clear shift can be seen towards the use of direct oral anticoagulants in oncology patients with venous thromboembolisms. Large-scale randomized clinical trials in oncology patients with deep vein thrombosis, aimed for primary and secondary prophylaxis of pulmonary embolism, have demonstrated a comparable degree of safety and not lesser efficiency of low molecular weight heparins or vitamin K antagonists in secondary prophylaxis of pulmonary embolism and deep vein thrombosis. The heads of the professional communities of the Western countries, as well as the Russian Society of Cardiology have recently changed their approach to primary prevention and to the treatment of deep vein thrombosis and pulmonary embolism in oncology patients [12–16].

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Risk factors of venous thromboses and pulmonary embolism in oncology patients

A number of risk factors of venous thromboembolism, for example, age, smoking, obesity, inactive lifestyle, arterial hypertension and diabetes mellitus, are related to the patient [17]. Other risk factors are related to the type and the location of the oncology process. As it is shown in table 1, some types of antitumor therapy also increase the probability of developing thrombi [18].

The age is a risk factor of venous thromboembolism both in patients with malignant neoplasms [20] and in the general population. In one retrospective research, the patients aged above 70 years and receiving chemotherapy, had an increased risk of developing venous thromboembolism comparing to younger patients (11% versus 6%) [21]. The functional status of the patients is also important: the decreased working capacity due to hypodynamia can increase the risk of venous thromboembolism [2].

Hereditary trombophilia is a significant risk factor that increases the probability of venous thromboembolism in oncology patients. The presence of a rare genetic risk factor, such as the deficit of antithrombin, of protein C, of protein S or of the factor V Leiden, increases the risk of venous thromboembolism at the young age [22]. Concomitant diseases, such as chronic pulmonary and renal diseases, anemia, infections and obesity — all of these increase the risk of venous thromboembolism in oncology patients 1.5-fold [20]. Finally, oncology patients with a past medical history of venous thromboembolism have 6 to 7 times higher risk of repeated venous thromboembolism comparing to cancer patients without venous thromboembolism [23].

Tumor location also affects the rate of venous thromboembolisms. The tumors located in the brain and in the pancreatic gland, are associated with the highest risk of pulmonary embolism [24]. Cancers of the stomach, esophagus, ovaries and lungs are also associated with high risk of deep vein thrombosis and pulmonary embolism. Especially dangerous are the hemoblastoses, the non-Hodgkin lymphomas and multiple myelomas [18]. The risk of venous thromboembolism increases upon regional or metastatic spreading of the malignant tumor [25], and the number of such patients is constantly increasing. About 50% of the patients with venous thromboembolism at the time of diagnosis already have metastases. The highest risk of deep vein thrombosis is reported during

Table 1

Risk factors for venous thromboembolism in cancer patients (modified from source [19])

Risk factors	
Related to the patient	Demographic data: elderly age, female gender Obesity Smoking Low physical activity Concomitant diseases (ischemic heart disease, hypertensive disease, atrial fibrillations, atherosclerosis, cardiac insufficiency, infectious diseases, sepsis, diseases of kidneys and liver, lung diseases, systemic diseases, diabetes mellitus) Past history of venous thromboembolism Hereditary trombophilia Number of platelets before therapy: ≥350×10^9/l, number of leucocytes before therapy: >11×10^9/l, hemoglobin level <100 g/l
Related to the oncology disease	Primary focus of cancer (lungs, colon/rectum, stomach, pancreatic gland, ovaries, prostate gland, urinary bladder, kidneys, brain, lymphoma, myeloma) Histogenesis of the tumor (adenocarcinoma) Malignant neoplasm stage: late stage of the tumor process, metastatic process Time from the inset of the diseases: more often during the first 3–6 months of the disease Significant enlargement of regional lymph nodes with the compression of adjacent vessels
Related to therapy	Major surgery Hospitalization Chemotherapy and anti-angiogenic medications Hormonal therapy Blood transfusions Medicinal products stimulating the erythropoiesis Presence of central vein catheter

the first 3 months after setting the adenocarcinoma diagnosis, while the probability of deep vein thrombosis eventually becomes slightly decreased. Nevertheless, when comparing the population of oncology patients to the comparable group of population not having cancer diseases, the risk of venous thrombosis in oncology patients remains increased all the time (from the moment of setting the diagnosis to 15 years of follow-up) [26].

Factors of deep vein thrombosis and pulmonary embolism, related to the treatment

Sadly, but the probability of venous thromboembolism also increases with a background of successful treatment for malignant diseases. Surgical interventions, some types of antitumor therapy and other therapeutic procedures can result in venous and arterial thromboembolisms. Minor pelvis and abdominal surgeries in oncology patients increase the risk of postoperative deep vein thrombosis and pulmonary embolism 2–3-fold comparing to the patients without oncological diseases and with similar interventions [27–30]. Systemic chemotherapy increases the risk of venous thromboembolism by a factor of 2–6 [31]. It was found that Cisplatin therapy doubles the risk of thromboembolic complications comparing to Oxaliplatin in patients with stomach and esophageal cancer [32]. Immunomodulating medicines used for multiple myeloma (Thalidomide, Lenalidomide), increase the risk of venous and arterial thromboembolisms [33], while the medicinal products suppressing the angiogenesis, such as Bevacizumab, containing monoclonal antibodies against vascular endothelium growth factor receptors (VEGFR), increase the risk of developing arterial thromboembolisms [34, 35]. Targeted therapy agents Sorafenib and Sunitinib increase the risk of thromboses [36]. Immune checkpoint inhibitors also increase the risk of both venous and arterial thromboembolism due to the cellular type of immune response, due to the expression of inflammatory cytokines and due to complement-mediated inflammation [37]. Supporting therapy with Erythropoietins, blood transfusions, often so necessary for oncology patients, also promote to developing venous thromboses in them [38].

Laboratory markers of oncology-associated thromboses

Some biomarkers indicate the increased risk of oncology-associated thromboses. High degree leukocytosis/thrombocytosis and low hemoglobin levels before chemotherapy increase the risk of venous thromboembolism [39]. These tests that are available in practice can be successfully used for the purpose of defining the probability of venous thrombosis [40].

D-dimer, a small fragment of the protein produced upon the degradation of fibrin, was investigated as a prognostic biomarker of venous thromboembolism in cases of oncology disease. High D-dimer levels were associated with elevated risk of venous thromboembolism [41]. It is worth noting that D-dimer levels often become elevated in oncology patients, even without the thrombosis: the levels are variable from one laboratory to another, and there is no general consensus on what levels of D-dimer can be considered an indicator of high risk of thrombosis.

Other molecules were also studied, including the P-selectin and the microparticles forming the tissue factor, along with their potential role in predicting venous thromboembolism. P-selectin was integrated into the risk assessment models together with the clinical factors [42]. As of today, the research works on the evaluation of the prognostic benefits of tissue factor microparticles show controversial results, and, in clinical practice, the risk scales are more commonly used.

Predicting the risk of venous thromboembolism using risk scales

It is very important to determine in advance, which patients with oncology diseases are subject to the highest risk of venous thromboembolism. For this purpose, the venous thromboembolism risk assessment models were developed [43]. The first and the most popular risk assessment model for venous thromboembolism in out-patient oncology patients was proposed in the research works headed by A.S. Khorana [39, 44]. The Khorana scale was developed based on the analysis of the data from 2701 patients, while its benefits were confirmed during the retrospective and prospective research works with the participation of more than 35,000 patients [45]. This scale was based on using 5 variables, such as the type of oncological disease, the values of clinical hematology panel parameters (hemoglobin, platelets and leucocytes) and the body mass index, which need to be evaluated before the initiation of chemotherapy. Each variable had a single point assigned, except for the high risk subclass, to which 2 points were assigned. The Khorana scale remains an instrument for risk assessment, which was included into practically all the recommendations.

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The novel research works show that using the Khorana scale can be useful for early detection of venous thromboembolism using ultrasound diagnostics. Despite this fact, currently, the international guidelines do not include this aspect, while in one of the multicenter research, the venous thromboembolism was detected in about 9% of the patients from the high risk group (>3 points of the Khorana scale) [46].

During the pilot research, it was shown that electronic alerting can be useful for early detection of deep vein thrombosis and may prevent hospitalization [47].

The evaluation of the risk of developing cancer-associated thromboses using the Vienna system, besides the five parameters mentioned above, also includes the levels of D-dimer and soluble P-selectin, which has increased the predicting value of the system, however, independent clinical trials have not confirmed it [42].

As for the arterial thromboses and embolisms, currently there is no verified instruments for risk assessment and predicting the arterial thromboembolisms in oncology patients.

Prophylaxis of venous thromboembolism in oncology patients during surgical intervention

Surgical intervention is a well-known risk factor for venous thromboembolism in oncology patients when compared to the patients without oncology diseases, undergoing surgical treatment [48]. All the patients with active malignant neoplasms with a past history of major surgical interventions, must receive medicinal prophylaxis of venous thromboembolism. The postoperative prophylaxis of thrombosis at the In-Patient Department is a currently accepted standard. But, in oncology patients, the risk of thrombosis is increased and, after the discharge from the in-patient department, the prolongation of thrombosis prevention in such patients at the out-patient phase would be logical. Several research works have studied the efficiency of prolonged anticoagulant therapy (up to 4 weeks) comparing to the intrahospital prevention of venous thromboembolisms (for 7 to 10 days) in oncology patients after surgery. The results have demonstrated a significant — from 12 to 4.8% (by 60%) — decrease in the rate of venous thromboembolism when using the prolonged prevention, with the risk of major hemorrhages and of fatal outcomes not being increased [49]. On that basis, the current standards of therapy from the American Society of Clinical Oncology (ASCO) recommend all the patients with malignant diseases scheduled for major surgical intervention, to use the pharmacological prevention of thromboses or unfractionated heparin at a dosage of 5000 U within 2 to 4 hours before surgery and every 8 hours after surgery, or low molecular weight heparin at a dosage of 40 mg from 10 to 12 hours before surgery and then 40 mg once daily after surgery in the absence of contraindications (active hemorrhage, risk of major hemorrhage and other contraindications).

The prevention of venous thromboembolism should be continued for 7 to 10 days. In high risk patients, for example, with restricted mobility, obesity, past episode of venous thromboembolism or in case of other additional risk factors, prevention of venous thromboembolism should be continued for up to 4 weeks after surgery. For patients with low risk level, the decision on the duration of the prophylaxis of venous thromboembolism shall be drawn up on an individual basis [12].

In some other recommendations, prolonged prophylaxis of venous thromboembolism after discharge from the in-patient department was also approved for up to 4 weeks for oncology patients with a history of major surgery in the abdominal cavity or in the minor pelvis [14, 16]. Practically all the recommendations for prolonged prophylaxis, as well as for the intrahospital prophylaxis, suppose the use of low molecular weight heparins.

Prophylaxis of venous thromboses in hospitalized oncology patients

Among the hospitalized patients with malignant neoplasms, a lot of concerns remain unclear regarding the issues of primary prevention of thrombosis, despite the fact that the interrelation between the oncology disease and the venous thrombosis is well known. According to the register of deep vein thrombosis in the USA, hospitalized patients with malignant neoplasms less often receive preventive treatment of venous thromboembolism comparing to other patients without oncology diseases (28% versus 35%). The main reasons include the active hemorrhage, the concerns on possible hemorrhages or thrombocytopenia [50].

As of today, there are no ideal medications and optimal schemes for preventing venous thromboembolisms among hospitalized oncology patients. J.I. Zwicker et al. [51] have confirmed the high efficiency of fixed dosages of Enoxaparin used for the prevention of deep vein thrombosis and have demonstrated that thrombo-prophylaxis with low molecular weight heparins with taking into consideration the weight of the patient is effective and safe.

For the purpose of the optimal prophylaxis of venous thrombosis, various scales are used, one of which is the Padua scale. In this scale, the maximum of 3 points is assigned in case of an active oncology disease and previous venous thromboembolism. In case of decreased mobility and the presence of known trombophilia, according to this scale, the risk grade is 2 points. One point is assigned in case of having a recent trauma and/or surgery (within a time period of 1 month), in case the patients are aged 70 years and older, in case of having a cardio-vascular disease or infectious/rheumatic disease, obesity (body mass index >30 kg/m^2) or concomitant hormonal therapy [52].

Sadly, despite the fact that all the abovementioned systems of estimation include the diagnosed oncology diseases, they do not take into account the risk probability depending on specific types of tumors. Besides, the analysis of literature sources shows that the preventive dosages of low molecular weight heparins, which are being ubiquitously used (Enoxaparin 40 mg; Dalteparin 5000 ME; Fondaparinux 2.5 mg), may be insufficient for decreasing the total rates of venous thromboembolisms and may be non-optimal for high risk groups of patients [53]. The capabilities of the Khorana scale to predict venous thromboembolisms in hospitalized patients were demonstrated during the retrospective research [54], where it was shown that higher benefits of preventing venous thromboembolisms were observed in patients with high Khorana indexes. However, it is quite evident that the existing scales are not comprehensive and there is a need for further research works on the implementation of risk assessment systems into clinical practice for hospitalized and out-patient oncology patients.

The duration of the prevention of venous thromboembolisms in oncology patients after hospitalization is also not yet defined conclusively. As shown by the EXCLAIM research (extended prophylaxis of venous thromboembolisms in patients with acute diseases and immobilization), the prolongation of anti-thrombotic prophylaxis for up to 28 days (comparing to standard 10 days) results in a statistically significant increase in the risk of hemorrhages with no additional decrease of the rates of venous thromboembolisms [55].

Despite the absence of specific data, also acknowledging the high risk of venous thromboembolisms in hospitalized oncology patients, the current recommendations from the professional societies, such as the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH), extrapolating the knowledge obtained during the research on the prevention of thromboses in patients with somatic diseases, include the following:

- in the absence of contraindications in the hospitalized patients with active malignant neoplasm and acute disease (cardiac insufficiency, acute respiratory disease with chronic pulmonary disease, acute infection, acute rheumatic disease and inflammatory intestinal disease), or in cases of their decreased mobility, the prescriptions shall include pharmacological prevention of venous thromboembolisms;
- the routine pharmacological prophylaxis of venous thromboembolisms is not indicated to patients admitted for undergoing minor procedures or chemotherapy, as well as to patients receiving administrations of stem cells or bone marrow transplantation [12, 16].

Prophylaxis of thrombosis in the out-patients with oncology diseases

Up to 74% of all the venous thromboembolisms related to cancer, occur exactly during the out-patient period [56]. The retrospective analysis of the medical insurance reports from the IMPACT (USA), conducted by G.H. Lyman et al. [57], indicates that the joint rate of venous thromboembolisms within 3.5 months from the initiation of chemotherapy is 7.3%, while in 12 months it reaches 13.5%. The rate of venous thromboembolisms varies significantly depending on the location of the oncology process and on the stage of diseases [57].

In the 1990-s, for the first time, the results were published on the thrombo-prophylaxis in oncology patients, and its was shown that the use of low Warfarin dosages in women with metastatic breast cancer results in a decrease of the relative risk of venous thromboembolism by 85%, with this, no increase was noted in the rate of hemorrhages comparing to the control group of patients [58]. Quite recently, several research works were carried out, devoted to the thrombo-prophylaxis in the out-patient settings among the patients with malignant neoplasms (pancreatic cancer and multiple myeloma), including the patients with high risk of venous thromboembolisms. During the PROTECHT trial (prophylaxis of thromboembolic during chemotherapy) [59], the participants included the patients with lung cancer, breast cancer, gastrointestinal tract cancers, as well as with the malignant tumors of the head /neck area and ovaries. The patients, according to the randomized sample,

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were receiving Nadroparin (3800 U) subcutaneously or placebo: venous thromboembolisms in patients of high risk group were reported in 4.5% and 11.1% of the cases, respectively. As for the rate of hemorrhages, the groups did not differ. Similar results were observed in the SAVE-ONCO research (Semuloparin for thromboprophylaxis in patients, receiving chemotherapy due to the presence of cancer), in which the patients with any metastatic or locally spreading solid tumor, receiving chemotherapeutic agents, were randomized into two groups, one of which was receiving the low molecular weight heparin Semuloparin, while the other group was receiving placebo. The research have demonstrated a significant decrease in the rate of developing venous thromboembolism in patients of the Semuloparin group without increasing the rate of serious hemorrhages [60]. The subgroup analysis of the data obtained in this research have shown that, for preventing a single case of thrombosis, it is sufficient to treat 25 patients from the high risk group.

In a recently updated Cochrane review [61] it was noted that primary thromboprophylaxis using low molecular weight heparins allows for significantly decreasing the rates of symptomatic venous thromboembolisms among the out-patients with oncology diseases, receiving chemotherapy. If the anticipated risk of venous thromboembolism is 7.1 per 100 patients, this means that 30 patients need to be treated in order to prevent a single thromboembolic event. These results once again confirm the necessity of stratifying the risk of thromboembolism in oncology patients for defining the groups of patients, in which the benefit significantly overweighs the risks of hemorrhages.

The benefits of anticoagulant therapy were proven during the research works in groups of patients with tumors showing high thromboembolic risk [62, 63]. The benefits of thromboprophylaxis were also reported in patients with multiple myeloma. In one of the research, a comparison was made of the efficiency and of the safety of thromboprophylaxis with low-dose aspirin or low molecular weight heparins in patients with newly diagnosed multiple myeloma, receiving Lenalidomide therapy. A decrease was shown in the rate of venous thromboembolism without serious hemorrhagic complications when using both the low molecular weight heparins and the aspirin [5]. Multiple myeloma is the only group of malignant neoplasms, in which it is justified to use aspirin for the prevention of venous thromboembolism.

Direct oral anticoagulants, especially factor Xa inhibitors, such as Apixaban, Rivaroxaban and Edoxaban, are well studied in patients with oncology diseases. Currently, three factor Xa inhibitors were approved by the regulating authorities in Europe and USA for the treatment of oncology-associated thromboses (in Russia — only Apixaban and Rivaroxaban). But the factor Xa inhibitors, or xabans (from the English Xa), were not certified for primary prophylaxis of venous thromboembolism, except for orthopedic surgery or some clinical situations. The dosage modes for factor Xa inhibitors for the prevention and treatment of venous thromboembolism are provided in table 2.

Data on the efficiency and safety of xabans during the primary prophylaxis of venous thromboembolism in oncology patients have been obtained at the beginning of 2019, when data became available from two large randomized controlled researches — CASSINI (Rivaroxaban for thromboprophylaxis in out-patients with cancer assigned to the high risk group) and AVERT (Apixaban for the prevention of venous thromboembolism in cancer patients), where the efficiency and the safety of xabans was evaluated for thromboprophylaxis in out-patients with active oncology disease and with high risks of venous thromboembolism. In general, both research works have shown the benefits of using direct oral anticoagulants in oncology patients for the purpose of primary prevention, which, however, is mitigated by the increased risk of hemorrhages. For the purpose

Table 2

Therapeutic and prophylactic doses of direct oral anticoagulants [19]

Drug	Dosage	
	Preventive	Therapeutic
Apixaban	2.5 mg twice daily	Initial dosage — 10 mg 2 times/day, 7 days, then 5 mg twice daily
Rivaroxaban	10 mg once daily	Initial dosage — 15 mg 2 times/day, 21 days, then 20 mg once daily
Edoxaban	Not used	60 mg/day, at least after 5 days of therapy, with low molecular weight heparin

of defining the role of direct oral anticoagulants in the primary prophylaxis of deep vein thrombosis and pulmonary embolism in oncology patients, further research is required. It must be stressed that the prescription of anticoagulants based only on the increase in the level of D-dimer, is insufficiently justified.

Summarizing the accumulated experience and the currently available international recommendations, the following can be summed up:

- the routine pharmacological prophylaxis is not indicated to all the patients with oncology diseases;
- the out-patients with oncology disease of high risk group (≥2 points of the Khorana scale before the initiation of chemotherapy) can be a justified group for using thromboprophylaxis with Apixaban, Rivaroxaban or low molecular weight heparins: the decision on the use of anticoagulants should be conferred with the patient taking into consideration the benefits and harms, the cost of medicinal products and the therapy duration;
- patients with multiple myeloma, receiving Talidomide or Lenalidomide (in combination with dexamethasone), shall receive thromboprophylaxis with Aspirin or low molecular weight heparin in case of low risk and with low molecular weight heparin in high risk situations [12, 16].

Treatment and secondary prophylaxis of venous thrombosis and pulmonary embolism: the choice of therapy and therapy duration

The correct treatment for venous thromboembolism in oncology patients is critically important, for both the recurrent venous thromboembolisms and the hemorrhages negatively affect the survival [5]. Currently, there are various available variants for antithrombotic therapy for oncology patients with thromboses. Traditionally, for the treatment of oncology-associated venous thromboembolism, Vitamin K antagonists were used. Low molecular weight heparins are superior comparing to vitamin K antagonists by the efficiency and the safety, and they still remain the main means for the treatment of thromboembolic events in oncology patients within the two last decades. The foundational CLOT research (comparison of low molecular weight heparins and Warfarin in cases of venous thromboembolism) was carried out in patients with oncology diseases and with acute symptomatic venous thromboembolism, compellingly proving the superior efficiency of low molecular weight heparins versus vitamin K antagonists during the long-term (6 months) treatment [64]. During the treatment period of 6 months, 8.0% of the patients in the Dalteparin group had recurrences of venous thromboembolisms, while in the group receiving vitamin K antagonists, recurrences of venous thromboembolisms were reported in 15.8% of the cases (p=0.002). No significant difference was found between the two groups in terms of the rate of any types of hemorrhages.

In a later CATCH research (comparison of hemostasis treatment methods in cancer patients), comparison was made of treatment results obtained with using low molecular weight heparin Tinzaparin at a dosage of 175 IU/kg once daily for 6 months and with using the treatment with Tinzaparin, initially for 5 to 10 days with further transition to Warfarin with achieving the target INR levels (international normalized ratio) of 2–3. Just like in the CLOT research, the rate of venous thromboembolisms has decreased from 10% in the Warfarin group to 6.9% in the Tinzaparin group, though the results were not statistically significant (p=0.07). The occurrence rate of serious hemorrhages was similar in both groups, while the rate of minor hemorrhages was significantly lower in the Tinzaparin group (11% and 16%; p <0.03) [65].

Based on the data from the CLOT research [64] and from the Cochrane review [66], international associations recommend low molecular weight heparins as the first line therapy for short-term and long-term therapy of oncology-associated venous thromboses and pulmonary embolism [12, 14]. However, such a therapy is not always applicable: frequent subcutaneous injections are the evident impediment for following the correct treatment mode. Besides, the presence of renal failure and the cost of low molecular weight heparins restrict the possibilities of their wide use. In real-life clinical practice, vitamin K antagonists are still often used in oncology patients with venous thromboses, taking into consideration the simplicity of oral intake and the relatively low cost, despite the fact that they are not recommended as the preferable treatment for oncology-associated venous thromboembolisms [67].

Currently, direct oral anticoagulants are recommended as the first line therapy in patients with deep vein thrombosis and pulmonary embolism without oncological diseases. Up until recently, their use in cases of oncology-associated thromboses was not recommended, however, the results of three research works on the direct comparison of direct oral anticoagulants and low molecular weight heparins became widely accessible. The HOKUSAI-VTE

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research (Edoxaban for the treatment of venous thromboembolism, associated with cancer) had randomized 1050 patients with oncology diseases and with acute symptoms or accidentally diagnosed venous thromboembolisms. One group was receiving Edoxaban (at a daily dosage of 60 mg) after the initiation of therapy with low molecular weight heparin — Dalteparin, while the comparison group continued Dalteparin therapy for 6 to 12 months. The follow-up duration was 9 months [6]. The main endpoint (cases of first repeated venous thromboembolism or major hemorrhage within 12 months) was observed in 12.8% of the patients in the Edoxaban group and in 13.5% in the Dalteparin group (OP=0.97; p=0.006). Edoxaban was not inferior comparing to Dalteparin in terms of anti-thrombotic efficiency regardless of the therapy duration (OP=0.97; p=0.006 for non-inferiority). By the recurrence rates of venous thromboembolisms, the groups of Edoxaban and Dalteparin did not differ (7.9% versus 11.3%; p=0.09), while the rate of major hemorrhages was higher when taking Edoxaban comparing to Dalteparin (6.9% versus 4.0% respectively; p=0.04). Hemorrhages were especially often observed in patients with gastrointestinal tract cancers (12.5% versus 3.6%; p=0.005).

The proofs of efficiency of direct oral anticoagulants were also obtained in the randomized SELECT-D research [68], in which 406 patients with symptomatic or asymptomatic venous thromboembolisms were randomized to receive Rivaroxaban (with a dosage of 15 mg twice daily for 3 weeks with further transition to 20 mg once daily) or Dalteparin (with a dosage of 200 IU/kg daily for 1 month, then 150 IU/kg daily for 6 months). After six months of follow-up, the cumulative rate of venous thromboembolism recurrences was significantly lower in the Rivaroxaban group comparing to the Dalteparin group (4% versus 11%; OR=0.43). By the rate of serious hemorrhages, the groups did not differ (6% versus 4% respectively; OR=1.83), while the rate of clinically significant small hemorrhages was significantly higher in patients receiving Rivaroxaban therapy (13% versus 4%, respectively; OR=3.76). Just like in the HOKUSAI research, the most serious hemorrhages in the Rivaroxaban group (in 7 out of 11) were reported in patients with tumors of the gastrointestinal tract, clinically significant small hemorrhages were also developing in the gastrointestinal tract (in 9 out of 25) or in the urogenital tract (in 11 of 25). When taking Rivaroxaban, hemorrhages were reported 3 times more often (36% versus 11%) then in the Dalteparin treatment group. More than half of the patients in these research works had metastases (53% and 58% respectively), of which about 70% were receiving active anti-tumor therapy. Moreover, the rate of venous thromboembolism in the group of low molecular weight heparins within the HOKUSAI-VTE and SELECT-D research works (11.3% and 11.0% respectively) was matching with the data obtained in similar research works — CLOT and CATCH (9% and 7.2%, respectively), and the rate of major hemorrhages was also similar (4% for HOKUSAI-VTE and SELECT-D versus 6% and 3% for CLOT and CATCH, respectively).

In another Apixaban research — CARAVAGGIO — a total of 1155 oncology patients with symptomatic or asymptomatic acute proximal deep vein thrombosis or pulmonary artery thromboembolism were randomized [69]. Patients were receiving Apixaban (at a dosage of 10 mg twice daily within the first 7 days, then 5 mg twice daily), or Dalteparin subcutaneously (at a dosage of 200 IU/kg once daily during the first month, then 150 IU/kg once daily). The groups were comparable by all the main clinical characteristics: about 60% of the patients were simultaneously receiving active anti-tumor therapy; 40% of the total number of patients in both groups had colorectal cancer and lung cancer. The recurrence of venous thromboembolism had occurred in 5.6% of the cases in the Apixaban group and in 7.9% in the Dalteparin group (OR=0.63; p <0.001 for non-inferiority). Major hemorrhages, the main clinical safety endpoint, were reported in 3.8% in the Apixaban group and in 4.0% for the Dalteparin group (HR=0.82; p=0.60). This is by what the CARAVAGGIO research differs from the previous similar research works, where the rate of hemorrhages in the group receiving direct oral anticoagulants was higher. Special mention should go to the hemorrhages in the gastrointestinal tract, the rate of which in the CARAVAGGIO research was similar in the Apixaban and Dalteparin groups.

In the ADAM-VTE small pilot research (Apixaban and Dalteparin for active venous thromboembolism, associated with malignant neoplasms), a decrease in the rate of venous thromboembolism recurrences was demonstrated in the Apixaban group without increasing the rate of hemorrhages [6].

Based on the accumulated data, the latest ASCO recommendations state that, for the purpose of long-term anticoagulant therapy (not less than 6 months) in cases of oncology-associated venous thromboembolisms, it is more preferably to use low molecular weight heparins or direct oral anticoagulants, which are more effective than vitamin K antagonists. Vitamin K antagonists can be used if low molecular weight heparins or direct oral

anticoagulants are not available. When using direct oral anticoagulants (except for Apixaban), the risk of serious gastro-intestinal hemorrhages is increased, just like the risk of hematuria in cases of urogenital tract tumors. The cautiousness when using the direct oral anticoagulants is also justified in other settings with a high risk of damage in the mucosal membranes. When selecting the direct oral anticoagulants, drug-to-drug interactions should be taken into account. Thus, factor Xa inhibitors should not be used simultaneously with potent inhibitors or inductors of P-glycoprotein or cytochrome P450 3A4 [12].

As of today, there are no research works that can evaluate the optimal duration of anticoagulant therapy in case of oncology-associated venous thromboembolisms. For the treatment of venous thromboembolisms in oncology patients, current guidelines have recommended using anticoagulants for at least 6 months. In patients with active oncology diseases, it is suggested to increase the duration of anticoagulant therapy. While the oncology process is active, the risk of venous thromboembolism recurrence in patients remains high, and the cessation of anticoagulant therapy due to the reasons not related to serious hemorrhage, results in the recurrences of venous thromboembolism [70]. Only in two prospective multicenter research works — DALTECAN (treatment for venous thromboembolism in oncology patients using Dalteparin for up to 12 months) and TiCAT (Tinzaparin in case of thromboses, related to cancer, lasting for more than 6 months) — the safety and the efficiency were proven for such an approach: the rate of venous thromboembolism recurrences has decreased from 4.5% and 5.7% to about 1% during the 7–12 months of therapy [71, 72]. These results indicate the benefits of prolonged treatment of venous thromboembolism in oncology patients. On the other hand, regardless of the medicinal product, the treatment of venous thromboembolism for some patients may become permanent. The necessity for long-term anticoagulation should be periodically revised, evaluating the additional risk factors, such as metastatic activity or progression of the disease, venous thromboembolisms in the past, current systemic chemotherapy or the use of thrombogenic drugs, on the one hand, and the risk of hemorrhages — on the other.

The current ASCO recommendations propose the following:

- anticoagulant therapy can be initiated with low molecular weight heparins (in case of normal renal functions, low molecular weight heparins are more preferable than non-fractioned heparin), with Fondaparinux, Apixaban or Rivaroxaban;
- low molecular weight heparin, Apixaban, Edoxaban or Rivaroxaban are more preferable than vitamin K antagonists for long-term anticoagulant therapy (for not less than 6 months);
- the use of direct oral anticoagulants is associated with an increased risk of hemorrhages, especially in cases of malignant neoplasms of the gastrointestinal tract;
- prolongation of anticoagulant therapy after the first 6 months should be taken into account for patients with metastatic tumors and/or when continuing the active antitumor therapy with periodical revision of the risk/benefit ratio of such therapy.

Asymptomatic and incidentally diagnosed venous thromboembolism

The venous thromboembolism that was detected upon scanning and that has no clinical manifestations at the moment of diagnosing, represents the half of all the cases of venous thromboembolism in oncology patients [6]. Besides the pulmonary embolism and deep vein thrombosis, the incidental findings also include thromboses of the visceral veins. In a group of patients with malignant neoplasms located in the gastrointestinal tract, deep vein thrombosis was incidentally diagnosed in half of the cases (35% of the total number of cases were pulmonary artery thromboembolisms), while the other thromboses were asymptomatic thromboses of the central vein catheter [73]. What should be done in situations like this, is not quite clear, however, retrospective research works and registers show that the data on the mortality and on the deep vein thrombosis recurrences do not differ in cases of asymptomatic and clinically manifesting venous thromboembolisms [74]. Based on this, the current recommendations propose a similar approach to therapy, meaning the long-term anticoagulant therapy both for incidentally diagnosed pulmonary embolism and in patients with symptomatic pulmonary artery thromboembolism.

In a recent ASH review [75], the treatment of incidentally diagnosed venous thromboembolisms should differ depending on the location of the thrombus. Anticoagulant therapy is clearly recommended for proximal thrombosis of the deep veins, for segmental pulmonary embolism and multiple subsegmental pulmonary embolism, which are prognostically significant. However, in cases of isolated subsegmental pulmonary embolism without the ultrasonographic

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signs of deep vein thrombosis in the lower limbs, it could be sufficient just to arrange the dynamic clinical and radiological follow-up.

In the treatment of isolated distal deep vein thrombosis, there is also no certainty. At least, two research works [76, 77] have shown that the risk of fatal outcome, recurrence and major hemorrhage is similar for deep vein thrombosis in the proximal and distal segments. These results allow for supposing that the distal deep vein thrombosis may aggravate the prognosis in patients with oncology diseases, while the anticoagulant therapy could be more preferable than the follow-up tactics.

At the current stage, there is insufficient data confirming the benefits of anticoagulant therapy, as well as insufficient data on the treatment dosages and therapy duration for distal thromboses of the deep veins [76, 77]. Finally, anticoagulant therapy in cases of visceral vein thrombosis could be useful for oncology patients with no high risk of hemorrhages, but the scientific data regarding this aspect are insufficient. The recommendations encourage to take an individual decision in each specific case [78]: in particular, incidentally detected venous thromboembolisms should be treated in the same way as the symptomatic ones, taking into consideration their similar Clinical outcomes, except for isolated subsegmental pulmonary embolism.

Repeated venous thromboembolisms with a background of anticoagulant therapy

The recurrence of venous thromboembolism with a background of anticoagulant therapy in oncology patients is not a rare occasion. Low compliance, temporary cessation of therapy due to hemorrhages or surgical procedures, inadequate dosing of anticoagulants, cancer progression or heparin-induced thrombocytopenia — here is the non-inclusive list of the possible causes of recurrent venous thromboembolism. Evidences for each specific treatment are sparse, and the International Society on Thrombosis and Haemostasis (ISTH) have empirically proposed for such cases to use low molecular weight heparins [78]. Patients which have a recurrence of venous thromboembolism, should be switched to therapeutic dosages of low molecular weight heparins, if they are currently receiving therapy with unfractionated heparin, vitamin K antagonists (with adequate control of the international normalized ratio) or direct oral anticoagulants. In patients with oncology disease and with a symptomatic recurrent venous thromboembolism, despite the optimal anticoagulant therapy with low molecular weight heparins, it is necessary to increase the dosage of the latter by 25%. In case when an improvement is observed, the increased dosage of low molecular weight heparins shall remain for the whole treatment period, and, in the absence of clinical effect, further dosage increase can be performed based on the peak values of anti-Xa activity [7]. For the purpose of preventing repeated pulmonary embolisms, in certain situations, a removable cava-filter (IVC) can be implanted [12].

Thus, the specific recommendations for some clinical situations are not based on the evidences, but rather on the opinion from the experts. The International Society on Thrombosis and Haemostasis (ISTH) recommends the following approach: patients with the recurrence of venous thromboembolisms, despite the anticoagulant therapy, shall be switched to low molecular weight heparins, if they are taking other anticoagulants, or they should continue the intake of low molecular weight heparins at higher dosage, beginning from the increase of the current dosage by 25%.

Cases with high risk of hemorrhages, patients with thrombocytopenia

Thrombocytopenia (platelet count less than 100×10^9/l) is a frequent complication of both the oncological process itself and the certain types of chemotherapy, in particular, in patients with hemoblastoses, undergoing the transplantation of hematopoietic stem cells. Despite the increased risk of hemorrhages in cases of thrombocytopenia, the thromboembolic risk in them does not decrease. Besides, as it was shown by the retrospective research [79], long-term thrombocytopenia (more than 30 days) is associated with a quadruple increase of the risk of venous thromboembolism recurrence. To equilibrate the risk of oncology-associated thrombosis and the risk of hemorrhages — this is the main problem in the treatment of thrombocytopenia patients. Not having scientifically proven data for such cases, when evaluating the individual risk, one should take into account the thrombosis burden (dimensions and location), the time from the onset of the event, past episodes of venous thromboembolism and its etiology. For example, catheter-related thrombosis is associated with lower rate of recurrences or pulmonary artery thromboembolism comparing to the thrombotic events. In the same manner, the distal deep vein thrombosis and accidental subsegmental pulmonary artery thromboembolism are, apparently, being referred to the events with lesser risk of massive pulmonary

embolism [80]. On the other hand, hemorrhage is more commonly seen in cases of allogenic transplantation of hematopoietic stem cells, with concomitant coagulation disorders and hepatic/renal failure. However, the risk of hemorrhages is poorly studied in the situations, when the platelet count is within a range from 10×10^9/l to 50×10^9/l. According to the latest recommendations from the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (SSC ISTH) [81], due to the higher risk of recurrence of venous thromboembolism at the acute phase (up to 30 days after the event), it is recommended to use the full dosage of the anticoagulant, if the platelet count exceeds 50×10^9/l. However, as soon as the number of platelets drops below this level, alternative strategies should be considered.

For patients with symptomatic segmental or more proximal pulmonary artery thromboembolism, proximal deep vein thrombosis or with the recurrence of deep vein thrombosis in the past, the indications may include a full-scale anticoagulant therapy and platelet transfusion (the threshold value is 40×10^9/l). On the contrary, for cases of distal deep vein thrombosis, asymptomatic subsegmental pulmonary embolism and catheter thromboses, the double decrease of the dosage is indicated or preventive administration of low molecular weight heparins, if the platelet count is from 25×10^9/l to 50×10^9/l. Generally, anticoagulant therapy shall be ceased in case of thrombocytopenia with less than 25×10^9/l of platelets. In some special situations, preventive dosages could be used even with the thrombocytopenia at the level of 10×10^9/l. The dosage modification strategy for anticoagulants is based on the consensus documents of the expert community and it has no sufficient evidence base [82].

The recurrence risk for pulmonary embolism or deep vein thrombosis decreases after the first 30 days, which is why in the subacute or in the chronic period, the dosage of anticoagulants can be decreased for the purpose of decreasing the risk of hemorrhages and preventing unnecessary blood transfusions. In particular, the decreased dosage (50% of the therapeutic dosage or preventive dosage of low molecular weight heparins) is recommended for the platelet counts from 25×10^9/l to 50×10^9/l. The possibility of temporary cessation of treatment should be considered with the platelet counts less than 25×10^9/l. In some patients with low risk of thrombosis recurrence, it is acceptable to stop the anticoagulant therapy during the whole thrombocytopenia period (with the platelet count of less than 50×10^9/l).

Low molecular weight heparins are currently the preferable anticoagulant for patients with thrombocytopenia. The data on the use of direct oral anticoagulants in patients with oncology-associated thromboses and severe thrombocytopenia (less than 50×10^9/l) are not present currently, though some evidence appear concerning the benefits of such tactics [83]. Based on the available data, installation of the cava-filter should be considered only in patients with absolute contraindication for anticoagulant therapy [84]. In accordance with the recommendations, patients with venous thromboembolism and thrombocytopenia (less than 50×10^9/l) should receive a full dosage of the anticoagulant and, probably, a platelet transfusion within the first 30 days after setting the diagnosis of venous thromboembolism. The preventive dosage of the anticoagulant can be effective and safe during the chronic phase of venous thromboembolism in patients with the platelet count from 25×10^9/l to 50×10^9/l.

Oncology patients with lesions in the brain

Patients with brain tumors have the highest rates of venous thromboembolisms among all the patients with oncology diseases, with rate being just the same as the one in the patients with malignant neoplasms of pancreatic gland and gynecological tumors. Symptomatic venous thromboembolisms develop in 19–29% of the glioma patients — the most widespread primary tumor of the brain.

There are no systematic reviews in the relation of intracranial lesions and the rates of venous thromboembolisms. We can more often see patients with metastases in the brain. In this case, approximately 20% develop venous thromboembolism. Despite the fact that the majority of thrombotic events develop after surgery, the risk of venous thromboembolism persists for the whole follow-up period. In a prospective research by A.A. Brandes et al. [85] with 77 patients having tumors of the central nervous system, which were followed up for over 2 years after surgery, the risk of deep vein thrombosis in 24 months had reached 32%. Currently, for this group of patients, the primary prophylaxis with anticoagulants is not recommended. The treatment for venous thromboembolisms in such patients is complicated by multiple factors, including concomitant diseases and bad working capacity, drug-to-drug interactions and, primarily, the possibility of intracranial hemorrhages, which can be life-threatening. Sadly, but, as of today, there are very few data that could help in making the correct decision, because the patients with intracranial

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tumors are, generally, not being included into large prospective research programs on anticoagulant therapy. The CLOT research had only 27 patients with brain tumors, in 2 of which, intracranial hemorrhages have developed. Special caution should be exercised when prescribing anticoagulants in patients with metastases in the brain, especially in some types of tumors, such as non-small-cell lung cancer or renal cell carcinoma [86].

The retrospective research employing the case-control method (by J. Donato et al. [87]) had attempted to define specifically whether the therapeutic dosage of anticoagulant increases the risk of intracranial hemorrhage. The authors have analyzed the data from 104 patients with venous thromboembolism and parenchymatous solid tumors and metastases in the central nervous system, receiving therapeutic dosages of Enoxaparin, and have compared them to the data from 189 control oncology patients with no anticoagulant therapy. The primary tumor of the brain and hematological malignant neoplasms were the exclusion criteria in the research. The intracranial hemorrhage was defined as the measurable when the focus volume was >1 ml, or as traceable with the volumes of <1 ml. Besides, each hemorrhage was classified as significant, if the hemorrhage volume exceeded 10 ml, and symptomatic — in case of neurological deficit, headache or nausea, changes in the cognitive functions, or if it required surgical intervention [88]. Based on the results of this research, the mean rate of intracranial hemorrhages in 1 year from the moment of treatment initiation was 19% in the Enoxaparin group and 21% in the control group, no statistically significant difference was observed between the groups. No statistically significant differences were detected when evaluating the individual malignant neoplasms with a similar rate of events in the Enoxaparin group and in the control group. The overall survival was also similar in the Enoxaparin group and in the control group (8.4 versus 9.7 months; p=0.65). The data from this research give ground for suggesting that low molecular weight heparins can be safely prescribed to patients with metastatic tumors of the brain without increasing the risk of intracranial hemorrhages.

The current ASCO recommendations do not consider the presence of intracranial lesions as an absolute contraindication for anticoagulant therapy. It is recommended to use an individual approach in each specific case, while among the anticoagulants, the preferable ones shall include low molecular weight heparins.

CONCLUSION

The approaches to the prevention and treatment of oncology-associated venous thromboses are rapidly changing, with new treatment schemes developing. The universally applicable approach, based on using only low molecular weight heparins, is being changed to the individual approaches due to the appearance of new data on the efficiency and safety of direct oral anticoagulants. The initiation of treatment with using direct oral anticoagulants is a novel recommendation in the majority of professional communities — it represents a shift in the paradigm of the treatment for oncology-associated venous thromboembolism. However, this also means a more complex treatment scheme with new issues appearing. The physicians must more thoroughly select the anti-thrombotic drug, must take into account the risks of recurrences of venous thromboembolism and hemorrhages, the potential drug-to-drug interactions, the preferences of the patient and they also must try to define the best strategy in each specific case.

As of today, the role of primary prevention of oncology-associated thromboses is still unclear. The duration of anticoagulant therapy is not yet completely understood in oncology patients with venous thromboembolism. It is difficult to describe the actions to be taken by the specialist in cases of asymptomatic thromboses, detected in the oncology patients during the screening procedures. Taking into consideration the fact that the cancer patient is referred to the group of increased risk in terms of developing thrombi and hemorrhages, the risk stratification still requires perfection. At the current stage, active research on biomarkers are carried out, including the genetic markers, for the purpose of defining the individual risk. The science is focused on transferring the clinical tests and translation research works into healthcare practice. This is an important social task, taking into consideration the costs, related to the treatment of oncology-associated venous thromboembolisms, for the healthcare system.

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and editing of the article; *I.N. Oleynikova* — literature search and analysis, collection and analysis of literary sources, writing of the text and editing of the article; *E.V. Plokhova*, *R.R. Khabazov* — collection of literature, editing of the article.

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CLINICAL CASE OF A NEW METHOD FOR THE OPERATIVE TREATMENT OF A REVERSIBLE FRACTURE OF A HILL–SACHS

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ABSTRACT

BACKGROUND: *The posterior dislocation of the humerus head occurs up to 4.5% of all cases of dislocated humerus. Low prevalence and difficulties in diagnosing this type of injury often lead to the formation of old shoulder dislocations. Old cases of back dislocation of the humerus head, especially with reversible bone defects, are accompanied by limitations of movement in the shoulder joint, expressed by pain syndrome. The presence of bone defects in the head of the humerus makes it necessary to replace the latter with bone or soft tissue structures, in surgical practice tendons of the subcutaneous and sub-carpal muscles are most often used. In old cases, scar post-traumatic rebirth is often impossible.* ***CLINICAL CASE DESCRIPTION:*** *The article presents a new method of operative treatment of the old clutch, in the framework of which the use of a new method of operative treatment of the reversal fracture of Hill-Sachs with a long-term stuck back dislocation of the shoulder is considered. The main goal, which is the operative treatment of reversible osteochondral defect up to 25% of the area of the humerus head, due to the deficiency of bone mass of the shoulder head. By moving the corrugated tendon of the long head of the bicep to the impaction zone and fixing it with anchor clamps in the defect zone, resulting in the stabilization of the shoulder joint.* ***CONCLUSION:*** *The outcome of this clinical case is restoration of the function of the shoulder joint and absence of clinical symptoms of instability in it in the late postoperative period. The use of the proposed method of operative treatment makes it possible to reduce the risks of developing postoperative restriction of movements in the joint, instability of the head of the humerus bone, especially in the long-term cases of dislocation of the head of the humerus.*

Keywords: *Hill–Sachs reversal fracture; posterior shoulder dislocation; remplissage; stabilization of the shoulder joint.*

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BACKGROUND

The posterior shoulder dislocation occurs in 2–4.5% of the cases of traumatic shoulder dislocations [1–3]. In 70% of the cases, the posterior shoulder dislocation is combined with a reverse osteochondral defect in the humeral head, known as the reverse Hill-Sachs fracture [1–3]. As a result of applying excessive traumatic force during the posterior shoulder dislocation, the soft-tissue structures, stabilizing the shoulder joint, are subject to damage, thus, due to the humeral head affecting the posterior margin of the articular surface of the scapula upon the internal rotation of the shoulder / abduction, an impression forms at the anterior-medial segments of the humeral head.

According to results shown by the Russian researches [3, 4], there exist the engaging and the non-engaging variants of the Hill-Sachs lesion, proposed by S. Burkhart and J. de Beer. Upon the engaged types of lesion, the axis of the posterior margin of the articular surface of the scapula coincides with the impression vector in the humeral head and the defect imitates the “hooking” of the posterior-inferior margin of the articular surface of the scapula. On the contrary, in cases of non-engaging lesions, the axis of the posterior margin does not match with the impression vector and the defect is not “hooking” the margin of the articular surface of the scapula [3, 4].

Unlike the true Hill-Sachs lesion, the reverse defects are usually not accompanied by significant loss of

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КЛИНИЧЕСКИЙ СЛУЧАЙ НОВОГО СПОСОБА ХИРУРГИЧЕСКОГО ЛЕЧЕНИЯ РЕВЕРСИВНОГО ПЕРЕЛОМА ХИЛЛА–САКСА ПРИ ЗАСТАРЕЛОМ ЗАЦЕПЛЕННОМ ЗАДНЕМ ВЫВИХЕ ПЛЕЧА

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АННОТАЦИЯ

Обоснование. *Задний вывих головки плечевой кости встречается в 4,5% всех случаев вывихов плечевой кости. Низкая распространённость и трудности в диагностике данного типа повреждения часто приводят к формированию застарелых вывихов плеча. Застарелые случаи заднего вывиха головки плечевой кости, особенно с реверсивными дефектами костной ткани, сопровождаются ограничением движений в плечевом суставе и выраженным болевым синдромом. Наличие костных дефектов головки плечевой кости обусловливает необходимость замещения последних костными или мягкотканными структурами (в хирургической практике наиболее часто применяются сухожилия подостной и подлопаточной мышц), что зачастую невозможно выполнить в застарелых случаях при рубцовом посттравматическом перерождении головки плечевой кости.*

Описание клинического случая. *В статье представлен новый способ хирургического лечения реверсивного перелома Хилла–Сакса при застарелом заднем вывихе плеча. Способ заключался в восполнении дефицита костной массы головки плеча (до 25%) путём перемещения гофрированного сухожилия длинной головки двуглавой мышцы плеча в зону импрессии и фиксации его анкерными фиксаторами в зоне дефекта, что привело к стабилизации плечевого сустава.*

Заключение. *Исходом данного клинического случая явились восстановление функции плечевого сустава и отсутствие клинических симптомов нестабильности в нём в позднем послеоперационном периоде. С нашей точки зрения, предложенный способ хирургического лечения позволяет уменьшить риск развития послеоперационного ограничения движений в суставе, нестабильности головки плечевой кости, особенно в застарелых случаях вывиха головки плечевой кости.*

Ключевые слова: *реверсивный перелом Хилла–Сакса; задний вывих плеча; ремплиссаж; стабилизация плечевого сустава.*

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the bone tissue mass in the humeral head. For the reason that such lesions rarely occur, they have not been described in such a detailed manner as the true engaged Hill-Sachs lesion [1–4].

In the primary diagnostics of such a condition, there is a number of difficulties, the main of which is the delayed diagnostics of the posterior dislocation, reaching up to 80% of the cases [3, 5], which is caused by incorrect radio-diagnostics or by the insufficient experience of the Orthopedic Traumatologist. The incorrect evaluation of the lesion type in the shoulder joint disorients the Orthopedic Traumatologist and results in possible mistakes in the further treatment tactics [3, 5, 6].

In order to stabilize the shoulder joint, except for case of reconstructing the structures, providing the joint stabilization, a number of authors recommend compensating the deficit of the bone tissue [3, 5]. As of today, various methods exist that are being used for surgical treatment of the impressed reverse Hill-Sachs fracture, with the methods being directed to replenishing the deficit of the bone mass in the humeral head. Three stages were established for the osteochondral defect of the humeral head depending

on the deficit of its bone mass: the minor one — less than 20%, the medium — from 20 to 45%, and the major one — more than 45% of bone mass loss [6]. In case of the minor osteochondral defect in the humeral head, McLaughlin's surgery is commonly used. The essence of the surgery is that the humeral head is being openly repositioned and the impression zone is being filled with the musculotendinous part of the subscapular muscle tendon.

Many of the surgical methods aimed for stabilizing the shoulder joint, not always achieve the desired result, which is why they are still a subject for discussions. The search for effective surgical methods for stabilizing the shoulder joint in cases of reverse Hill-Sachs lesion is still showing its topicality.

We are presenting a clinical case of successful surgical treatment in a patient with a long-standing engaged shoulder dislocation and with a reverse Hill-Sachs fracture (the defect of the humeral head was 25% of the articular surface of the humeral head) using a novel method of surgical treatment.

CLINICAL EXAMPLE

Information about the patient

The male patient B., aged 60, was admitted to the clinics on 14.10.2020 with the complaints of pain in the left shoulder joint and limited motility in it.

Disease history data. The left shoulder joint trauma was inflicted by an episode of falling from a bicycle on his own left arm being extended. Having the complaints of pain in the left shoulder joint and significant restriction of motion amplitude, the patient has visited the Trauma Care facility, where (after the radiology and clinical examination), the diagnosis set was the "Bruise of the left shoulder joint". The procedures performed included the limb immobilization using scarf bandage and administering the pain medication. Within the next two weeks, the pain syndrome did not resolve, the patient was experiencing significant restriction in the functions of the shoulder joint. Upon repeated visit, the patient again underwent immobilization of the upper limb. Only in 5 weeks the patient has referred to the clinical hospital.

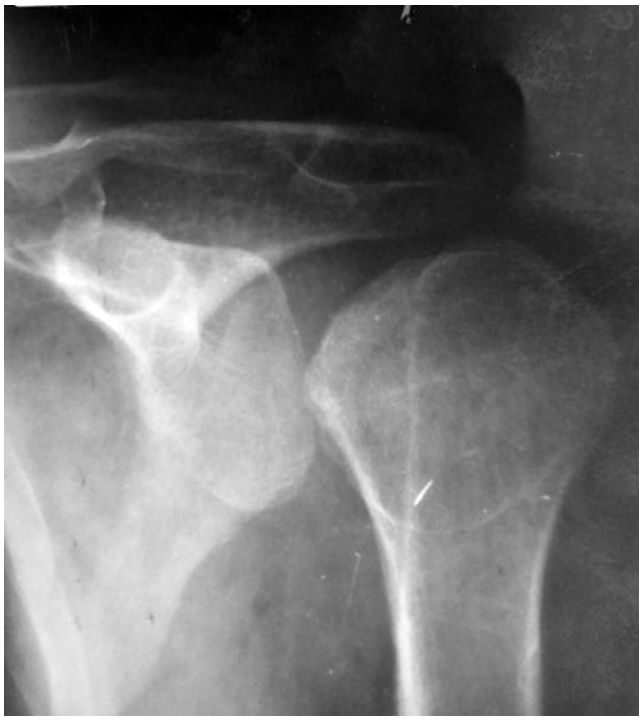

Fig. 1. X-Ray of the shoulder joint of patient (direct projection) before surgery.

Physical diagnostics

Upon the clinical examination, the findings were the following: the left arm is hanging along the trunk at the internal rotation position. Moderate hypotrophy was found in the left deltoid muscle. No deformation was found in the joint, but the palpation reveals some degree of depression along the anterior surface. The palpation of the joint is painless. Passive abduction and flexing in the shoulder — up to 60°, painful. The active abduction is impossible, flexing — up to 45°. The results of using the spiral computed tomography have revealed a defect in the anterior-medial surface of the humeral head; the area of the impression (into the spongy part of the bone) is 25% of the area of the humeral head, while the inclination angle (the misalignment between the vertical plane and the scapular body axis) is 60°.

Provisional diagnosis

Based on the data from the clinical-instrumental examination, the diagnosis set was the following: "Long-standing engaged posterior dislocation of the humeral head, reverse Hill-Sachs fracture (osteochondral lesion in the anterior segment of the humeral head with an impression defect in the bone tissue with a defect area of 25% of the articular surface of the humeral head)"; Fig. 1.

Treatment

At the pre-operation planning phase, as a result of long-term history of humeral head dislocation (5 weeks) and the presence of a minor osteochondral defect in the humeral head (the humeral head defect area is 25% of the articular surface of the humeral head), performing the following surgical intervention was planned: open-access repositioning of the humeral head with filling the defect with the tendon of the subscapular muscle (McLaughlin's surgery).

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Surgery performed on 16.10.2020. Within the settings of the endotracheal (intubation) anesthesia, the deltoid-pectoral access was used to open the left shoulder joint. Mobilization of the shoulder joint was carried out by means of dissecting the scars in the articular cavity, the head of the humeral bone was set free. Upon the revision, the humeral head is located at the backward position, engaging the posterior margin of the articular surface of the scapula (Fig. 2). Other findings included an osteochondral defect in the anterior area of the humeral head. The impression area of the humeral head is located medially from the minor tubercle and has an area of 0.5×1 cm with the depth of up to 0.5 cm. The humeral head defect in the anterior-upper part represents an impression fracture, the volume of which is 2.8 cm^3. Using the surgical elevator, the dislocation of the humeral head was repositioned with further preparing a bed for filling the defect area (French — remplissage — *filling the defect*) using the subscapular muscle tendon (Fig. 3). However, the attempts of remplissage with submerging the cicatricially deformed tendon of the subscapular muscle into the defect area were unsuccessful. The intraoperative decision was to transfer the tendon of the long head of the biceps muscle into the impression zone at the humeral head for filling the bone mass volume in the humeral head. Further procedures included the fixation of the tendon in the defect zone using two anchor screws (Fig. 4). For this purpose, the tendon of the long head of the biceps muscle was transferred to the impression zone. The proximal part of the tendon of the long head of the biceps muscle, originating from its attachment point, was tensioned and fixated near the upper pole of the impression using anchor fixation devices. The distal part of the tendon of the long head of the biceps muscle was tensioned in the opposite direction and also fixated using anchor fixation devices near the lower pole of the defect. With this, the impression zone had a corrugated tendon adjacent to it, which was filling the defect in the humeral head (Fig. 5). No further dislocation or semiluxation was observed when the humeral head was positioned at the critical points.

Dynamic changes and outcomes

The postoperative period was showing no abnormalities; the limb was immobilized with the scarf bandage. The control radiology images show the correct positioning of the humeral head within the shoulder joint, with the humeral head projection zone showing the presence of two anchor fixation devices (Fig. 6). The immobilization with scarf bandage was used for 3 weeks with further restoring the mobility in the shoulder joint.

When analyzing the results of the surgical method proposed, the evaluation included such criteria as the presence of clinical symptoms of shoulder joint instability, the severity of the pain syndrome when moving the shoulder and the amplitude of active and passive movements in the shoulder joint. As a result

Fig. 2. Schematic representation of the horizontal section of the shoulder joint with a posterior dislocation of the shoulder with a Hill-Sachs defect hooked over the posterior edge of the glenoid.

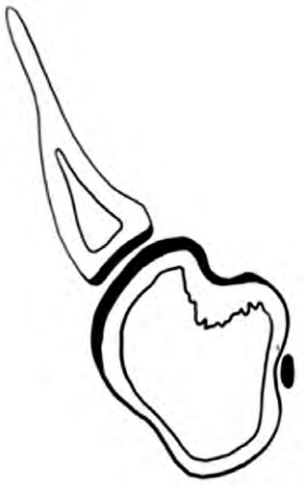

Fig. 3. Schematic representation of the horizontal section of the shoulder joint after reduction of the posterior dislocation of the shoulder.

Fig. 4. Schematic representation of the horizontal section of the shoulder joint after filling the defect of the humerus head with a corrugated tendon with the length of the biceps head.

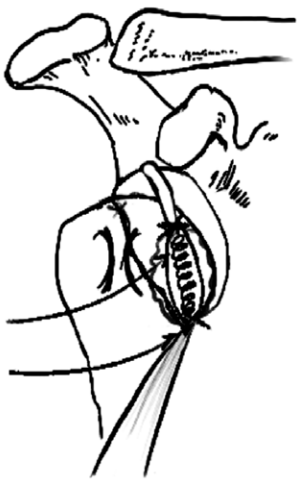

Fig. 5. Schematic representation of the vertical section of the shoulder joint after filling the defect of the shoulder head with a corrugated tendon of the long biceps head.

of surgical treatment, we have managed to completely restore the functioning of the shoulder joint. The complete amplitude of active and passive movements in the shoulder joint has restored in 5 weeks.

Prognosis

The patient has reported a good treatment result and he could re-gain the previous level of physical activity. The analysis of the obtained results performed 3 years after surgery, has demonstrated the absence of clinical symptoms indicating shoulder joint instability, as well as the absence of pain syndrome when moving the limb, no restriction was found in terms of active and passive movements in the shoulder joint, no sense of joint instability was reported by the patient (Fig. 7).

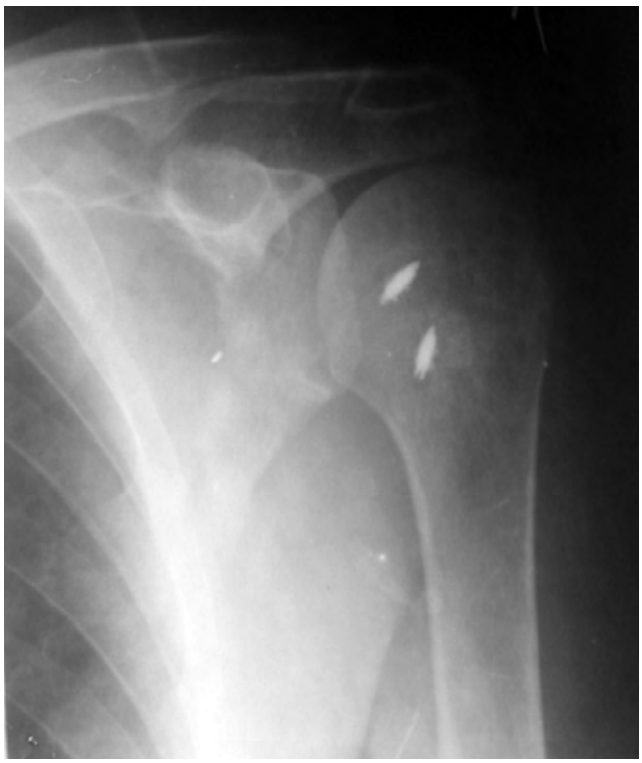

Fig. 6. X-Ray of the shoulder joint of patient (direct projection) after surgery.

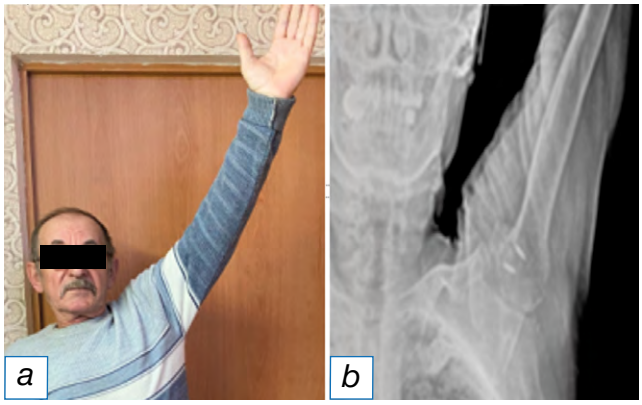

Fig. 7. Appearance of patient, 3 years after surgery (*a*); X-Ray of the shoulder joint of patient, direct projection (*b*).

DISCUSSION

The McLaughlin surgery (modified by Neer) is being used in cases of medium degree osteochondral defects of the humeral head. The principle of the surgery includes submerging the subscapular muscle into the defect zone in the minor tubercle along with its tendon. The benefit of the said surgery comparing to other surgical techniques is the more massive and complete filling of the defect in the humeral head [7]. P.G. Kogan et al. [8] use the method of humeral head osteochondral defect plasty using the bone cement. The essence of the method is that, in order to compensate the deficit in the humeral head, bone cement should be used along with screw reinforcement, with the bone cement being used to form the head surface. Bone replacement surgeries are used in cases of the humeral head osteochondral defects having an area of 30–50% [3, 4]. The methods of using the free bone autotransplant or the allograft, as well as the reverse endoprosthesis replacement of the shoulder joint — all of the these are used when filling the large osteochondral defects in the humeral head [4].

The surgical tactics of treating the patients with reverse Hill-Sachs lesion is still disputable and depends both on the bone mass deficit in the humeral head and on the level of activity observed in the patient [9].

With the increase of the time from the moment of the shoulder dislocation episode, the soft-tissue structures stabilizing the shoulder joint undergo degenerative changes along with the ossification of the tissues surrounding the shoulder joint. This leads to the formation of a dense conglomerate, not allowing (in the majority of cases) for restoring it or using them in terms of stabilizing the shoulder joint [10]. When dealing with long-standing engaged shoulder dislocations associated with difficulties in terms of preserving the soft-tissue structures of the shoulder, upon dissecting the cicatricially transformed tissues of the shoulder joint cavity, it is not always possible to preserve or to restore the cicatricially transformed tendon of the subscapular muscle, which is why using it to fill the humeral head defect is not possible [11]. A number of authors suppose that the thickness of the cicatricially transformed tendon of the subscapular muscle complicates placing it into the longitudinal defect of the humeral head, while filling the defect with the tendon may result in restriction of the motion range in the shoulder joint [12].

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From our point of view, the choice of surgical treatment tactics for cases of reverse Hill-Sachs fracture depends on the dimensions and on the depth of the humeral head defect. In case of the osteochondral defect in the humeral head (up to 25% of the humeral head area), a remplissage method can be employed with using the tendon of the long head of the biceps muscle. The method of surgical treatment for cases of reverse Hill-Sachs fracture proposed by us, has been applied for an invention — 2023132902/20(072680) on 11.01.2024.

CONCLUSION

The method for surgical treatment developed by us, can be recommended in cases when the impression area in the humeral head is up to 25% of the humeral head surface area, with the inclination angle being 60°. In cases of the reverse Hill-Sachs fracture, the use of remplissage with the tendon of the long head of the biceps muscle can represent a competitive method for comparing it to other surgical techniques.

ADDITIONAL INFORMATION

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Authors' contribution. *S.N. Tikhonenkov* — search and analytical work, writing the text of the article, examining the patient, treating patients; *A.Yu. Lebedev* — search and analytical, patient treatment, writing the text of the article; *G.M. Dubrovin* — treatment management, discussion of the study results. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

Consent for publication. A written voluntary informed consent was obtained from the patient to publish a description of the clinical case in the journal "Journal of Clinical Practice", including the use of his medical data (results of examination, treatment and observation) for scientific purposes (date of signing 14.10.2020).

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