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THE EVALUATION OF THE HEMODYNAMICALLY SIGNIFICANT STENOSIS OF THE CAROTID ARTERIES: ANALYZING THE RESULTS FROM THE DUPLEX SCANNING OF VESSELS, FROM THE COMPUTED TOMOGRAPHIC AND THE TRANSCATHETER X-RAY CONTRAST ANGIOGRAPHY

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ABSTRACT

BACKGROUND: *Atherosclerotic stenosis of the carotid arteries is one of the main reasons of stroke, of transient ischemic attacks, of developing cognitive disorders and of incapacitating the population. The key indication to invasive treatment for this disease is the degree of stenosis in the carotid artery, due to which the most important problem in the diagnostics is the maximally precise evaluation of the stenosis degree. The duplex scanning of the carotid arteries is a safe, non-invasive and relatively inexpensive visualization method, which is the first line of diagnostics. The precision of measuring the stenosis and the occlusion of the carotid artery, according to the ultrasound examination data, varies from 70% to 90%. At the same time, the degree of stenosis, measured using various methods, does not always match.* ***AIM:*** *to compare the data obtained by duplex scanning of the brachiocephalic arteries and by other instrumental diagnostics methods in terms of the precision of measuring the percentage of stenosis in the carotid arteries, as well as to analyze the reasons of discrepancies between the obtained data.* ***METHODS:*** *The research is based on the retrospective analysis of case history data from the patients hospitalized to the Vascular Surgery Department of the Federal State Budgetary Institution «Federal Scientific and Clinical Center» under the Russian Federal Medical-Biological Agency during the period from 01.05.2023 until 20.05.2024. The obligatory inclusion criteria for the analysis were the presence of the main disease of the I65 group according to the ICD-10 and undergoing at least one of the examination types within the settings of the FSBI «Federal Scientific and Clinical Center» under the Russian Federal Medical-Biological Agency (duplex scanning, computed tomographic angiography, transcatheter X-ray contrast angiography). The statistical processing was done using the Statistica software pack version 10.0 (StatSoft).* ***RESULTS:*** *The conducted research has shown that there is no complete matching between the data from the transcatheter X-ray contrast angiography, the computed tomographic angiography and the duplex scanning. The analysis of the reasons of discrepancies when measuring the degree of stenosis in the orifices of the internal carotid arteries from the results of duplex scanning and computed tomographic angiography has allowed for isolating three main groups: the human factor (operator-dependent, 30.4%), the anatomic factor (23.2%) and the differences in descriptions (46.4%).* ***CONCLUSION:*** *Upon examining the patients, it is necessary to strictly follow the algorithm of diagnosing the stenoses of the carotid arteries, beginning from the duplex scanning of the extracranial segments of brachiocephalic arteries as the most accessible and highly informative method. Computed tomographic angiography of this vascular segment is required for selecting the patients for surgical treatment, for it is necessary to keep in mind the potential risk of developing the contrasted nephropathy and the risks of radiation exposure. A properly done ultrasound examination allows for not only decreasing the number of discrepancies between these two diagnostic methods, but also to avoid the necessity of conducting such an invasive radio-contrasting method as angiography.*

Keywords: *duplex; carotid artery internal; carotid stenosis; reasons for discrepancies; data comparison.*

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ОЦЕНКА ГЕМОДИНАМИЧЕСКИ ЗНАЧИМОГО СТЕНОЗА СОННЫХ АРТЕРИЙ: АНАЛИЗ РЕЗУЛЬТАТОВ ДУПЛЕКСНОГО СКАНИРОВАНИЯ СОСУДОВ, КОМПЬЮТЕРНО-ТОМОГРАФИЧЕСКОЙ И ЧРЕСКАТЕТЕРНОЙ РЕНТГЕНОКОНТРАСТНОЙ АНГИОГРАФИИ

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АННОТАЦИЯ

Обоснование. *Атеросклеротический стеноз сонных артерий является одной из основных причин инсульта, транзиторной ишемической атаки, развития когнитивных нарушений, инвалидизации населения. Ключевым показанием к инвазивному лечению данного заболевания является степень стеноза сонной артерии, в связи с чем важнейшей проблемой диагностики является максимально точное определение выраженности стеноза. Дуплексное сканирование сонных артерий является безопасным, неинвазивным, относительно недорогим методом визуализации, являясь первой линией диагностики. Точность определения стеноза и окклюзии сонной артерии по данным ультразвукового исследования составляет от 70% до 90%. Вместе с тем степень стеноза, определённая разными методами, не всегда совпадает.* ***Цель исследования*** *— сопоставить данные дуплексного сканирования брахиоцефальных артерий и других инструментальных методов диагностики в точности определения процента стеноза сонных артерий, а также провести анализ причин расхождения полученных данных.* ***Методы.*** *Исследование основано на ретроспективном анализе данных историй болезни пациентов, госпитализированных в отделение сосудистой хирургии ФГБУ ФНКЦ ФМБА России в период с 01.05.2023 по 20.05.2024. Обязательными критериями включения в анализ являлись наличие основного заболевания группы I65 по МКБ-10 и выполнение любых двух исследований в условиях ФГБУ ФНКЦ ФМБА России (дуплексное сканирование, компьютерно-томографическая ангиография, чрескатетерная рентгеноконтрастная ангиография). Статистическая обработка проводилась с использованием пакета программ Statistica версии 10.0 (StatSoft).* ***Результаты.*** *Обнаружено отсутствие полного совпадения между данными чрескатетерной рентгеноконтрастной ангиографии, компьютерно-томографической ангиографии и дуплексного сканирования. Анализ расхождений в оценке степени стеноза устьев внутренних сонных артерий по результатам дуплексного сканирования и компьютерно-томографической ангиографии позволил выделить три основные группы причин: человеческий фактор (операторзависимость, 30,4%), анатомический фактор (23,2%), различия описаний (46,4%).* ***Заключение.*** *При обследовании пациентов необходимо строго придерживаться алгоритма диагностики стенозов сонных артерий, начиная с дуплексного сканирования экстракраниальных отделов брахиоцефальных артерий как наиболее доступного и высокоинформативного метода. Компьютерно-томографическая ангиография данного сосудистого бассейна необходима при отборе пациентов для хирургического лечения, так как необходимо помнить о потенциальном риске развития контрастной нефропатии и радиационного воздействия. Качественно выполненное ультразвуковое исследование позволяет не только снизить число противоречий между этими двумя методами диагностики, но и избежать необходимости проведения такого инвазивного рентгеноконтрастного метода исследования, как ангиография.*

Ключевые слова: *дуплексное сканирование; внутренняя сонная артерия; стеноз сонной артерии; причины расхождений; сопоставление данных.*

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BACKGROUND

Atherosclerotic stenosis of the carotid arteries is an important cause of stroke, of transient ischemic attack, of developing cognitive disorders and of incapacitating the population. It is not very often when it is considered a marker of systemic atherosclerotic vascular lesions, commonly being associated with the ischemic heart disease and with the lesions in the arteries of the lower limbs [1].

According to data from the World Health Organization, in 2021, within the territorial borders of the Russian Federation, the ischemic stroke was the cause of death of more than 200 000 persons, which makes it the third most frequent cause of death in the country at that year [2]. In the worldwide statistics, stroke is the second leading cause of incapacitation and mortality [3–5]. Every year worldwide approximately 6 million people die of this disease, approximately 5 million become disabled[1] [6]. The most widespread causes of cerebral infarction are the stenotic-occlusive lesions of the brachiocephalic arteries [7, 8].

Currently, when providing medical aid to the patients with the lesions in the carotid arteries, first of all, it is necessary to follow the two officially validated documents: "The national recommendations on managing the patients with the diseases of the brachiocephalic arteries" (2013) [5] and the guidelines from the Ministry of Health of the Russian Federation "Occlusion and stenosis of the carotid artery" (2016) [9]. In 2022, a Russian Consensus on the diagnostics and treatment of patients with the stenosis of the carotid arteries was also published, which, however, was not approved by the Ministry of Health of the Russian Federation and which has a recommendatory value.

One of the main indications to the invasive treatment is the degree of stenosis in the carotid artery [5]. Hence, the most important diagnostic problem is the maximally precise determination of the severity of stenosis. It is also important to note that the main diagnostic criteria were compiled based on the two large trials conducted in 1980–1990 and based only on the angiography findings [10, 11].

As of today, the examination of the patients with suspected atherosclerotic lesions in the carotid arteries includes several instrumental diagnostics methods: the duplex scanning (DS) of the brachiocephalic arteries, the computed tomographic angiography (CTA) and the transcatheter X-ray contrast angiography (AG).

With every passing year, the number of surgical interventions in the brachiocephalic arteries irreversibly grows. The surgeons show the tendency of preferring the usage of data from the computed tomographic angiography without taking into account the results of vascular duplex scanning (due to the dependence of visualization by means of DS on a specific operator).

Research aim — to compare the data obtained during the duplex scanning of brachiocephalic arteries, conducted at the Federal State Budgetary Institution "Federal Scientific and Clinical Center for Specialized Types of Medical Aid and Medical Technologies" under the Federal Medical-Biological Agency" (FSBI "Federal Scientific and Clinical Center" under the Russian Federal Medical-Biological Agency) with other instrumental diagnostics methods in terms of the precision of measuring the percentage of stenoses in the carotid arteries, as well as to analyze the reasons of discrepancies in the obtained data.

METHODS

Research design

A retrospective analysis was conducted with including the data from the case histories of the patients hospitalized the Vascular Surgery Department of the FSBI "Federal Scientific and Clinical Center" under the Russian Federal Medical-Biological Agency during the period from 01.05.2023 until 20.05.2024. The analysis included the anonymized case history data (gender, age, conducted surgical interventions in the carotid system vessels) along with the examination protocols for brachiocephalic arteries (DS, CTA, AG).

Conformity Criteria

Inclusion criteria: the presence of the main disease from the I65 group (occlusion and stenosis of the pre-cerebral arteries, not resulting in a cerebral infarction) according to the International Classification of Diseases (10th revision) and undergoing at least one of the examinations within the premises of the FSBI "Federal Scientific and Clinical Center" under the Russian Federal Medical-Biological Agency (duplex scanning, computed tomographic angiography, transcatheter X-ray contrast angiography).

Research findings

The comparative analysis also included the data on the differences observed when assessing the percentage of stenosis in the orifices of the internal carotid arteries when using two of the three methods (if any). The main analysis of discrepancies was carried

[1] World Health Organization [Internet]. Health affairs. Available from: https://www.who.int/ru Accessed: March 3, 2025.

out in groups: the percentage of stenosis according to CTA data minus the percentage of stenosis according to DS data (CTA-DS) and the percentage of stenosis according to DS data minus the percentage of stenosis according to AG data (DS-AG).

Statistical analysis

The statistical processing was done using the ''Statistica'' software package Version 10.0 (StatSoft). Due to the impossibility of following the normal distribution criteria, the statistical analysis was undertaken with using the non-parametric statistics criteria. The statistical significance was stated as the value of p <0.05. As for the quantitative indicators, the continuous variables were presented as the median and the lower/upper quartiles (Me [25%; 75%]). The differences of the quantitative indicators were assessed using the Mann-Whitney U test.

RESULTS

Research sample (participants)

Data from the case histories of 207 patients were analyzed, of which 140 (68%) were males and 67 (32%) were females, the mean age at the moment of hospitalization of which was 68.9 years (median — 69 years with a range from 42 to 89 years), with the mean age of males significantly differing from the mean age of females — 67.7 vs. 71.4, respectively (Z=2.9; p=0.003).

All the 207 patients were undergoing diagnostic examinations: CTA — 189, DS — 164, AG — 21, with 16 patients having all the mentioned types of examinations (all of them being operated). Before the conduction of AG, CTA was always carried out. The combined diagnostics by means of CTA and DS was reported for 146 patients.

All the patients were divided into groups by the number of imaging methods involved in the examination. The distribution of methods among the patients operated during the present hospitalization (n=171), is shown in Fig. 1.

Primary findings

We have arranged a detailed analysis of data in two groups of patients: 16 individuals in which all the three types of examinations were carried out (Group 1); 130 individuals undergoing CTA and DS (without the inclusion of the patients from Group 1; Group 2).

In 16 patients of the Group 1, the described findings included lesions in 27 internal carotid arteries (ICA) with the stenoses of various degree of intensity: upon the paired comparison of the data from three methods (CTA-DS, CTA-AG, DS-AG), no significant differences were found (Fig. 2). Predominantly, the scattering

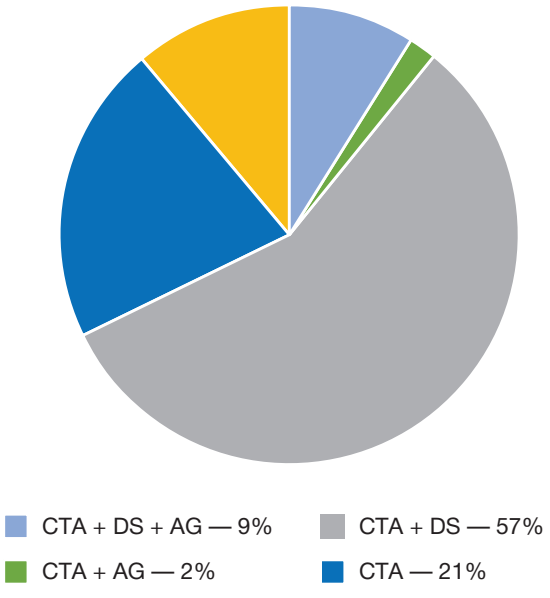

Fig. 1. The structure of pre-operational examination in patients with hemodynamically significant stenosis of the carotid arteries. CTA — computed tomographic angiography; DS — duplex scanning of the brachiocephalic arteries; AG — transcatheter X-ray contrast angiography. [From the archive of the Federal State Budgetary Institution «Federal Scientific and Clinical Center» under the Russian Federal Medical-Biological Agency, 2025. Published for the first time].

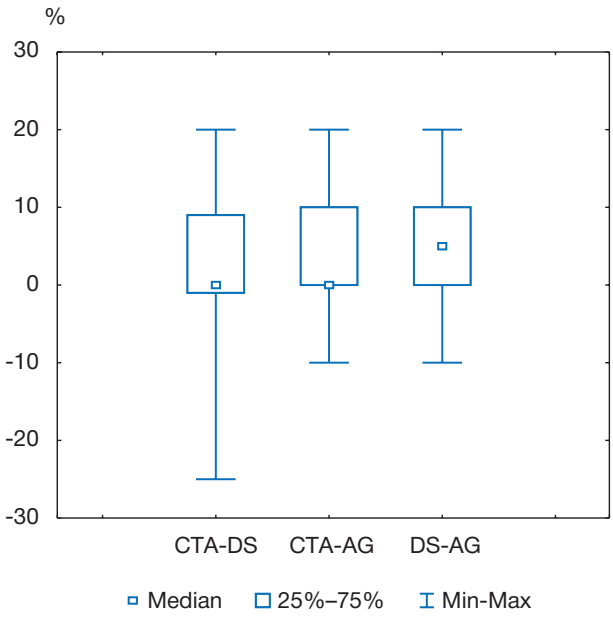

Fig. 2. Paired comparison of the results from three diagnostic methods. CTA — computed tomographic angiography; DS — duplex scanning of the brachiocephalic arteries; AG — transcatheter X-ray contrast angiography. [From the archive of the Federal State Budgetary Institution «Federal Scientific and Clinical Center» under the Russian Federal Medical-Biological Agency, 2025. Published for the first time].

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of data was 10%. Higher scattering of data was found for DS.

The detailed analysis of the detected 5 (18.5%) cases of discrepancies >10% has demonstrated the following:

Patient No. 68: the percentage of stenosis acc. to DS data was higher comparing to the CTA by 15%, but the stenosis was hemodynamically insignificant, due to which further AG was done only on the contralateral side, where there was a hemodynamically significant atherosclerotic plaque.

Patient No. 206: underestimation of stenosis comparing to CTA by 10%, comparing to AG — by 15%.

Patient No. 141: according to data from DS, the stenosis is 20% less than comparing to data from CTA and AG, probable cause — underestimation of hemodynamic criteria.

Patient No. 189: the patient from the ICU with the diagnosis of acute cerebrovascular event on the left side; underestimation of stenosis according to data from DS by 20%.

Patient No. 185: according to data from DS, the stenosis is 25% higher comparing to data from CTA, but the DS result was completely matching with the AG findings.

A total of 130 patients from the group 2 — 202/260 (77.7%) ICA — had atherosclerotic plaques. The distribution of differences in evaluating the stenoses between CTA and DS is shown in Fig. 3. In 149/202 (73.8%) ICA, there were no deviations or they were within the range of 10%, in 23/202 (11.4%) — from 15 to 20%, in 15/202 (7.4%) — ≥20%, with the predominance of higher stenosis degree in the results of the DS — 26 (12.9%) cases, while lower percentage of stenosis was found in 12 (5.9%) cases.

For the purpose of comparison, data were analyzed on the severity of stenoses in the ICA orifices using the methods of CTA and DS comparing to the AG data, for particularly this method is the gold standard in assessing the stenoses. The groups of AG-CTA and AG-DS (Fig. 4) did not show any differences, though it is necessary to note that the transcatheter X-ray contrast angiography was done only in 21 patients and only with an evaluation of stenosis degree in the zone of interest.

When analyzing the discrepancies in evaluating the degree of stenosis in the orifices of the ICA on the results of DS and CTA >10% (56 ICA in both control groups with the exclusion of two cases, where the DS findings differed from only one of the control methods — AG or CTA), several causative factors can be pointed out.

- The human factor, or the operator dependence (17 patients, 30.4%): in this group, we have summarized the discrepancies of >10%, revealed when analyzing the medical documentation, but without the presence of other evident cause.

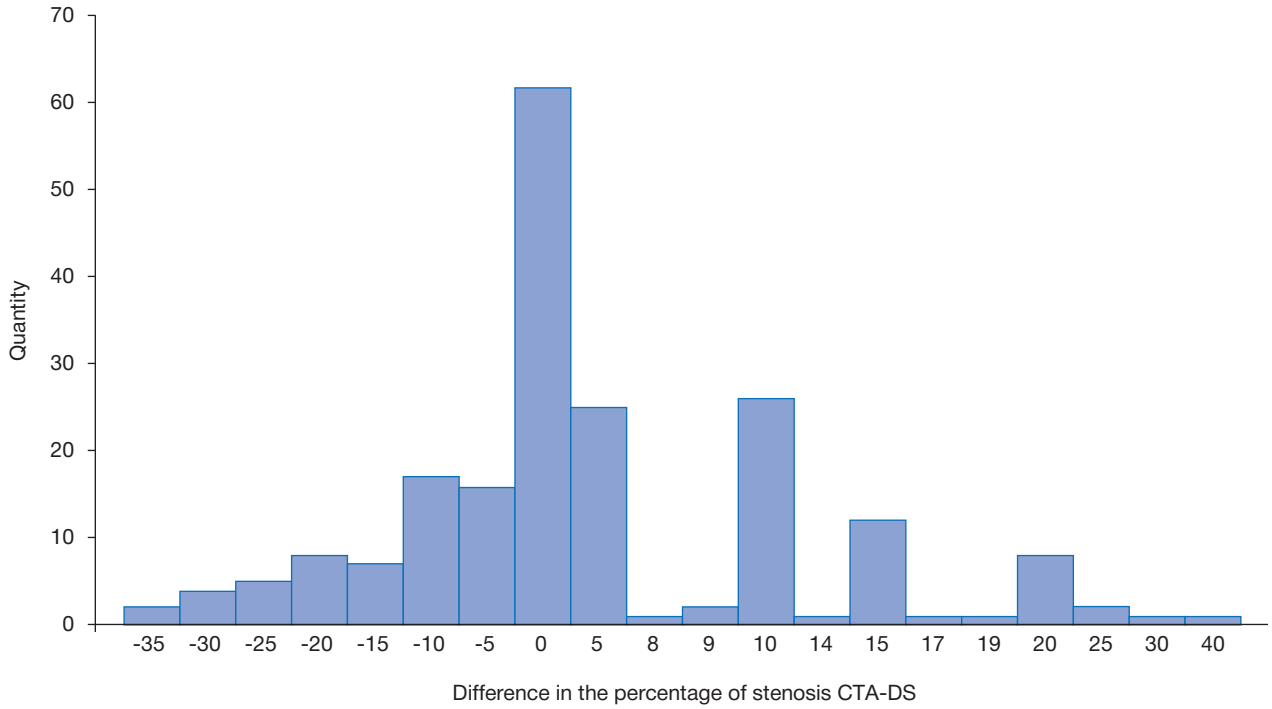

Fig. 3. The histogram of the distribution of differences in evaluating the stenoses in the orifices of the internal carotid arteries (CTA data minus DS data). CTA — computed tomographic angiography; DS — duplex scanning of the brachiocephalic arteries; АГ — transcatheter X-ray contrast angiography. [From the archive of the Federal State Budgetary Institution "Federal Scientific and Clinical Center" under the Russian Federal Medical-Biological Agency, 2025. Published for the first time].

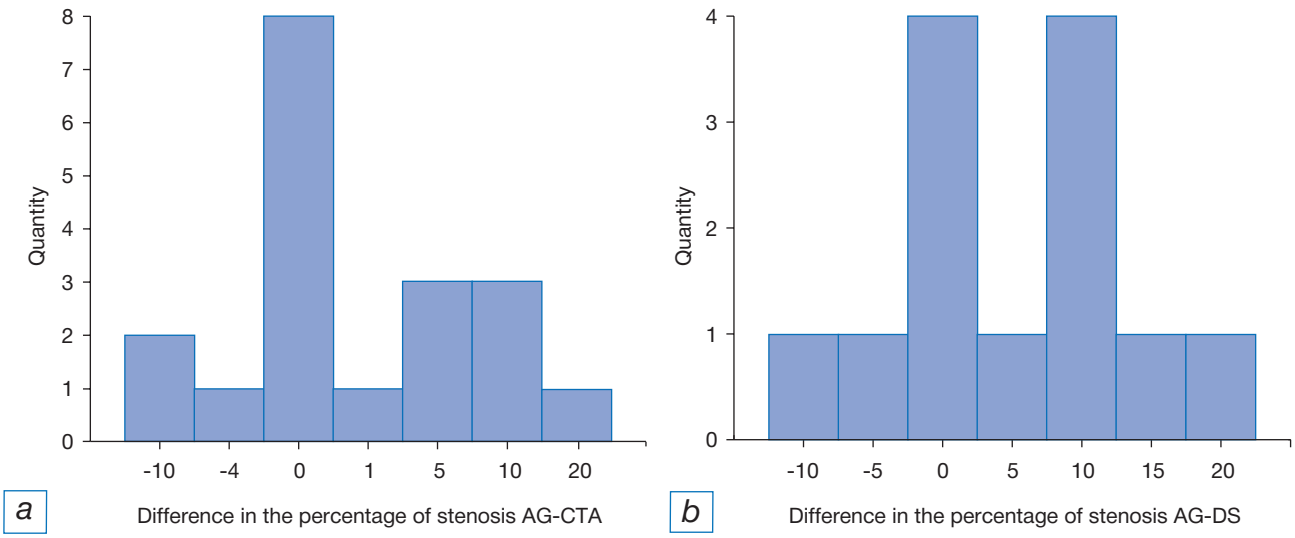

Fig. 4. The histogram of the distribution of differences in evaluating the stenoses in the orifices of the internal carotid arteries: *a* — AG data minus CTA data; *b* — AG data minus DS data. CTA — computed tomographic angiography; DS — duplex scanning of the brachiocephalic arteries; AG — transcatheter X-ray contrast angiography. [From the archive of the Federal State Budgetary Institution «Federal Scientific and Clinical Center» under the Russian Federal Medical-Biological Agency, 2025. Published for the first time].

- The anatomic factor (13 patients, 23.2%): this group summarized all the discrepancies, which were based on the difference in the interpretation of the degree of stenosis by the anatomical landmarks (visualization of the carotid bifurcation, of the orifice and of the proximal segment of ICA).
- Description differences (26 patients, 46.4%): in this group, we have summarized the cases in which there was a clearly trackable difference in the interpretation of data from different examinations. This group included the discrepancies related to the visualization of plaques (10%, 15% by the CTA data) and the discrepancies in evaluating the stenoses (less than 50%). The separation of the group of plaques "without significant stenosing" according to the CTA data was not taken into account. This group also contained the cases when the difficulties were occurring when interpreting the hemodynamical data for the stenoses.

Thus, the conducted research has shown that there is no complete matching between the data from AG, CTA and DS. When evaluating the degree of stenoses in the ICA orifices, the DS data were equivalent to the CTA data. The widely known drawback of ultrasound diagnostics is the dependence of the examination results on the operator, which may lead to differences in interpreting the obtained data not only between several specialists, but even upon the repeated examinations done by the same specialist. The operator dependence of ultrasonic methods leads to the necessity of using confirmatory methods (CTA, AG) when selecting the candidates for surgical treatment. We have found that the highest percentage of discrepancies between CTA and DS was related to the cases of stenoses reaching up to 50%, not least because of the difference in the criteria for evaluating such stenoses. The less frequent, but more significant reason of discrepancies was the difference in the interpretation of some anatomic structures and in the circulation criteria.

DISCUSSION

X-ray contrast angiography is the gold standard in the diagnostics of the lesions in the arteries, however, as of today, the higher significance in the diagnostics of the carotid artery stenosis, as well as in making the clinical decisions on determining the indications to surgical interventions is gained by the duplex scanning of the brachiocephalic arteries[1].

The duplex scanning of the carotid arteries is a safe, non-invasive and relatively inexpensive visualization method. This method allows for evaluating the circulation in the bulb and in the proximal part of the ICA. The distal ICA segments are not always accessible for scanning [2]. Generally, when evaluating the stenosis using the DS method, it is recommended to pay attention not only to the planimetric changes, but also to the specific features of circulation [12].

As the confirmatory examination for the setting the definitive diagnosis and for evaluating the necessity and the type of surgical treatment,

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contrast-enhanced methods are required, such as the X-ray contrast transcatheter angiography, the magnetic resonance angiography or the computed tomographic angiography [2].

The clinical significance of computed tomographic angiography is due to the anatomical correctness of the method, as well as to the possibility of obtaining information on the very corrugated vessels, the small diameter vessels and on the distal areas of vascular system[1].

The transcatheter X-ray contrast angiography remains a diagnostic standard in patients with the lesions in the extracranial arteries, however, the risks for the patient and the financial cost are the limitations for angiography as a screening method. Direct angiography is also indicated for cases of obtaining controversial findings on the results of other non-invasive methods[1]. The literature data confirm that the combined use of two non-invasive methods (DS with magnetic resonance angiography or CTA) allows for avoiding the use of radiocontrast angiography. However, even when using two methods, an insufficiently precise determination of the degree and spreading of stenosis was found in almost 20% of the patients [5].

In the research work by R.M. Daolio et al. [13], presenting an analysis of the systematic review based on the Cochrane data base and compiled in 2022, the authors have provided the evidence of high diagnostic precision of color DS, especially in terms of differentiating the stenoses of the carotid arteries with a degree of up to 50% and in the range of 50–99%. The review has included 22 articles with an analysis of 4957 instrumental examinations of this vascular system, on the results of which, a conclusion was made that the precision of evaluating the stenosis and the occlusion of the carotid artery when using the ultrasound examination varies from 70% to 90%.

In accordance with clinical recommendations from the Ministry of Health of the Russian Federation [14] and the recommendations from the World Health Organization[1], the examination of the carotid arteries should start from color DS of the brachiocephalic arteries. Later on, either the magnetic resonance tomography or the CTA can be conducted. In case of proper execution of these examinations and in case when the results are matching, the decision on surgical treatment can be drawn up without the need for radiocontrast angiography. In case when the examination findings are controversial or in case of insufficient visualization of the arteries, using the X-ray contrast angiography remains obligatory.

Research limitations

The absence of unified standards of describing (anatomic landmarks, criteria that are obligatory for describing, terms in the protocols) due to the absence of the recommendations for such methods as the DS of the brachiocephalic arteries and the CTA of the brachiocephalic arteries, as well as the absence of general standards for these two methods, complicates the interpretation of the conclusions even within a single medical institution. Particular difficulties may develop when comparing the data on stenoses with a degree of less than 50%.

CONCLUSION

When arranging the examination of the patients, it is necessary to strictly follow the diagnostics algorithm for stenoses of the carotid arteries, beginning from the duplex scanning of the extracranial segments of brachiocephalic arteries as the most accessible and highly informative method. The computed tomographic angiography of this vascular system is necessary when selecting the patients for surgical treatment, for it is necessary to keep in mind the potential risk of developing contrasted nephropathy and of the radiation exposure. The proper execution of the ultrasound examination allows for decreasing the number of discrepancies between these two diagnostic methods, which means decreasing the necessity for performing the angiography.

ADDITIONAL INFORMATION

Author contribution. *N.S. Nosenko* — concept and design of the study, literature review, collection and analysis of literary sources, writing the text and editing the article; *E.M. Nosenko* — scientific revision of the manuscript, concept and design of the study, editing of the article; *D.S. Alemasova* — literature review, collection and analysis of literary sources, writing the text and editing the article; *T.V. Dedy* — scientific revision of the manuscript. 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.

Ethics approval. The protocol of the retrospective study was agreed upon by the Local Ethics Committee of the Federal State Budgetary Institution FNCC of the FMBA of Russia (minutes of the meeting of the LEK No. 12-2024 dated 11.11.2024).

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THE EFFECTS OF SARCOPENIA ON THE COMPLICATIONS AFTER ESOPHAGECTOMY WITH SIMULTANEOUS PLASTY OF THE ESOPHAGUS

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ABSTRACT

BACKGROUND: *Large meta-analyses have proven the negative effects of sarcopenia on the rates of postoperative complications and mortality, on the duration of the postoperative stay at the In-Patient Department and on the 1-, 3- and 5-year survival of the patients. However, given that in coloproctology and emergency surgery, the effects of sarcopenia on the outcomes are undoubtful, in the esophageal surgery the results are extremely controversial.* ***AIM:*** *to evaluate the effects of sarcopenia on the complications in patients after esophagectomy with simultaneous esophageal plasty.* ***METHODS:*** *At the National Medical Research Center of Surgery named after A.V. Vishnevsky (NMRCS), a retrospective computed-tomographic diagnostics of sarcopenia was carried out among the patients (n=111) before undergoing esophagectomy with simultaneous esophageal plasty due to the presence of benign or malignant diseases of the esophagus. The perioperative management of all the patients was carried out within the framework of the programs of rationally accelerated perioperative rehabilitation. For the purpose of quantitative evaluation of sarcopenia, the musculoskeletal index was measured. Using the logistic regression, we have evaluated the effects of preoperational sarcopenia on the postoperative complications.* ***RESULTS:*** *Sarcopenia of various degree of intensity was diagnosed in 95 (85.6%) patients. The analysis of the adjusted odds ratios did not reveal any statistically significant relation between sarcopenia and postoperative complications.* ***CONCLUSION:*** *The experience gained at the NMRCS has shown that high-quality surgical technique together with competent perioperative management are able to alleviate the negative effects of sarcopenia on the postoperative complications.*

Keywords: *sarcopenia; esophagectomy; esophagoplasty; accelerated rehabilitation.*

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BACKGROUND

Sarcopenia is a progressive decrease of muscle mass and physical strength. Upon the introduction of the term in 1989, it was associated only with aged patients [1]. Later sarcopenia was acknowledged not only a worldwide problem, but also a separate disease [2]. The age-related muscular atrophy begins from 40 years of age and progressively deteriorates after 60 [3], including the cases of developing secondarily due to inflammatory or oncological diseases, neurological disorders, decreased physical activity and nutritional insufficiency [4]. Sarcopenia is being diagnosed in one out of every two persons after 80 years of age and in one out of every ten worldwide [5]. Currently, active research is carried out on the effects of sarcopenia on the postoperative complications in all the fields of surgery. Large meta-analyses have proven the negative effects of sarcopenia on the rates of postoperative complications and mortality, on the duration of postoperative stay at the In-Patient Department and on the 1-, 3- and 5-year survival of patients [6-9]. Despite the topicality of the problem, the gold standard of sarcopenia diagnostics is still not approved. For the quantitative evaluation of the muscle mass, computed tomography (CT) is often used to measure the musculoskeletal index and the psoas muscle index [10, 11].

Esophagectomy with simultaneous esophageal plasty is a high-risk intervention associated with high rate of complications and hospital mortality. The evaluation of the risk factors of developing

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ВЛИЯНИЕ САРКОПЕНИИ НА ОСЛОЖНЕНИЯ ПОСЛЕ ЭЗОФАГЭКТОМИИ С ОДНОМОМЕНТНОЙ ПЛАСТИКОЙ ПИЩЕВОДА

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АННОТАЦИЯ

Обоснование. *Крупные метаанализы доказали негативное влияние саркопении на частоту послеоперационных осложнений и летальности, длительность послеоперационного пребывания в стационаре и 1-, 3- и 5-летнюю выживаемость пациентов. Однако если в колопроктологии и экстренной хирургии влияние саркопении на исходы не вызывает сомнения, то в хирургии пищевода результаты крайне противоречивы.* ***Цель исследования*** *— оценить влияние саркопении на осложнения у пациентов после эзофагэктомии с одномоментной эзофагопластикой.* ***Методы.*** *В Национальном медицинском исследовательском центре хирургии им. А.В. Вишневского (НМИЦХ) провели ретроспективную компьютерно-томографическую диагностику саркопении пациентам (n=111) перед эзофагэктомией с одномоментной эзофагопластикой по поводу доброкачественных и злокачественных заболеваний пищевода. Периоперационное обеспечение всех пациентов проходило в рамках программы рационально ускоренной периоперационной реабилитации. Для количественной оценки саркопении измеряли скелетно-мышечный индекс. С помощью логистической регрессии оценили влияние предоперационной саркопении на послеоперационные осложнения.* ***Результаты.*** *Саркопению разной степени выраженности диагностировали у 95 (85,6%) пациентов. Анализ скорректированных отношений шансов не выявил статистически значимой ассоциации между саркопенией и послеоперационными осложнениями.* ***Заключение.*** *Опыт НМИЦХ показал, что качественная хирургическая техника вкупе с грамотным периоперационным обеспечением способны нивелировать негативное влияние саркопении на послеоперационные осложнения.*

Ключевые слова: *саркопения; эзофагэктомия; эзофагопластика; ускоренная реабилитация.*

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complications during esophagectomy and their prevention is a promising direction of scientific search, however, while in coloproctology [9] and emergency surgery [8] the effects of sarcopenia on the outcomes are undoubtful, in the surgery of the esophagus, the results are extremely controversial [12, 13].

Research aim — to evaluate the effects of sarcopenia on the complications in patients after esophagectomy with simultaneous esophageal plasty.

METHODS

Research design

A single-center retrospective research was carried out with 500 primary esophagectomies with simultaneous esophageal plasty. At the first stage after evaluating the complications, the patients were divided into two groups for the purpose of defining the risk factors of developing complications. During the second stage of the research, the same parameters were assessed in patients, in which measurements were undertaken of the musculoskeletal index and sarcopenia was ruled out. The third stage included re-grouping of the patients with the CT-diagnostics of sarcopenia for evaluating its effects on the development of postoperative pneumonia. Additionally, an attempt was made to compile a predictive model indirectly evaluating the musculoskeletal index, based on the basic anthropometric and clinical-laboratory findings.

Conformity criteria

Inclusion criteria. Initially, the research work was including all the patients, in which the primary

esophagectomy with simultaneous esophageal plasty was carried out within the framework of the program of rationally accelerated perioperative rehabilitation (the RUPOR program). The inclusion criterion of the sarcopenia research was the presence (at the premises of the research facility) of the pre-operational CT-images, obtained at least 3 months before the intervention, having no artifacts complicating the interpretation.

Non-inclusion criteria: low quality of pre-operational CT-images, absence of past CT-data in the archive

Exclusion criteria: emergency surgical interventions

Research facilities

The research work was conducted at the Federal State Budgetary Institution "National Medical Research Center of Surgery named after A.V. Vishnevsky" under the Ministry of Health of the Russian Federation (NMRCS).

Research Duration

The duration of the retrospection was from 2012 until 2024.

Medical procedure description

The RUPOR program included the obligatory examination of the patient by the interdisciplinary team at the pre-hospital phase. All the patients had their body mass index (BMI) measured along with determining the Charlson Comorbidity Index (CCI), with the degree of anesthetic risk evaluated using the standards of the American Society of Anesthesiologists (ASA), the risk of cardiac complications was assessed using the Lee Criteria, while the risk of nutritional insufficiency was estimated using the Nutrition Risk Screening 2002 (NRS-2002), among other studied parameters were also the clinical-laboratory and instrumental findings. If necessary, the patients were receiving the pre-operative preparation measures. During the intraoperative period, normothermia and normovolemia were maintained along with the protective pulmonary ventilation and prevention of postoperative nausea and vomiting, of thromboembolic and infectious complications.

All the patients from the test group were undergoing a sub-/total esophagectomy with simultaneous esophageal plasty. On the morning of the first postoperative day, the patients were transferred to a specialized department with removing the urinary catheter and the pleural draining tube provided the aerostasis was maintained and less than 400 ml of discharge was produced. In a routine manner, all the patients were instructed to avoid oral intake of water until postoperative day 5 (the day of the first radiology or CT-control); infusion therapy was prescribed along with complete parenteral feeding. In case of the satisfactory quality of the cervical co-junction (positive intraoperative evaluation of the viability of the gastric transplant and of the esophageal stump) and in the absence of aspiration or incompetent (leaking) anastomosis upon the radiology control, the patients were allowed to drink water from day 1 and to sip from postoperative day 2. The intake of strained food was possible from postoperative day 3 after a satisfactory secondary radiology control. Postoperative complications were evaluated using the unified register of the Consensus group on complications during esophagectomy (Esophagectomy Complications Consensus Group, ECCG) [14]. Isolated hydrothorax related to the early removal of the pleural draining tube (on postoperative day 1) was not considered a complication.

Research outcomes

Main research outcomes. An evaluation of postoperative complications after esophagectomy with esophageal plasty; evaluation of the effects of sarcopenia on the post-operative complications in general and postoperative pneumonia in particular.

Additional research outcomes. Compiling a predictive model, indirectly evaluating the musculoskeletal index based on the basic anthropometric (body weight, height, BMI) and clinical-laboratory (blood levels of hemoglobin, iron, albumin, transferrin and total protein) parameters.

Subgroup analysis

For the purpose of quantitatively evaluating the sarcopenia, we have measured the musculoskeletal index using CT-sarcometry. The measurements were carried out using the axial CT-scans at the level of L3 vertebral bone. The threshold range of the attenuation coefficient varied from -29 to +150 Hounsfield units (HU). A volume of all the skeletal muscles was calculated at the scan zone (paraspinal, major psoas, oblique and rectus abdominal muscles) with excluding other structures. The measurements were carried out by semiautomatic method in the Slicer 5.6.2. software. The segmentation of the image within the pre-set densitometric values was done automatically, while the structures not related to the muscle tissue were removed manually (Fig. 1, 2). The musculoskeletal index was calculated as a ratio of the area of skeletal muscles (cm^2) to the square value of the patient height (m^2). The threshold values

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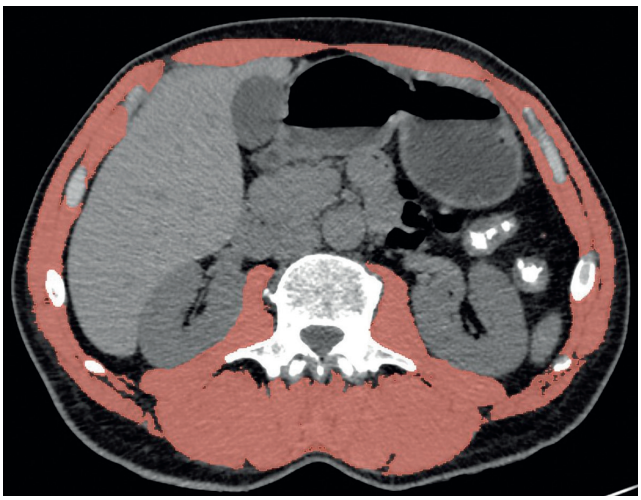

Fig. 1. Preoperational computed tomography image of the patient without sarcopenia (the area of the muscle tissue is 215.5 cm^2, the musculoskeletal index is 63 cm^2/m^2). The muscle tissue is highlighted with red color. Axial projection, soft-tissue window.

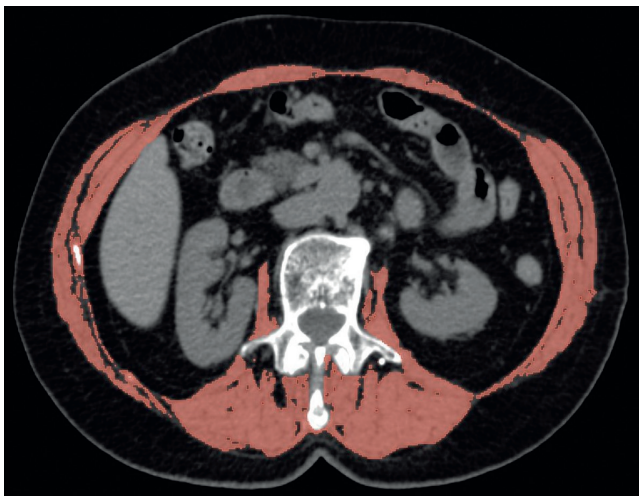

Fig. 2. Preoperational computed tomography image of the patient with sarcopenia (the area of the muscle tissue is 44.5 cm^2, the musculoskeletal index is 17 cm^2/m^2). The muscle tissue is highlighted with red color. Axial projection, soft-tissue window.

of musculoskeletal index, below which the status of the muscle tissue was considered as sarcopenia, were the classical Prado criteria — 52.4 cm^2/m^2 for males and 38.5 $cm^2/м^2$ for females [15]. For the purpose of simplification of the interpretation of the obtained values, they were presented not as absolute values, but as a ratio of the obtained value to the lower margin of the reference ranges for the given gender (musculoskeletal index). Besides, all the patients at the pre-operative stage had their BMI, body mass and height measured along with the levels of hemoglobin, iron, albumin, transferrin and total protein in blood.

Methods of registration of outcomes

For the diagnostics of postoperative complications (pneumonia, incompetence of anastomosis and necrosis of the transplant), the procedures included a CT examination of the chest cavity organs and of the abdominal cavity with oral contrasting on the first and fifth, or on the third and seventh post-operative days. Besides, the same examination was carried out in cases of sudden worsening of the patient's status. Other complications were suspected based on the clinical data with further verification with the aid of laboratory and instrumental methods.

Statistical analysis

The sample size was not pre-calculated.

The descriptive statistics for categorical variables was presented by the absolute and the relative rates, and for quantitative variables — by the mean values (standard deviation, SD) and the median ([min; max]); tables 1, 3 and 6 also provide the *p* values for testing the null hypothesis on the absence of association between the factors and the development of complications. For the categorical factors, the χ^2 (chi-square) test was used, while for the quantitative ones — the t-test.

A basic model of logistic regression was compiled for the evaluation of the probability of developing complications, including the main factors of developing complications. The selection of factors for the basic model was undertaken based on the domain terms. The statistical procedures of building the model (for example, stepwise regression) were not used. The age and the gender were added to the model as "universal confounders". The evaluation of the nutritional status of the patient, the severity of the concomitant diseases and the complexity of the intervention were indirectly presented by the BMI, by the comorbidity index and by the duration of surgery, respectively.

The main analysis of the association for the factors of interest with the development of complications after surgery was carried out using the logistic regression; a factor of interest was added to the basic model. For the odds ratios, calculated by means of logistic regression, *p*-values and 95% confidence intervals were provided, calculated by the Wald's method using robust evaluations of the standard errors (HC4 sandwich estimator). The analysis of the correctness of the models was carried out visually using the QQ-plots for residuals, the residuals vs. fitted plots, the scale-location diagrams and the residuals-leverage plots, as well as the partial residuals plots. In all the cases, the quality of the models was satisfactory.

For the evaluation of the predictive power of the statistical association between the variables, the Pearson correlation was used. For building the predictive model, we have used the multifactorial linear regression. The evaluation of the predictive quality of the obtained model was carried out using the adjusted coefficient of determination (adjusted R2).

No adjustments for multiple comparisons were used. The available case analysis was applied with no imputation of data. The tests were conducted at the significance level of α=0.05.

RESULTS

Research sample (participants)

At the NMRCS, the analysis included 500 medical records of the patients, in which primary esophagectomy was done with simultaneous esophageal plasty due to its benign (54%) or malignant (46%) diseases within the framework of the RUPOR program during the period from 2012 until 2024. The pre-operative preparation was done in 27.8% of the patients, of which, the correction of the nutritional status was required in 21.8% of the cases, and of the concomitant diseases — in 7%.

All the patients from the test group underwent sub-/total esophagectomy, 2.6% — combined with gastrectomy or subtotal proximal resection of the stomach. All the surgeries were done using the open transthoracic (44.6%) or transhiatal (55.4%) access with the formation of manual cervical anastomosis. In 92.6% of the patients, the gastric tube was used for esophagoplasty. During the combined esophagogastrectomy and in cases of the stomach not being suitable for esophagoplasty, the reconstruction was undertaken using the colon (6.2%). In case of a significant deficit in the length of the gastric tube (1.2%), a combined transplant was used, for which the gastric tube was dissected from the duodenum, and the diastasis formed was replaced with a pedunculated jejunal segment. The median of the surgery duration was 390 minutes.

From the year 2017, 97.4% of the patients were extubated in the surgery room and transferred to the intensive care unit (ICU) for further follow-up. The median of patients stay at the Intensive Care Unit was 0.67 days.

The program of early oral nutrition was applied to 96 (19.2%) patients. Postoperative complications were found in 146 (29.2%) patients. In 50 (10%) patients, postoperative pneumonia has developed. The incompetence of esophageal anastomosis (leakage) was diagnosed in 11 (2.2%) cases, also, in 11 (2.2%) patients, apical necrosis of the conduit was verified, while the additional 11 (2.2%) having a subtotal necrosis of the transplant. The median of stay at the In-Patient Department was 9 postoperative days, while the hospital mortality was 1.4%.

In the subgroup of patients with conducted CT-diagnostics of sarcopenia, 33 (30%) were receiving the pre-operative preparation, of which 19 (17%) included the correction of nutritional status (tube/parenteral/combined feeding), 13 (11.7%) underwent diagnostic coronarography, after which 3 (3%) underwent the transcutaneous coronary intervention, 2 (2%) — coronary artery bypass grafting. Before the scheduled esophagectomia, 2 (2%) patients underwent carotid endarterectomy, in 1 (1%) patient, a constant electronic cardiac pacemaker was installed. After surgery, all the patients were extubated at the surgery room and transferred to the Intensive Care Unit. The median of stay at the Intensive Care Unit was 0.7 days, the median of postoperative stay at the In-Patient Department was 9 days. Complications after surgery were reported in 34% of the cases. The postoperative pneumonia was diagnosed in 14 (13%) patients. Incompetence of esophageal anastomosis was found in 3 (3%) patients, while the apical necrosis of the gastric tube was found in 2 (2%). The hospital mortality in the test subgroup was 0%.

Primary findings

At the first stage of the research, after an evaluation of the complications, 500 patients were divided into two groups with or without complications (table 1).

Postoperative complications were statistically significantly more often diagnosed in older patients (p=0.0011). The duration of the intervention and anesthesia, the type of access, the ASA and the comorbidity index also significantly differed in a group of patients with postoperative complications (p <0.001).

The results obtained based on the basic regression model, are provided in table 2. The model included the age and gender as the “universal confounders”, the BMI (as the evaluation of the nutritional status of the patient), the comorbidity indexes (the evaluation of the severity of the concomitant diseases) and the duration of surgery (an evaluation of the complexity of surgery). The analysis of the adjusted odds ratios did not show any statistically significant association between the probability of developing complications and the age, the gender, the BMI and the comorbidity index, despite the fact, that the mean age statistically significantly differed between groups during the one-way

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Table 1

Basic descriptive statistics of the patients included into the research

Parameter	Patients		Total (*n*=500)	*p*
	no complications (*n*=354)	with complications (*n*=146)		
Age, years				
Mean (SD)	55.0 (13.7)	59.4 (13.3)	56.3 (13.7)	0.0011
Median [min; max]	57.0 [18.0; 89.0]	61.0 [19.0; 89.0]	59.0 [18.0; 89.0]	
Gender:				
• male	202 (57.1%)	97 (66.4%)	299 (59.8%)	0.065
• female	152 (42.9%)	49 (33.6%)	201 (40.2%)	
Weight, kg				
Mean (SD)	69.7 (16.3)	70.2 (15.5)	69.8 (16.1)	0.71
Median [min; max]	68.0 [34.0; 125]	69.0 [37.0; 105]	69.0 [34.0; 125]	
Body mass index:				
Mean (SD)	24.1 (5.19)	24.0 (4.84)	24.0 (5.09)	0.89
Median [min; max]	23.7 [14.4; 40.0]	22.8 [15.1; 37.2]	23.5 [14.4; 40.0]	
Classification of body mass index:				
<18.5 kg/m^2	54 (15.3%)	20 (13.7%)	74 (14.8%)	0.57
18.5–24.9 kg/m^2	161 (45.5%)	74 (50.7%)	235 (47.0%)	
>25 kg/m^2	139 (39.3%)	52 (35.6%)	191 (38.2%)	
Smoking:				
• no	268 (75.7%)	98 (67.1%)	366 (73.2%)	0.063
• yes	86 (24.3%)	48 (32.9%)	134 (26.8%)	
NRS-2002:				
Mean (SD)	2.70 (0.826)	2.80 (0.902)	2.73 (0.849)	0.25
Median [min; max]	3.00 [1.00; 5.00]	3.00 [1.00; 5.00]	3.00 [1.00; 5.00]	
No data	1 (0.3%)	1 (0.7%)	2 (0.4%)	
Comorbidity index:				
Mean (SD)	3.12 (2.42)	4.22 (2.49)	3.44 (2.49)	<0.001
Median [min; max]	3.00 [0; 10.0]	4.00 [0; 10.0]	3.00 [0; 10.0]	
Lee scale:				
Mean (SD)	1.20 (0.490)	1.32 (0.610)	1.24 (0.530)	0.034
Median [min; max]	1.00 [0; 3.00]	1.00 [0; 3.00]	1.00 [0; 3.00]	
ASA:				
Mean (SD)	2.57 (0.666)	2.80 (0.650)	2.64 (0.669)	<0.001
Median [min; max]	3.00 [1.00; 4.00]	3.00 [2.00; 4.00]	3.00 [1.00; 4.00]	
Loss of body weight >10% per 6 months:				
• no	256 (72.3%)	102 (69.9%)	358 (71.6%)	0.66
• yes	98 (27.7%)	44 (30.1%)	142 (28.4%)	
The total volume of intraoperative infusion therapy taking into consideration fulfilling the losses, ml/kg per hour				
Mean (SD)	4.45 (1.67)	4.36 (1.69)	4.42 (1.68)	0.61
Median [min; max]	4.30 [-0.751; 14.0]	4.28 [0; 9.93]	4.29 [-0.751; 14.0]	
The duration of surgery, min				
Mean (SD)	391 (99.9)	437 (111)	404 (105)	<0.001
Median [min; max]	370 [230; 755]	438 [240; 780]	390 [230; 780]	

Table 1

Continued

Parameter	Patients		Total (*n*=500)	*p*
	no complications (*n*=354)	with complications (*n*=146)		
The duration of anesthesia, min				
Mean (SD)	484 (109)	529 (125)	497 (116)	<0.001
Median [min; max]	463 [300; 850]	520 [300; 880]	480 [300; 880]	
Access:				
• transthoracic	132 (37.3%)	90 (61.6%)	222 (44.4%)	<0.001
• transhiatal	222 (62.7%)	56 (38.4%)	278 (55.6%)	
Transplant type:				
• gastric tube	329 (92.9%)	134 (91.8%)	463 (92.6%)	0.9
• intestinal tube	21 (5.9%)	10 (6.8%)	31 (6.2%)	
• combined	4 (1.1%)	2 (1.4%)	6 (1.2%)	
Incompetence of anastomosis or sub-/total necrosis of the conduit:				
• yes	0 (0%)	33 (22.6%)	33 (6.6%)	<0.001
• no	354 (100%)	113 (77.4%)	467 (93.4%)	
Musculoskeletal index before surgery (adjusted for gender):				
Mean (SD)	0.704 (0.317)	0.633 (0.250)	0.680 (0.297)	0.2
Median [min; max]	0.592 [0.193; 2.24]	0.551 [0.321; 1.20]	0.589 [0.193; 2.24]	
No data on MSI	281 (79.4%)	108 (74.0%)	389 (77.8%)	
Musculoskeletal index before surgery:				
Mean (SD)	32.3 (14.6)	29.7 (13.1)	31.4 (14.1)	0.36
Median [min; max]	28.8 [10.1; 86.4]	24.6 [14.5; 63.0]	27.4 [10.1; 86.4]	
No data on MSI	281 (79.4%)	108 (74.0%)	389 (77.8%)	

Note. Here and in the table 3: CO is the standard deviation; min; max are the minimum and maximum values, respectively.

Table 2

Risk factors of developing complications (500 patients)

Parameter	Adjusted odds ratio (OR)			
	Odds ratios	*p*	95% CI	
			L	U
Constant	0.0794	0.003	0.0151	0.417
Age, years	1.01	0.489	0.984	1.03
Females	0.809	0.333	0.526	1.24
Body mass index	0.975	0.209	0.937	1.01
Comorbidity index	1.13	0.062	0.994	1.28
Surgery time, min	1.00	0.001	1.00	1.01

Note. *p* value for the «model-submodel» test type — the likelyhood ratio is 0.44; the values were rounded to the third significant figure, the *p*-values were rounded to the third decimal place. Here and in the table 4, 5: CI — Confidence interval; L — lower; U — upper.

(unifactorial) analysis. It is important to note that the confidence intervals for the effect of the age, for the female gender and for the comorbidity index are sufficiently wide and include clinically significant values. Despite the absence of statistical significance, it cannot be claimed that there is no practically significant association of the probability of developing complications with the gender, the age or the comorbidity index.

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During the second stage, the same descriptive statistics parameters were evaluated in a subgroup of patients, which had their muscle mass volume measured (table 3), with that the sarcopenia of various degree was diagnosed in 95 (85.6%) patients.

Postoperative complications statistically significantly more often were diagnosed in patients with higher degree of anesthetic risk (p=0.0042) in case of long-term (p=0.046) transthoracic interventions (p=0.017), while the age and the comorbidity index did not statistically significantly differ in the groups. Despite the fact that mean BMI value in both groups was comparable, the distribution of patients with the body weight deficit and excess statistically significantly differed (p=0.049). The mean value of the musculoskeletal index before surgery was also comparable between the groups and did not statistically significantly differ.

For a more detailed analysis of the effects of the musculoskeletal index on the risk of developing complications, unifactorial (table 4) and multifactorial (table 5) regression models were built with the inclusion of the basic parameters, tested in a large sample of patients. Both models did not demonstrate a statistically significant association of the musculoskeletal index with the probability of developing postoperative complications, nevertheless, taking into consideration the wide confidence intervals for OR (both adjusted and non-adjusted), there is insufficient data to rule out the presence of clinically significant association of the musculoskeletal index with the development of complications. Based on the obtained data, within the frameworks of the RUPOR program, the musculoskeletal index and sarcopenia were not associated with the development of postoperative complications in a statistically significant manner.

Additional findings

We have tried to compile a predictive model, indirectly estimating the musculoskeletal index based on the basic anthropometric and clinical-laboratory findings. For this compilation, we have examined the inter-relation of the musculoskeletal index with the BMI, the body mass, the height, the levels of hemoglobin, iron, albumin, transferrin and total protein in blood. The most close relation was found for the musculoskeletal index and the BMI (r=0.37), the body mass (r=0.35) and the albumin levels (r=0.3), where "r" is the Pearson correlation coefficient. As for the other

Table 3

Basic descriptive statistics (111 patients): evaluation of sarcopenia in groups with or without complications

Parameter	Patients		Total (n=111)	p
	no complications (n=73)	with complications (n=38)		
Age, years				
Mean (SD)	56.5 (14.5)	59.1 (14.5)	57.4 (14.5)	0.37
Median [min; max]	58.0 [25.0; 84.0]	62.0 [19.0; 82.0]	61.0 [19.0; 84.0]	
Gender:				
• male	40 (54.8%)	23 (60.5%)	63 (56.8%)	0.71
• female	33 (45.2%)	15 (39.5%)	48 (43.2%)	
Weight, kg				
Mean (SD)	70.8 (16.7)	66.5 (16.3)	69.3 (16.6)	0.19
Median [min; max]	70.0 [42.0; 110]	64.0 [37.0; 105]	69.0 [37.0; 110]	
Body mass index:				
Mean (SD)	24.5 (5.50)	23.3 (4.81)	24.1 (5.28)	0.23
Median [min; max]	24.6 [14.8; 37.9]	22.2 [15.6; 36.3]	23.9 [14.8; 37.9]	
Classification of body mass index:				
<18.5 kg/m^2	11 (15.1%)	5 (13.2%)	16 (14.4%)	0.049
18.5–24.9 kg/m^2	27 (37.0%)	23 (60.5%)	50 (45.1%)	
>25 kg/m^2	35 (47.9%)	10 (26.3%)	45 (40.5%)	
Smoking:				
• no	55 (75.3%)	26 (68.4%)	81 (73.0%)	0.58
• yes	18 (24.7%)	12 (31.6%)	30 (27.0%)	

Table 3

Continued

Parameter	Patients		Total (*n*=111)	*p*
	no complications (*n*=73)	with complications (*n*=38)		
NRS-2002:				
Mean (SD)	2.67 (0.728)	2.84 (0.718)	2.73 (0.725)	0.24
Median [min; max]	3.00 [1.00; 4.00]	3.00 [2.00; 5.00]	3.00 [1.00; 5.00]	
Comorbidity index:				
Mean (SD)	3.82 (2.67)	4.29 (2.40)	3.98 (2.58)	0.35
Median [min; max]	4.00 [0; 10.0]	4.00 [0; 10.0]	4.00 [0; 10.0]	
Lee scale:				
Mean (SD)	1.33 (0.554)	1.42 (0.599)	1.36 (0.569)	0.43
Median [min; max]	1.00 [1.00; 3.00]	1.00 [1.00; 3.00]	1.00 [1.00; 3.00]	
ASA:				
Mean (SD)	2.64 (0.609)	2.95 (0.462)	2.75 (0.579)	0.0042
Median [min; max]	3.00 [1.00; 4.00]	3.00 [2.00; 4.00]	3.00 [1.00; 4.00]	
Loss of body weight >10% per 6 months:				
• no	55 (75.3%)	25 (65.8%)	80 (72.1%)	0.4
• yes	18 (24.7%)	13 (34.2%)	31 (27.9%)	
The total volume of intraoperative infusion therapy taking into consideration fulfilling the losses, ml/kg per hour				
Mean (SD)	4.44 (1.82)	4.30 (1.24)	4.39 (1.64)	0.63
Median [min; max]	4.29 [1.55; 14.0]	4.21 [2.17; 7.24]	4.22 [1.55; 14.0]	
The duration of surgery, min				
Mean (SD)	399 (93.1)	442 (113)	414 (102)	0.046
Median [min; max]	390 [240; 625]	438 [260; 780]	405 [240; 780]	
The duration of anesthesia, min				
Mean (SD)	491 (101)	539 (127)	507 (112)	0.044
Median [min; max]	480 [300; 730]	533 [330; 880]	495 [300; 880]	
Access:				
• transthoracic	33 (45.2%)	27 (71.1%)	60 (54.1%)	0.017
• transhiatal	40 (54.8%)	11 (28.9%)	51 (45.9%)	
Transplant type:				
• gastric tube	65 (89.0%)	34 (89.5%)	99 (89.2%)	1
• intestinal tube	6 (8.2%)	3 (7.9%)	9 (8.1%)	
• combined	2 (2.7%)	1 (2.6%)	3 (2.7%)	
Incompetence of anastomosis or sub-/total necrosis of the conduit:				
• yes	0 (0%)	5 (13.2%)	5 (4.5%)	0.0072
• no	73 (100%)	33 (86.8%)	106 (95.5%)	
Musculoskeletal index before surgery (adjusted for gender):				
Mean (SD)	0.704 (0.317)	0.633 (0.250)	0.680 (0.297)	0.2
Median [min; max]	0.592 [0.193; 2.24]	0.551 [0.321; 1.20]	0.589 [0.193; 2.24]	
Musculoskeletal index before surgery:				
Mean (SD)	32.3 (14.6)	29.7 (13.1)	31.4 (14.1)	0.36
Median [min; max]	28.8 [10.1; 86.4]	24.6 [14.5; 63.0]	27.4 [10.1; 86.4]	

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Table 4

Unifactorial (one-way) regression model: the evaluation of the effects of sarcopenia on the probability of developing postoperative complication

Parameter	Unadjusted odds ratio (OR)			
	OR	*p*-value	95% CI	
			L	U
Constant	0.954	0.929	0.339	2.69
The musculoskeletal index before surgery	0.402	0.227	0.0918	1.76

Table 5

Multifactorial regression model: the evaluation of the effects of sarcopenia on the postoperative complication

Parameter	Adjusted odds ratio (OR)			
	OR	*p*-value	95% CI	
			L	U
Constant	0.239	0.421	0.00734	7.80
Age, years	1.02	0.591	0.961	1.07
Females	0.803	0.628	0.331	1.95
Body mass index	0.932	0.145	0.848	1.02
Comorbidity index	0.990	0.947	0.730	1.34
Surgery time, min	1.01	0.032	1.00	1.01
Musculoskeletal index before surgery	0.506	0.467	0.0809	3.17

factors, the correlation coefficient of the module did not exceed 0.18.

After building a multifactorial linear model, none of the factors (gender, BMI, body weight, height, levels of hemoglobin, iron, albumin, transferrin and total protein in blood), included into the model, was statistically significantly associated with the musculoskeletal index (Fig. 3). The total *p*-value for the whole model was 0.07, the adjusted coefficient of determination (R^2) was 0.12. Hence, the potential of studied factors for predicting the musculoskeletal index is weak. These factors poorly describe the variability of the index. The basic anthropometrical and clinical-laboratory parameters do not predict sarcopenia in patients with the diseases of the esophagus.

Undesirable phenomena

Postoperative complications were reported in 146 (29.2%) patients. The most frequent complication was the postoperative pneumonia — 50 (10%) patients. Cardiac rhythm disorders (expressed as atrial fibrillations) were diagnosed in 30 (6%) cases, incompetence of the esophageal co-junction — in 11 (2.2%), necrosis of the transplant — in 22 (4.4%), of which 11 (2.2%) patients had an apical necrosis of the conduit, requiring conservative therapy, while another 11 (2.2%) had a sub-/total necrosis of the transplant, which was accompanied by its extirpation and by the elimination of the esophago- and gastro-/jejunostomas.

DISCUSSION

This article presents a single-center experience of perioperative managing of esophagectomy with simultaneous esophageal plasty within the framework of the RUPOR program. Retrospectively, using the radial diagnostics methods, sarcopenia was diagnosed in 85.6% of the patients. Despite such a high occurrence rate, it did not affect the complications after esophagectomy within the premises of the NMRCS.

In the scientific literature worldwide, the data on the effects of sarcopenia on the postoperative complications is controversial. In 2019, the first meta-analysis was published, describing the effects of sarcopenia on the treatment outcomes in esophageal cancer patients [16]. The authors came to the conclusion that sarcopenia worsens the long-term prognosis for the patients (3- and 5-year survival). After 4 years, the other meta-analyses based on the updated worldwide

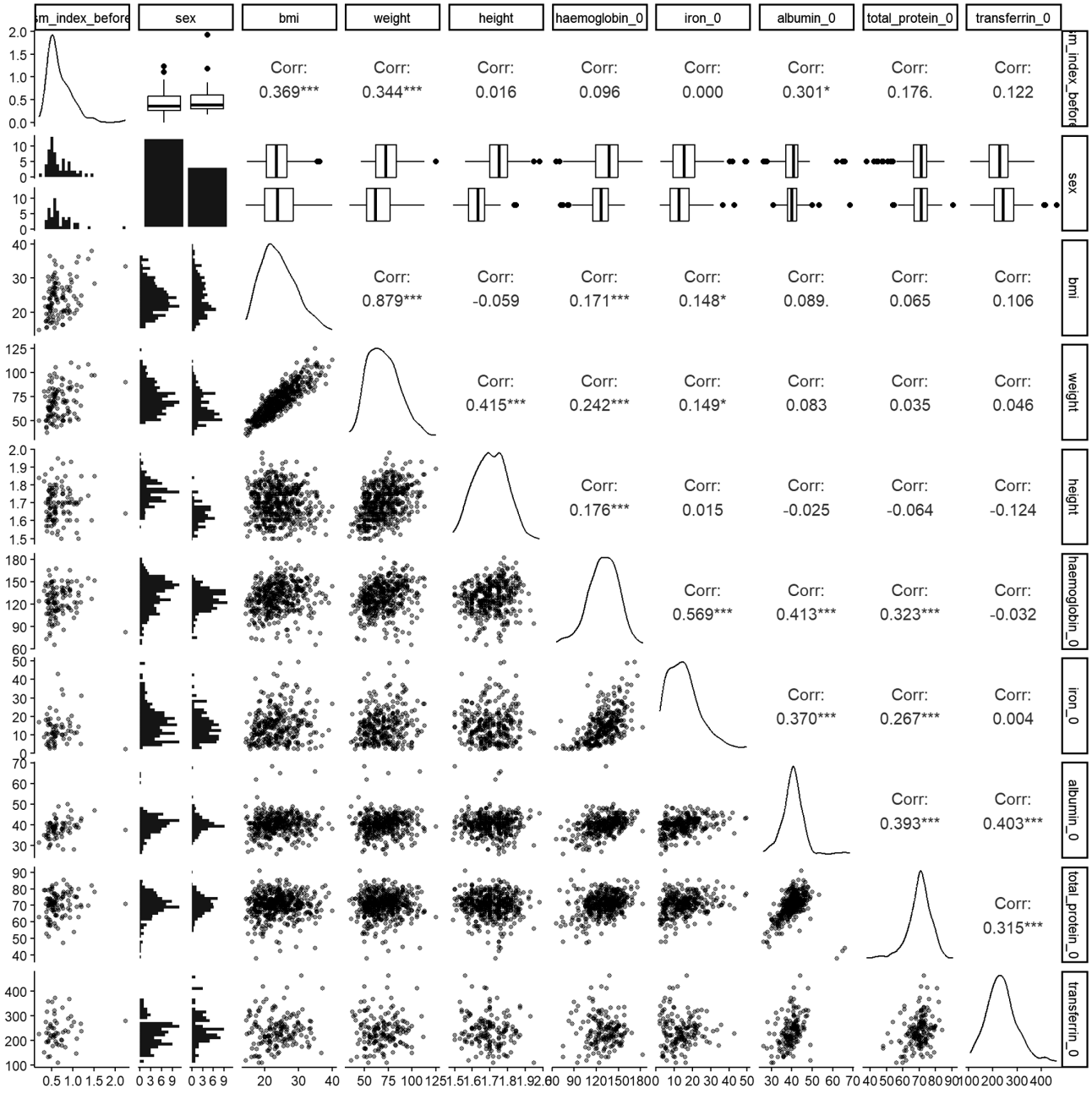

Fig. 3. Paired scattering diagrams and Pearson correlation coefficients for the risk factors of developing complications in general (musculoskeletal index, gender, body mass index, body weight, height, levels of hemoglobin, iron, albumin, transferrin and total protein in blood).

data have concluded that sarcopenia is an independent risk factor for postoperative complications in general, for the incompetence of anastomosis and respiratory complications in particular, and it significantly decreases the total and the relapse-free survival in patients with esophageal cancer [17, 18].

Upon the detailed review of the articles included into the meta-analysis, the inhomogeneity of the studied patients stands out. The occurrence rate of sarcopenia in groups varies from 15–16.5% [19, 20] to 70–75% [13, 21], which is partially related to the absence of a unified standard of CT-diagnostics of sarcopenia. The investigators have evaluated various muscle groups and quantitative parameters, more often determining the musculoskeletal index, but some articles included the measurements of the psoas muscle index [21–23] and even the volume of the masticatory muscles [24]. When evaluating the musculoskeletal index, various reference ranges were used. Some investigators were applying the classical Prado criteria (52.4 cm^2/m^2 for males and 38.5 cm^2/m^2 for females) [15], others were decreasing the lower

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reference range for males down to 43 cm^2/m^2 in cases of the BMI <25 kg/m^2 [25, 26] and were insignificantly changing the values for females. However, more interesting are the research results themselves, used for proving the effects of sarcopenia on the postoperative complications. Thus, in a research by B. Soma et al. [26], including 109 patients, sarcopenia was diagnosed in 44% of them. In sarcopenia patients, the duration of stay at the Intensive Care Unit was increasing from 5 to 6 days, the hospitalization — from 33 to 46 postoperative days, the rate of anastomosis incompetence — from 17.5% to 20%, while the rates of postoperative pneumonia — from 11% to 33%. The research was finalized with a conclusion that sarcopenia significantly increases the rate of respiratory complications. In other research, sarcopenia was increasing the rate of complications from 36% to 63% [27], with all of these data, all the patients were intraoperationally receiving a nutritional jejunostoma with an installation of the decompression nasogastral tube and the pleural draining tube was removed on the eighth postoperative day. U. Fehrenbach et al. [12] have analyzed the treatment results in 85 patients with diagnosing complications in 72% of the cases and the incompetence of anastomosis — in 12.8%. The research has shown that sarcopenia patients had a significantly longer hospitalization period — from 19 to 32, while in cases of sarcopenic obesity — from 24 to 71 postoperative days, but S.R. Siegal et al. [28] did not find a relation between sarcopenia and increased morbidity, mortality or relapse-free survival rate in a large sample of patients (n=173) and the occurrence rate of sarcopenia (73.4%).

Due to the high-quality surgical technique employed by the operating surgeon, to the adequate perioperative management and preoperational preparation of the patients, even in cases of sarcopenia (85.6%), it can be possible to maintain a relatively low rate of postoperative complications (34%) in general, of pneumonia (13%) and of the incompetence of the anastomosis (3%) in particular, with the duration of postoperative period being up to 9 postoperative days.

Research limitations

It is worth noting that all the research works were evaluating only the patients with esophageal cancer. At the NMRCS, only 54% of surgeries were undertaken due to the presence of the oncology disease. In the other patients, the interventions were carried out due to the presence of benign diseases of the esophagus (esophageal stricture, cardial achalasia grade IV, grade II short esophagus, fistula). It is the possible reason of such a high occurrence of sarcopenia, for in cases of benign diseases, the mean body weight loss is higher and the disease history is longer. For the statistical processing of the information, we have employed the logistical regression, but not the standard dichotomization of the continuous variable used in other articles. The logistical regression provides a higher probability of detecting the relation between the data and ruling out the effects of sarcopenia on the outcomes of treatment in the patients [29, 30].

CONCLUSION

Esophagectomy with simultaneous esophageal plasty is a surgery associated with high risk of complications and mortality. Due to the implementation of the RUPOR program developed at the NMRCS, the rates of life-threatening complications (pneumonia, incompetence of anastomosis, necrosis of the transplant) and mortality after reconstructive interventions were significantly lower comparing to the worldwide data. Sarcopenia was diagnosed in 85.6% of the NMRCS patients — and this is a significant and proven factor, worsening the treatment results for the patients, however, based on the analysis of our data, sarcopenia does not affect the development of postoperative complications. The experience from the NMRCS has shown that the high-quality surgical technique together with proper perioperative management can alleviate the negative effects of sarcopenia.

ADDITIONAL INFORMATION

Author contribution. *N.B. Kovalerova* — treatment of patients, data collection, writing the text of the article; *D.V. Ruchkin* — the operator of all surgical interventions, management of patient treatment and discussion of the results of the study; *O.V. Strunin* — search and analytical work, discussion of the results of the study; *D.E. Okonskaya* — radiological diagnostics, writing the text of the article; *A.V. Mazurok* — radiological diagnostics. 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.

Ethics approval. The organization of the study was approved by the local Ethics Committee of the The National Medical Research Center of Surgery named after A. Vishnevsky of the Ministry of Health of

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EXPERIMENTAL DIGITAL ATLAS OF BLOOD SUPPLY ZONES OF THE INTERNAL CAROTID ARTERY

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ABSTRACT

BACKGROUND: *The compilation of a neuroanatomic atlas based on a large sample is essentially a fundamental research work, but compiling a digital atlas during the epoch of wide usage of radiodiagnostics methods in the clinical and experimental practice along with using the artificial intelligence systems brings a significant applied relevance to the research. Rats are the main species of laboratory animals, in which the studies of modeling the ischemic stroke, of testing the cerebroprotective drugs and of developing new strategies of regenerative therapy of stroke consequences are carried out. At the present moment, there is no available and comprehensive digital atlas of the arterial blood supply of the rat brain, while single research works are based on small groups of animals and their histological description. Within this context, it is deemed very interesting and important to take the first step in addressing this issue.* ***AIM:*** *to compile an atlas of blood supply zones within the intracranial branches of the internal carotid artery in the settings of experimentally induced occlusion of the medial cerebral artery.* ***METHODS:*** *The archived data were used from the magnetic resonance imaging scans in rats with modeling the transient occlusion of the medial cerebral artery with a monofilament (n=243). The system of automatic brain segmentation based on artificial intelligence was used for objective mapping of the cerebral infarction area, the obtained data were added to a single coordinate space, unified and analyzed for highlighting the arterial blood supply zones.* ***RESULTS:*** *A digital atlas of the arterial circulation was compiled based on the intravitam data of high-resolution magnetic resonance imaging with an isotropic voxel.* ***CONCLUSION:*** *The compiled atlas may be used for increasing the quality of modeling the cerebral infarction by means of transient occlusion of the medial cerebral artery with a monofilament and it allows for using the additional objective parameters in the evaluation of the treatment effects in cases of experimentally induced ischemic stroke. The methodology developed by us is applicable for high-performance retrospective analysis of the neurovisualization data from the ischemic stroke patients, obtained within a framework of the implementation of the Vascular Medicine Program in the Russian Federation.*

Keywords: *ischemic stroke; rats; blood supply; Magnetic resonance imaging; artificial intelligence.*

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BACKGROUND

In order to solve the modern scientific tasks, the researchers have to master and apply the new methods of data processing and analysis at a deeper levels [1]. The technological advances progress more and more, which promotes to developing the applied research, however, there is also a decrease in the attention to the fundamental science [2]. The

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ЭКСПЕРИМЕНТАЛЬНЫЙ ЦИФРОВОЙ АТЛАС ЗОН КРОВОСНАБЖЕНИЯ ВЕТВЕЙ ВНУТРЕННЕЙ СОННОЙ АРТЕРИИ

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АННОТАЦИЯ

Обоснование. *Создание нейроанатомического атласа на большой выборке данных является, по сути, фундаментальным трудом, но создание цифрового атласа в эпоху широкого применения методов лучевой диагностики в клинической и экспериментальной практике, а также систем искусственного интеллекта придаёт исследованию значимое прикладное значение. Крысы являются основным видом лабораторных животных, на которых происходят исследования по моделированию ишемического инсульта, тестированию церебропротекторных препаратов и разработке новых стратегий регенеративной терапии последствий инсульта. На данный момент не существует полноценного цифрового атласа артериального кровоснабжения мозга крыс, а единичные работы опираются на небольшие группы животных и их гистологическое описание. В связи с этим представляется крайне интересным и важным сделать первый шаг для освещения данной проблемы.* ***Цель исследования*** *— создать атлас зон кровоснабжения интракраниальных ветвей внутренней сонной артерии в условиях экспериментальной окклюзии средней мозговой артерии.* ***Методы.*** *Архивные данные магнитно-резонансных исследований крыс с моделью транзиторной окклюзии средней мозговой артерии монофиламентом (n=243). Систему автоматической сегментации мозга на основе искусственного интеллекта использовали для объективной разметки области инфаркта мозга, полученные данные приводили в общее координатное пространство, объединяли и анализировали для выделения зон артериального кровоснабжения.* ***Результаты.*** *Создан цифровой атлас артериального кровоснабжения на основании прижизненных данных магнитно-резонансной томографии высокого разрешения с изотропным вокселем.* ***Заключение.*** *Созданный атлас может применяться для повышения качества моделирования инфаркта мозга путём транзиторной окклюзии средней мозговой артерии монофиламентом и позволит использовать в оценке эффектов терапии экспериментального ишемического инсульта дополнительные объективные параметры. Разработанная нами методология применима для высокопроизводительного ретроспективного анализа данных нейровизуализации пациентов с ишемическим инсультом, полученных в рамках реализации сосудистой программы в Российской Федерации.*

Ключевые слова: *ишемический инсульт; крысы; кровоснабжение; магнитно-резонансная томография; искусственный интеллект.*

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present article is devoted to studying the distribution of arterial blood supply zones in the brain of the rats, which, already more than 150 years are deemed the most popular laboratory animals for modeling various diseases during the experimental biomedical research works [3]. The experimental model of ischemic stroke, based on the transient occlusion of the medial cerebral artery using a monofilament, allows for achieving the maximally precise reproduction of the pathogenetic processes occurring upon the development of the two most frequent variants of ischemic stroke — the atherothrombotic and the cardioembolic one with the reperfusion phenomenon [4, 5]. Despite the high popularity of this model, until the present moment, there is no high-resolution digital atlas of the arterial blood supply zones, which could be integrated into the modern methods of automatic processing of radiology visualization data. The corresponding descriptions of small series of MRI-scans [6] and histology examinations on this issue [7, 8] did not lead to the compilation of such an instrument.

The implementation of the artificial intelligence systems into the translational research on ischemic stroke [9–11] makes this task even more topical. This is, most particularly, due to the fact that similar systems, including the systems of morphometric analysis and of segmenting the foci of damaging the brain matter with taking into consideration the anatomical positioning and others, at a certain stage of their functioning require the usage of a digital atlas, which serves as the basis for the analysis. One of the benefits of the methods of intravitam brain visualization in the experimental animals is the possibility to shorten the sample size and to obtain objective data on the anatomy without the necessity of euthanizing. Magnetic resonance imaging (MRI) as one of such methods [12], allows for accumulating a mass of digital data, required for compiling such an atlas.

Research aim — to compile a digital atlas of the blood supply zones of the intracranial branches of the internal carotid artery in the settings of the experimental occlusion of the medial cerebral artery.

METHODS

Research design

This research work is a single-center (conducted using the data obtained at a single laboratory), experimental (conducted using the data from the laboratory animals) and retrospective one (all the data used during the research, were obtained as a result of other experimental activities).

Conformity criteria

Inclusion criteria. The research included the retrospective data from magnetic-resonance scans of the rat brain with a model of acute focal ischemia and with the protocol including the isotropic T2-weighted images.

Exclusion criteria. The exclusion criteria used when evaluating the archival data, were the absence of brain infarction area according to data from MRI and the absence of the required impulse sequence in the scanning protocol.

Research facilities

The archival MRI data from the experimental animals were obtained using the Wistar rats at the "Medical Nanobiotechnology" Center for Collective Use within the premises of the Federal State Autonomous Educational Institution of Higher Education "Pirogov Russian National Research Medical University" under the Ministry of Health of the Russian Federation (Pirogov RNRMU). Within the framework of obtaining these data, it was found that, during the previous experiments, the animals were housed in standard conditions (12h dark/light mode, 22±2°C, 45–65% humidity) in groups of 4–5 animals per cage (before) and as a single animal per cage after modeling the ischemic stroke with a free access to water and to the standard rodent diet. All the surgical interventions and MRI procedures were carried out under general inhalational anesthesia, which was administered via the animal anesthesia system (E-Z-7000 Classic System; E-Z-Anesthesia Systems). The induction of anesthesia was initiated by 3.5–4% Isoflurane (Aerrane, Baxter HealthCare Corporation), while maintaining the anesthesia included the use of 2–2.5% Isoflurane. When modeling the experimental brain infarction, a mixture of anesthetic agent and atmospheric air was used, while during the MRI scans, pure oxygen was supplied. During all the surgical interventions and during the MRI scanning, the body temperature of the animals was maintained at 37°C. At the end of the follow-up period, the animals were euthanized using the induction chamber (E-Z-7000 Classic System; E-Z Anesthesia Systems) and inhalational anesthesia with a lethal isoflurane dosage. Later on, directly before transcardiac perfusion, they were additionally receiving a lethal dosage of Zoletil. All the animal-based experimental results were described according to the ARRIVE recommendations.

Research duration

The retrospective analysis of the archival data included the research activities performed by a group of researchers from 2017 until 2024.

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Research description

In order to compile an atlas of the blood supply system of the intracranial branches of the internal carotid artery, the archival MRI data from the experimental animals were used, obtained during the modeling of temporary occlusion of the medial cerebral artery with monofilament.

The cerebral infarction induced within the framework of the other scientific research works by the group of authors, was modeled by means of a transient (90 minutes) occlusion of the right medial cerebral artery with a monofilament introduced via the external carotid artery into the internal carotid artery [13]. The monofilament has a silicone tip with a length of 4 mm and with a diameter of 0.37 mm (monofilament 4-0, Doccol Corporation), due to which, depending on the depth of its location, it is possible to cease the circulation in the arteries, located close to the area of the origination of the medial cerebral artery.

As for the objective control of the cerebral infarction focus, all the animals were undergoing MRI-scanning by means of the tomography device for small laboratory animals — ClinScan (Bruker BioSpin) with a magnetic field induction of 7 Tesla.

Statistical analysis

For the most objective segmentation of the cerebral infarction focus, we have used a previously trained software algorithm with an aid of the artificial intelligence system. This system was created on the basis of the Swin-UNETR transformer [14] as one of the most recent neuronal network architectures, demonstrating high quality when segmenting the medical data from the radiology diagnostics methods. All the data processing was carried out using the Python programming language [15]. The obtained data on the segmentation of the cerebral infarction was added to the unified coordinate space by means of using the SimpleITK pack [16] and the pre-prepared template of rat brain (registrations were done in the template). Here, all the segmentation data were integrated and analyzed using the 3D Slicer software pack [17].

RESULTS

Research sample

The research included a total of 243 archived trials, in which isotropic T2-weighted images were obtained (using the impulse sequence 3-dimensional rapid spin echo with a SPACE mode of excitation angle modification, with the voxel size of 0.2×0.2×0.2 mm, with the time repetition and the echo-signal time of 4000 and 251 msec, respectively).

Primary findings

In order to compile an atlas of the blood supply systems of the intracranial branches of the internal carotid artery according to MRI data, we have used an artificial intelligence system, allowing for significant segmenting the cerebral infarction zone after the occlusion of the medial cerebral artery (Fig. 1). The obtained results of segmenting the experimental cerebral infarction were registered in a unified coordinate space using the rat brain template (Fig. 2, a). Based on the obtained segmentation files, summarized in a single coordinate system, the thermal maps of the rates of developing the cerebral infarction foci were compiled (see Fig. 2, b).

The search of blood supply zones of the main intracranial branches of the internal carotid artery (subcortical and cortical areas of the medial cerebral artery, of the anterior choroid artery and of the hypothalamic arteries) was performed in several stages. In accordance with the sequence of arteries originating from the internal carotid artery, the filament, introduced into its lumen, may cause an occlusion of its various branches (Fig. 3, a). Knowing the sequence of origination of arteries, one can differentiate the animals, in which, upon the deep positioning of the filament, there is no infarction focus in the system of the proximal branches of the internal carotid artery, and

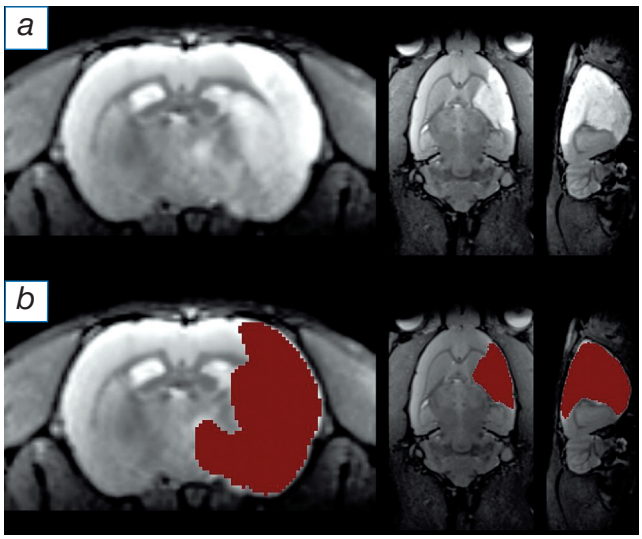

Fig. 1. An example of segmentation of the cerebral infarction using artificial intelligence: *a* — T2-weighted images in the axial, frontal and sagittal planes (from the left side to the right), in which the right hemisphere contains a visualized hyperintensive infarction focus in the brain; *b* — automatic segmentation of the cerebral infarction focus (marked with red color).

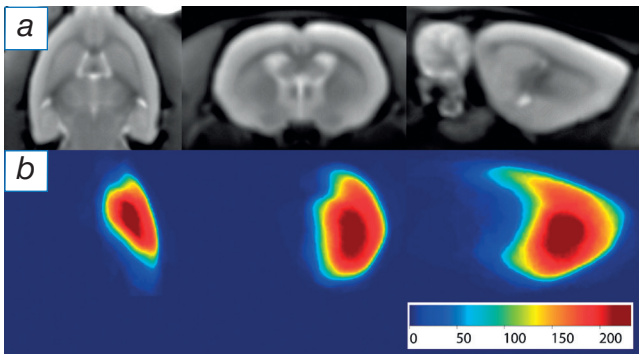

Fig. 2. The rate of the cerebral infarction focus positioning among the experimental animals in a model of temporary occlusion of the right medial cerebral artery (obtained by summarizing all the foci of cerebral infarction in a single coordinate space): *a* — inactive brain template, in which the data registration was made (as a reference); *b* — the rate of cerebral infarction locations: the warmer is the color, the more often this part of the brain was affected (a color scale is provided with describing the correlation of the color and the averaged values).

from the animals with insufficiently deep positioning of the filament, in which the infarction focus does not involve the distal branches of the internal carotid artery (see Fig. 3, a).

The first stage of compiling the atlas was generating the thermal maps of lesion focus development depending on the extent of cerebral infarction: 0–25 mm^3, 0–50 mm^3, 0–75 mm^3, 0–100 mm^3, 0–200 mm^3, 0–300 mm^3, 25–75 mm^3, 50–150 mm^3, 100–200 mm^3, 200–300 mm^3, 300–500 mm^3, 200–500 mm^3, 150 mm^3 and more. The obtained thermal maps were visually analyzed using the Otsu's method; the procedures included a primary segmentation of the areas of interest. During the second stage, automatic filtration was carried out in terms of inclusion and/or exclusion (into the summarized thermal map) of scanning data that included (and/or did not include) the reference points selected at the first stage for the area of the cerebral infarction: a total of five such combinations were selected. The resulting thermal maps were analyzed as an addition to the ones compiled during the fist stage, along with their marking with overlaying the areas with the blood supply from the selected branches of the internal carotid artery. At the final stage, smoothening of contours was done with searching the optimal borders between the blood supply systems for evening out the overlaying areas.

The obtained atlas of blood supply zones of the main intracranial branches of the internal carotid artery is provided in Fig. 3 (b), with its three-dimensional reconstruction — in Fig. 3 (c).

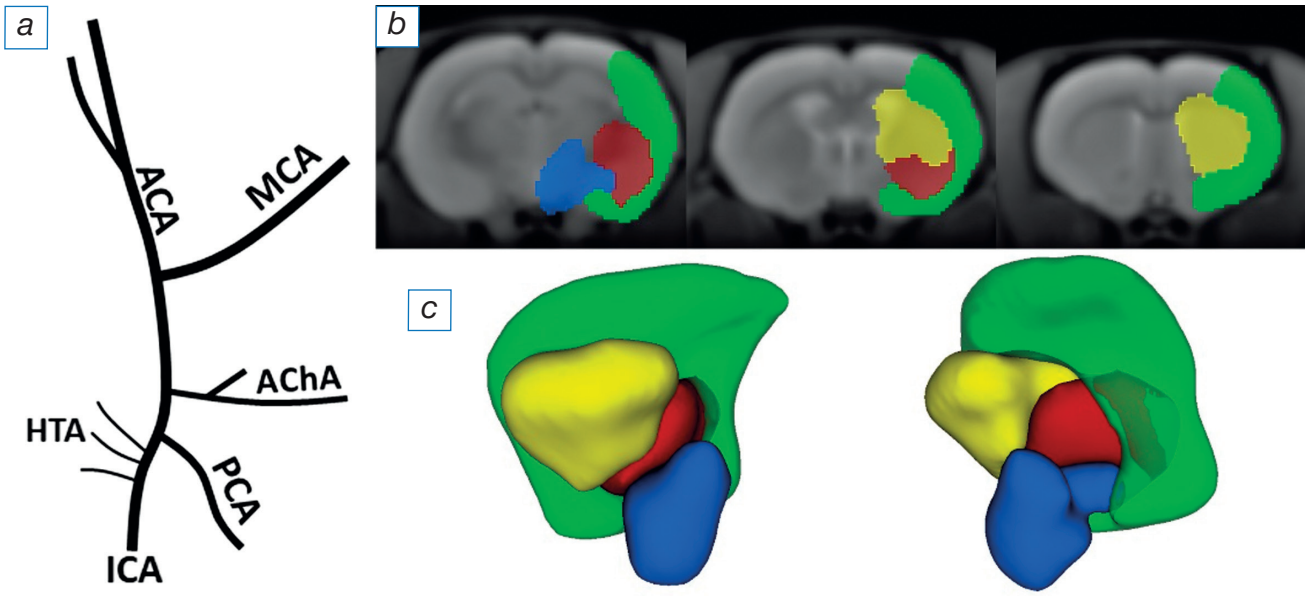

Fig. 3. The pattern of origination of the intracranial branches of the internal carotid artery and the compiled atlas of their blood supply zones: *a* — the chart showing the origination of the intracranial branches of the internal carotid artery (compiled based on the data obtained by Z. He et al. [7]); *b* — sequential slices in the axial plane with the location of blood supply zones in them (green color marks the zone of the cortical branches of the medial cerebral artery, yellow — the zone of the medial cerebral artery, supplying the subcortical area, red — the zone of anterior choroid artery, blue — the zone of hypothalamic arteries); *c* — three-dimensional reconstruction of the atlas of blood supply zones for the intracranial branches of the internal carotid artery (color marking identical to point "*b*"). ICA — internal carotid artery; PCA — posterior cerebral artery; MCA — median cerebral artery; AChA — anterior choroid artery; HTA — hypothalamic arteries.

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DISCUSSION

The digital atlas of blood supply zones of the major intracranial branches of the internal carotid artery compiled by us, may be used for the objective and quantitative evaluation of the rates of developing various types of cerebral infarction (hemispheric, subcortical, hypothalamic) in a model of transient occlusion of the medial cerebral artery. Based on these data, it is possible to adjust the filament parameters (the length of the silicone tip and its diameter), as well as to predict the possible complications, for example, such as hyperthermia upon damaging the hypothalamus [18]. The benefit of this research is that, for the first time, an atlas of the blood supply zones is compiled based on the large (more than 200 scans) set of data obtained using the non-invasive method with high spatial resolution in rats (an isotropic voxel measuring 0.2×0.2×0.2 mm was used). In the majority of existing trials, for the evaluation of the blood supply zones, the approach used included either ex vivo histological staining of the brain in ischemia [7, 8] or MRI with anisotropic slices and with a small sample size, without compiling the blood supply atlas [6]. Similar atlases of blood supply zones already exist for mice [19, 20], compiled based on the data from single experimental animals, due to which they poorly reflect the variability of their location.

It is worth noting that the proposed approach to compiling an atlas of arterial blood supply zones, based on analyzing the experimental data and described in the present article, has a potential for its adaptation and its application in clinical practice. During the time of implementing the Vascular Medicine Program in the Russian Federation, a significant number of neurovisualization data was accumulated from the ischemic stroke patients. Its retrospective analysis with taking into consideration the demographic and clinical characteristics and based on the methodology developed by the authors, can contribute to obtaining new fundamental knowledge in the field of vascular neurology.

Research limitations

The main downside of this research is compiling the atlas only for the blood supply zones of the intracranial branches of the internal carotid artery on the right side. However, the model of transient occlusion of the medial cerebral artery with a monofilament is the gold standard and the most wide-spread model in translational pre-clinical research on the ischemic stroke as the most closely related in terms of pathophysiology [21–23]. The limitation on the evaluation side can also be reduced at the data registration stage by its reflecting. The possible downside is also the usage of a specialized protocol (isotropic T2-weighted images with using the impulse sequence of the 3-dimensional rapid spin echo with modifiable excitation angle) at the stage of compiling the atlas, however, the atlas itself may be used outside the context of operating with artificial intelligence, and its registration is possible with any T2-weighted images, including the anisotropic ones.

CONCLUSION

For the first time ever, based on the sample size of more than 200 high-resolution intravitam MRI-scans, a digital atlas was compiled that is describing the blood supply zones of the major intracranial branches of the internal carotid artery. This atlas is applicable within the framework of translational research in the most relevant experimental model of ischemic stroke — the transient occlusion of the medial cerebral artery with a monofilament. The methodology developed by us is applicable for high-performance retrospective analysis of neurovisualization data from the patients with ischemic stroke, obtained as a part of the implementation of the Vascular Medicine Program in the Russian Federation.

ADDITIONAL INFORMATION

Author contribution. *I.L. Gubskiy*, *D.D. Namestnikova*, *E.A. Cherkashova*, *I.S. Gumin* — data preparation and analysis, writing program code, writing article text; *I.L. Gubskiy*, *L.V. Gubsky*, *V.P. Baklaushev*, *V.P. Chekhonin*, *K.N. Yarygin* — concept development, resource provision, text 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.

Ethics approval. This work was performed on an archival data set, the acquisition of which as part of the scientific work of the authors' team was approved by the Ethics Committee of the Pirogov Russian National Research Medical University (protocol No. 22/2023 dated 15.12.2023), and in accordance with Directive 2010/63/EU of the European Parliament and of the Council of the EU on the protection of animals used for scientific purposes.

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

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DETERMINING THE EFFICIENCY OF LOW-INTENSITY LASER RADIATION EXPOSURE WITH A WAVELENGTH OF 445 NM APPLIIED TO THE GINGIVAL AREA ACCORDING TO THE DATA FROM LASER DOPPLER FLOWMETRY

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ABSTRACT

BACKGROUND: *Currently, the list of diode semiconductor lasers in surgical dental practice is expanded due to the development of the blue laser. The topical issue is the evaluation of the effects of laser radiation with a wavelength of 445 nm on the microcirculation of oral cavity mucosa.* ***AIM:*** *to assess the effects of 445 nm laser radiation with a 0.1 Watt power on the microcirculation and the lymphatic flow in the gingival area using the method of laser Doppler flowmetry.* ***METHODS:*** *The efficiency of laser radiation with a wavelength of 445 nm in the gingival area was determined by the data from laser Doppler flowmetry. Dynamic changes of the basal circulation and basal lymphatic flow in the area of the attached keratinized gingiva in the teeth of the mandible were evaluated in healthy volunteers: the numerical values obtained for the microcirculation were measured along with its variability and the coefficient of variation before and after laser therapy. Statistical analysis and visualization of the obtained data were performed using the R 4.4.2 statistical calculations medium.* ***RESULTS:*** *In a total of 20 volunteers, the method of laser Doppler flowmetry has shown a significant increase of the microcirculation values in the gingival tissues upon the exposure of the laser radiation with a wavelength of 445 nm to the gingiva (gum).* ***CONCLUSION:*** *An increase of the circulation rates in the gingival tissues upon the exposure of the low-intensity laser radiation with a wavelength of 445 nm indicates the presence of a therapeutic effect caused by the blue laser. The procedures of preventing the diseases of the parodontal tissues are recommended to be supplemented by photobiomodulation with using the blue laser technology at a power of 0.1 W.*

Keywords: *microcirculation; laser Doppler flowmetry; blue laser; low-level laser irradiation; photobiomodulation.*

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BACKGROUND

In modern dental practice and in the treatment of inflammatory or inflammatory-destructive diseases of the parodontal tissues, the low-intensity laser radiation (or Low Level Laser Therapy (LLLT)) of red or infrared spectrum is widely used [1–3]. LLLT provides a biostimulating, anti-inflammatory, analgesic and regenerative effect in the parodontal tissues [4, 5]. The mechanism of action of LLLT is related to the photochemical reactions taking place in the cells under the effects of laser radiation. The absorption of light by the chromophores leads to an activation of the cellular enzymes, to an increased synthesis of adenosinetriphosphate and to an improvement in the oxygenation of tissues [6, 7].

The results of laser Doppler flowmetry (LDF) indicate an improvement of the microcirculation in the mucosal membrane of the papillary and marginal gingiva, an increase of the capillary circulation and a growth of the vasomotor activity in the vessels when the conventional scheme of parodontal therapy is complemented by the use of laser radiation with a wavelength of 632.8 nm, 650 nm, 810 nm, 850 nm, 890 nm or 980 nm [1, 8–11]. The normalization of local circulation promotes to the dehydration of tissues and to the decreased severity of swelling. All of these factors contribute to general increase of trophic processes in the gingival tissues [3, 12].

Currently, the list of diode semiconductor lasers available for use in dental practice is extended by the inclusion of the medical blue laser with a radiation

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ОПРЕДЕЛЕНИЕ ЭФФЕКТИВНОСТИ ВОЗДЕЙСТВИЯ НИЗКОИНТЕНСИВНЫМ ЛАЗЕРНЫМ ИЗЛУЧЕНИЕМ ДЛИНОЙ ВОЛНЫ 445 НМ НА ОБЛАСТЬ ДЕСНЫ ПО ДАННЫМ ЛАЗЕРНОЙ ДОППЛЕРОВСКОЙ ФЛОУМЕТРИИ

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АННОТАЦИЯ

Обоснование. *В настоящее время перечень диодных полупроводниковых лазеров для хирургической стоматологической практики расширен благодаря появлению медицинского синего лазера. Актуальным представляется изучение влияния лазерного излучения длиной волны 445 нм на микроциркуляцию слизистой оболочки полости рта.* ***Цель исследования*** *— изучить влияние лазерного излучения длиной волны 445 нм при мощности 0,1 Вт на микроциркуляцию и лимфоток в области десны методом лазерной допплеровской флоуметрии.* ***Методы.*** *Эффективность воздействия лазерным излучением длиной волны 445 нм на область десны установлена по данным лазерной допплеровской флоуметрии. Изучена динамика базального кровотока и базального лимфотока в области прикреплённой кератинизированной десны зубов нижней челюсти: определены числовые значения показателя микроциркуляции, величины его изменчивости и коэффициента вариации до и после лазерной терапии. Статистический анализ и визуализация полученных данных проведены с использованием среды для статистических вычислений R 4.4.2.* ***Результаты.*** *У 20 добровольцев методом лазерной допплеровской флоуметрии выявлено достоверное увеличение показателя микроциркуляции в области тканей десны при воздействии лазерным излучением длиной волны 445 нм на область десны.* ***Заключение.*** *Увеличение скорости кровотока в тканях десны при воздействии низкоинтенсивным лазерным излучением длиной волны 445 нм указывает на наличие у синего лазера терапевтического эффекта. В профилактические мероприятия заболеваний тканей пародонта рекомендуется включать процедуры фотобиомодуляции с применением технологии синего лазера мощностью 0,1 Вт.*

Ключевые слова: *микроциркуляция; лазерная допплеровская флоуметрия; синий лазер; низкоинтенсивное лазерное излучение; фотобиомодуляция.*

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wavelength of 445±40 nm. All over the world, the manufacturers of blue lasers claim this technology as being the best for surgical preparation of the soft tissues, for the radiation with a wavelength of 445±40 nm is to a greater extent absorbed by hemoglobin, oxyhemoglobin and melanin comparing to the laser radiation of the infrared spectrum [13, 14]. In clinical practice, dental lasers of the infrared range are used both for laser surgery and for laser therapy. The topical issue is the capabilities of using laser radiation with a wavelength of 445 nm for LLLT of the mucosa in the oral cavity with a perspective of an addition of this manipulation into the set of therapeutic procedures used in cases of inflammatory diseases of the parodontal tissues.

Aim: to evaluate the effect of laser radiation with a wavelength 445 nm and with a power of 0.1 Watt on the microcirculation and lymphatic flow in the gingival area by means of using the method of laser Doppler flowmetry.

METHODS

Research design

In order to detect the signs of the 445 nm wavelength low-intensity laser radiation affecting the microcirculation in the parodontium, we have arranged an observational prospective interventional non-randomized and non-controlled research. When compiling the design of the clinical research, the PICO method was used (table 1).

Conformity criteria

Inclusion criteria: age from 18 years and older; patients of female and male gender; presence of healthy parodontium; an established diagnosis of "Chronic catarrhal gingivitis"; the presence of written voluntary informed consent from the patient for the participation in the research.

Non-inclusion criteria: age under 18 years; pregnancy, breast-feeding; intake of antiaggregants or anticoagulants by a patient; established diagnosis of "Parodontitis"; presence of a pernicious habit of smoking; periodic or constant intake of narcotic medications; oral breathing type; past medical history of concomitant diseases, affecting the system of peripheral blood supply (diabetes mellitus, arterial hypertension, metabolic syndrome); abnormal development of the facial skeleton (small roof of the atrium of the oral cavity, insufficient height of the alveolar margin of the mandible, dense location of the teeth in the anterior group at the mandible, high attachment of the mentalis muscles); myofunctional disorders (increased tone of the mentalis muscles); presence of orthodontic constructions in the oral cavity.

Exclusion criteria: the inefficiency of the diagnostic procedure due to unforeseen circumstances (for example, allergy to laser radiation).

Research facilities

The clinical research was carried out at the Department of Surgical Dentistry of the Institute of Dentistry named after E.V. Borovsky under the Federal State Autonomous Educational Institution of Higher Education "I.M. Sechenov First Moscow State Medical University" of the Ministry of Health of Russia.

Research Duration

The clinical research work was including 20 volunteers and it was carried out during the period of 2023–2024.

Medical Procedure Description

For the purpose of defining the possibilities and the practicability of using laser radiation with a wavelength of 445 nm as the energy source for laser therapy and for photobiomodulation of parodontal tissues, we have measured the parameters of microcirculation of blood and lymph in the oral cavity mucosa upon the exposure to low-intensity laser radiation in the gingival area (manipulation code A22.07.008).

The clinical research procedures were carried out in the morning, at daylight hours, with the patient positioned seated in the dental chair with the back support at an angle of 100 degrees, the patient's head positioned on the head rest. The holder of the diagnostic probe of the "LAZMA-D" analyzer was positioned on the mucosa in the zone of the attached keratinized gingiva of teeth 4.2–4.3 on the vestibular side (Fig. 1). The examination zone was selected using the method of convenient judgment-based sample. For the purpose of ruling out the artifacts when recording the perfusion, we have used the standard system consisting of a support stand and the optical fiber clamp.

The microcirculation of blood and lymph was estimated according to the data obtained by LDF, which was arranged before the LLLT being applied to the gingival area (for obtaining the control values) and in 25 minutes after its completion — for detecting the therapeutic effect. The duration of each measurement was 120 seconds.

Table 1

Flow-chart of the research design

Parameters	Designation of the symbol in this research
P	Patients (volunteers) with healthy parodontium
I	Intervention — LLLT exposure with a wavelength of 445 nm to the gingival area
C	Comparison of the results obtained using laser Doppler flowmetry before and after the LLLT exposure at a wavelength of 445 nm applied to the gingival area in volunteers
O	Outcome — determining the quality of microcirculation of blood and lymph in the examined volunteers after the LLLT procedure at a wavelength of 445 nm in the gingival area

Note. P — population, I — intervention, C — comparison, O — outcome. LLLT — low-intensity laser radiation.

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The exposure of the laser radiation with a wavelength of 445 nm (ALTA BLUE, "VPG LASERONE", Russia) was applied to the gingival area of the teeth 4.2–4.3 on the vestibular and the lingual side with a power of laser radiation being 0.1 W using the contactless method — a dynamic technique of spiral movements following the continuous wave pattern (CW) and the non-initiated fiber, lasting 30 seconds on each side (Fig. 2). The distance from the tip of the light guide to the surface of the gingiva was 4.5–5 mm. The area of exposure zone was 2 cm^2. Upon the completion of the procedure, the display of the ALTA BLUE laser equipment was showing the "total energy" value of 6 J. The power density was 3 J/cm^2.

In 25 minutes, the area of the conducted medical procedure was repeatedly examined using the same diagnostic method (LDF).

The measurement of the values of the basal circulation and lymphatic flow in the gingival area upon the exposure of laser radiation with a wavelength of 445 nm was carried out using the LDF method. The evaluation of the functional status of the microcirculation system in the gingiva was carried out using the "LAZMA ST" computerized diagnostic laser analyzer.

The "LAZMA ST" laser diagnostic analyzer (LLC "LAZMA" Research and Production Enterprise, Russia) consists of the "LAZMA-D" analyzer of peripheral circulation along with the lymphatic flow and tissue co-enzymes, also including a "LAZMA-TEST" assembly intended for temperature and electro-stimulation functional tests (Marketing authorization for medical product issued on 08.06.2017 with a number № RZN2017/5844). For the fulfillment of the objectives of the given research, we have used the "LAZMA-D" analyzer with a software version 3.0.2.384.

During the course of the LDF, such medical-biological characteristics as the peripheral circulation rate (the measure of microcirculation) and the peripheral lymphatic flow rate, were also evaluated. The value of the microcirculation rate parameter is proportional to the product of the number of red blood cells and the mean rate of its motion in the capillaries. The value of the peripheral lymphatic flow is proportional to the product of the number of scatterers in the lymphatic flow and the mean rate of its motion [15].

After a LDF session, the studied diagnostic characteristics of the basal circulation and lymphatic flow were displayed on the monitor as the colored dopplergrams and the numeric values: the microcirculation rate (*M*), the value of its variability (σ) and the coefficient of variation (*Kv*).

The coefficient of variation (*Kv*) determines the vasomotor activity of the microcirculation vessels in percents (%): $Kv=(\sigma/M)\times100\%$.

Based on the obtained data, it is deemed possible to determine the status of the microcirculation in the examined area.

Statistical analysis

The research sample was determined using the Sample size formulas based on the results of similar research published earlier [16].

The statistical analysis and the visualization of the obtained data were provided using R 4.4.2 statistical calculation media (R Foundation for Statistical Computing, Vienna, Austria). For the qualitative

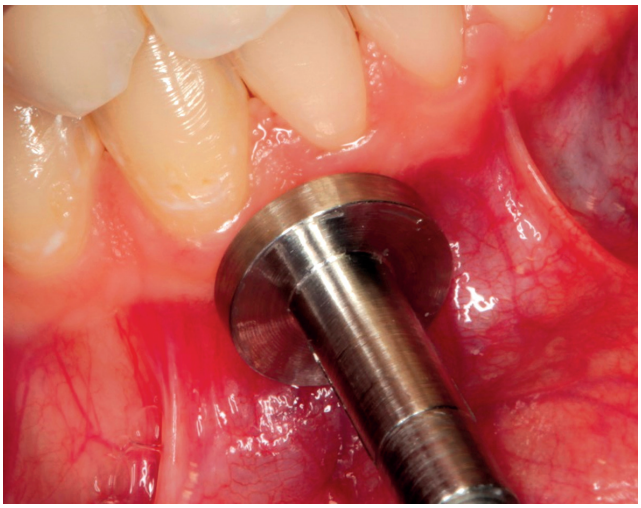

Fig. 1. The positioning of the diagnostic probe during the procedure of laser Doppler flowmetry.

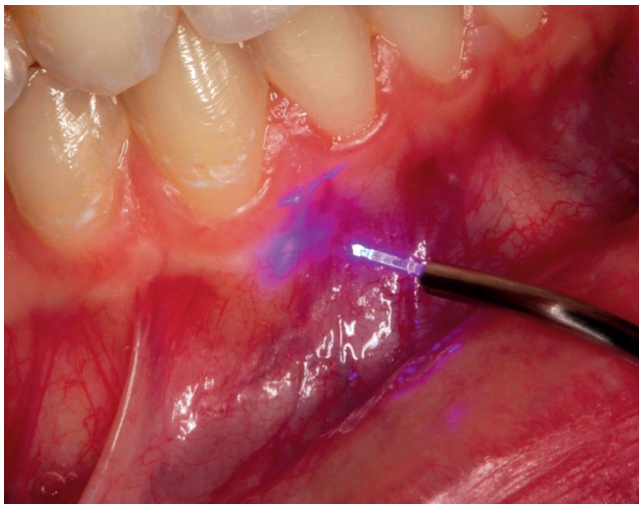

Fig. 2. The procedure of low-intensity laser radiation in the gingival area of the teeth 4.2–4.3 in a practically healthy volunteer.

parameters, the mean value, the standard deviation, the median and interquartile range were calculated; the distribution pattern was determined using the Shapiro–Wilk test.

RESULTS

Research sample (participants)

The test group included 20 volunteers — the IV- and V-year students of the Institute of Dentistry named after E.V. Borovsky, of which 10 were young men and 10 were young women aged 22–24 (mean age 22.9±0.8) years, having no pernicious habits, with no signs of inflammation in the parodontal tissues and with no past medical history of somatic diseases.

Seven to ten days prior to the examination, all the participants underwent professional oral hygiene procedures. On the day of the trial initiation, the volunteers were not taking caffeine-containing beverages. In order to participate in the research, the volunteers were visiting us 3 hours after meals and after undergoing an individual oral hygiene procedure. Within 25 minutes, the patients were informed on the purpose of the research and on the LDF method, also having their oral cavity examined with determining the dental status. This amount of time was enough for the volunteers to get a complete emotional and physiological rest. The personal data and the photos of the patients were encrypted and added to the previously compiled Google-form, which was later filled with the LDF results.

Main research outcomes

Upon the exposure of laser radiation with a wavelength of 445 nm on the gingival areas in 20 volunteers, the LDF parameters were then changing (Fig. 3). In healthy volunteers, the mean value of peripheral blood circulation (*M*) was 19.28±0.61 perf.U. The mean value of the variability of microcirculation rates (*σ*) was 3.07±0.1 perf.U. The value of the coefficient of variation (*Kv*) was calculated using the formula and it was reaching 15.92±0.66%. After the LLLT procedure, the findings included a statistically significant increase in the blood microcirculation rate (*M*) — by an average of 3.07 perf.U. (22.36±1.2; 95% CI 2.44–3.71; p <0.001). Statistically significant changes in the variability of the microcirculation value (*σ*) were not reported (p=0.319). However, after the LLLT procedure, we have found an increase in the variability of this parameter: its standard deviation has increased 6.71-fold (95% CI 4.33–10.4; p <0.001) (Fig. 3). After the LLLT procedure, we have observed an increase of the coefficient of variation (*Kv*) by an average of 1.52% (14.4±3.04; 95% CI 0.14–2.9); p=0.032). A statistically significant increase was also shown for the standard deviation of this parameter — by a factor of 4.62 (95% CI 2.98–7.15; p <0.001).

The mean value of the lymph microcirculation rate (*M*) was 0.4±0.07 perf.U. The mean value of the variability of the microcirculation rate (*σ*) was 0.12±0.04 perf.U. The value of the coefficient of variation (*Kv*) was calculated using the formula and it was reaching 30.6±7.3% (Fig. 4).

After the exposure of the 445 nm wavelength laser radiation on the gingival area, the parameter value of the lymph microcirculation rate (*M*) did not significantly change.

Undesirable phenomena

No undesirable phenomena were reported when using the LLLT procedure during the research activities.

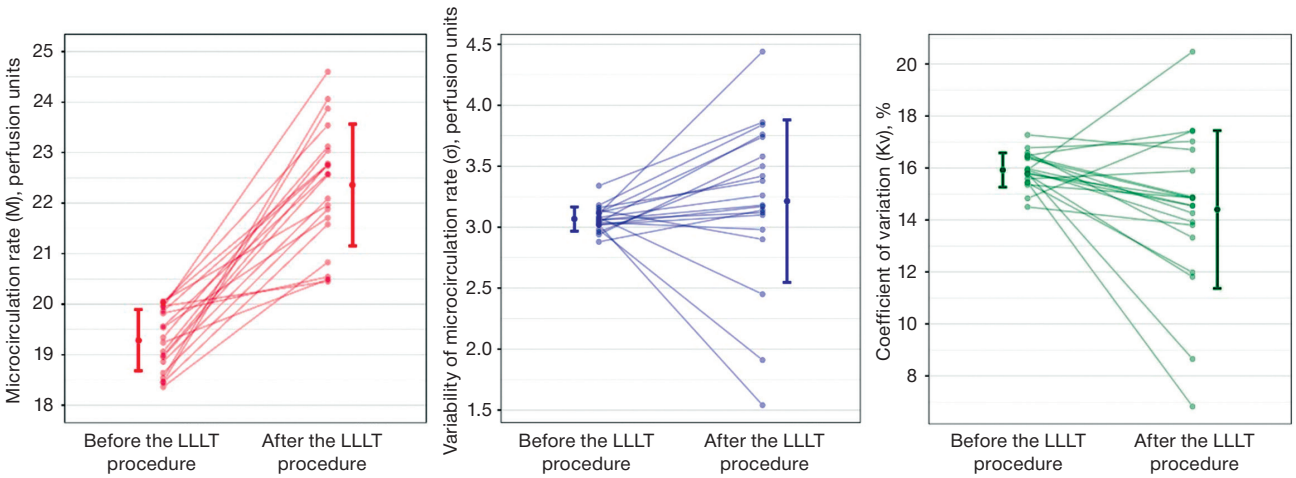

Fig. 3. Dynamic changes of the parameters of basal microvascular circulation in the gingiva, determined using the method of laser Doppler flowmetry, upon the exposure of laser radiation with a wavelength of 445 nm and with a power of 0.1 Watt.

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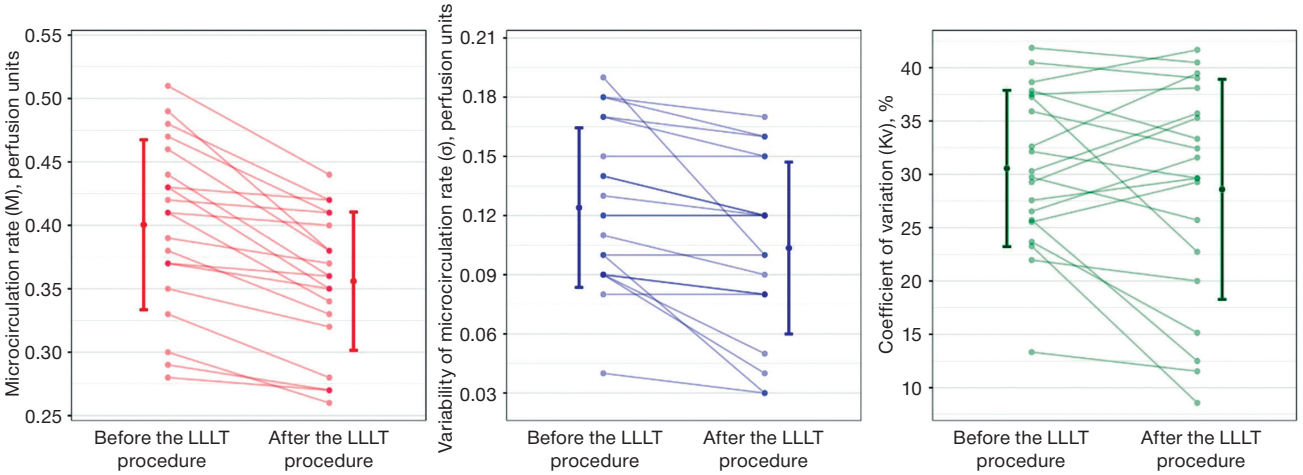

Fig. 4. Dynamic changes of the basal gingival lymphatic flow, determined using the method of laser Doppler flowmetry, upon the exposure of laser radiation with a wavelength of 445 nm with a power of 0.1 Watt.

DISCUSSION

Our research work was the first one that has assessed the exposure of the low-intensity blue laser radiation on healthy parodontal tissues. The findings included a slight but significant change in the values of basal circulation in the gingival tissues.

From the year of 2015, the worldwide dental society began using the "photobiomodulation" term to describe the LLLT procedure in the area of the healthy tissues [17]. Photobiomodulation is a potentially effective and non-invasive method of improving the microcirculation processes [10]. A contactless exposure of the laser radiation on the tissues with a small power values results in a number of physiological processes at a cellular level and at the tissue level [9].

The anti-inflammatory effect of laser radiation in cases of red and infrared range manifests at a power of 0.1–0.5 Watts and, to a greater extent, in case of minimal power values (0.1 W) [9]. It is also known that the maximal value of the physiotherapeutic exposure value — 0.5 W — is reaching the levels of the ablation mode of the blue laser. With a power of laser radiation reaching 0.7 W, the blue laser can dissect the oral cavity mucosa [18]. The practicable aspect of interest was the maximal remoteness from the power rates specific for the surgical application of the blue laser. Specifically for this reason, this clinical research was performed with selecting the laser radiation of 0.1 W for affecting the zone of attached keratinized gingiva.

The basis of the biological response in the tissues of the living organism after a low power laser radiation is the phenomenon of activating the Ca^{2+}-dependent reactions in the cells, which manifests as the increase of the redox-potential in the mitochondria, as the increase in the synthesis and the accumulation of adenosinetriphosphate, as the activation of DNA and RNA synthesis [9]. The absorption of laser energy by chromophores leads to an activation of cellular enzymes, to an increase in the parameters of oxidative metabolism parameters and to the stimulation of microcirculation along with an improvement of tissue oxygenation [19].

The increase of the circulation rates in the gingival areas after an application of laser radiation with a wavelength of 445 nm is accompanied by a decrease in the rates of lymphatic flow, which can be explained by the specific physiological features of microcirculation: upon the increase in the blood flow rates, the hydrostatic pressure in the capillaries also raises, which complicates the filtration of fluid in the interstitial space. The increase of the pressure also promotes to re-absorption of liquid from the interstitium back to the blood, decreasing the volume of fluid, accessible for the formation of the lymph. Upon the acceleration of the circulation, it shortens the time of contact between the blood and the capillary walls, which decreases the possibility of fluid diffusion into the interstitial space [15]. Similar to the findings from T.N. Safonova et al. [20], an increase of the circulation rate determines the decrease in the lymphatic flow rate and promotes to the acceleration of the oxidative processes in the gingival tissues. In our research, we have also observed the tendency to decreasing the lymphatic microcirculation rates, though not achieving the threshold of statistical significance.

In case of impairments in the functioning of the microcirculation network, there occurs the deceleration of the circulation, the changes in the shape and the number of functioning of the capillaries, with developing a venous congestion, which results in the formation

of cyanosis of mucosa in the papillary and marginal gingiva [21, 22].

The exposure of laser radiation with a wavelength of 445 nm at a power of 0.1 W within 1 minute on the gingival area of a single tooth causes an increase in the circulation rate in the parodontal tissues in healthy volunteers. In the accessible literature, there is no scientific data on the effects of blue laser radiation on the microcirculation in the gingival tissues when using larger power rates. The experiments have shown that, when not following the LLLT methodical guidelines of the power not exceeding 0.5 W, heating develops in the parodontal tissues of the laboratory animals (up to 52.3°C), which is significantly higher than the threshold values (42°C) [23]. It is known that the peak of laser radiation absorption by hemoglobin corresponds to the wavelength of the blue range of the spectrum [10]. When using the laser radiation power that is close to the ablation threshold, the LLLT procedure can result in the aggregation of red blood cells and blood clotting. Based on the obtained results and on the scientifically justified facts when arranging the activities for preventing the parodontal diseases, it is recommended to undergo the photobiomodulation procedures with using the blue laser technology at a power of 0.1 W.

Laser Doppler flowmetry is an objective and non-invasive method of functional diagnostics of microcirculation in the superficial tissues, allowing for continuous registration of circulation and lymphatic flow at the real time mode [15, 24]. The main measured parameters in LDF are the dynamic changes of microcirculation and the spectral elements of the fluctuations of circulation and lymphatic flow in the tissues [15, 25]. These parameters depend on multiple physiological, pathological and physical factors, such as the gender, the age, the emotional status of the person, the presence of vascular abnormalities, the presence of metabolic diseases, the air temperature in the functional diagnostics office etc. [15, 26–29], due to which, for objectivization of the results obtained during the functional examination, we have used the preliminary preparation of the patients within 25 minutes.

A perspective aspect is the evaluation of the specific features of microcirculation in the gingival area upon the exposure of laser radiation with a wavelength of 445 nm in patients with the diagnosis of “Gingivitis and parodontitis”.

Research limitations

The limitation of the research is that it is single-center and non-randomized. Also, another fact that we count as a limitation is the absence of the aim of evaluating the additional microcirculation parameters, accessible for analysis when using the «LAZMA ST” laser diagnostic equipment.

CONCLUSION

For the first time, an information was obtained on the possibilities of clinical application of the innovative laser technology with a wavelength of 445 nm during the photobiomodulation of the parodontal tissues. The estimation of the effects of blue laser on the gingival microcirculation was undertaken with a power of laser radiation being 0.1 W. This power parameter is maximally remote from the value, in which the blue laser can provide a contactless separation of the oral cavity mucosa. The obtained results on the increase of circulation rate at laser radiation power of 0.1 W indicate the possibility of using this photobiomodulation mode in clinical practice.

ADDITIONAL INFORMATION

Author contribution. *N.V. Romanenko* — concept and study design, conducting a clinical trial, manuscript writing, statistical data processing, final scientific editing, formulation of conclusions; *E.V. Tulskikh* — participation in a clinical trial, data collection and statistical analysis; *N.M. Kirsanova* — participation in a clinical trial, data collection, literature review; *S.V. Tarasenko* — final scientific editing, general 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.

Ethics approval. The clinical trial was approved by the local ethics committee of the Federal State Autonomous Educational Institution of Higher Education “I.M. Sechenov First Moscow State Medical University” of the Ministry of Health of the Russian Federation on February 16, 2023 (LEK Protocol № 03-23 dated February 16, 2023).

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THE DETECTION OF EROSIVE CHANGES IN THE JOINTS OF HANDS AND FEET IN RHEUMATOID ARTHRITIS: A COMPARISON OF ULTRASOUND AND RADIOLOGY METHODS

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ABSTRACT

BACKGROUND: *The detection of bone tissue erosions in cases of rheumatoid arthritis has a fundamental importance for the purpose of defining the treatment strategy and it indicates the unfavorable outcomes. It is recognized that the sensitivity of X-ray in detecting the bone tissue erosions is lower comparing to the ultrasound examination, especially at the early stages of the disease. The application of non-invasive and safe methods for the diagnostics of rheumatoid arthritis opens new possibilities for successful treatment.* ***AIM:*** *to compare and to evaluate the results of ultrasound and radiological detection of destructive changes in the joints of the hands and feet in rheumatoid arthritis patients.* ***METHODS:*** *The research included 76 patients with an established diagnosis of rheumatoid arthritis. Radiography and ultrasound examination of the joints in the hands and feet were carried out at the moment of enrollment into the research and later on in 1 and 4 years.* ***RESULTS:*** *The findings included a slight degree of correlation between the two absolute values — the number of joints with erosions according to the data from the ultrasound examination and according to the radiology examination findings. The rate of progression of the erosive changes was more pronounced in the data from ultrasound examination comparing to the radiology findings: from 0.5 [0; 1] to 2.5 [0; 6.0] (p=0.001) and from 0 [0; 1] to 0 [0; 3] (p=0.001), respectively. When evaluating the comparability of the two methods used for detecting the erosive changes in the joints of the hands and feet at each observation point by means of using the Bland–Altman method, it was shown that the results from both methods partially reach the outside of the margins of two standard deviations, which indicates the low degree of agreement between them. The mean difference between the measurements was -0.38 (95% CI -0.63…-0.13) before treatment, -1.15 (95% CI -1.5…-0.79) at the follow-up point of 12 months and -1.52 (95% CI -2.32…-0.73) in 4 years, which indicates the presence of systematic deviations. No correlation was detected between the difference in the number of joints with erosions and the mean number of joints with erosions according to the ultrasound examination and according to the radiography findings.* ***CONCLUSION:*** *Ultrasound examination and radiography are not equivalent methods of detecting erosions in rheumatoid arthritis, however, ultrasound examination helps detecting early progression of the process, which is a key to successful therapy of rheumatoid arthritis.*

Keywords: *rheumatoid arthritis; erosions; ultrasound examination; radiography.*

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BACKGROUND

Currently, the visualization is reaching its new stage, not only in the diagnostics of rheumatic diseases, but also in the evaluation of its course and prognosis. High-precision methods, used in modern medical equipment, allow for evaluating not only the structure of the object, but also to arrange the dynamic imaging, which may give additional information for detecting the diseases at the early and pre-clinical stages [1–3].

Detecting the bone tissue erosions in rheumatoid arthritis has a fundamental importance for the purpose of defining the treatment strategy, for the structural lesions play an important role in the diagnostics,

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ВЫЯВЛЕНИЯ ЭРОЗИВНЫХ ИЗМЕНЕНИЙ СУСТАВОВ КИСТЕЙ И СТОП ПРИ РЕВМАТОИДНОМ АРТРИТЕ: СРАВНЕНИЕ УЛЬТРАЗВУКОВОГО И РЕНТГЕНОГРАФИЧЕСКОГО МЕТОДОВ

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АННОТАЦИЯ

Обоснование. *Обнаружение костных эрозий при ревматоидном артрите имеет решающее значение для определения стратегии лечения и указывает на неблагоприятные исходы. Считается, что чувствительность рентгенографии в выявлении эрозий костей ниже, чем при ультразвуковом исследовании, особенно на ранних стадиях заболевания. Применение неинвазивных и безопасных методов диагностики ревматоидного артрита открывает новые возможности для успешного лечения.* ***Цель исследования*** *— сравнить и оценить результаты ультразвукового и рентгенографического выявления деструктивных изменений суставов кистей и стоп у больных ревматоидным артритом.* ***Методы.*** *В исследование включены 76 пациентов с установленным диагнозом ревматоидного артрита. Рентгенография и ультразвуковое исследование суставов кистей и стоп проводились на момент включения в исследование, далее через 1 и 4 года.* ***Результаты.*** *Наблюдалась слабая степень корреляции между двумя абсолютными значениями количества суставов с эрозиями по данным ультразвукового исследования и рентгенографии. Темп нарастания эрозивных изменений в большей степени отмечался по данным ультразвукового исследования, чем при рентгенографии: от 0,5 [0; 1] до 2,5 [0; 6,0] (p=0,001) и от 0 [0; 1] до 0 [0; 3] (p=0,001) соответственно. При оценке сопоставимости двух методов определения эрозивных изменений суставов кистей и стоп в каждой точке наблюдения с помощью анализа Блэнда–Альтмана показано, что результаты обоих методов частично выходят за пределы двух стандартных отклонений, что свидетельствует о низкой степени согласия между ними. Средняя разница между измерениями показателей составила -0,38 (95% ДИ -0,63…-0,13) до лечения, -1,15 (95% ДИ -1,5…-0,79) при наблюдении через 12 месяцев и -1,52 (95% ДИ -2,32…-0,73) при наблюдении через 4 года, что указывает на систематические отклонения. Корреляции между разницей количества суставов с эрозиями и средним количеством суставов с эрозиями по ультразвуковому исследованию и рентгенографии не выявлено.* ***Заключение.*** *Ультразвуковое исследование и рентгенография не являются эквивалентными методами обнаружения эрозий при ревматоидном артрите, однако ультразвуковое исследование помогает выявить раннее прогрессирование процесса, что является ключом к успешной терапии ревматоидного артрита.*

Ключевые слова: *ревматоидный артрит; эрозии; ультразвуковое исследование; рентгенография.*

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indicating the unfavorable outcomes [4]. Currently, the gold standard for the visualization and quantitative evaluation of bone tissue lesions in patients with rheumatoid arthritis is radiography [5], while the standard method of evaluating the structural lesions in cases of rheumatoid arthritis is the modified Van der Heijde Sharp score (SHS) [6].

According to the recommendations from the European Alliance of Associations for Rheumatology (EULAR) on using the visualization of joints in the

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clinical therapy of rheumatoid arthritis, radiography must be used as a first choice visualization instrument for detecting the lesions in the joints (bone tissue erosions and narrowing of the articular fissures) [7].

As it is known, the sensitivity of radiography in detecting the bone tissue erosions is lower comparing to other visualization methods, such as Magnetic resonance imaging (MRI), ultrasound examination (USE) and computed tomography, especially at the early stages of the disease [8–12], opening new possibilities for the non-invasive and safe diagnostics.

High labour-intensity and cost of MRI, being a significant downside of the technology, determines the preference of ultrasound examination [9] — an accessible and relatively inexpensive examination method not related to the exposure of ionizing radiation, which is used for the evaluation of the status practically in all the joints during a single examination. Ultrasound examination of the joints allows for evaluating not only the synovitis and the lesions in the peri-articular tissues, but also the structural lesions of the articular surface, for example, detecting the erosive changes. According to the results from a number of research works, ultrasound examination allows for detecting more erosions than radiography, also having a higher sensitivity and specificity [13]. There are several qualitative and semiquantitative systems of ultrasonographic evaluation [14–19], but, up to the present moment, there is no commonly used standardization method. Ultrasound examination is an attractive method for the evaluation of bone tissue erosions in cases of early rheumatoid arthritis, when the possibilities of radiography are limited by low sensitivity. Based on the large publication base, it can be concluded that ultrasound examination is a reliable tool for the evaluation of erosions in cases of rheumatoid arthritis [9, 20, 21].

The detection of bone tissue erosions by means of ultrasound examination has not only a diagnostic value, but it also predicts the development of rheumatoid arthritis in cases of non-differentiated arthritis in patients with antibodies to cyclic citrullinated peptide, also precedes the development of structural changes in the radiography images in rheumatoid arthritis patients [22], with the bone tissue erosions in the radiography images being rarely detectable in the group of individuals positive for antibodies to the cyclic citrullinated peptide, not predicting the development of rheumatoid arthritis.

At the present moment, the literature worldwide contains an insufficient number of trials comparing the visualization methods for assessing the destructive changes in the joints, while the published sources contain controversial data on the comparison of these two methods. Thus, the research by J. Grosse et al. [22] has shown that, when using the ultrasound to evaluate the joints in patients with rheumatoid arthritis, 2 times more erosions of the joints were found comparing to radiography (SHS scores). The conclusions from the authors of one of the recent researches, stating that ultrasound examination and radiography of the erosions are well in agreement and that ultrasound examination plays an auxiliary role in assessing the destructive process [23], was the basis for the conduction of our research.

Research aim — an assessment of the possibilities of ultrasound examination in the visualization of destructive changes in cases of rheumatoid arthritis comparing to the gold standard — the radiography.

METHODS

Research design

A prospective observational single-center research was carried out in patients with rheumatoid arthritis with the aim of comparing the two methods (radiography and ultrasound) in detecting the erosions of articular surfaces.

Conformity Criteria

Inclusion criteria:

- validated presence of RA in accordance with the classification criteria for RA (ACR/EULAR 2010);
- age over 18 years;
- high or moderate activity of the disease at the moment of inclusion (SDAI ≥ 11, swollen and painful joints ≥ 3 + ESR (Westergren) ≥ 28 mm/h or CRP ≥ 10 mg/l).

Exclusion criteria:

- active tuberculosis, positive Mantoux test (papula ≥ 5 mm) and/or the presence of suspiciousness in terms of an active tuberculosis process based on the radiological changes in the lungs combined with positive Diaskintest or QuantiFERON test;
- the presence of viral hepatitis B, infection of hepatitis B virus;
- the presence of oncological diseases within the last 10 years;
- demyelinating diseases of the nervous system;
- severe cardiac insufficiency;
- active bacterial or viral infection;
- allergic reaction to proteinic medicines in the past medical history;
- pregnancy or breast-feeding.

Research facilities

The research was conducted with the participation of patients with rheumatoid arthritis, which were under long-term supervision and were receiving therapy at the Federal State Budgetary Scientific Institution "Scientific Research Institute of Rheumatology named after V.A. Nasonova" (FSBSI V.A. Nasonova SRIR) [24].

Research Duration

The research was conducted during the period from 2015 until 2022.

Medical procedure description

The ultrasound examination was carried out using the Logiq 9 (GE, USA) and MyLabTwice (ESAOTE, Italy) devices and using the multi-frequency linear probe (10–18 MHz) with the technique of Power Doppler, the parameters of which were adapted for the registration of low-speed flows (PRF 300–600 Hz, low filter, dynamic range 20–40 dB). During the process of examination, 7 articular zones were evaluated in the palms and feet on the clinically dominating side (wrists, II and III metacarpophalangeal, II and III proximal interphalangeal, II and V metatarsophalangeal joints).

The ultrasonography sings of destructive changes (erosions), according to the criteria from the international network on the improvement of the evaluation of results in rheumatology (Outcome Measures in Rheumatology Clinical Trials, OMERACT), was the deepening of the bone tissue contour, visualized in two perpendicular sections, with a width of more than 2 mm and with a depth of more than 1 mm [25]. The estimation of destruction was performed using the binary accounting system (present/absent) for each examined joint (a number of joints with erosions) in three points: at the moment of enrollment into the trial, in 12 months of therapy and after 4 years of follow-up. The dynamic (quantitative and qualitative) parameter of the increase in the number of joints with erosions was also used. For the quantitative evaluation of radiological changes, the Sharp's method was used (modified by van der Heijde) before treatment, in 12 months and 4 years after the treatment initiation [6].

For the comparison of the two methods for evaluating the destructive changes, we have used the evaluation of the identical articular zones with counting the number of joints with erosions according to the data from radiography and ultrasound examination for the purpose of alleviating the specific features of ultrasonic visualization and the radiographic evaluation (the primarily benefits of the ultrasonic method in the evaluation of joints, where the ultrasonography access is possible from three sides, for example, metacarpophalangeal joints II and V, and the benefit of radiography is the intra-articular evaluation).

To estimate the possibilities of using ultrasound examination for the diagnostics of erosive changes in cases of rheumatoid arthritis, both methods were used simultaneously and compared at all the stages of follow-up.

Statistical analysis

The statistical processing of the results was carried out using the Statistica software package ver. 8.0 (StatSoft, USA), including the commonly used methods of parametric and non-parametric analysis. For the parameters, the distribution of which differed from the normal one, when comparing the two groups, the Mann-Whitney test was used, the results were presented as the median (Me) [25th; 75th percentile]. For the graphic comparison of the results obtained using various methods, the Bland–Altman method was applied. The differences were considered statistically significant at the $p < 0.05$.

RESULTS

Research sample (participants)

The general characteristics of the patients with rheumatoid arthritis, included into the research (n=76), is presented with dynamic follow-up data in table 1.

Primary findings

According to the data from radiography of the palms and feet, erosions were found in 30% of the patients before treatment initiation, in 39% of the patients one year after the treatment initiation and in 66% at the end of the research, according to the data from ultrasound examination — in 50, 75 and 71%, respectively. The median of the number of joints with erosions detected by USE was higher than for radiography, with gradual progression of changes during the process of follow-up (see table 1).

The estimation of the relation between the two methods at three stages of the trial has shown a weak degree of relation between the absolute values — the number of joints with erosions, evaluated using the ultrasound examination and radiography (r=0.36; p=0.001) before treatment: in 15 patients with ultrasonographic signs of erosions, they were not revealed according to the data obtained when using the radiography (a total of 38 patients with detected erosions according to the data from ultrasound

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Table 1

General characteristics of the patients with rheumatoid arthritis (*n*=76), Me [25; 75]

Parameters	On enrollment	In 1 year	In 4 years
Age, years	53.5 [44.0; 61.5]	-	-
Duration of disease, months	6.0 [4.0; 16.5]	-	-
Number of swollen joints	7 [5; 11.5]	0 [0.0; 2.0]	0.5 [0.0; 3.0]
Number of painful joints	9.5 [5.0; 14.5]	1.0 [0.0; 3.5]	3.5 [0.0; 6.5]
DAS28	5.53 [4.54; 6.15]	2.64 [1.98; 3.92]	3.61 [2.64; 4.79]
SDAI	28.5 [19.38; 40.14]	4.52 [1.7; 11.63]	9.68 [3.59; 18.29]
CDAI	26.25 [17.25; 36.5]	4.0 [1.5; 11.0]	9.0 [3.35; 17.95]
ESR, mm/h	34.5 [8.5; 50]	10.0 [4.0; 24.0]	20.0 [12.0; 34.0]
CRP, mg/l	11.4 [1.1; 35.4]	2.5 [0.2; 6.1]	2.8 [1.15; 7.35]
RF (+), *n*	66 (87%)	-	-
A/B to CCP(+), *n*	63 (83%)	-	-
Percentage of patients with Rg-erosions, Sharp's method, %	47	53	66
Percentage of patients with Rg-erosions in the examined joints, %	30	39	58
Ultrasonographically determined number of joints with erosions	0.5 [0.0; 1.0]	2.0 [0.5; 3.0]	2.5 [0.0; 6.0]
Radiologically determined number of joints with erosions	0.0 [0.0; 1.0]	0.0 [0.0; 1.0]	1.0 [0.0; 3.0]

Note. DAS-28 (Disease Activity Score-28) — index of inflammatory activity of rheumatoid arthritis; SDAI — Simplified Disease Activity Index of rheumatoid arthritis; ESR — erythrocyte sedimentation rate; CRP — C-reactive protein; RF (+) — positive test for Rheumatoid factor; A/B to CCP(+) — positive test for antibodies to cyclic citrullinated peptide; X-ray/US — radiological/ultrasound examination.

examination and 23 patients with erosions according to the data from radiography). One year after treatment initiation, the correlation was also weak (r=0.29; *p*=0.01), while after 4 years of follow-up is has become more clear (r=0.502; *p*=0.001).

We have analyzed the consistency of measurement results obtained using different methods. The method of Bland–Altman has demonstrated a dependence of the difference between the ultrasonography and the radiography results on the mean number of joints with erosions, obtained using two methods (Fig. 1). All the graphs were compiled within a standardized range of ±1.96 standard deviations, showing the expected scattering of differences between two measurements.

The lower and the upper limits of agreement at the first point were -2.55 and 1.79 respectively, with the dislocation to -0.38 for radiography. Upon the correlation analysis, the findings showed a dependence of the

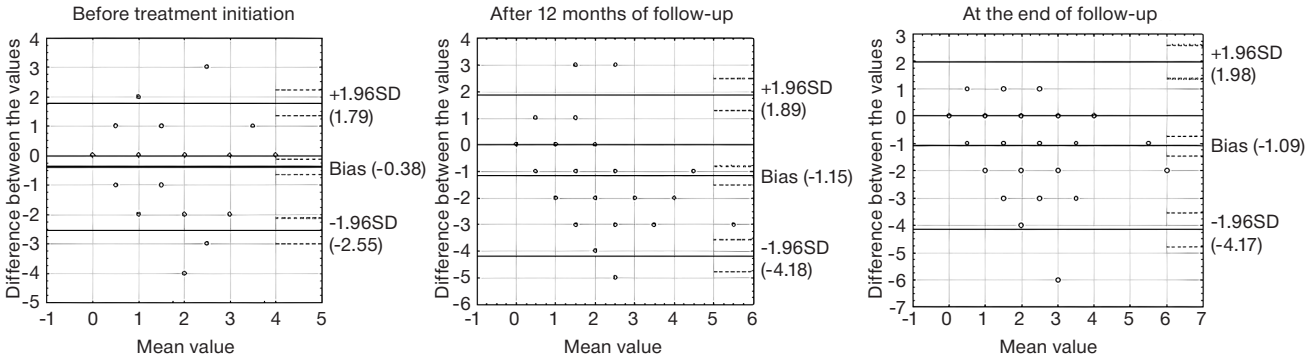

Fig. 1. The dependence of the difference in the number of joints with erosions, measured ultrasonographically and radiologically, on the mean value. Bland–Altman plot: upon enrollment (before treatment initiation), in 1 year from the moment of treatment initiation and at the end of the research.

difference in the values on its means when using the two methods (Fig. 2). After a year of follow-up (the second point), the limits of agreement have expanded (-4.18 for the lower and 1.89 for the upper), the dislocation has also become more significant (-1.15). The dependence of the difference between the values on its mean value was also statistically significant (see Fig. 2). After 4 years of follow-up (the third point), the abovementioned tendencies persisted: the lower and the upper limits of agreement were -4.17 and 1.98, respectively, the dislocation was significant (-1.09), there was also a statistically significant relation of the difference between the values and their means (see Fig. 2).

Thus, despite the presence of a mild to moderate correlational relationship between the ultrasonography and the radiology methods, the Bland–Altman analysis shows a systematic discrepancy due to the significant deviation of the absolute values, the results are partially out of the ranges of two standard deviations, with a demonstrated statistically significant relation of the difference in the values and their mean values.

Taking into consideration the absence of agreement between the two methods in a single point and a more frequent detection of erosions when using the ultrasonography, a conformity was analyzed between the ultrasound examination and the radiography in various follow-up time points. Due to the fact that ultrasonography detects erosions earlier and more frequent than radiography, the ultrasonographic method at the beginning of follow-up and after a year of treatment (the first and the second points) was compared to the radiography results after 4 years of follow-up (the third point). Upon the comparison of the results from the ultrasound examination at the first point and from radiography — at the third one, a moderate correlation was found in the relationship between the number of joints with erosions, evaluated using two methods (r=0.46; p=0.001). The average deviation of the radiography results comparing to the data obtained using the ultrasound examination was -0.13, the lower range was -2.49, the upper was 2.23 (Fig. 3, *a*). The correlation coefficient was 0.014 (p=0.9),

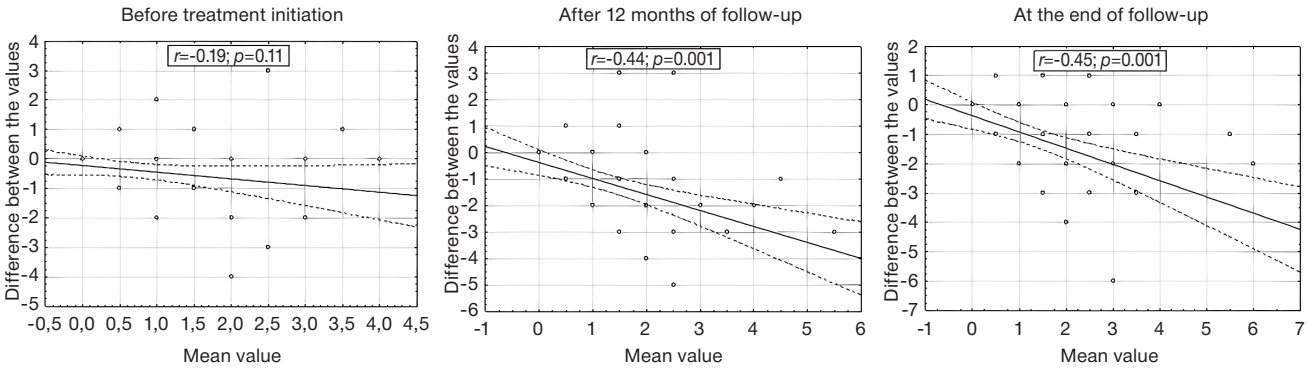

Fig. 2. The dependence of the difference in the number of joints with erosions, measured ultrasonographically and radiologically, on the mean value for the two methods of detecting erosions: upon enrollment (before treatment initiation), in 1 year from the moment of treatment initiation and at the end of the research.

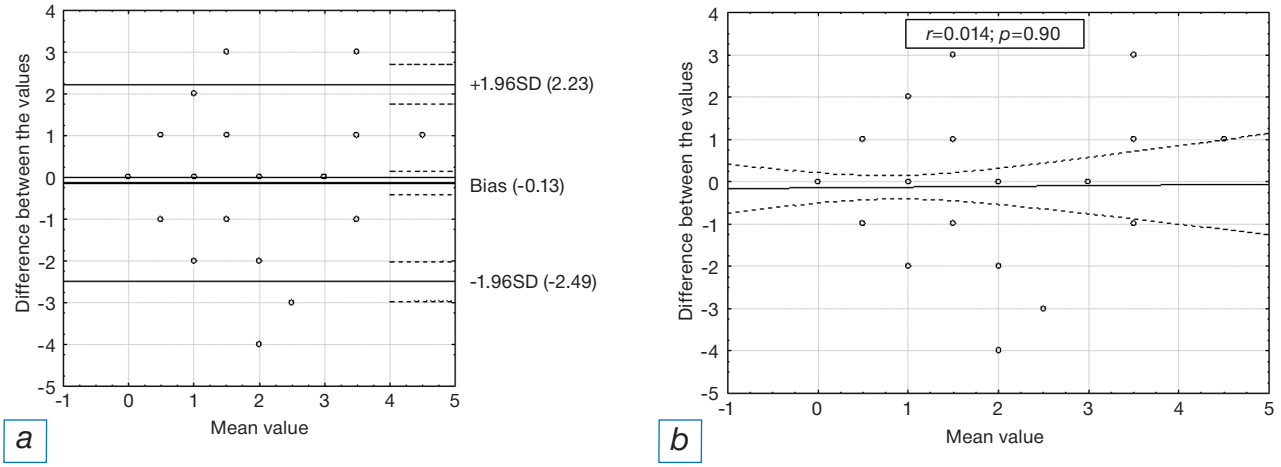

Fig. 3. The dependence of the difference in the number of joints with erosions, measured using ultrasound method upon enrollment and radiologically at the end of follow-up, on the mean values: *a* — Bland–Altman plot; *b* — correlations.

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5% of the values were outside the interval of two standard deviations (see Fig. 3, *b*).

The similar analysis was carried out when comparing the ultrasonography results after one year of follow-up and the radiography results at the end of the follow-up period. There was a moderate statistically significant dependence between the two changes (r=0.31; *p*=0.006). The Bland–Altman analysis has shown a deviation of the results being -1.07, with the lower range of -3.94 and the upper being 1.8. The correlation coefficient was -0.35 (*p*=0.0015; r^2=0.13); 4% of the values did not fit into the ranges of two standard deviations.

The Bland–Altman analysis has shown minimal discrepancy of the results upon the comparison of ultrasonography at the first point and of the radiography at the third one. The mean difference between both measurements is -0.13, only 5% of the values do not fit into the range of two standard deviations and there was no detected dependence of the measured difference on the mean parameter value — the number of joints with erosions. Only the high ranges of the agreement do not allow for concluding on the 100% equivalence of two methods, which is probably related to the available limitations.

The comparison of the results for the second and the third point has shown a significant systematic discrepancy.

Thus, the ultrasound examination is not an equivalent for the radiological method of detecting erosive changes in the joints of the palms and feet, but it is comparable to the radiological detection of erosions after 4 years of follow-up.

DISCUSSION

We have conducted a comparative evaluation of the results of measuring the destructive changes in the joints of the palms and feet using the ultrasound examination and the radiography in patients with a slight (median — 6 months) duration of the disease. A total of 1/3 of the patients at the moment of their inclusion into the research had erosions detectable by radiography, which allowed for adequately tracing the progression of destructive changes within 4 years of follow-up. The gold standard of detecting destructive changes is the radiography, despite its exclusion from the classification criteria for rheumatoid arthritis issued in 2010 [26]. This is due to delayed (as it was also shown by our research) development of erosions, absence of which at early stages shall not provide the possibility of early diagnostics of rheumatoid arthritis. The exclusion are the patients, in which a long-term inactive disease is suspected, which can be classified as non-rheumatoid arthritis, while the presence of typical erosions could allow for setting the correct diagnosis [27]. It is also necessary to point out that the detection of erosive changes at early stages is a prognostically unfavorable factor [4, 8, 11, 19], due to which, the search of the methods of early and accessible detection of erosions in cases of rheumatoid arthritis is still in progress [28–30].

The data obtained by us allow for stating the significance of ultrasound examination as a predictive method in the evaluation of destructive changes, meaning the most agreement of the methods in cases of 4 years interval between them. The absence of agreement in the simultaneous use of the methods can be explained by the presence of limitations (for example, partial accessibility of the ultrasonographic evaluation of the bone tissue contour with an intra-articular location, the subjectiveness of the method, the examination of the limited number of joints). We have found that the ultrasound detection of erosions occurs significantly earlier comparing to the radiological examination and, hypothetically, the time difference is not less than 4 years.

The early detection of erosions using the ultrasound examination is described in a number of research articles comparing the visualization methods with simultaneous evaluation in each joint. In one of the recent reviews, an analysis was undertaken to estimate the sensitivity and specificity of ultrasound examination of the locomotor system for the purpose of identifying the synovitis and early erosive changes in small joints for cases of rheumatoid arthritis. In the sample provided, the sensitivity and specificity of ultrasound examination for detecting early erosions of the bones was 58% and 94%, respectively, including the described earlier detection of erosive changes by the data from ultrasound examination comparing to radiography [9].

The comparison of two methods for detecting erosive changes was carried out using the correlation analysis (kappa-test) in several research works from foreign authors, where it was shown that the estimated degree of agreement was not high (from 0.59 to 0.74) [11, 13]. Our research showed similar findings and it led to the conclusion that ultrasound examination is an effective and earlier method of detecting erosions, with the statistical discrepancy of two methods being minimal at the moment of enrollment into the trial and increasing during the follow-up (from -0.38 on enrollment to -1.15), which indicates the more often

ultrasonographic detection of destructive changes with the increase in the duration of the disease.

Similar results were demonstrated by U.M. Dohn et al. [31]: based on their results, in accessible areas, ultrasound examination also has high precision in terms of detecting and evaluating the erosions in rheumatoid arthritis patients. Also interesting is the research by R.H. Mohammed et al. [32] on comparing the capabilities of ultrasound examination and radiography in the diagnostics of early rheumatoid arthritis: of the 720 palm joints examined using the ultrasound, erosions were detected in 23 (3%) joints of 7 (18%) patients comparing to radiography, where the erosions were detected in 7 (1%) palm joints in 3 (8%) patients. Thus, the number of palm joints with erosions detected by ultrasound examination was 3.28 times more than the number detected using radiography images. Similarly, the number of patients with erosions in palm joints based on the data from ultrasound examination was 2.33 times higher than the number detected in the radiography images. These differences were statistically significant.

CONCLUSION

We have not found any proof of equivalence for the ultrasound examination and the radiography in detecting erosions in the joints of the palms and feet. With an increase in the follow-up time, the relation of changes detectable using the ultrasound examination and the radiography becomes more significant, but the clinical value of such a late detection of erosions in cases of rheumatoid arthritis is doubtful.

The detected delayed agreement of radiological and ultrasonographic detection has a great importance in further validation and clinical implementation of ultrasound examination for detecting the destructive arthritis in patients with early stages of rheumatoid arthritis.

ADDITIONAL INFORMATION

Author contribution. *A.V. Smirnov* — general concept, search and analytical work, processing and discussion of research results, writing the text of the article, X-ray evaluation; *O.G. Alekseeva* — search and analytical work, processing and discussion of research results, participation in recruitment and management of patients, ultrasound examination; *S.I. Glukhova* — statistical processing and discussion of the results of the study; *M.V. Severinova* — participation in ultrasound examination and filling out thematic maps; *E.L. Nasonov* — general concept and search and analytical work; *A.V. Volkov* — search and analytical work and processing and discussion of research results and writing the text of the article and 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.

Ethics approval. The study was approved by the Local Ethics Committee of V.A. Nasonova Scientific Research Institute of Rheumatology, in accordance with the protocols No. 25 of 12/03/2015 and No. 11 of 06/18/2020. All participants in the study provided voluntary informed consent in order to participate in the research.

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SELECTIVE DORSAL RHIZOTOMY IN CEREBRAL PALSY: THE EFFICIENCY AND THE SPECIFIC FEATURES OF REHABILITATION

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ABSTRACT

Selective dorsal rhizotomy is one of the methods used for surgical correction of spasticity in the muscles of the lower limbs with high level of evidence among the patients with cerebral palsy. At the same time, the long-term positive results after surgery can be achieved only when combining surgical treatment with rehabilitation activities. The provided literature review contains a historic reference on the development of the technology along with the current data on the efficiency of surgical intervention with the analyzed research results in terms of the methods and the specific features of rehabilitation among the patients with the diagnosis of cerebral palsy after selective dorsal rhizotomy. Just like other treatment methods, selective dorsal rhizotomy does not exclude the probability of developing complications, but the individual approach during the course of combined, long-term and intensive rehabilitation, as well as following the clinical protocols, can minimize these risks. Stable improvement of motor functions, as well as an increase in the quality of life among patients after selective dorsal rhizotomy and combined rehabilitation courses, confirm the efficiency and the perspectivity of this method.

Keywords: *cerebral palsy; selective dorsal rhizotomy; spasticity; rehabilitation; physical therapy.*

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INTRODUCTION

In the Republic of Kazakhstan, just like worldwide, cerebral palsy takes one of the leading places among the incapacitating diseases in children and adolescents. As of the year of 2022, the number of disabled children aged 0–17 years in Kazakhstan was 104,260, of which there were 61,047 boys and 43,213 girls. In 29% of the cases, the causes of cerebral palsy were the diseases of the nervous system. Thus, according to data from the Bureau of National Statistics under the Agency for Strategic Planning and Reforms of the Republic of Kazakhstan, in 2022, a total of 14,387 children were registered with newly developing disability, of which 8,497 were boys and 5,890 were girls[1, 2]. Worldwide, each 1,000 of newborns has 2 to 3 cases of cerebral palsy [1]. The spasticity in this type of disease is the predominant type of motor activity impairment (85.8%) [2].

The basis of the pathogenetic mechanism of developing spasticity is the loss of inhibitory control (the disinhibition) over the segmental motor mechanisms on the side of the central neurons and spinal reflexes up to the complete disinhibition of the latter. In cases of spastic diplegia, the hypertone in the lower limbs is more pronounced comparing to upper limbs. The research works with the participation of 1,050 children with the diagnosis of cerebral palsy have studied the spasticity of separate muscles in the lower limbs before and after treatment: the evaluation included the tone of the hip adductor muscle, the hip flexor

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СЕЛЕКТИВНАЯ ДОРСАЛЬНАЯ РИЗОТОМИЯ ПРИ ЦЕРЕБРАЛЬНОМ ПАРАЛИЧЕ: ЭФФЕКТИВНОСТЬ И ОСОБЕННОСТИ РЕАБИЛИТАЦИИ

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АННОТАЦИЯ

Селективная дорсальная ризотомия — один из методов оперативной коррекции спастичности мышц нижних конечностей с высоким уровнем доказательности у пациентов с церебральным параличом. Вместе с тем долгосрочные положительные результаты после операции могут быть достигнуты только при комбинации оперативного лечения с реабилитационными мероприятиями. В представленном обзоре литературы дана историческая справка о создании технологии, приведены современные данные об эффективности оперативного вмешательства, проанализированы результаты исследований касательно методов и особенностей реабилитации пациентов с диагнозом церебрального паралича после селективной дорсальной ризотомии. Как и другие методы лечения, селективная дорсальная ризотомия не исключает вероятности осложнений, но индивидуальный подход при проведении комплексной, продолжительной и интенсивной реабилитации, а также соблюдение клинических протоколов способны минимизировать эти риски. Стойкое улучшение двигательных функций, а также повышение уровня качества жизни пациентов после селективной дорсальной ризотомии и комплексных курсов реабилитации подтверждают эффективность и перспективность данной методики.

Ключевые слова: *церебральный паралич; селективная дорсальная ризотомия; спастичность; реабилитация; физическая терапия.*

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muscles, the popliteal tendons of hip muscles (the biceps, the semimembranous and the semitendinous muscles of the posterior surface of the hip), the rectus femoris muscle, the knee extensor/flexor muscles, the gastrocnemius and the soleus muscles. It was shown that the spasticity in the lower (560 patients; 53.3%) and upper (490 patients; 46.7%) limbs decreases the quality of life among the patients, which especially affects the possibilities of unsupported movement or walking using special aids [3–6].

The methods of correcting the muscle hypertonus in cases of cerebral palsy can be divided into the conservative and the surgical ones. The operative methods include the intrathecal implantation of the Baclofen pump, the selective dorsal rhizotomy (SDR) and orthopedic surgeries [4–9].

The attitude to the SDR worldwide is ambiguous as of today: some countries are actively implementing it into clinical practice, others use it in single cases or do not use at all. This being said, in 2021, the results of a research were published, in which comparison was made for the use of three methods for correcting the spasticity in cases of cerebral palsy — the SDR, the injections of botulinal toxin A and the intrathecal therapy with Baclofen — in various European countries. The highest number of the SDR was performed in Scotland

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(59 surgeries) and Sweden (45 surgeries), with Sweden, besides using the SDR, actively using the injections of botulinal toxin A (646 procedures) and the intrathecal therapy with Baclofen (84 procedures). At the same time in Finland and Iceland, there were no registered cases of using the SDR [10]. In Kazakhstan, the SDR method is included into the current clinical protocol of treating cerebral palsy[3], but the research works on the rates of using this surgery were not carried out yet in the republic.

SELECTIVE DORSAL RHIZOTOMY: THE HISTORY AND THE PRESENT DAYS

The first description of the clinical use of the SDR is dated 1908, when one of the founders of the German and Global Neurosurgery Otfrid Foerster has first carried out four lumbosacral dorsal rhizotomies. Later he has published a report containing the data about 26 patients, 3 of which have deceased, 15 had a stable remission and 8 had a recurrence. In 1978, an Italian Neurosurgeon Victor Fasano has presented a new concept of the surgical methods — the functional dorsal rhizotomy. The principle of the method is the intraoperative evaluation of the abnormal muscle response to electric pulses. The new method has allowed for excising only the bundles, which were responsible for the "abnormal" muscular response. In 1982, the Neurosurgeons Warwick Peacock and Leila Arens modified the SDR for its use at the level of the cauda equina [11]. According to the review [7], W. Peacock in 1986 implemented the SDR in large Pediatric Centers all across the territory of the United States of America. As of today, this method is known worldwide and is used in many Neurosurgery centers as a method for correcting spasticity in cerebral palsy patients, where a sufficient amount of good results was obtained regarding both the short-term and the long-term perspective [6, 8, 12–15].

I. Novak et al. have published a systematic review, in which they have defined the botulinal toxin, the intrathecal Baclofen, the Diazepam and the SDR as the "green light" means in the treatment of cerebral palsy [2], but, of all listed methods, only the SDR provides the patients with a constant decreased muscle tone during the post-surgery period [16, 17]. The positive result remained not only within the timeframes of 3, 6, 12 and 24 months, but also 25 years after surgery [6, 8, 13, 16–19].

In England, a cohort efficiency research was carried out with using the SDR in five neurosurgery centers, where children aged 3–9 years underwent follow-up for 24 months. The main criteria for the SDR outcome were the gait analysis, the results of using the Ashworth spasticity scale and the Gross Motor Function Measure (GMFM-66), the quality of life among the cerebral palsy adolescents as determined by using the CP-QoL questionnaire. Eventually, after 2 years, the GMFM-66 value has increased in almost all the children (137 participants): the total increment was 3.2 units a year; significant improvement was observed in the parameters of the quality of life — practically in all the examined areas [14].

A similar multicenter research was carried out in Germany within the premises of three centers 12 and 24 months after surgery. The criteria for the evaluation of the SDR efficiency included the Ashworth scale, the GFMCS classification of motor functions in cerebral palsy patients and the GMFM-88 gross motor functions measuring scale. Positive changes were reported, with all the parameters measured in 24 months being significantly higher. For example, the Ashworth scale score (when evaluating the right hip adductor muscle) in 12 months has improved in 68% of the participants, in 24 months — in 71%, while the GMFM-88 has increased by 7% and 1 (2%) child had signs of worsening [5].

In 2022, the results of a cross-sectional research became available, the one that has studied the motor skills and the life aspects among the patients that had the SDR surgery more than 25 years ago. The comparison group included healthy volunteers of the same age. Upon the examination of the muscles, no significant difference was detected in the muscle tone between the groups. The muscle strength was shown to be lower in patients with the SDR surgery, they also had persisting restriction of the range of motion in the joints of the lower limbs. The psychological health parameters had no differences from the healthy group, but the physical parameters were not approaching the age-corrected reference ranges. This research has shown a positive long-term effect of the SDR.

The SDR surgery is to be proposed for the patients, the scale indexes in which correspond to the GMFCS levels II–III, but some authors recommend arranging the surgery among the children with more expressed impairments (GMFCS levels IV–V). During a multicenter

[3] Clinical Protocols of the Ministry of Health RK-2023 (Kazakhstan) [Internet]. Infantile cerebral palsy: clinical protocol for diagnosis and treatment (Approved by the Joint Commission on the quality of medical services of the Ministry of Health of the Republic of Kazakhstan from 15 December 2023. Protocol No. 199). Available from: https://diseases.medelement.com/disease/детский-церебральный-паралич-кп-рк-2023/17822. Accessed: 15.01.2025. (In Russ.)

research, C.S. Gillespie et al. [8] have studied the efficiency of the SDR among 144 patients with spastic diplegia of GMFCS grade IV–V with dynamic evaluation after one year. Positive dynamic changes were noted in terms of correcting the spasticity, the conclusion was made that the improvement is not as significant as it is in the GMFCS II–III patients (the results obtained when using the GMFM-66 scale has increased by an average of 2.4 units), 30.9% have reported about re-gaining the urinary bladder functions. This has allowed for recommending the use of the SDR in patients with spastic diplegia and with the IV–V class of gross motor functions [8].

It was shown that the SDR effectively decreases the spasticity and improves the mobility of the joints without significant negative effects in terms of the morphology of the muscle tissue and of the locomotor system. Moreover, the use of neuromuscular skeletal modeling during the research has shown an increase of muscle strength when walking (in operated children). According to the opinion from B.A. MacWilliams et al. [19], the SDR, comparing to other treatment methods, shows a clear prolonged effect on the relaxation mechanisms that are required for walking. Long-term monitoring with clinical measurements of local spasticity in patients that have received this surgery, has shown positive dynamic changes with partial or significant regress of motor disorders [4, 19–25]. The discrepancies presented in the literature on the evaluation of the SDR [26] can be explained by small sample size and/or by the absence of objective parameters for the obtained results, by the short follow-up duration after surgery and by medical-social rehabilitation [4, 27].

The end result can also depend on the complications occurring during the course of surgery and at the post-surgery period, which, in turn, can be short-term (lasting less than 1 year after surgery) and remote (occurring after a period of more than 1 year), transient or non-transient, structural or non-structural. The short-term complications, which result in a delay of rehabilitation, may include the CSF leak, the impaired sensitivity, the pulmonary or gastro-intestinal complications (nausea, vomiting, constipations) and the dysfunction of urinary tracts. The remote complications include the deformation of the vertebral column (8.4–20.5%) and spondylosis. The development of remote complications can be related to the early age of the patient (the younger the patient, the higher the risk of deformation in the vertebral column), to the Cobb angle (more than 30 degrees) and to the past history of scoliosis [26, 27].

REHABILITATION

Rehabilitation is an integral component in the combined treatment of the cerebral palsy patients after the SDR [8, 14, 16, 17]. The ability of children to improve the quality of walking after the SDR combined with physical therapy methods was proven [6]. When assessing the obtained data, 86% of respondents have noted that rehabilitation has fundamental importance for the success of surgery [12].

Early rehabilitation period begins right after surgery. The opinions of the authors vary regarding the day of initiating physical therapy, with this, the majority of them recommend beginning rehabilitation on day 1–2 after surgery [28]. The authors proposing the rehabilitation activities from day 3–4, justify their opinion by the fact that early verticalization and excessive physical load can become the cause of early postoperative complications, such as CSF leak and an increase of pain syndrome. On day 3, in the absence of contraindications, it is permissible to change the position on the bed — turning and early passive kinesiotherapy. From days 4–7 of the postoperative period, the intensity of physical exercises is being gradually increased, the patient is permitted to sit on the edge of the bed or the chair, to stand on hands and knees, to stand up with aid and support for training the body balance and postural control. Beginning from weeks 2 and 3, it is allowed to start the training sessions on the correct walking pattern, simultaneously perfecting the self-care habits [16]. In the absence of complications, as well as taking into consideration the age and the rehabilitation potential, further activization of the patient is possible 3 days after surgery, performing balancing exercising — in 7 days [6]. The tactics of managing the patients after the SDR is defined by their functional status. Patients of GMFS classes II–III are subject to the transition to the rehabilitation department on days 4–5, where they receive physical therapy for 2 weeks. After discharge, all the patients undergo rehabilitation activities at a rate of up to 4–5 times a week for 6 months, then the periodicity of physical therapy is once in two years [3].

In Kazakhstan, there is an experience of long-term (15 months) clinical follow-up of 4 patients aged 4–8 years with the diagnosis of cerebral palsy after the SDR, of which 2 patients have spastic diplegia (GMFCS III) and 2 patients have tetraparesis (GMFCS IV). Physical therapy was prescribed from days 2–3 and included a set of strength exercises with an accent to the following groups of muscles: hip abductors and foot dorsiflexion muscles. On day 3, the procedures included early positioning of the patients using the spinal assistant

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(sitting posture) for the purpose of eliminating the pelvic retroversion and changing the 90 degrees angle between the body axis and the hip axis. From month 2, positioning was initiated using the sitting posture and the spinal assistant, in case of positive changes, verticalization followed (carried out with the help of special rehabilitation means). The tool for evaluating the efficiency of the SDR combined with rehabilitation was the International Classification of Functioning, Disability and Health. The examinations were carried out in 6 and 15 months after surgery. The authors came to the conclusion that the SDR effectively decreases the spasticity level in the target muscles, promotes to developing new motor skills, such as verticalization and mobility, also shortening the risk of progression for the acquired locomotor system disorders [29].

CONCLUSION

Selective dorsal rhizotomy is a highly effective method of surgical correction of spasticity in cerebral palsy patients, which is confirmed by multiple research works. The use of the SDR allows for achieving a significant decrease of the muscle tone, for improving the mobility in the joints and for increasing the functional capabilities in the patients, however, for achieving optimal results, it is important to employ the combined treatment program that includes not only the surgery itself, but also the long-term and structurized rehabilitation.

The efficiency of the SDR is due to its ability to selectively affect the nerve roots, which provides a decrease in the spasticity with no significant changes in the structure of the muscle tissue and of the locomotor system. The key factor of success is the postoperative rehabilitation. The optimization of timings and intensity of rehabilitation activities allows for minimizing the risks of complications and promotes to faster restoration of the functional skills. The long-term results of the SDR include the improvement of motor skills, the decrease of mobility restrictions and the increase in the quality of patients' life, which is confirmed by follow-up data with a duration of more than 25 years.

Despite the proven efficiency of the method, its application is accompanied by potential complications, which requires employing an individual approach to selecting patients and thorough following the clinical protocols.

Thus, the integration of the SDR into the combined treatment of the cerebral palsy patients is a promising vector of the modern Medicine, providing an improvement of the quality of life for children and adolescents with this disease.

ADDITIONAL INFORMATION

Author contribution. *D.B. Kurmanova* — concept development, literature search and analysis, data interpretation, data discussion, article writing; *S.T. Turuspekova*, *V.S. Lisnic* — concept development, literature analysis, data interpretation, data discussion, article editing; *G.A. Mukhambetova* — data discussion and interpretation, article editing; *B.K. Demisinova*, *N.K. Mamashayev* — data discussion. 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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MODERN POSSIBILITIES OF TREATING BRAIN TUMORS: INTRAOPERATIVE TECHNOLOGIES IN NEUROONCOLOGY

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ABSTRACT

The fundamental principle of neurooncology is the maximal removal of the tumor, simultaneously minimizing the effects on the healthy brain structures. In cases of malignant gliomas, the extent of resection still remains a critical parameter, which significantly affects the prognosis of the disease. The results from numerous trials show that the increase of the resected tumor volume correlates with improved survival rates. This review provides the data on the innovative intraoperative therapeutic technologies, developed for improving the treatment outcomes among the patients with brain tumors. It is important to note that each of these technologies has its benefits and limitations. For example, laser interstitial thermotherapy provides the ability of highly precise destruction of tumor cells with minimal damaging of the surrounding healthy tissues, however, it requires special equipment and qualified personnel. Photodynamic therapy is distinguished by selective affecting the tumor, but its efficiency depends on the type of photosensibilizing agent used and on the depth of light penetration. Brachytherapy, in turn, provides the possibility of local tumor irradiation, minimizing the effects on the surrounding structures, but it can require a long-term following up the patient after the procedure. Thus, the use of modern intraoperative methods gives access to new perspectives in neurooncology, providing a more precise and sparing destruction of tumors with preserving the functional activity of the healthy brain structures. However, the success of their use depends on further development of technologies, on increasing the qualification of specialists and on the close interactions of the scientific community with the industry and with the regulating authorities.

Keywords: *neurosurgery; oncology; technologies; laser interstitial thermal ablation; photodynamic therapy; brachytherapy; innovations; glioma; glioblastoma.*

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INTRODUCTION

The fundamental principle of neurooncology is to maximally resect the tumor, simultaneously minimizing the effects on the healthy structures of the brain. In cases of high-grade gliomas (HGG), the extent of resection still remains a critical parameter, which significantly affects the prognosis of the disease. Numerous research works show that the increase of the volume of resected tumor correlates with improved survival rates [1–3]. However, it is important to take into account that the excessively aggressive surgical approach can result in the development of new neurological disorders in a patient, which, in turn, can negatively affect the overall survival, especially concerning the tumors, located in the functionally important areas of the brain [4]. Even despite the progress in the surgical techniques, the risk of recurrences remains high due to the presence of residual infiltrative cells at the border of the tumor and beyond its margins. This determines the necessity of constant searching and implementing new intraoperative technologies, capable of increasing the precision of tumor visualization and providing

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СОВРЕМЕННЫЕ ВОЗМОЖНОСТИ ЛЕЧЕНИЯ НОВООБРАЗОВАНИЙ ГОЛОВНОГО МОЗГА: ИНТРАОПЕРАЦИОННЫЕ ТЕХНОЛОГИИ В НЕЙРООНКОЛОГИИ

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АННОТАЦИЯ

Основополагающий принцип нейроонкологии заключается в том, чтобы максимально удалить опухоль, одновременно минимизировав воздействие на здоровые структуры головного мозга. В случае злокачественных глиом объём резекции продолжает оставаться критическим параметром, который существенно влияет на прогноз болезни. Результаты многочисленных исследований показывают, что увеличение объёма удалённой опухоли коррелирует с улучшенными показателями выживаемости. В данном обзоре представлены инновационные интраоперационные терапевтические технологии, созданные для улучшения исходов лечения пациентов с опухолями головного мозга. Важно отметить, что каждая из этих технологий имеет свои преимущества и ограничения. Например, лазерная интерстициальная термотерапия обеспечивает высокоточную деструкцию опухолевых клеток с минимальным повреждением окружающих здоровых тканей, однако требует специального оборудования и квалифицированного персонала. Фотодинамическая терапия отличается избирательным воздействием на опухоль, но её эффективность зависит от типа используемого фотосенсибилизатора и глубины проникновения света. Брахитерапия, в свою очередь, предоставляет возможность локального облучения опухоли, минимизируя воздействие на окружающие структуры, но может требовать длительного периода наблюдения за пациентом после процедуры. Таким образом, применение современных интраоперационных методов открывает новые перспективы в нейроонкологии, обеспечивая более точную и щадящую деструкцию опухолей при сохранении функциональной активности здоровых структур мозга. Однако успех их применения зависит от дальнейшего развития технологий, повышения квалификации специалистов и тесного взаимодействия научного сообщества, индустрии и регуляторов.

Ключевые слова: *нейрохирургия; онкология; технологии; лазерная интерстициальная термоабляция; фотодинамическая терапия; брахитерапия; инновации; глиома; глиобластома.*

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the possibility of detecting and eliminating the microscopically small remnants of the tumor cells along the margins of the post-operative cavity after the main stage of resecting the tumor. Due to that, special importance is gained by modern methods of intraoperative diagnostics, such as the fluorescent navigation, the spectroscopy and the molecular visualization, which allow the surgeon to better navigate at the operative field and to more precisely determine the margins between the healthy tissues and the tumor. These approaches promote to decreasing the risk of damaging the healthy tissues and to increasing

the radicality of the surgical intervention, which can potentially improve the remote treatment results.

For the purpose of preventing the continued growth of HGG cells, actively invading the normal nerve tissue, the exclusive importance is being gained by the methods of intraoperative therapy, such as the laser interstitial thermotherapy, the intraoperative brachytherapy, the photodynamic and the sonodynamic therapy.

The analysis of modern literature performed in this article, has allowed for characterizing the novel technologies of intraoperative therapy, to examine their current status and to evaluate the clinical results of their use in neurooncology.

Methodology of searching the trials

The search in the PubMed, Google Scholar and eLibrary electronic data bases was carried out in Russian and English languages using the following key words and their combinations: «neurosurgery»; «oncology»; «gliomas»; «glioblastoma»; «laser interstitial thermoablation»; «photodynamic therapy»; «brachytherapy».

The algorithm of selecting the sources consisted of several stages (Fig. 1). During the process of screening, the review authors have independently analyzed the titles and the abstracts of the selected articles, checking their conformity to the review topic; then, full-text manuscripts were assessed for the conformity to the inclusion criteria (publication in Russian or English languages; the article is a literature review or a clinical trial; the article is published in the peer-reviewed scientific journal; the article describes the use of intraoperative technologies in neurooncology). Ultimately, the present review has enlisted 63 research works.

LASER INTERSTITIAL THERMOTHERAPY

Laser interstitial thermotherapy (LITT) is a minimally invasive ablation method, employing the thermal energy for destroying the tumor tissue [5]. The procedure is being undertaken at the stereotaxic manner, usually under the control of magnetic resonance tomography and under general anesthesia. For the introduction of the optical fiber, a small opening is created, through which, the low-energy laser radiation is being delivered for a period of 3–4 hours [6]. The heat created during this procedure destroys the blood-brain barrier, for a certain time period (up to 4–6 weeks after the procedure) improving the penetration of the medicinal products [7]. The immunomediated death of tumor

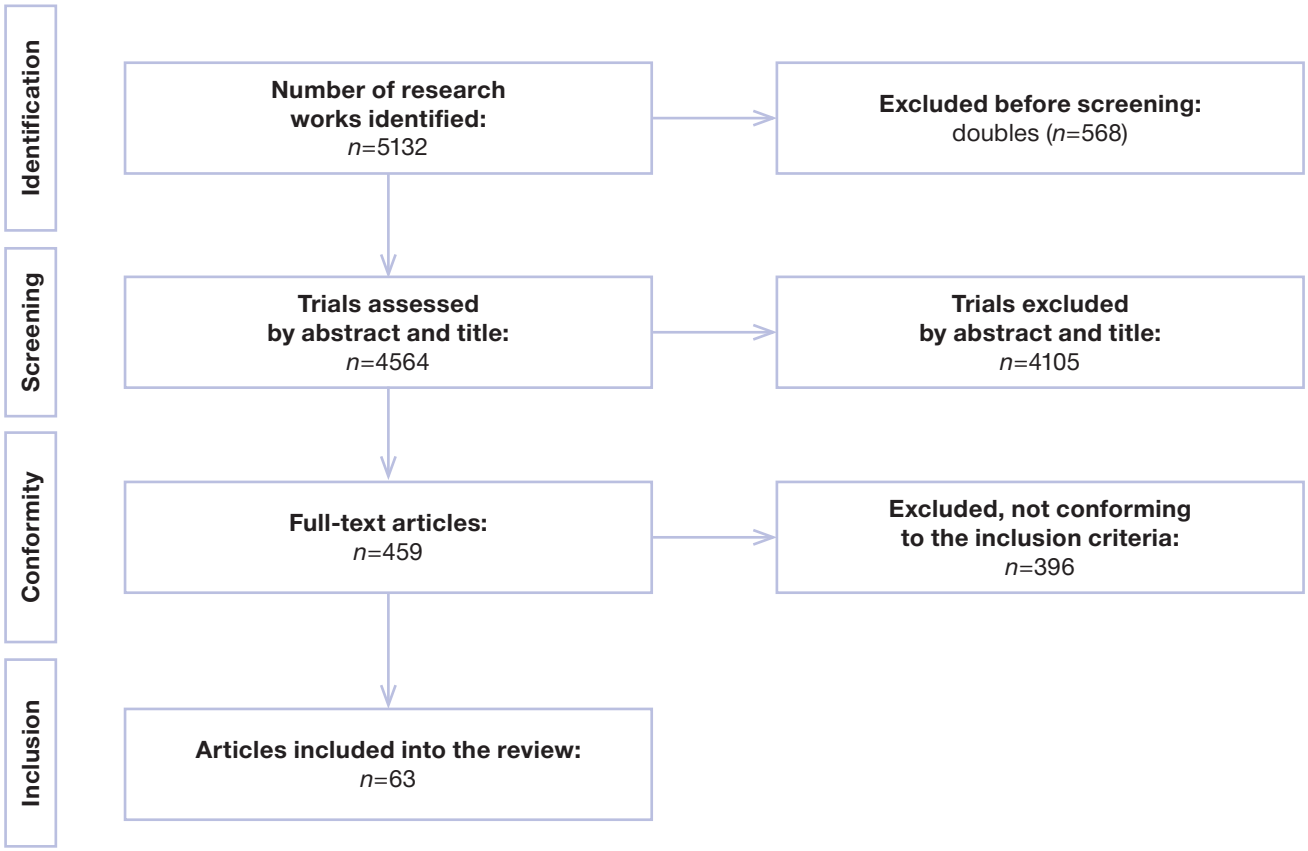

Fig. 1. Algorithm of searching the research works.

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cells, induced by LITT hyperthermia, in combination with the immunotherapy, can contribute to overcoming the blood-brain barrier and stimulating the cellular anti-tumor immune response, in particular, due to using the inhibitors of immune checkpoints [7, 8]. At the present moment, only the first phase of the trial is completed, with the research work being devoted to the combined use of LITT and monoclonal antibodies against the programmed death-ligand 1 (PD-L1) — the Avelumab, additional research is expected [9, 10].

As of today, two LITT systems are being actively used — the NeuroBlate (predominantly in neurooncology) and the Visualase (more often used for the treatment of drug-resistant epilepsy) [11–13]. Both devices can be used in accordance with various indications.

The NeuroBlate system, approved in 2009 by the Food and Drug Administration of the USA (FDA), is a controlled magnetic resonance device for performing the LITT procedures, employing laser hyperthermia for the purpose of *in situ* local heating the targets [14]. The first phase of clinical trials with the participation of patients suffering from the recurrent HGG, was arranged in 2013 in a group of 10 patients, the mean survival of which was 10.5 months [15]. The LAANTERN (Laser Ablation of Abnormal Neurological Tissue Using Robotic NeuroBlate System; NCT02392078) trial is a large research work supported by Monteris, during which, for a period of 5 years beginning from 2015, a total of 3000 patients were enlisted from various medical centers. One of the first to examine the efficiency of LITT in cases of newly diagnosed and recurrent wild type glioblastoma were the researchers J.F. de Groot et al. [16]. According to the results of their trial that included 29 patients with newly diagnosed and 60 patients with recurrent tumor, the median of overall survival among the patients with the newly diagnosed disease was comparable to the results observed in cases of standard surgical resection. Also, data were published on the treatment efficiency for metastatic lesions in the brain and for epilepsy [17, 18]. Besides, NeuroBlate is being tested within the framework of the randomized REMASTER controlled trial (REcurrent Brain Metastases After SRS Trial; NCT05124912), studying the brain metastases, as well as within the PENSAR (NCT05075850) international trial devoted to evaluating the neuropsychological outcomes, the results of which demonstrate the mean overall survival of 16.4 months and the relapse-free survival of 11.93 months. The median survival rate after using the LITT was almost 9 months, while in case of surgical resection this parameter has varied within a range of 5–13 months, which confirms the efficiency of minimally invasive alternative traditional surgery in case of newly diagnosed and recurrent IDH-positive glioblastomas with a short recovery period and lower risk of adverse effects.

The Visualase System approved by the FDA in 2008, was initially developed for the treatment of drug-resistant temporal epilepsy and since then it became a subject for numerous research works [19, 20]. Current trials, such as the SLATE, evaluate the safety and efficiency of Visualase in the treatment of mesial temporal epilepsy [21]; research works are being undertaken on the application of Visualase in the treatment of brain tumors [22, 23]. Thus, P.R. Jethwa et al. [22] have reported about a case series with the participation of 20 patients with brain tumors, 17 of which have previously used other types of therapy. The authors have noted that all the procedures have allowed for achieving a high precision of laser exposure (83.8%), and the majority of patients could leave the hospital already on the next day after surgery.

Despite the fact that direct comparisons between the NeuroBlate and the Visualase systems are lacking, both of them are demonstrating positive results and are being studied in the on-going clinical trials.

INTRAOPERATIVE BRACHYTHERAPY

Intraoperative brachytherapy represents a method of introducing radioactive materials directly into the tumor zone or near it before local radiation therapy. This approach can be used both inside the cavities of the organism and in the inter-tissue spaces [24]. Due to the directed effects of high radiation dosages on the tumor with minimal damaging the adjacent healthy tissues, the treatment efficiency gets increased [25].

Initially, brachytherapy was developed as an additional method of fighting malignant tumors in the abdominal cavity organs, but, at the modern level of technology, it is widely used in the treatment of various types of tumors, including the neoplasms in the central nervous system, in the prostate, in the mammary gland, in the female reproductive organs and in the eyes [26–29]. There are two main types of brachytherapy — the high-dose rate (HDR) and the low-dose rate (LDR).

During the HDR, the radiation source is being introduced into the tumor area for a short period of time (several minutes), being extracted afterwards. In case of the LDR, the radioactive material is left at the affected zone at least for several days, as a maximum —

for long (permanent) time [30]. After the main surgical intervention, into the resulting cavity, the radioactive isotope granules are commonly being placed, such as Cesium-131 (Cs-131), Iodine-125 (I-125) and Iridium-192 (Ir-192), the half-life of which ranges from several days to several weeks [31, 32].

In a number of clinical research works, the confirmation was obtained for the safety and efficiency of using brachytherapy for the treatment of brain tumors. Thus, S.T. Magill et al. [32] have used I-125 brachytherapy in 42 patients with atypical or recurrent meningiomas. The results have demonstrated that the mean duration of the recurrence-free period was 20.9 months for atypical and 3.3 years for recurrent meningiomas. E. Dagnew et al. [33] have observed similar findings in the research with the participation of 26 patients with brain metastases, where the local tumor control was reaching 96%, while the median of overall survival was 17.8 months. However, both research works have reported complications associated with the necrosis of the brain tissue due to radiation-induced damage, which, probably, was related to high initial dosage of I-125, characterized by relatively high disintegration energy (35 keV) and by the long half-life (59.4 days) [31]. This is why Cs-131, having an optimal ratio of energy (30 keV) and the half-life (9.7 days), has become the most preferable radioactive isotope for low-dose brachytherapy.

In the phase I/II clinical research conducted by A.G. Wernicke et al. [34], the procedures of permanent implantation of Cs-131 granules were performed in 24 patients with newly diagnosed metastases in the brain. One year later, the authors have observed 93.8% of local tumor control with no serious adverse effects related to radiation exposure. Similar results of controlled toxicity were also obtained during the other phase I/II trial with the participation of 15 patients [35].

After the successful use of Cs-131 in the low-dose mode of brachytherapy, the Gammatile (USA) device was made, representing the Cs-131 granules embedded into a collagen carrier, which is intended for the intracavitary implantation after surgery. The efficiency of this device was verified during the STaRT trial (Surgically Targeted Radiation Therapy), which has enlisted 11 patients with 16 HGG tumor foci (12 recurrent and 4 treatment-naive) [36]. The use of Gammatile has provided the local remission of 83% tumors within 12 months, while among the treatment-naive tumor cases this parameter was 100%. Currently, there is a ROADS phase III clinical trial going on, comparing the results of using Gammatile with the results of post-operative stereotactic radiosurgery (SRS). The completion of this research is planned for 2027 [37].

Among the recent advances in onco-radiology, it is important to note the Xoft Electronic Brachytherapy intraoperative balloon electronic brachytherapy systems (Axent, USA), which deliver the miniature source of X-ray radiation directly to the bed of the tumor, avoiding the necessity of using radioactive isotopes and the cost intensive equipment [25]. The radiation sources are being delivered via the applicator devices, providing a high dose of radiation to the surrounding tissues. The Intrabeam system by Zeiss (Germany) works as a miniature linear accelerator, creating a high-dose radiation for immediate radiation therapy after surgery with a minimal exposure of healthy tissues. A multicenter research by M. Huss et al. [38] with the use of these systems has demonstrated an improvement of overall survival by 25% in 3 years after the intervention.

The Xoft Axxent system (iCAD), equipped with a compact X-ray tube and a tungsten target, is showing high precision and safety of its radiation. Its ability to rapidly decrease the dosage helps minimizing the effects of radiation in the surrounding healthy tissues, with is especially valuable when operating in the vulnerable areas, such as the brain. Initially developed for the treatment of mammary gland and skin cancer, the Axxent system, due to its flexible software, can generate the dosage rate that is comparable with such radioactive isotopes as Ir-192, with no additional regulatory or logistical difficulties related to the usage of radioactive materials [39].

The Elekta Esteya (Sweden) is also an effective electronic solution for brachytherapy, initially developed for the treatment of non-melanoma skin cancers, but later extended for using during the intraoperative treatment of HGG due to its compact construction and its advanced capabilities of regulating the dosage rates. Using the 69.5 kV voltage, the Esteya system is capable of providing high power when using the low-energy X-ray beam, which increases its safety both for the patients and for the medical staff. The design of the Esteya system allows for conducting a precisely directed treatment, minimizing the radiation exposure to the non-targeted areas, making it attractive for using in neurooncology [39].

PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) represents a treatment method which combines using the light source and the non-toxic photosensibilizing agents for destroying the tumor cells [40]. The light is pointed directly at the

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tumor via the optical fibers, located inside or within the cavity forming after resecting the tumor [41]. Under the effects of the light with a specific wavelength and intensity, the photosensibilizing agent becomes activated, then producing the active oxygen species [7, 42]. These compounds react with the cellular components, causing the free-radical-induced death of tumor cells [42]. Currently, the most widely used photosensibilizing agent for PDT in cases of HGG is the 5-Aminolevulinic acid (5-ALA) [7, 43] — the precursor of the photoactive porphyrins (the fluorescent agent and simultaneously the source of active oxygen species) in the tumor tissues. The PDT-combined fluorescent navigation, mediated by 5-ALA, has become the object of multiple current clinical trials.

The efficiency of PDT, to a significant extent, is due to the selective accumulation of photosensibilizing agents in the malignant tumor cells, which is related to their ability to bind to the low density lipoproteins — the important components of the cellular membrane [42, 44]. As a result, the tumor cells, which rapidly reproduce and have high biosynthetic demands, devour the low density lipoproteins and the photosensibilizing agents at a much higher rate comparing to the healthy cells.

The anti-tumor effects of PDT are diverse. Besides the direct destruction of tumor cells by means of oxidative damage, PDT also causes ischemia in the tumor, damaging its vascular network and suppressing the formation of new blood vessels [45]. Besides, PDT stimulates both the innate and the adaptive immune reactions, which uncovers the interesting perspectives for clinical trials [45].

Hemerion (France) has developed a photosensibilizing agent named Pentalafen and the Heliance device, which are being introduced into the tumor before surgery and intraoperationally [46]. The aim of the INDYGO (INtraoperative photoDYnamic Therapy for GliOblastomas; NCT03048240) staged clinical research conducted at the facilities of the Lille University Hospital, was the evaluation of safety and efficiency of the intraoperative 5-ALA-mediated PDT after a fluorescent navigation surgery [47]. The research included only 10 patients with newly diagnosed HGG during a period from May 2017 until June 2018 [47]. Upon the completion of the research in April 2021, the provisional analysis of the results did not show any significant adverse effects, while the overall survival and the progression-free survival rates for a period of 12 months were 60% and 80%, respectively [48]. The next stage of the INDYGO research is the DOSINDYGO (Dose Finding for Intraoperative Photodynamic Therapy of Glioblastoma; NCT04391062) trial — a multicenter phase II clinical trial on determining the maximal tolerable dose of 5-ALA-mediated PDT [49]. Currently, an active recruitment of participants is still going on, the completion of the research is planned for September 2025.

The research by A.Yu. Rynda et al. [50] has assessed the efficiency of intraoperative PDT in patients with HGG of supratentorial location (n=161). The patient cohort was divided into the main group receiving PDT (n=80) and the comparison group without PDT (n=81). The usage of intraoperative technologies within the structure of the combined treatment for malignant gliomas has significantly increased the median overall survival in Grade III patients to 39.1±5.5 months, in Grade IV patients — up to 20.7±4.7 months, also increasing the inter-recurrent period. No serious complications were observed that were related to the use of the photosensibilizing agent.

Thus, the application of the intraoperative PDT within the structure of the combined treatment for malignant gliomas promotes to an increase in the overall survival and in the inter-recurrent period, making this method a perspective direction in neurooncology.

SONODYNAMIC THERAPY AND FOCUSED ULTRASOUND

Sonodynamic therapy (SDT) represents an alternative method of treatment, which employs a non-toxic sonosensitizing compound together with focused ultrasound exposure for destroying the tumor cells [51]. The focused ultrasound transfers acoustic energy via the ultrasonic transducer into the target tissue areas with high spatial precision. Just like PDT, the sensitizer is mainly concentrated in the tumor cells, which allows for performing a targeted ablation. The basic mechanism of action of the focused ultrasound includes the formation of the cavitation effect (from the Latin cavitas — the emptiness), during which, the induction of ultrasonic waves results in a series of alternating cycles of high and low pressure, causing the formation and further implosion (a type of explosion) of microbubbles with heating the surrounding tissues [51]. The microbubbles mechanically disrupt the blood-brain barrier, temporarily increasing its permeability, which facilitates the localized delivery of medicines [52].

Currently, there are two leading companies that work on the development of the technologies related to the use of focused ultrasound for impairing the integrity of the blood-brain barrier in the treatment of gliomas:

InSightec Ltd. (Israel) has developed an improved system of focused ultrasound exposure under the magnetic resonance tomography control, and CarThera (France) has developed a SonoCloud low-intensive contact ultrasonic system. During the phase I clinical research, which had recruited 17 recurrent glioblastoma patients, A.M. Sonabend et al. [53] have demonstrated the safety and efficiency of the transient impairment of the blood-brain barrier permeability using the SonoCloud device, as well as an improved delivery of albumin-bound Paclitaxel and Carboplatin through the blood-brain barrier. One of the most studied SDT sensitizers is the same 5-ALA compound. Currently, SonALAsense (USA) is conducting a single-center phase 0 clinical trial with an evaluation of safety and efficiency of increased SDT dosage rates combined with 5-ALA (SONALA-001) in the treatment of HGG (NCT04559685).

Such technologies as SDT and focused ultrasound, offer innovative solutions for the treatment of tumors that are hard to access. The usage of non-toxic compounds and ultrasound for targeted destruction of tumor cells represents a promising strategy, which will help improving the treatment results and lowering the risk of adverse effects. It is important to continue the research and development in this field to optimize the existing treatment methods and to increase their efficiency.

THE MODERN FOCUS OF SCIENTIFIC DEVELOPMENT

The entirety of the novel intraoperative treatment methods indicates the significant progress in the neurosurgery of brain tumors, offering specialized instruments for overcoming the high recurrence rate and for solving the complex issues of HGG therapy. Such methods as the LITT, PDT and SDT, focused ultrasound and brachytherapy, demonstrate a synergetic effect comparing to classic resection, promoting to the preservation of a large extent of healthy tissue and to the improvement in the quality of life for the patients. In parallel with such physical effects, local chemotherapeutic approaches are being developed that ensure the maximal efficiency directly in the lesion focus. For example, Carmustine (Bischlorethylnitrosourea, BCNU), an alkylating agent (the nitrosourea derivative) that was initially used for the treatment of gliomas by means of intravenous injection and that was later introduced (in the form of biodegradable plates containing Carmustine (Gliadel)) into the cavity remaining after removing the tumor [54]. The plate format, intended for decreasing the systemic toxicity, simultaneously ensures the localized exposure at the margins of the resection area [54]. In the meta-analysis conducted by L. Zhao et al. [55], the combination of surgical resection of tumor with the introduction of Carmustine plates has prolonged the overall survival in patients with newly diagnosed multiform glioblastomas for 2–4 months. Nevertheless, despite the positive results, the usage of Carmustine plates, for a number of reasons, has not yet become the standard treatment of glioblastomas, including due to the significant technical difficulty of the procedure. In addition to that, in the meta-analysis by A. Bregy et al. [56], the rate of complications observed when using the Carmustine plates, was exceeding the value of 42% (most commonly — seizures and cerebral edema), even taking into consideration the observed decrease in the number of systemic adverse effects for the plate form of Carmustine. Additional barriers for wide implementation of Carmustine plates include the high costs and the logistical difficulties of using the method in the settings of the operating room.

The modern focus of scientific development is aimed predominantly at the HGG, which represent a serious problem due to their high occurrence rates, the resistance to the existing treatment methods and the unfavorable prognosis. The survival rates remain extremely low, despite many years of research and the progress in technologies [57]. The two key biological features of HGG — the heterogeneity of the tumor and its ability to spread outside the contrasted zone — require a combined integration of various technologies and therapeutic strategies [58]. As of today, the combinations of various high-tech methods are used, such as surgery with fluorescent control and the exoscopy and Raman spectroscopy combined with LITT, PDT, SDT and focused ultrasound exposure. These methods are combined with the immunotherapy with checkpoint inhibitors and with the conventional chemoradiation therapy. For the purpose of further perfecting the therapy, more precise *in vitro* and *in vivo* models are required, which are capable of reproducing the heterogeneous origin of HGG [59, 60]. The limited representation of the existing pre-clinical models complicates the course of translational trials [60]. Besides the biological challenges related to the heterogeneity of tumors, it must be kept in mind that the implementation of new technologies in surgery is inevitably accompanied by an increase of costs and of the duration of training for specialists.

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There is a topical need for increasing the number of phase 0 and I clinical research works. As noted by the STARD-CNS recommendations [61], special attention must be paid to the possible mistakes when designing the trials, especially concerning the new fluorophores. These early research stages are critically important for the evaluation of safety, applicability and preliminary efficiency of new technologies, opening the path for more large-scaled testing of the promising treatment methods at the next stages. The important aspect of the wide implementation of new methods of intraoperative diagnostics and therapy is obtaining the approval for clinical application from the regulatory authorities (for example, FDA), which itself is a long-term and complex process. Due to that, the experience of registering Gliolan, a medicinal product that is based on 5-ALA, can represent a valuable lesson [62]. Within the framework of this process, the 5-ALA was approved by the FDA, which allowed the researchers to repurpose its use from therapy to the intraoperative visualization tool. This example demonstrates the significance of flexibility and innovativeness in the process of transitioning the laboratory science innovations into clinical practice.

CONCLUSION

The active development of new technologies and treatment methods in neurooncology represents a remarkable example of human inventiveness for increasing the efficiency of treating the poorly curable gliomas of high degree of malignancy. Each of the intraoperative therapeutic technologies described in the review, contributes greatly into the improvement of the treatment outcomes for patients with brain tumors. Thus, LITT provides the precise elimination of the tumor cells, minimally affecting the adjacent healthy tissues, however, this procedure requires specialized equipment and experienced specialists. PDT directly affects the tumor, but the efficiency of the method is determined by the type of photosensibilizing agent used and by the depth of penetration of the activating light beam. Brachytherapy, in turn, allows for performing local irradiation of the tumor, limiting the effects in the surrounding areas, nevertheless, after this procedure, the patient may require a long-term follow-up period.

The cooperation between the scientific community, the industry and the regulating authorities can play a key role in the successful implementation of the reviewed technological innovations into clinical practice.

ADDITIONAL INFORMATION

Author contribution. *A.I. Nafikov*, *R.I. Minnigaleev* — concept and design of the study, editing of the article; *E.R. Yarullina* — collection and analysis of literary sources, preparation and writing of the text of the article; *E.M. Magomedova* — collection and analysis of literary sources, preparation and writing of the text of the article; *K.G. Soboleva* — literature review, collection and analysis of literary sources, writing the text and editing the article; *M.M. Sobolev* — search and analysis of literature, writing the text of the article; *O.R. Egamova*, *Yu.A. Kirillova*, *A.A. Harutyunyan* — data collection and analysis, editing the manuscript; *E.M. Magomedova* — data collection and analysis, participation in the writing of the manuscript; *K.G. Soboleva*, *F.A. Tokhova*, *N.A. Abbasova*, *Kh.Kh. Saadueva*, *I.F. Yarmeev* — data collection and analysis, writing the text of the manuscript. 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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DIAGNOSTIC CAPABILITIES OF MAGNETIC RESONANCE IMAGING IN ASSESSING THE MYOCARDIAL PERFUSION IN CASES OF ISCHEMIC DISORDERS

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ABSTRACT

Magnetic resonance imaging (MRI) of the heart has proven itself as an important tool for the evaluation of myocardial perfusion and for the diagnostics of myocardial ischemia. Due to its high spatial resolution and absence of X-ray radiation, MRI of the heart allows for precise diagnosing subendocardial ischemia without any adverse effects, which makes it a valuable method for detecting the ischemic heart disease. Recent advances in cardiac MRI and in post-processing have allowed for moving from qualitative to quantitative evaluation of the stress perfusion cardiac MRI, which has significantly increased the objectiveness and the precision of diagnostics. Quantitative evaluation of myocardial perfusion using the MRI provides a possibility of objective evaluation of myocardial ischemia, which can contribute to improved detection of coronary microvascular dysfunctions. The integration of quantitative perfusion MRI with other methods, such as the kinematic MRI, the delayed increase of gadolinium levels and the T1/T2-mapping, allows for deeper understanding the pathophysiology and improving the prediction of outcomes for various cardio-vascular diseases. The review addresses modern research works on cardiac MRI with regard to diagnostics and predicting of ischemic heart disease, coronary microvascular dysfunctions or non-ischemic cardiomyopathy, focusing on the quantitative approach in the evaluation of myocardial perfusion and its potential use in clinical practice.

Keywords: *magnetic resonance imaging; MRI of the heart; myocardial perfusion; coronary artery disease; CMD; coronary artery disease; CAD; prediction of cardiovascular diseases.*

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INTRODUCTION

Stress perfusion magnetic resonance imaging (MRI) of the heart has become an important method for the diagnostics of myocardial ischemia due to its high spatial resolution and the ability to detect subendocardial ischemia, making it preferable comparing to the radio-isotopic methods, such as single-photon emission computed tomography (SPECT) and positron-emission tomography (PET), especially taking into consideration the absence of radiation exposure [1, 2]. Moreover, MRI of the heart allows for performing a combined evaluation of the cardiac activity within a single examination, including the analysis of the contractile functions of the myocardium (using kinematography), the detection of myocardial fibrosis and scars by means of using the method of late increase of the gadolinium levels (late gadolinium enhancement, LGE), as well as the characterization of myocardial tissues using the parametric mapping. These methods complement the routine stress cardiac MRI that is used for the evaluation of myocardial perfusion, providing a more detailed understanding of the structure and functions of the cardiac muscle [1].

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ДИАГНОСТИЧЕСКИЕ ВОЗМОЖНОСТИ МАГНИТНО-РЕЗОНАНСНОЙ ТОМОГРАФИИ В ИССЛЕДОВАНИИ МИОКАРДИАЛЬНОЙ ПЕРФУЗИИ ПРИ ИШЕМИЧЕСКИХ СОСТОЯНИЯХ

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АННОТАЦИЯ

Магнитно-резонансная томография (МРТ) сердца зарекомендовала себя как важный инструмент для оценки миокардиальной перфузии и диагностики ишемии миокарда. Благодаря высокому пространственному разрешению и отсутствию рентгеновского излучения МРТ сердца позволяет точно диагностировать субэндокардиальную ишемию без каких-либо побочных эффектов, что делает её ценным методом для выявления ишемической болезни сердца. Недавние достижения в области МРТ сердца и постпроцессинговой обработки позволили перейти от качественной к количественной оценке стресс-перфузионной МРТ сердца, что значительно повысило объективность и точность диагностики. Количественная оценка миокардиальной перфузии с помощью МРТ предоставляет возможность объективно оценить степень ишемии миокарда, что может способствовать улучшенному выявлению коронарной микрососудистой дисфункции. Интеграция количественной перфузионной МРТ с другими методами, такими как кинематическая МРТ, позднее повышение уровня гадолиния и T1/T2-картирование, позволяет глубже понять патофизиологию и улучшить прогнозирование исходов различных сердечно-сосудистых заболеваний. В обзоре рассматриваются современные исследования МРТ сердца в диагностике и прогнозировании ишемической болезни сердца, коронарной микрососудистой дисфункции и неишемической кардиомиопатии с фокусом на количественный подход в оценке миокардиальной перфузии и её потенциальное применение в клинической практике.

Ключевые слова: *магнитно-резонансная томография; МРТ сердца; миокардиальная перфузия; ишемическая болезнь сердца; ИБС; коронарная микрососудистая дисфункция; КМД; прогнозирование сердечно-сосудистых заболеваний.*

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Modern advances in the field of scanning sequences and data processing allow for performing the quantitative analysis of myocardial perfusion, which promotes to the transition from qualitative to quantitative assessment of stress perfusion, providing a more objective diagnostics of ischemic changes. Quantitative methods may turn out to be useful for detecting coronary microvascular dysfunctions (CMD) and for studying the pathogenesis of non-ischemic cardiomyopathy. As a result, the area of application for the stress perfusion MRI of the heart becomes significantly expanded.

The research work also contains an analysis of current literature data concerning the diagnostics and prediction of ischemic heart disease (IHD), CMD and non-ischemic cardiac disease with an accent to the role of perfusion cardiac MRI.

List of abbreviations

HCM — hypertrophic cardiomyopathy
DCM— dilated cardiomyopathy
IHD — ischemic heart disease
CMD — coronary microvascular dysfunction
MRI — magnetic resonance imaging (tomography)
SPECT — single-photon emission computed tomography
PET — positron-emission tomography
HFpEF — heart failure with preserved ejection fraction
AUC — area under the curve
CFR — coronary flow reserve
ECV — extracellular volume
FFR — fractional flow reserve
GLS — global longitudinal strain
LGE — late gadolinium enhancement
MACE — major adverse cardiovascular events
MBF — myocardial blood flow
MPR — myocardial perfusion reserve
MPRI — myocardial perfusion reserve index

Methodology of searching the research works

The search of the trials was undertaken in the following data bases: eLibrary, PubMed/MEDLINE and Google Scholar until December 2024, using the following key words: «myocardial ischemia», «cardiovascular magnetic resonance», «coronary artery disease», «microvascular dysfunction», «heart failure». As a result of the search, a total of 4803 articles were found in the PubMed/MEDLINE data base, 3982 — in Google Scholar and 1989 — in the eLibrary.

As the first stage, the authors have excluded the duplicates, while the screening phase with an assessment of abstracts and titles of the detected research works was aimed to evaluate the conformity to the topic of the present review. The next phase included an evaluation in accordance with the following inclusion criteria: the research published in Russian or in English; the research is published in a peer-reviewed scientific journal; the research was undertaken using humans or animals; the research being a literature review or an original article containing the abovementioned key words; the research describes the application of cardiac MRI in the diagnostics of IHD severity degree, in characterizing the functional impairment of coronary microvessels and in the assessment of the prognostic significance of these parameters in patients with various cardio-vascular diseases, including IHD, hypertrophic and dilated cardiomyopathy, as well as heart failure with preserved ejection fraction. Ultimately, 71 trials were included into the review.

DIAGNOSTIC SIGNIFICANCE OF MAGNETIC RESONANCE IMAGING OF THE EPICARDIAL CORONARY ARTERIES

Increased spatial resolution of MRI allows for detecting the subendocardial ischemia by means of qualitative visual evaluation, which provides higher diagnostic precision comparing to SPECT in the diagnostics of IHD [1].

More than 10 years ago, the CE-MARC large single-center prospective randomized research has demonstrated that the stress MRI is superior comparing to the SPECT in terms of the efficiency (area under the curve [AUC] — 0.89 vs. 0.74, respectively, p <0.0001) in detecting the clinically significant IHD, which was defined as ≥70% narrowing of the vessel lumen according to data from invasive coronary angiography [3]. Further analysis of the CE-MARC trial performed by P.P. Swoboda et al. [4], included a comparison of the diagnostic precision of the stress-LGE and stress-rest methods for detecting the ischemia. When using the stress-LGE method, ischemia was detected as the perfusion defect with no signs of infarction according to data from delayed LGE-visualization, while the stress-rest method detects ischemia by the presence of perfusion defect solely upon the stress-visualization. It was found that the stress-LGE method demonstrates higher diagnostic precision with a sensitivity of 75.6% and with the specificity of 93.1% comparing to the stress-rest method, which had a sensitivity of 73.6% along with a specificity of 93.1%.

The evaluation of the spreading degree of myocardial infarction with the aid of LGE represents an important benefit of cardiac MRI, increasing the diagnostic precision in detecting the obstructive IHD. In a recent Phase III clinical trial, A.E. Arai et al. [5] have evaluated the diagnostic precision of stress perfusion MRI of the heart comparing to SPECT in terms of detecting the significant IHD, defined as more than 70% stenosis in the results of coronary angiography. The authors have revealed that stress-MRI of the heart has better diagnostic characteristics with an AUC of 0.88 comparing to the AUC 0.74 for SPECT (p <0.001)

The PACIFIC-2 research was a prospective comparative trial aimed at the evaluation of the

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diagnostic efficiency of qualitative stress perfusion MRI of the heart, of the qualitative 99mTc-SPECT and of the quantitative 15O-H2O PET in detecting the hemodynamically significant IHD using the parameter of fractional flow reserve (FFR) <0.8 as a standard criterion. In this research, the quantitative PET was superior comparing to the qualitative perfusion MRI of the heart and comparing to the SPECT in terms of the AUC values and precision (0.76, 0.66 and 0.66; 70%, 70% and 67%, respectively), however, there were no significant differences detected in the total diagnostic precision between these three methods. It is important to note that, within the framework of this protocol, PET had a benefit of quantitative analysis, while the heart MRI and SPECT were evaluated qualitatively [6].

Each of the methods mentioned above has its specific features, benefits and limitations. MRI of the heart and SPECT in the diagnostics of myocardial ischemia are based predominantly on the visual evaluation, while PET more often relies on the quantitative evaluation of the myocardial circulation. This is due to the fact that PET is capable of providing precise and reproducible measurements of the circulation in the myocardium, both in the stress state and at rest – due to practically linear relation between the indicator uptake and its concentration. The comparative trials on the visualization of myocardial perfusion constantly demonstrate high diagnostic precision for PET. Nevertheless, despite these benefits, PET also has significant drawbacks, including high cost and short half-life of the used radionuclides. The latter requires either the presence of nearly located cyclotron or the use of special radioactive markers with longer half-lives, such as flurpiridaz (18F) [7], which may limit the accessibility of PET.

Despite the advance in modern visualization technologies, SPECT remains the most widely used method for evaluating the myocardial ischemia, mainly due to its high accessibility. One of the key benefits of SPECT is the possibility of conducting the examination in the settings of physical loading, which is especially important for patients with contraindication to pharmacological stress-tests [8]. However, this method is characterized by relatively low spatial resolution, which limits its diagnostic precision comparing to such methods as PET and MRI of the heart [9]. Another important problem is the radiation load, making this method potentially unsafe for some categories of patients.

Cardiac MRI, on the contrary, has a significant benefit due to the fact that it is not associated with radiation exposure, providing high spatial resolution and detailed information on the impairment of the myocardium by means of using the LGE method as a part of combined examination protocols. Nevertheless, there are certain limitations related to the presence of metallic implants and to the necessity of using contrasting agents, which can be problematic for patients with chronic kidney diseases or implanted medical devices. New developments, such as ferumoxytol — based contrasting agents for patients with chronic renal failure [10] and the methods of broadband visualization for patients with metallic implants [11], can aid in overcoming these limitations.

SPECT represents a modern approach to the visualization of myocardial perfusion, allowing for performing a complete quantitative evaluation of myocardial blood flow (MBF) by means of dynamic scanning [12]. Just like the stress perfusion MRI of the heart, SPECT combines the possibilities of evaluating the perfusion with the evaluation of the morphology in the coronary arteries, similar to the one provided by the coronary angiography [13]. However, despite these benefits, SPECT has a number of limitations related to the necessity of using iodine-containing contrasting agents and to the exposure of ionizing radiation, which constitutes a specific problem for patients with severe chronic kidney diseases or for the young men.

Thus, each of the mentioned visualization methods has its benefits and limitations, which has to be taken into account when choosing the optimal approach for a specific patient.

PROGNOSTIC SIGNIFICANCE OF MAGNETIC RESONANCE IMAGING OF THE HEART IN TERMS OF DETECTING THE IMPAIRMENT OF CORONARY ARTERIES

The quantitative methods of cardiac perfusion MRI have significantly progressed over the recent years and they are still being actively researched. The diagnostic precision of cardiac stress perfusion MRI was evaluated by A.D. Villa et al. [14] with the involved physicians having various levels of training and experience. The results have demonstrated that the third level certified specialists from the European Society of Cardiology (ESC) / the European Association of Cardiovascular Imaging (EACVI) were able to detect clinically significant IHD in 83.6% of the cases, while the second level examiners have achieved a precision of 65.7%, with the first level showing only 55.7% (p <0.001). In this research, the automatic quantitative analysis has demonstrated the results comparable to

those obtained by the third qualification level physicians (86.3% of the cases; p=0.56).

In another auxiliary research (CE-MARC), it was shown that the stress-MBF and the myocardial perfusion reserve (MPR), when measured using the quantitative stress perfusion MRI of the heart, were reaching the AUC of 0.89 (95% CI: 0.83–0.96) and 0.87, respectively, for detecting the clinically significant IHD (stenosis exceeding 70%). The AUC values obtained upon the visual evaluation by an expert, were 0.88 (95% CI: 0.81–0.95). The differences in diagnostic precision between quantitative and visual evaluation were not statistically significant (p=0.72). Besides, the addition of MBF values at rest for calculating the myocardial perfusion reserve (MPR) did not result in a significant increase in AUC (p=0.79) [15].

The recent research by R. Crawley et al. [16] has evaluated the diagnostic precision of automated high-resolution perfusion mapping in detecting the clinically significant IHD. The investigators have found that, with the MBF of ≤1.94 ml/g per minute and the MPR of ≤1.97, one can effectively identify the clinically significant IHD (FFR ≤0.80) when examining the coronary arteries (AUC 0.85 and 0.96, respectively, p <0.001 for both parameters). Thus, the quantitative stress perfusion MRI of the heart can provide an objective and precise evaluation of myocardial ischemia.

The qualitative evaluations of stress perfusion MRI can underestimate the ischemic load in patients with multivascular IHD [17, 18]. T. Kotecha et al. [19] have analyzed the diagnostic efficiency of quantitative perfusion mapping comparing to visual evaluation of cardiac perfusion MRI in detecting multivascular lesions in the coronary arteries. The authors have found that the ischemic load, detected using the quantitative mapping, was significantly higher in cases of multivascular lesions comparing to the ischemic load evaluated visually (in cases of tri-vascular involvement — 100% versus 56%, in cases of the bivascular one — 63% versus 41%; p <0.001), however, significant differences were not shown for single-vessel impairment (25% versus 25%). Hence, the quantitative mapping of perfusion more precisely defines the degree of impairment in the coronary arteries comparing to the visual evaluation methods. This is an additional important benefit of quantitative approaches in evaluating the perfusion by means of cardiac MRI in the diagnostics of the impairment in epicardial coronary arteries.

Cardiac MRI plays an important role in assessing the severity of IHD, allowing for precise determination of the ischemic changes and the zones of myocardial infarction. This makes the method an indispensable tool for risk stratification in IHD patients. In a large multicenter retrospective research named SPINS [20], which has investigated the prognostic significance of cardiac stress-MRI in patients with stable angina, a total of 2349 patients were enlisted from 13 medical institutions in USA. The mean follow-up time was 5.4 years. The patients, which had no signs of ischemia or LGE, have shown low rates of fatal outcomes (all-cause) and low rates of nonfatal myocardial infarction (<1%) with the need for coronary re-vascularization (from 1% to 3%). In contrast, patients with signs of both ischemia and LGE had a more than four-fold increase in the all-cause mortality rates or in the rates of nonfatal myocardial infarction, along with a ten-fold increase in the need of coronary re-vascularization.

Recently, an evaluation of the efficiency of cardiac stress-MRI was carried out for the purpose of risk stratification in more specific population groups. T. Pezel et al. [21] have assessed the long-term prognostic factors of cardiac stress perfusion MRI among 2,295 patients with cardio-vascular risk factors, but without the confirmed IHD. During a mean follow-up period of 8.3 years, major adverse cardiovascular events (MACE) were reported in 203 participants. Ischemia and previously undetected myocardial infarction, revealed by using the MRI of the heart, became a potent predictor of developing MACE and fatal outcomes caused by cardiac failure. T. Pezel et al. [22] have also investigated the long-term prognosis of coronary re-vascularization, conducted based on the cardiac MRI findings, i.e. any re-vascularization performed within 90 days after the MRI. The research included 31,762 patients with suspected IHD, the mean follow-up time for which was 6.0 years. The trial has shown that stress- induced ischemia and LGE were the independent predictors of all-cause mortality. Besides, re-vascularization based on the cardiac MRI findings, was associated with lower mortality rates among the patients with ischemia in ≥6 segments (severe degree), but it did not show any benefits in patients with the ischemia of <6 segments (mild or moderate degree) [22].

M. Kinnel et al. [23] have investigated the prognostic value of cardiac stress perfusion MRI in patients with known diseases of the coronary arteries with a mean follow-up time of 4.2 years. The induced ischemia was acknowledged as a significant predictor of MACE. The presence of ischemia was associated with the development of MACE with an adds ratio of 3.52 and with the fatal outcomes for cardio-vascular reasons

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with an odds ratio of 2.55. LGE was also shown to be an independent predictor for unfavorable outcomes.

Adenosine is often used as a vasodilating agent during the research works on the evaluation of the prognostic value of cardiac MRI. Adenosinetriphosphate provides vasodilating and haemodynamic effects similar to the one in adenosine [24, 25]. Due to the acceptable cost and accessibility issues shown for other medicinal products, adenosinetriphosphate is widely used in the countries of the Asian-Pacific region [26–28] and in some European states [25], as well as in the Russian Federation [1, 24]. M.Y. Ng et al. [29] have arranged a research work, in which 208 patients with suspected IHD underwent stress perfusion MRI of the heart using adenosinetriphosphate. Within a mean follow-up period of 3.3 years, the patients with stress-induced ischemia had higher MACE rates. Independent predictors of developing MACE were the stress-induced ischemia (odd ratio — 3.63), the decrease in the left ventricle ejection fraction and the presence of myocardial infarction.

The absolute coronary flow reserve (CFR), defined using the phase-contrasted kinematic MRI (kin-MRI), is an excellent prognostic value for MACE and for cardiovascular-related death in patients with known or suspected IHD [30, 31]. Phase-contrasted kin-MRI allows for quantitative evaluation of the circulation in the coronary sinus, which is about 96% of the total circulation in the left ventricle [32]. By measuring the circulation in the coronary sinus, both at the stress conditions and at rest, one can calculate the total CFR, which is a ratio of the total circulation in stress to the total basal circulation in the coronary sinus.

S. Nakamura et al. [28] have investigated the auxiliary prognostic value of the stress perfusion MRI of the heart and of the CFR, measured using phase-contrasted kin-MRI, in 933 patients with suspected IHD. With the median duration of follow-up being 5.3 years, the analysis of Kaplan–Meier curves has shown a significant difference in the event-free survival between groups with the total CFR <2.5 and the absolute CFR >2.5 (p <0.001), as well as between patients with or without ischemia (p <0.001). The combination of stress perfusion MRI of the heart and the absolute CFR has significantly improved the risk stratification. The prognosis was comparable in the subgroups with ischemia and CFR >2.5 and without ischemia and CFR <2.5 (p=0.731). Thus, stress perfusion MRI of the heart and the phase-contrasted kin-MRI for the purpose of defining the absolute CFR have shown an additional prognostic value for cardio-vascular events.

The quantitative evaluation of stress perfusion by means of cardiac MRI allows for evaluating both the total stress MBF and the total flow reserve without the necessity of using the phase-contrasted MRI-visualization of the coronary sinus. K.D. Knott et al. [33] have assessed the prognostic value of the absolute stress MBF and of the MPR using the quantitative stress perfusion cardiac MRI. Their research, that included 1,049 patients with suspected IHD, has shown that both the stress MBF and the MPR were independently related to the risk of fatal outcome and MACE. In particular, the corrected odds ratios for fatal outcome and MACE were 1.93 and 2.14 for each 1 ml/g per minute of decreased stress MBF vs. 2.45 and 1.74 for each unit of MPR decrease, respectively.

The quantitative evaluation of MBF and MPR using stress perfusion cardiac MRI allows for precisely evaluating the risk in IHD patients. Updated recommendations from the American Heart Association (AHA, 2023) on managing chronic IHD encourage using the cardiac MRI for the quantitative evaluation of MBF for the purpose of improving the risk stratification [34]. The precise risk stratification with the aid of quantitative cardiac stress perfusion MRI can contribute to drawing up justified clinical decisions by means of identifying the patients, in which re-vascularization or optimal medication therapy can bring the maximal benefit.

CORONARY MICROVASCULAR DYSFUNCTION

The term «coronary microvascular dysfunction» describes a spectrum of structural and functional changes in the coronary microcirculation, leading to impaired MBF and ultimately to myocardial ischemia [35]. CMD develops due to functional and/or structural changes in the microcirculation [35]. The functional mechanisms may include impaired vasodilation and/or microvascular spasm. The impairments of vasodilation can result from endothelium-dependent and/or endothelium-independent mechanisms. The endothelium-dependent mechanisms are related to the decreased synthesis and/or accelerated degradation of nitrogen oxide (NO) and other relaxing factors, produced by the endothelium, which limits the ability of the vessels to dilate [36]. The endothelium-independent mechanisms include the impaired relaxation of the smooth muscles of the vessels and the increased reaction to vasoconstricting mediators [35]. The microvascular spasm is a part of a spectrum of vasomotor disorders and it is closely related to the dysfunction of the endothelium, in which the vasoconstricting tonus prevails [37]. The

structural changes manifest as the narrowing of the lumen in the intramural arterioles and capillaries, by perivascular fibrosis, by the decreased number of capillaries and by the accumulation of the glycation end-products [38, 39].

Diagnostics of coronary microvascular dysfunction by means of stress perfusion magnetic resonance imaging of the heart

The cardiac stress perfusion MRI allows for evaluating the condition of both the epicardial coronary arteries and the microcirculation. If the patients having no impairment in the epicardial coronary arteries show impaired perfusion caused by stress, this can indicate the presence of CMD. The cardiac MRI, just like the PET, allows for quantitative determination of the MBF at rest and upon pharmacologically induced stress, which helps in precisely diagnosing the CMD. In their research, H. Rahman et al. [40] evaluated 75 patients with chest pain, but without IHD. CMD was defined by the invasive parameter — the CFR <2.5. The results have demonstrated that MPR has a high diagnostic precision (AUC 0.88) and it is superior comparing to the visual evaluation (AUC 0.60) for the diagnostics of CMD. Visual evaluation had a precision of only 58% with a sensitivity of 41% and with the specificity of 83%. A single parameter of stress MBF was proven to be insufficient for the diagnostics of CMD. The research emphasizes the importance of using the combination of stressed and basic measurements of perfusion for precise detection of CMD.

The distinction between the epicardial IHD and CMD is complicated upon visual evaluation of the cardiac stress perfusion MRI, however, the quantitative stress perfusion MRI of the heart allows for differentiating these two conditions. T. Kotecha et al. [41] have evaluated the efficiency of quantitative cardiac stress perfusion MRI in the detection of clinically significant IHD (FFR <0.80), as well as in its differential diagnostics with CMD (FFR >0.80; index microvascular resistance [IMR] <2.5). The results have demonstrated that foci with epicardial IHD had significantly lower values of MBF and MPR comparing to CMD foci and to the normal areas. The MBF values (in cases of stress) being ≤1,94 ml/g per minute were effective in detecting the clinically significant IHD, while the total MBF value (in stress) of <1.82 ml/g per minute was showing the presence of tri-vascular lesions and CMD.

The MPR index, calculated based on the cardiac MRI data (myocardial perfusion reserve index, MPRI), is a reliable semiquantitative parameter, reflecting the microvessels' ability to dilate. This parameter is calculated as the ratio of circulation increase upon loading to the increase in the circulation at rest, normalized as compared to the increase in the left ventricle circulation [42]. W. Zhou et al. [43] have investigated the long-term prognosis in CMD patients having symptoms of ischemia, but without the impairment of the epicardial coronary arteries, by means of using the semi-quantitative analysis of cardiac stress-MRI. Within a follow-up period of 5.5 years, MACE was developing in 15.6% of the patients. The risk of developing MACE in patients having the MPRI of ≤1.47 was 3 times higher than in patients with the MPRI of >1.47. The multivariate analysis has confirmed that MPRI is an independent predictor of developing MACE. The complete quantitative evaluation of the perfusion by means of cardiac MRI can provide even more precise stratification of risk. Further studies are required for the evaluation of the prognostic value of the quantitative stress perfusion cardiac MRI in CMD patients.

Diabetes mellitus and coronary microvascular dysfunction

L. Jiang et al. [44] have studied CDM in a model of streptozotocin-induced diabetes mellitus in pigs (12 animals) using the quantitative myocardial perfusion by means of cardiac MRI. The animals underwent the procedures of longitudinal quantitative perfusion MRI of the heart in 2, 6, 10 and 16 months from the beginning of the experiment. The research has shown that MPR significantly decreases eventually, which indicates the progression of CMD along with the development of the disease. The MPR decrease also correlates with the increase in fasting blood glucose and glycol-hemoglobin (HbA1c), with a decrease in the longitudinal strain of the left ventricle and with an increase in the left ventricle remodeling index. Histological examination has shown an increase in the collagen volume fraction, which indicates the development of interstitial fibrosis in the myocardium, while the density of the microvessels remained unaltered at the initial stages of diabetes mellitus [44]. These data show that the decrease of MPR occurs earlier than the changes in the microvessel density, and it is related to the structural and functional changes in the coronary microvessels.

J.L. Yeo et al. [45] have examined 205 patients with type 2 diabetes and 40 healthy volunteers as the control group. In patients with type 2 diabetes, MPR was significantly lower comparing to the control group

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(1.78±0.55 and 2.00±0.63 ml/g per minute, respectively; p=0.032). MPR in diabetic patients was also decreased comparing to the control group (2.82±0.83 vs. 3.18±0.82; p=0.020). These results allow for suggesting that CMD may play the key role in the pathogenesis of cardiomyopathy associated with type 2 diabetes mellitus in humans.

Diastolic dysfunction and diabetes mellitus

Diastolic dysfunction is widely spread worldwide and it is associated with unfavorable outcomes in patients with diabetes [46]. A.S. Bojer et al. [47] have investigated the relation of the extracellular volume (ECV) of the myocardium and the MBF with the diastolic function of the heart in patients with type 2 diabetes mellitus. The research included 205 patients with type 2 diabetes and 25 individuals of the control group, in which ECV and MBF were measured at rest and in stress along with evaluating the MPR during the cardiac MRI. An increase of the ECV, indicating the interstitial myocardial fibrosis, was independently related to the worsening of diastolic functions, in particular, with a decrease of the early peak filling rate (ePFR) and with an increase of the maximal volume of the left atrium (LAmax). The increased MBF and MPR values upon loading were related to the improvement of the diastolic function, in particular, with the improvement of the early diastolic myocardial relaxation, as indicated by the lateral parameters and by the mean E/e value. These data show that diffuse myocardial fibrosis and CMD contribute to the development of diastolic dysfunction in the left ventricle in cases of type 2 diabetes, with the myocardial fibrosis affecting the myocardial elasticity and the CMD — the early relaxation of the myocardium. This emphasizes the importance of affecting both the fibrosis and the CMD in the treatment of cardio-vascular complications in patients with type 2 diabetes.

NON-ISCHEMIC CARDIOMYOPATHY

The primary non-ischemic cardiomyopathy, such as the hypertrophic cardiomyopathy and dilated cardiomyopathy, are related with the progression of diffuse myocardial fibrosis. The use of LGE and parametric mapping of the myocardium during the cardiac MRI is considered a reliable method for the differential diagnostics of various types of cardiomyopathy, for predicting outcomes and selecting the therapeutic strategies [48–51]. A recent prospective multicenter research has shown that ECV is an independent prognostic marker, both for the cardiac failure and for the arrhythmia — related events, in patients with dilation cardiomyopathy [52]. Besides myocardial fibrosis, CMD can be the additional key abnormality in cases of non-ischemic cardiomyopathies.

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is characterized by complex interactions between the cellular dysbalance, the interstitial fibrosis with thickened fibers surrounding the myocytes, the abnormalities in the mitral valve and in the sub-valvular structures of the heart, as well as the remodeling of coronary microvessels along with the hypertrophy of cardiomyocytes. These structural changes in cases of HCM serve as a basis for developing the CMD, which then leads to recurrent myocardial ischemia with the increased need of oxygen [38]. Though CMD manifests in hypertrophic or cicatricial areas of the myocardium, it can develop in the visually normal segments. The decrease of MBF without impairing the coronary arteries is a characteristic feature of HCM.

R.K. Hughes et al. [53] have arranged a case-control research, in which they evaluated the MBF and MPR among the genetically typed and HCM-positive individuals, but without the clinical hypertrophy in the left ventricle. The results have demonstrated that positive genotype individuals without hypertrophy in the left ventricle show a decrease of MPR (2.77±0.83) comparing to the control group (3.24±0.63; p=0.009), which indicates the presence of impaired MPR even in the absence of significant hypertrophy of the left ventricle and myocardial fibrosis. This confirms that CMD is present even among the HCM mutation carriers without evident clinical manifestations.

G. Joy et al. [54] have studied the microstructure of the myocardium and the functions of the microvessels by means of diffusion tensor imaging and stress perfusion, comparing these parameters in patients with the subclinical and the manifesting form of HCM, as well as in healthy volunteers. The authors have found significant differences in the microstructural characteristics between the groups compared, with the values of the fractional anisotropy being 0.32 (95% confidence interval [CI] 0.30–0.33) for subclinical forms of HCM and 0.28 (95% CI 0.25–0.30) for manifesting forms of HCM comparing to 0.34 (95% CI 0.33–0.36) in healthy individuals (p <0.001). Significant changes were also found the MBF parameters: 2.46±0.54 ml/g per minute for subclinical HCM, 1.77±0.52 ml/g per minute for manifesting HCM and

2.77±0.62 ml/g per minute in the control group (p <0.05). These significant changes within the structure of the myocardium and in the functions of the microvessels, both in cases of subclinical and manifesting HCM, may serve as a marker of early manifestations of HCM.

C.E. Raphael et al. [55] have investigated the factors predicting the development of cardiac failure in HCM, paying special attention to myocardial fibrosis and to the status of the microvessels. The authors came to the conclusion that the end-systolic volume index of the left ventricle and the degree of fibrosis in the myocardium (%LGE) are important predictors of future episodes of cardiac failure. The hazard ratio (HR) for the end-systolic volume of the left ventricle was 1.44 (95% CI: 1.16–1.78; p=0.001), while for the %LGE, calculated per each 10% of increase, — 1.44 (95% CI: 1.14–1.82; p=0.002). Within the multivariate analysis, the significant predictors of cardiac failure were the age (HR 1.37; 95% CI: 1.06–1.77; p=0.02) and the presence of mitral regurgitation (HR 2.6; p=0.02). With this, the presence or the degree of induced perfusion defect according to visual evaluation were not related with the outcomes (p=0.16 and p=0.27 respectively).

The quality of myocardial perfusion itself is not considered a predictor of developing cardiac failure. Quantitative perfusion MRI of the heart can become more informative for detecting CMD in cases of HCM, but additional research works are required for the evaluation of its prognostic role in HCM patients.

Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is characterized by an increase in the dimensions of the left ventricle and by the decrease in its contractile functions, with this, there are no signs of significant stenosis in the coronary arteries [56]. Despite the absence of classic IHD, several research works in the filed of nuclear medicine have revealed a decrease of MPR in DCM patients, which may indicate the presence of CMD as the main cause of the disease [57–59]. Though DCM is traditionally considered a non-ischemic form of cardiomyopathy, these data suggest that chronic or recurrent hypoperfusion of the myocardium may lead to myocardial fibrosis and remodeling in cases of DCM [59–61].

A. Gulati et al. [61] have investigated the interrelation between the stress perfusion parameters, MBF and MPR, along with the remodeling of the left ventricle, in DCM patients. The research work included a quantitative evaluation of the MBF parameters at rest and in stress among 65 DCM patients comparing to 35 healthy volunteers of the control group. The results have demonstrated that, in DCM patients, the total MBF at rest was significantly higher comparing to the healthy volunteers, but the total MBF measured during stress was decreased, resulting in an alteration of MPR. Besides, the MBF during stress and the MPR were significantly decreased in patients with the left ventricle ejection fraction ≤35% comparing to the patients with the LV ejection fraction being >35%. The segments of the myocardium with LGE at rest and during stress had lower MBF values comparing to the segments showing no LGE.

M. Takafuji et al. [62] have compared the absolute CFR values measured using the phase-contrasted MRI, in 26 DCM patients and 26 healthy individuals. The results have demonstrated that the total CFR was significantly lower in DCM patients (2.87±0.86) comparing to the control group (4.03±1.47; p=0.001). The multicomponent linear regression analysis has revealed that global longitudinal deformation of the left ventricle (global longitudinal strain, GLS) is the only independent predictor of the total CFR (β=-0.558, p=0.003). These data confirm the hypothesis that CMD in cases of DCM promotes to subendocardial hypoperfusion, affecting the longitudinal structure of the myocardium and decreasing the GLS.

Despite the fact that previous trials have provided the convincing evidence of the relation between DCM and CMD, larger prospective research works are necessary for investigating the correlations between CMD and myocardial fibrosis in DCM patients.

HEART FAILURE WITH PRESERVED EJECTION FRACTION

Heart failure with preserved ejection fraction (HFpEF) is a clinical syndrome, which is accompanied by symptoms and signs of heart failure, despite the normal or almost normal ejection fraction of the left ventricle [63]. The diastolic dysfunction is the key hemodynamical component of HFpEF. This process is characterized by the unfavorable remodeling of the left ventricle, by cardiometabolic dysfunction and by interstitial myocardial fibrosis. Besides, CMD can play an important role in the pathogenesis of HFpEF [64, 65]. A recent research work on PROM-HFpEF has shown that 75% of the HFpEF patients had CMD (CFR index <2.5 during Doppler echocardiography) [66, 67]. In a pre-planned DIAMOND-HFpEF trial that was assessing the CMD in HFpEF patients using cardiac MRI, it was found that CMD (MPR <2.0) was revealed

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in 70% of the HFpEF patients comparing to 48% in the control group. CMD was associated with the worst clinical outcomes, such as increased mortality and hospitalization rates in HFpEF patients. The research work also did not reveal any significant correlation between MPR and myocardial fibrosis, which allows for suggesting that CMD and fibrosis may independently affect the pathophysiology of HFpEF [68].

C. Siggins et al. [69] have investigated the interrelation between various biomarkers and cardiac MRI parameters in 19 HFpEF patients and in 15 healthy volunteers of the control group. The multiparametric analysis of cardiac MRI data and of the biomarkers has revealed 7 such factors which significantly correlate with ECV, and 6 — with MPR, however, only one biomarker was significantly correlating both with the ECV and with the MPR. The results have demonstrated that myocardial fibrosis and CMD may manifest differently in HFpEF patients. This observation has allowed for suggesting that the metabolic syndrome, the kidney diseases and the systemic inflammation may take part in the development of myocardial fibrosis and chronic heart failure [69].

PROBLEMS AND PERSPECTIVES OF QUANTITATIVE PERFUSION MAGNETIC RESONANCE IMAGING OF THE HEART

Quantitative perfusion MRI of the heart represents a modern method of evaluating the MBF and MPR with high spatial and temporal resolution capability. Unlike the qualitative perfusion MRI, based on the subjective visual evaluation of perfusion defects, quantitative MRI allows for measuring the absolute circulation parameters in milliliters per gram of myocardium per minute (ml/g per minute), which significantly increases the precision of diagnostics and reduces the effects of the human factor [70].

The main stages of quantitative perfusion MRI are the following:

- administration of contrasting agent (gadolinium-based);
- dynamic scanning with high frame rate for the evaluation of the contrasting agent entering the myocardium;
- analyzing the time of transit for the contrasting agent in the myocardium by means of kinetic modeling;
- calculating the absolute MBF values at rest and upon pharmacologically induced stress (usually with adenosine or regadenoson);
- evaluation of the MPR as the ratio of MBF in stress to the MBF at rest.

Clinical application of quantitative perfusion magnetic resonance imaging

Evaluation of the ischemic heart disease. The quantitative perfusion MRI, allowing for highly precise detection of hemodynamically significant stenoses of the epicardial coronary arteries, is comparable to the invasive coronary angiograph and FFR. In the CE-MARC research, the quantitative MRI has shown a sensitivity of 86% and a specificity of 83% in the diagnostics of IHD, which is comparable to SPECT and PET [3, 4, 15].

Detection of coronary microvascular dysfunction. CMD is characterized by impaired myocardial perfusion in the absence of significant stenoses in the coronary arteries. Quantitative MRI allows for precise diagnosing the CMD, measuring the MBF and MPR. The MPR values of <2.0 indicate the presence of microvascular impairment and may be used for predicting the unfavorable cardio-vascular events.

Risk stratification in patients with cardio-vascular diseases. Quantitative perfusion MRI has a high prognostic value. In the SPINS trial including patients with normal MBF values and with the absence of LGE, the five-years survival rate was >99%, while in patients with a significant MBF decrease, the risk of serious cardio-vascular events was increasing 4-fold [20].

The quantitative perfusion MRI of the heart has shown a significant potential in the diagnostics, in developing therapeutic strategies and in predicting various cardio-vascular diseases, especially after the implementation of methods for creating the high-quality images and quantitative evaluation of myocardial perfusion [70]. Recent research works emphasize a vast potential of this method in the settings of its wide use in medical practice, however, for the successful transition from scientific research to everyday clinical practice, it is necessary to solve several key tasks.

1. Absence of unified standards for processing the data and processing the results.

   One of the main problems is the absence of unified standards for data collection and further processing of information. For example, the saturation in T1 mode occurs in the left ventricle, when the concentration of the contrasting agent exceeds a certain value during the first injection of gadolinium, but in the myocardium this effect can be insignificant. In order to manage this, two basic approaches are used — the double-bolt method and the method of double sequence, which help avoiding the excessive saturation of the left ventricle and preventing the artifacts occurring during the first injection of the contrasting agent. However,

despite this, the problem remains topical, for there are differences in the platforms from various CMR manufacturers, in the voltages of the magnetic field, in the contrast infusion protocols, in the scanning settings and in the post-processing methods, including the algorithms of kinetic modeling.

2. The non-coordination in quantitative parameters of MBF.
   Various cardiac MRI platforms may show different MBF values, which complicates clinical interpretation and decision-making. It is necessary to draft a unified standard for the evaluation of circulation, which shall allow for eliminating these differences and for increasing the diagnostic precision.
3. Variability of MBF changes.
   There is a high variability in MBF measurements, which affects the precision of diagnostics and can depend on various factors, such as the operator skills, the experience of using specific software, the quality of the software itself and the operating conditions of the equipment. The solutions for this problem can include the operator training programs, the standardization of protocols and the development of automated data processing systems.
4. Incorrect circulation kinetics models.
   There are multiple various kinetic models for the evaluation of circulation, each one providing various results. The selection of the optimal model is a difficult task, requiring thorough analysis and testing. This problem is aggravated by the absence of consensus opinion on the best model for quantitative evaluation of circulation.
5. The necessity of a reliable validation system.
   For increasing the reliability and precision of the quantitative perfusion MRI of the heart, a validation system is required, which should include the verification of kinetic models, the verification of MBF measurement accuracy and the standardization of data processing protocols.
6. Improper data processing.
   Its is necessary to develop a reliable system for the storage and processing of data, which shall provide the accurate preservation and reproduction of the information acquired by means of cardiac MRI. Automated data processing systems can help minimizing the errors and increasing the precision of the analysis.
7. Developing the software tools based on artificial intelligence.
   Using the cutting-edge technologies of artificial intelligence, such as machine learning, can help decreasing the variability and increasing the accuracy of measurements, especially when processing large data sets.
8. Support from the experts.
   Arranging the training sessions for specialists and providing support from the experts play an important role in the successful implementation of cardiac MRI in clinical practice. Standardized courses and trends can help training the qualified personnel, which promotes to the effective operation when using the new technologies.
9. Solving the problems of training and certification.
   Arranging specialized courses and training programs can help solving the problem of the lack of qualified staff, capable of operating this new technology. Developing a system of accreditation exams is also important for confirming the qualification of a specialists.

The prespectives of quantitative perfustion magnetic resonance imaging

The promising trends of development in this field include the following:

- automation of the analysis using artificial intelligence (algorithms of machine learning shall allow for standardizing data processing and reducing the variability);
- integration with other MRI methods (combination of quantitative perfusion with T1/T2-mapping and phase-contrasted kin-MRI improves the combined evaluation of the myocardium);
- developing new contrasting agents (using ferumoxytol instead of gadolinium in patients with renal failure);
- implementation of testing standards (introducing the international reference values for MBF and MPR shall allow for increasing the reproducibility of the method);
- expanding the clinical indications (using this method in cases of cardiomyopathy, inflammatory heart diseases and post-Covid complications).

The quantitative perfusion MRI of the heart is a promising tool for diagnostics and for risk stratification in cases of cardio-vascular diseases. Its implementation is especially important for detecting the CMD, for assessing the severity of ischemia and for predicting the outcomes, however, for the successful integration of the method into clinical practice, there is a need for overcoming the elimination of technical limitations along with the analysis standardization and with the automatization of data processing.

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CONCLUSION

The quantitative evaluation of cardiac perfusion MRI provides a possibility of objective and precise diagnosing the IHD, also allowing for better recognition of CMD, which previously was difficult to evaluate when using qualitative visual evaluation. Quantitative perfusion MRI of the heart also provides a more precise prognostic stratification for various heart diseases, including the hypertrophic cardiomyopathy, the dilated cardiomyopathy and the heart failure with preserved ejection fraction, which is an additional capability in understanding the pathophysiology underlying the non-ischemic cardiomyopathies, such as the hypertrophic cardiomyopathy and dilated cardiomyopathy, as well as the cardiac failure with preserved ejection fraction. The quantitative MRI of myocardial perfusion, especially when combined with functional evaluation of the MRI data and with determining the characteristics of the tissues, can aid in more detailed investigation of the coronary macro- and microcirculation, which shall promote to better understanding of the nature of myocardial ischemia.

ADDITIONAL INFORMATION

Author contribution. *E.R. Pogrebnichenko* — concept and design of the study, data analysis, writing the article; *A.S. Mameshova*, *Z.A. Akhmedbekova*, *P.T. Tedurova* — collection of material, data processing, statistical analysis; *M.A. Kamilov* — manuscript critical revision; *E.A. Alibekov*, *K.M. Gazimagomedov*, *Ch.S. Saipullaev*, *N.Yu. Popov*, *A.L. Abdulaev* — interpretation of results, participation in discussion and editing of the manuscript; *Kh.S. Nasueva* — methodological support, coordination of group work; *M.M. Bakarova*, *Z.V. Erkenova* — technical editing of the article, search and analysis of data. 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 CONSOLIDATION OF FRACTURES OF THE DISTAL METAEPIPHYSIS OF THE RADIAL BONE IN PATIENTS WITH DIABETES MELLITUS: PROBLEMS AND SOLUTION APPROACHES

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ABSTRACT

The fractures of the distal segment of the radial bone in diabetes mellitus patients is a problem which requires special attention, for the processes of healing in such patients are slower and are often accompanied by a number of complications. This article reviews the basic mechanisms affecting the consolidation of fractures in diabetes patients, including the metabolic disorders, the hyperglycemia, the micro- and macroangiopathy, the polyneuropathy and other systemic abnormalities. An analysis was carried out of the specific features of the anatomy of the distal metaepiphysis of the radial bone, which make it vulnerable to fractures that are difficult to heal. The research provides a detailed analysis of the factors inhibiting the regeneration of the bone tissue, such as the accumulation of glycation end-products, the increased activity of the osteoclasts, the decreased immune protection and the high risk of infectious complications. Also, the methods were highlighted that are used for prevention and treatment, including the control of glucose levels, the correction of vitamin D deficit, the repositioning of the fractured bone fragments and the reliable immobilization. The research emphasizes the necessity of combined approach to the treatment of fractures in diabetes patients, with taking into consideration both the orthopedic and the endocrinological aspects.

Keywords: *diabetes mellitus; fracture of the radial bone; consolidation; hyperglycemia; osteoporosis; microangiopathy; immobilization.*

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INTRODUCTION

According to the data from 2022, published in "The Lancet" journal, the number of adults with diabetes mellitus (DM) worldwide has exceeded 800 mln people, increasing more than four times from 1990 [1]. One of the systemic complications of DM is the metabolic disorder of the bone tissue, which leads to the decrease in its strength, to developing osteoporosis and to the increased risk of fractures in patients both with type 1 and type 2 diabetes [2.3].

In recent years, special attention is paid to investigating the impairments of the regeneration processes in the bone tissue in diabetic patients. It was found that the healing of fractures in such patients is significantly complicated and is accompanied by higher rate of complications [4, 5]. This is due to the following set of factors: hyperglycemia, angiopathies, polyneuropathy, decreased immune protection and dysfunction of the osteoblasts.

The most frequent clinical models for investigating the bone tissue regeneration in cases of DM are the fractures in the zones with anatomically vulnerable structure, in particular — fractures of the distal metaepiphysis of the radial bone, or the so-called "typical fractures" [6]. These fractures are properly illustrating both the general and the specific mechanisms of impaired regeneration in patients with diabetes mellitus.

Thus, the analysis of the specific features of the consolidation of fractures of the radial bone in DM patients may serve as a basis for wider understanding the pathogenesis of impaired bone tissue healing in cases of this disorder [7–9].

Aim of the review — to summarize the modern outlooks on the pathogenesis of impaired bone tissue regeneration in cases of diabetes mellitus, with an accent to the clinically significant example — fractures of the distal metaepiphysis of the radial bone. The main pathophysiological mechanisms were considered, which

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КОНСОЛИДАЦИЯ ПЕРЕЛОМОВ ДИСТАЛЬНОГО МЕТАЭПИФИЗА ЛУЧЕВОЙ КОСТИ У ПАЦИЕНТОВ С САХАРНЫМ ДИАБЕТОМ: ПРОБЛЕМЫ И ПУТИ РЕШЕНИЯ

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АННОТАЦИЯ

Переломы дистального отдела лучевой кости у пациентов с сахарным диабетом — это проблема, которая требует особого внимания, так как процессы заживления у таких пациентов протекают медленнее и сопровождаются рядом осложнений. В данной статье рассматриваются основные механизмы, влияющие на консолидацию переломов у пациентов с диабетом, включая метаболические нарушения, гипергликемию, микро- и макроангиопатию, полинейропатию и другие системные изменения. Анализируются особенности анатомии дистального метаэпифиза лучевой кости, которые делают его уязвимым к переломам и сложным для заживления. В работе приводится детальный разбор факторов, тормозящих регенерацию костной ткани, таких как накопление конечных продуктов гликирования, повышенная активность остеокластов, снижение иммунной защиты и высокий риск инфекционных осложнений. Освещаются также методы профилактики и лечения, включая контроль уровня глюкозы, коррекцию дефицита витамина D, репозицию костных отломков и надёжную иммобилизацию. Подчёркивается необходимость комплексного подхода к лечению переломов у пациентов с диабетом, учитывающего как ортопедические, так и эндокринологические аспекты.

Ключевые слова: *сахарный диабет; перелом лучевой кости; консолидация; гипергликемия; остеопороз; микроангиопатия; иммобилизация.*

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are complicating the consolidation of fractures, also, the approaches were submitted for the prevention and treatment, taking into account both the general and the local aspects of bone tissue regeneration in DM patients.

Algorithm of searching the publications

This review was based on the publications, submitted during the period from 2018 until 2024 to the PubMed bibliographical system. The key words that were used for selecting the articles are the following: diabetes mellitus type 1 and 2, fractures of the distal metaepiphysis of the radial bone, consolidation, ankylosis, pseudoarthrosis, aseptic necrosis, hyperglycemia, RANK, RANKL.

The selection of articles was carried out taking into consideration the following criteria:

- Estimation of the factors affecting the process of bone regeneration, including the distal metaepiphysis of the radial bone in patients with diabetes mellitus and the ways of preventing the development of complications;
- Information on the specific features of the consolidation of typical fractures of the radius is the main method of conducting the clinical research or the object of the literature review.

As a result of searching with using the key words in the PubMed search engine, a total of 93 publications were found, of which 62 were full-text articles completely matching the selection criteria and were included into the scientific review.

ANATOMIC-BIOMECHANICAL SPECIFIC FEATURES OF THE DISTAL SEGMENT OF THE RADIAL BONE

The distal metaepiphysis of the radial bone has its specific features of the anatomic structure and biomechanics, which affect the rate of developing fractures in this area [10].

The distal segment of the radial bone has a thin cortical layer and relatively large spongy bone part, which decreases its resistance to compression and torsion forces. The radial bone in its distal part has a deviation angle from the axis of the forearm, which makes the bone more vulnerable to fractures upon falling onto the extended arm, for the impact force is distributed inhomogeneously [11].

A number of features of anatomy and blood supply of the distal segment of the radial bone increases the risk of developing complicated fractures in this area, as well as the risk of impaired consolidation, such as ankylosis of the radiocarpal joint, pseudoarthrosis and developing an aseptic necrosis of the radial bone [12].

The distal metaepiphysis of the radial bone has a complex anatomy with the presence of articular surfaces, processes and multiple foramens for the passage of vessels and nerves. Fractures in this area can damage multiple small vessels, altering the blood supply of the bone tissue [13]. The blood supply of the distal segment of the radial bone is relatively limited, some vessels are terminal and have no anastomoses, due to which the collateral vessels cannot always compensate the damage of the main vessels in cases of fracture. This makes the bone very susceptible to the impairment of blood supply and to developing aseptic necrosis [14]. After falling on the extended hand, the forearm muscles are at tension, which can destabilize the bone fragments, impeding their correct consolidation [15]. This increases the risk of bone fragments dislocation and of the complications, such as pseudoarthrosis.

SPECIFIC CLINICAL FEATURES OF THE CONSOLIDATION OF FRACTURES IN CASES OF DM

In patients with diabetes mellitus, the specific features of the consolidation of typical fractures in the radial bone are due to not only the anatomical characteristics of the bone, but also due to the systemic abnormalities, characteristic for this disease. Diabetes mellitus is accompanied by the development of osteoporosis and by the increased fragility of bones [16].

In cases of type 1 diabetes, the basis of the pathogenesis of the bone tissue remodeling includes the decreased activity and impaired differentiation of the osteoblasts. On the other hand, for type 2 diabetes, the characteristic features include hyperinsulinemia, promoting to an increase in the division and in the differentiation of osteoblasts and, as a result, to the increased values of bone mineral density (BMD). High BMD values in type 2 diabetic patients are combined with slower bone tissue metabolism, which results in a decrease in the bone strength.

Diabetes mellitus not only increases the risk of developing fractures, but also affects the processes of bone tissue regeneration, impairing it [17]. This is due to the fact that, in patients with this disease, the processes of bone tissue metabolism are also impaired along with the bone remodeling [18.19].

THE MECHANISMS OF DAMAGING THE BONE TISSUE REGENERATION IN DIABETES MELLITUS

One of the complications of diabetes mellitus, affecting the consolidation of fractures, is the micro- and macroangiopathy, which leads to a decrease of BMD, to the slower formation of the osteotylus, as well as to the increased risk of developing complications [20]. Microangiopathy develops due to long-term hyperglycemia and concomitant metabolic disorders. It plays a significant role in the impairment of the consolidation of fractures in diabetic patients [21]. The mechanisms of developing the microangiopathy include the non-enzymatic glycation of proteins in the basal membrane of the capillaries and other components of microvessels in the settings of increased glucose levels. This leads to the accumulation of glycation end-products, impairing the structure and function of the vascular wall and increasing the thickness of the basal membrane, resulting in an impaired blood supply of the bone tissue [22]. In the settings of hyperglycemia, there occurs an increase in the formation of free radicals, which damage the endothelial cells and contribute to the development of endothelial dysfunctions, the result of which is the impairment of the microcirculation [23].

The mechanisms of developing macroangiopathy also include the dyslipidemia. Diabetic patients often show increased blood levels of cholesterol and triglycerides, which promotes to developing atherosclerosis, and, consequently, results in an impaired blood supply of the bone tissue, as well as an activation of the renin-angiotensin-aldosterone system, regulating the blood pressure along with the water and salt balance. In cases of diabetes, its activity increases, owning also to the development of diabetic nephropathy, which promotes to developing hypertension and aggravates the damaging of the vessels [24].

As mentioned earlier, the distal segment of the radial bone has a number of specific features of its blood supply, capable of resulting in an impaired fracture healing and developing complications. Angiopathy

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that develops with a background of diabetes mellitus, even more aggravates the situation, increasing the timings of fracture healing due to slower formation of the osteotylus, also increasing the risks of developing aseptic necrosis or pseudoarthrosis in the distal segment of the radial bone in groups of patients with this disease [25, 26].

Another factor affecting the processes of the consolidation of fractures in the distal segment of the radial bone in patients with diabetes mellitus is the polyneuropathy.

Diabetic neuropathy actually can negatively affect the consolidation of fractures, including the fractures of the radial bone, though its role is no that evident as it is in cases of angiopathy [27]. Neuropathy can impair the normal innervation of the bone tissue, affecting the balance between the osteoblasts and osteoclasts. This can shift the balance towards resorption, weakening the bone and complicating its healing after the fracture [28]. It is important to note that diabetic polyneuropathy leads to a deceleration of the inflammatory response: the inflammation process is a necessary stage of healing the fracture, while the neuropathy can suppress this process, resulting in an insufficient inflammation, which negatively affects the consolidation [29].

In case of the radial bone, these mechanisms can be especially expressed, for this bone is subject to significant loads in everyday life [30].

Diabetes mellitus causes a number of metabolic disorders, significantly affecting the processes of the consolidation of fractures, including the fractures of the radial bone [31].

The metabolic disorders include hyperglycemia, deficit of insulin and deficit of vitamin D. Hyperglycemia provides the environment for the development of diabetic complications. In the settings of elevated glucose levels, glycation of the proteins occurs, due to which, the glycation end-products form and an increase is observed in the production of the active oxygen species and of the factors increasing the number and the activity of osteoclasts: RANK, RANKL, tumor necrosis factor (TNF) [32, 33].

THE EFFECTS OF CHRONIC INFLAMMATION AND CYTOKINES ON BONE REGENERATION IN DIABETES MELLITUS

Diabetes mellitus is characterized by chronic subclinical inflammation, which provides systemic and local effects on the processes of bone tissue regeneration. The key role in this process is played by the pro-inflammatory cytokines, such as TNF, IL-1β, IL-6 and IFN-γ, the levels of which are significantly increased after a long-term hyperglycemia [23].

TNF is one of the central inflammation mediators, affecting not only the differentiation of the osteoclasts via the RANK/RANKL pathway, but also directly suppressing the activity of the osteoblasts, suppressing the expression of bone matrix genes and inhibiting the synthesis of type I collagen [34]. Besides, TNF induces the expression of RANKL in the osteoblast-like cells, increasing the bone resorption.

IL-1β and IL-6 activate the osteoclastogenesis and slow down the reparative function of the osteoblasts. The increased concentration of IL-6 is associated with slowed consolidation of fractures and worse formation of the osteotylus [34].

Diabetes also promotes to the development of an unfavorable inflammatory micro-environment in the fracture zone. The accumulation of AGEs (advanced glycation end-products) activates the RAGE receptors on the cells of the immune system, the osteoblasts and the osteoclasts, inducing the production of cytokines and ROS (reactive oxygen species), which promotes to the persistence of low-intensity inflammation in the area of the trauma.

Additionally, the thing that should be kept in mind is the effects of hyperglycemia on the MSC (mesenchymal stem cells). In the settings of DM, a depletion develops in the population of MSC along with a decrease in their proliferative activity, impaired differentiation to the osteogenic lineage and increased tendency to developing an apoptosis [17, 28]. This leads to a decrease in the regenerative potential of the bone and to the impaired remodeling.

The activation of inflammasomes was also described (for example, NLRP3), induced by glucose and AGEs, which initiate cellular inflammation and a cascade of producing IL-1β and IL-18. These cytokines additionally increase the damage of the bone tissue and intervene with the regeneration.

Thus, the dysbalance between the pro-inflammatory and the regenerative signals in diabetes mellitus leads to the formation of the defective bone matrix, to the impairment of the vascularization and to the complicated consolidation of fractures.

The role of cytokines and growth factors in the impaired regeneration of the bone tissue in cases of diabetes mellitus

Besides the metabolic disorders, chronic inflammation and vascular abnormalities, the important pathogenetic mechanism of impaired consolidation

of the bone tissue in cases of diabetes mellitus includes the changes in the signaling pathways of the key cytokines and growth factors, regulating the osteogenesis, angiogenesis and restoration of the matrix. The abnormalities in the functioning of the TGF-β, IGF-1 and FGF, as well as in the interleukins (IL-1β, IL-6, IL-17) are currently considered as the central element of weakening the regeneration processes in DM patients.

TGF-β: the weakening of the bone tissue response and of the angiogenesis

Transforming Growth Factor Beta (TGF-β) is one of the main mediators of bone tissue regeneration. It regulates the differentiation of osteoblasts, the synthesis of type I collagen, the remodeling and vascularization in the fracture zone. However, in the settings of diabetes, a significant impairment can be observed in the transmission of the signal via the TGF-β/Smad2/3 cascade, which results in the inhibition of the osteogenic activity of the mesenchymal stem cells (MSC) and the delay in the formation of mature bone tissue [17, 35].

According to the data from the research work by M. Becerikli et al. [35], in cases of DM, a hyperglycemia-induced decrease develops in the phosphorylation of Smad2/3 along with the decrease in the expression of TGFBR1/2 receptors. This alters the formation of the osteotylus, decreases the expression of Runx2 and Col1a1 — the key genes of osteogenic differentiation. Moreover, it was found that the decrease in the activity of TGF-β in diabetes is accompanied by the suppression of angiogenesis by means of a decrease in VEGF and HIF-1α production, which additionally worsens the restoration of the bone tissue.

The confirmation for this is the data from the research by R.K. Singh et al. [36], which has shown that the restoration of the activity of the TGF-β/Smad signal pathway by using the nanocarriers transporting the TGF-β1 significantly improves the osteogenesis, stimulates the neo-angiogenesis and accelerates the healing of fractures in the animals with induced diabetes.

IGF-1 and the anabolic signaling deficit

The insulin-like growth factor 1 (IGF-1) plays the key role in the formation of the bone tissue: it increases the proliferation of osteoblasts, the collagen synthesis, the differentiation of MSC and the remodeling of the matrix. In DM patients, the IGF-1 level decreases due to the insulin insufficiency and due to the resistance to the IGF-1/PI3K/Akt signaling pathway, which leads to the decrease in the anabolic activity of the bone tissue [37].

The experimental research works have demonstrated that the administration of IGF-1 or the activation of its signaling cascade promotes to the restoration of the expression of osteogenic factors and accelerates the formation of the osteotylus in diabetic animals [38].

FGF-signals and angiogenesis

The family of Fibroblast Growth Factors (FGF), especially FGF-2, participates in the processes of vascularization, reparation and stimulation of the osteogenic differentiation of MSC. DM impairs the expression of FGFR receptors and the activation of MAPK/ERK pathways, which suppresses the proliferation of stem cells, decreases the vascularization of the damage zone and worsens the quality of the newly formed bone tissue [34].

Interleukins and inflammatory micro-environment

IL-1β, IL-6, IL-17 are the pro-inflammatory cytokines, the level of which is steadily increased in patients with DM. These substances:

- suppress the activity of osteoblasts,
- activate osteoclastogenesis,
- impair the balance between the resorption and the formation of the bone tissue.

IL-6 also hinders the mineralization of the bone matrix, while the IL-17 increases the inflammatory background and the destruction of the bone tissue by means of the activation of Th17-cells [34].

Thus, the decrease in the activity of TGF-β, IGF-1 and FGF, as well as the interleukin dysbalance, lead to the disruption of bone tissue healing in cases of DM, both by means of the suppression of osteogenesis and via the suppression of angiogenesis. These signaling pathways are the promising targets for targeted therapy aimed at the improvement of the consolidation of fractures in patients with diabetes mellitus.

Glycation of collagen

Glycation of proteins and accumulation of glycation end-products play a substantial role in the impaired consolidation of fractures in cases of diabetes mellitus.

In the settings of hyperglycemia, the structure and properties of collagen are altered, which makes it less strong, less elastic and less resistant to enzymatic cleavage. As a result of this, a less strong osteotylus forms, which is susceptible to damage and has a slower healing rate [39].

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Glycation hinders the formation of normal transverse cross-links between collagen molecules, which provide strength and stability of the bone matrix. This even more weakens the bone tissue and complicates the consolidation.

The accumulation of glycation end-products, such as pentosidine, affects the process of mineralization, making the bone tissue more fragile [40]. They also bind to their receptors on various cells, including macrophages and osteoclasts, activating them and stimulating the output of pro-inflammatory cytokines. The activity of pro-inflammatory cytokines in the fracture area impairs the normal healing and promotes to the bone tissue resorption [41].

Glycation end-products directly suppress the functions of osteoblasts, decreasing their ability to synthesize new bone matrix and to participate in mineralization [34].

Vitamin D deficiency

In cases of diabetes mellitus, impaired metabolism of vitamin D was noted. One of the reasons of altered structure of the bones in diabetes mellitus is the deficit of calcium, developing due to the deficit of vitamin D, as well as due to the dysbalance of its absorption and increased washout. During the animals tests, it was shown that the decrease of insulin levels results in an impaired absorption of calcium in the duodenum. Besides, in diabetes mellitus, the increased elimination of calcium with urine was reported, caused by hyperglycemia [42].

An important role in the altered consolidation of the bone is played by vitamin D. The disruption of its metabolism in diabetes mellitus develops due to the damaging of intestinal cells and due to the decrease in their ability to absorb vitamin D from food in the settings of hyperglycemia, as well as due to the development of diabetic nephropathy: in diabetes, the functions of the kidneys may become impaired, which results in a decrease in the production of vitamin D [43].

Impaired vitamin D metabolism in cases of diabetes leads to the suppression of the functions of osteoblasts, promotes to the decreased absorption of calcium and slows the processes of fracture consolidation [44].

The important role in the process of the osteotylus formation is played by insulin, which has a stimulating effect on the bone matrix and the formation of cartilage. Due to this, in the settings of insulin deficit, osteopenia develops. The deficit of this hormone results in decreasing collagen synthesis by the osteoblasts [45]. In rats with untreated diabetes mellitus, the collagen synthesis level in the zones of fractured bones was decreasing by 50–55%, which was resulting in the worsening of the mechanical properties of the newly formed tissue [46].

Insulin also takes part in the paracrine regulation of the process of consolidation of fractures. A decrease in the insulin levels leads to the dysbalance in the synthesis of the growth factors, such as the basal fibroblast growth factor, the insulin-like growth factor-1, the platelet-derived growth factor, the transforming growth factor beta and the vascular endothelial growth factor. These factors are necessary for the normal consolidation of fracture, and in the settings of their deficit, the proper restoration of bone does not take place [46].

Diabetes mellitus significantly increases the risk of developing osteomyelitis due to the combination of factors related to the decrease of the immune protection. Osteomyelitis extremely negatively affects the consolidation of fractures, facilitating the development of complications [47].

The processes affecting the inhibition of the factors of immune protection and promoting the development of infectious complications, include the impaired functions of the neutrophils and macrophages, which promotes to the decrease of the production serum antibodies in the settings of hyperglycemia [48].

As a result of these factors, the consolidation of fractures in patients with osteomyelitis developing with a background of diabetes mellitus, can be significantly hindered. This may lead to the development of such complications as fracture nonunion, pseudoarthrosis and ankylosis [49].

The effects of microangiopathy and diabetic neuropathy on the regeneration of the bone tissue

Among the systemic complications of diabetes mellitus, negatively affecting the consolidation of fractures, special significance is gained by the microangiopathy and the diabetic polyneuropathy. These pathological processes impair the vascularization and the innervation of the bone tissue, worsening the delivery of oxygen, nutrients and growth factors, required for normal bone tissue healing.

Microangiopathy in DM develops with a background of long-term hyperglycemia, leading to the non-enzymatic glycation of the proteins in the vascular wall and in the basal membrane of the capillaries. This promotes to the thickening of the basal membrane, to the decrease in the capillary permeability and to the development of endothelial dysfunctions [21].

In the settings of chronic hyperglycemia, an increase is observed in the production of ROS, which results in the damage of endothelial cells and impaired microcirculation. Simultaneously, the RAGE pathways also show signs of activation related to the accumulation of AGEs, which additionally worsens the function of the vessels [41].

These processes are especially crucial in the zones with anatomically restricted blood supply, such as the distal metaepiphysis of the radial bone. In DM, the microangiopathy significantly decreases the quality and the speed of developing the osteotylus, also increasing the risk of aseptic necrosis [15].

The additional contribution into the impaired blood supply of the bones belongs to the macroangiopathy, associated with the atherosclerosis of major vessels, the dyslipidemia and the activation of the renin-angiotensin-aldosterone system. These changes aggravate the ischemia in the tissues, especially in patients with concomitant diabetic nephropathy [43].

Diabetic polyneuropathy is another important factor, negatively affecting the regeneration of the bone. Impaired innervation of the bone tissue affects the balance between the osteoblasts and the osteoclasts, including the effects induced by means of neuropeptides (for example, CGRP, SP) and inflammation mediators. Upon decreasing the sensitivity and the tone of sympathetic and sensory nerves, the local regulation of circulation also becomes impaired along with the aggravated microcirculation and with a decreased regenerative response [28].

Besides, neuropathy is associated with a decrease of the inflammatory response, required at the early stages of bone tissue healing. The suppression of the activity of macrophages and lymphocytes in the damage zone leads to insufficient inflammation and to the weakened osteoinduction, disrupting the initiation of the reparative processes [29].

The functional activity of osteoblasts also suffers from the deficiency of neurotrophins, the decrease of which is described in cases of diabetic neuropathy, which impairs theirs proliferation and differentiation [30].

Thus, microangiopathy disrupts the blood supply of the bone tissue, decreases the delivery of oxygen and growth factors, while the diabetic neuropathy weakens the neurogenic regulation of osteogenesis and the immune response. In total, these mechanisms significantly decrease the efficiency of reparative processes in cases of fractures in DM patients, increasing the risk of delayed consolidation, pseudoarthroses and other complications.

Immune mechanisms of impairing the bone tissue regeneration in cases of diabetes mellitus

Besides vascular, metabolic and hormonal disorders, the key role in the impairment of the processes of the consolidation of the bone tissue in patients with diabetes mellitus is played by the immune cells participating in the initiation and regulation of inflammation, osteogenesis and remodeling. As of today, it was found that T-lymphocytes, macrophages, NK-cells and other cells of the innate immune response actively interact with the cells of the bone tissue and significantly affect its restoration.

$CD4^+$ T-helpers and $CD8^+$ cytotoxic T-lymphocytes take part in the regulation of inflammation and osteogenesis. In cases of diabetes mellitus, the observed findings include a shift of the subpopulations of $CD4^+$-cells towards the Th1/Th17-phenotype, associated with the increased production of IFN-γ, IL-17 and TNF, which stimulate the bone resorption and suppress the osteoblastogenesis [34].

Special significance has the activation of Th17-cells, increasing the expression of RANKL on the osteoblast-like cells and, as a result, stimulating the differentiation of osteoclasts. This disrupts the balance between bone tissue formation and resorption and leads to the prevailing of destructive processes.

$CD8^+$ T-cells also contribute to the pathological cascade, producing TNF and IFN-γ. Their accumulation in the damage zones in DM patients is associated with an increase in the osteoclastic activity and chronic inflammation [32].

Tissue macrophages play an ambivalent role in bone tissue regeneration. Classically, the activated M1-macrophages provide the initiation of inflammation, producing IL-1β, TNF and ROS, also (alternatively), the activated M2-macrophages take part in the resolution of inflammation and in the initiation of reparative processes (including angiogenesis and osteogenesis).

In diabetes, a dysbalance can be observed towards the M1-phenotype, which results in persisting inflammation, decreased levels of VEGF and TGF-β, inhibition of osteogenic differentiation and poor formation of the osteotylus [36].

Besides, the glycation of matrix proteins and the activation of RAGE receptors on macrophages increase the expression of pro-inflammatory mediators, which supports the chronization of inflammation and aggravates the quality of healing.

Natural killers (NK-cells), as a part of the innate immune response, also take part in the inflammatory

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microenvironment of bone tissue regeneration. In cases of DM, their activity changes with a shift of the cytokine profile towards the increased production of IFN-γ, which aggravates the inflammation and the resorption of the bone tissue [28].

Moreover, NK-cells can interact with osteoclasts and macrophages, increasing inflammation and modulating the immune response in the fracture zone.

Thus, in cases of diabetes mellitus, intensive disorders of the immune homeostasis occur: the predominance of Th1/Th17-profile, the activization of M1-macrophages, the decrease in the activity of M2-cells and the functional shifts in the functioning of $CD8^+$ and NK-cells. These changes support chronic inflammation, promote to bone tissue resorption and suppress the regenerative processes, creating the unfavorable environment for the consolidation of fractures.

Medication treatment effects

Some research works investigate the use of thiazolidinediones, as a factor affecting the processes of healing the fractures, including the ones of the distal metaepiphysis of the radial bone, in patients with diabetes mellitus. However, currently there is no unambiguous opinion from the researchers about the effects of substances of this group on the bone tissue [50].

Negative effects of taking the substances from the thiazolidinediones group:

1. Some research works have demonstrated that the use of these medications may lead to a decrease in the mineral density of the bone tissue and may increase the risk of fractures. Thiazolidinediones simultaneously inhibit the differentiation of osteoblasts and activate the differentiation of osteoclasts, which results in loss of bone mass by means of decreasing the formation of the bone tissue and increasing the bone tissue resorption.

2. The experimental researches in animals have demonstrated that the substances from the group of thiazolidinediones may slow down the formation of the osteotylus and may worsen its mineralization [51].

For the prevention of abnormalities of the consolidation of fractures, including the typical fractures of the radial bone, and the development of complications in patients with diabetes mellitus, it is necessary to apply the measures aimed at the mitigation of risk factors, as well as to create optimal conditions for the healing of the bone tissue (Table 1) [52].

PROPHYLAXIS AND TREATMENT APPROACHES

The main directions of the preventive measures are the following:

1. Control of glycemia. This is the key factor of preventing the abnormalities of the healing of fractures. It is necessary to aim for achieving and maintaining the individual target levels of glycosylated hemoglobin (HbA1c) [53]. By no means unimportant is teaching the patients on the self-control of blood glucose levels. Regular control of the blood glucose levels allows for timely adjusting the treatment and for preventing the hyperglycemia [54].

2. Prevention and treatment of angiopathy. These methods include the control of blood pressure and the

Table 1

The results of clinical research of the consolidation of fractures in cases of DM

Authors (year)	Research design	Population	DM type	Fracture location	Primary findings
Pscherer et al. (2019) [8]	Prospective observation	Patients with DM and without DM (*n*=120)	Type 1 and 2 diabetes	Distal segment of the radial bone	Healing delayed by 3 weeks, the risk of complications is higher 3.4-times
Malige et al. (2022) [16]	Retrospective analysis	Patients with type 2 DM (*n*=87)	Type 2 diabetes	Distal segment of the radial bone	Late surgery (>5 days) — growth of the number infections and nonunion
Tulipan et al. (2021) [31]	Literature review	Summary of research on type 2 DM	Type 2 diabetes	Forearm (tot.)	Decreased remodeling, despite the normal BMD
Wang et al. (2019) [45]	Meta-analysis	Analysis of more than 20 research works with the total *n* >10 000	Type 1 and 2 diabetes	Various zones	Increased risk of nonunion (OR 1.42), repeated fractures

Note. DM — diabetes mellitus; OR — odds ratio.

levels of cholesterol and triglycerides in blood, which helps preventing the development and the progression of angiopathy. Timely detection and treatment of vascular complications of diabetes promotes to the improvement of blood supply in the bone tissue [55].

3. Anatomic reposition of the fractured bone fragments. In order to provide an optimal healing of the fracture, it is necessary to maximally precisely match the bone fragments, restoring the normal anatomy of the bone, creating the favorable environment for the formation of the osteotylus.

Also important is the choice of the optimal repositioning method [56]. In patients with diabetes mellitus, if possible, closed reduction of the fractured bone fragments is more preferable. This type of repositioning minimizes the risk of developing infections, also providing faster healing of fractures. However, closed reduction is not always an effective method, having a number of contraindications, in which open reduction is the only method accessible for the correction of fractures: open or unstable fractures, fractures with the interposition of the soft tissues, fractures with significant displacement of the fractured bone fragments, fractures with a concurrent damaging of vessels and nerves, as well as long-standing fractures. When choosing the open reduction as a method for treating the fractures, it is necessary to thoroughly control the blood glucose level and to provide a prevention of infectious complications [57].

4. Reliable immobilization. In order to prevent the dislocation of fragments and to create stable conditions for the formation of osteotylus, reliable fixation of the fracture is necessary. This is especially important in diabetic patients, in which healing can be delayed. The immobilization method (plaster splint, orthesis, external fixation device, internal fixation) is to be chosen depending on the type of fracture, its location and the status of the soft tissues [58]. In cases of stable fractures, the preferable fixation method is an orthesis. The benefits of this fixation method include the possibility to control the status of the skin above the fracture area, to carry out the hygienic procedures, also applying less pressure to the soft tissues, providing the prevention of circulation disorders, of developing edemas and contractures.

However, in case of unstable fractures or fractures with significant displacement of the fractured bone fragments, the orthesis cannot assure the sufficient fixation for the correct consolidation of the fracture, in such cases it is more practicable to use a plaster splint or other splints.

The external and internal fixation devices shall be used in cases of inefficiency of the conservative methods, however, these methods are accompanied by the risk of infectious complications [59].

5. The correction of vitamin D deficit: All the diabetic patients receive the recommendations to regularly check their blood vitamin D levels. In case of detecting vitamin D deficit, it is necessary to prescribe the corresponding therapy for achieving and maintaining the optimal level [60].

6. Timely treatment of osteomyelitis. When suspecting the presence of osteomyelitis, it is necessary to arrange a combined examination and to initiate treatment as soon as possible. The treatment of osteomyelitis should include the usage of effective antibiotics following the sufficient dosages and duration [61].

4. The optimization of medication therapy: When prescribing the medicinal products for the treatment of diabetes, it is necessary to take into account their potential effects on bone tissue and the risk of fractures.

If possible, priority shall be given to the medicines which do not negatively affect the BMD and do not increase the risk of fractures [62].

The correction of micro-environment as a strategy of improving the consolidation of fractures in cases of DM

In patients with diabetes mellitus, the local microenvironment in the fracture zone is characterized by increased oxidative stress, chronic inflammation, hypoxia, deficit of angiogenic factors and impaired differentiation of the bone lineage cells. This is why in recent years, more and more attention is paid to the active modulation of the tissue microenvironment as a direction for the prevention and treatment of delayed consolidation.

1. Decrease of the oxidative stress

Chronic hyperglycemia induces the formation of reactive oxygen species (ROS), which impair the functions of the osteoblasts, damage the vascular endothelium and increase the secretion of pro-inflammatory cytokines [34].

The correction measures include the following:

- using antioxidants (alpha-lipoic acid, vitamin E, N-acetylcysteine),
- inhibitors of NADPH-oxidase,
- using nanocarriers with antioxidant activity (for example, Cerium nanoparticles [36]).

2. Repolarization of macrophages

The elimination of M1-domination and the stimulation of the transition to M2-phenotype of macrophages promotes to the restoration of angiogenesis and osteogenesis. This can be achieved by the following:

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- local administrations of TGF-β1, IL-4, IL-10,
- using the biomaterial stimulating the M2-response (for example, hydrogels, enriched with antioxidants and growth factors),
- therapy aimed at blocking the RAGE-signaling [35].

3. Improvement of angiogenesis

Angiopathy and hypoxia at the fracture zone in cases of DM impair the reparation. In order to stimulate the neo-vascularization, the following methods are used:

- local delivery of VEGF, FGF-2,
- HIF-1α stimulators,
- PRP (platelet-rich plasma) containing the angiogenic and regenerative factors.

4. Support of osteogenic differentiation

The administrations of IGF-1, BMP-2, TGF-β1 along with using mesenchymal stem cells (MSC) allow for restoring the osteogenic potential and normalizing the processes of remodeling [[37].

5. Biomaterials and carriers

Modern developments include the biocompatible matrices, capable of the following:

- suppression of inflammation,
- delivery of the growth factors and antioxidants,
- formation of supporting environment for cellular migration and differentiation [36].

The correction of the micro-environment is the most important component of the regenerative strategy in cases of impaired consolidation of bones in DM patients It should be combined with the systemic correction of hyperglycemia and of the osteometabolic disorders, but aimed directly at the tissue conditions required for the effective healing.

CONCLUSION

Patients with diabetes mellitus have an increased risk of fractures due to the development of osteoporosis, as well as the high risk of impaired consolidation due to metabolic disorders, circulation and innervation disorders, as well as the risk of developing infectious complications. For the successful treatment of fractures of the radial bone in diabetic patients, it is necessary not only to provide the anatomically correct repositioning and reliable immobilization, but also to correct the systemic disorders characteristic for diabetes, paying special attention to the optimization of glycemic control, to the correction of vitamin D deficit and to the prevention of infectious complications. In case of the absence of competent treatment of fractures of the distal segment of the radial bone in patients with diabetes mellitus, the development of such complications as aseptic necrosis, pseudoarthrosis and ankylosis of the radiocarpal joint is possible. The recommendations include arranging a multidisciplinary management of such patients with the participation of the physicians of the following specialties: internists, endocrinologists and surgeons.

ADDITIONAL INFORMATION

Author contribution. *P.A. Tebeneva* — concept and design of the study, editing of the article; *A.A. Makulova* — scientific revision of the manuscript, collection and analysis of literary sources, preparation and writing of the text of the article. 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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ORIGINAL STUDY ARTICLES

ORGANIZING THE LABORATORY TESTING PROCEDURES IN ISCHEMIC STROKE PATIENTS

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ABSTRACT

BACKGROUND: *Arranging the laboratory tests for the patients presenting with suspected ischemic stroke, represents an important task for medical organizations. Further treatment tactics may depend on the results of such tests, due to which, it is necessary to assure its high quality at all the stages of laboratory diagnostics.* ***AIM:*** *An optimization of the pre-analytical and analytical stages of laboratory testing for the admitted patients, shortening the testing turnaround time (TAT) along with drawing up the organizational decisions together with the clinicists and the quality control department.* ***METHODS:*** *The analysis and the rehearsal of the logistical aspects of all the processes related to the hospitalization of acute ischemic stroke patients were arranged by means of organizing the in-house drills and the time tracking of the operations at the admission ward and at the express-laboratory.* ***RESULTS:*** *After performing the in-house timed drills, a number of problems was revealed, both at the admission ward and at the express-laboratory, solving of which has allowed for optimizing the working processes, facilitating the pre-analytical stage and shortening the time of issuing the results. An in-house directive was issued on providing medical aid to the stroke patients, standard operations procedures were drafted and additional adjustments were introduced into the laboratory and medical information systems. The analysis of the regulatory basis has provided a possibility for specificating a number of immunohematological tests for stroke patients and shortening the costs of reagents and expendable materials.* ***CONCLUSION:*** *For the decreasing the total TAT down to 20 minutes for the purpose conforming the quality criteria, it is necessary to shorten the time of pre-analytical and analytical stages. Each medical organization is recommended to arrange the time tracking of all the processes of stroke patient admission for detecting the most time-intensive activities.*

Keywords: *ischemic stroke; laboratory tests; quality criteria; turnaround time, TAT.*

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BACKGROUND

The necessity of performing certain laboratory tests within the shortest possible period of time after hospitalization to the in-patient department for the patients with suspected ischemic stroke is regulated by a number of regulatory documents: the procedure of providing medical aid to the patients with cerebrovascular accidents (CVA) [1], the standard of specialized medical aid for cases of cerebral infarction [2], the clinical recommendations on ischemic stroke [3] and the Directive issued by the Ministry of Health on the criteria for evaluating the quality [4]. The main task with this background is the rapid obtaining the results for the purpose of ruling out the contraindications for undergoing thrombolytic therapy and conducting the differential diagnostics with other diseases having the similar clinical patterns. The lists of laboratory tests and the timings of fulfilling the tests in the abovementioned documents differ (table 1). One of four documents listed above regulates the timing of the tests as being 20 minutes from the admission of the ischemic stroke patient to the in-patient department. The Procedure of providing medical aid contains less strict requirements — 20 minutes from the moment of drawing the blood sample. Within this context, for the purpose of assuring the quality of providing medical aid, it is necessary to refer to the maximum list of tests (platelet count, blood glucose, activated partial thromboplastin time, international normalized ratio)

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ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ

ОРГАНИЗАЦИЯ ЛАБОРАТОРНЫХ ИССЛЕДОВАНИЙ ПРИ ОКАЗАНИИ ПОМОЩИ ПАЦИЕНТАМ С ИШЕМИЧЕСКИМ ИНСУЛЬТОМ

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АННОТАЦИЯ

Обоснование. *Организация лабораторных исследований пациентам, поступающим с подозрением на ишемический инсульт, является важной задачей для медицинской организации. От результатов этих исследований может зависеть дальнейшая лечебная тактика, в связи с чем необходимо обеспечение высокого качества на всех этапах лабораторной диагностики.* ***Цель исследования*** *— оптимизация преаналитического и аналитического этапа лабораторных исследований у поступающих пациентов, сокращение времени оборота теста (turnaround time, TAT) и выработка организационных решений совместно с врачами-клиницистами и отделом контроля качества.* ***Методы.*** *Изучение и отработка логистики всех процессов, касающихся госпитализации пациентов с острым ишемическим инсультом, проводились путём внутренних учений и хронометража в приёмном отделении и экспресс-лаборатории.* ***Результаты.*** *После внутренних учений и хронометража был выявлен ряд проблем как в приёмном отделении, так и в экспресс-лаборатории, решение которых позволило оптимизировать рабочие процессы, облегчить преаналитический этап и сократить время выдачи результатов. Был утверждён внутренний приказ по оказанию помощи пациентам с инсультом, разработаны стандартные операционные процедуры, внесены дополнительные настройки в лабораторную и медицинскую информационные системы. Анализ нормативной базы дал возможность конкретизировать перечень иммуногематологических исследований у пациентов с инсультом и сократить затраты на реагенты и расходные материалы.* ***Заключение.*** *Для уменьшения общего TAT до 20 минут в целях соответствия критериям качества необходимо сокращение времени на преаналитический и аналитический этапы. Каждой медицинской организации рекомендуется провести хронометраж всех процессов при поступлении пациента с инсультом для выявления наиболее времязатратных действий.*

Ключевые слова: *ишемический инсульт; лабораторные исследования; критерии качества; время оборота теста; TAT.*

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and the minimal time for issuing the result (20 minutes from the admission to the in-patient department).

Upon planning the opening of the Department for patients with acute cerebral circulation disorders, the laboratory of the Federal State Budgetary Institution “Federal Center of Brain Research and Neurotechnologies” under the Federal Medical-Biological Agency (FSBI FCBRN of the RFMBA) has received a task of organizing the procedures of conducting emergency laboratory tests for the presenting patients in accordance with the current regulatory documents — within 20 minutes from the hospitalization moment. This time interval includes the time required for assessing the patient, for issuing the referrals for testing, for drawing the blood sample, for the transportation of test tubes to the laboratory, the centrifugation, the testing procedures and the issuance of the result.

Research aim — optimizing the pre-analytical and analytical stages of laboratory tests with taking into consideration the time tracking data for all the procedures related to the laboratory tests among the presenting patients for the purpose of shortening the test turnaround time (TAT).

Table 1

The list of laboratory tests for stroke patients

Regulatory document	List of tests	Time to completion
Procedure of providing medical aid to CVA patients	• Platelet count • Glucose • INR • APTT	Within 20 min from the moment of drawing the blood sample
Standard of specialized medical aid in cases of cerebral infarction	• Glucose • Blood pH • INR • Blood group and rhesus-factor • Blood-transmitted infections • Coagulation tests • Clinical hematology panel • Blood biochemistry panel • Clinical urinalysis	Timings not provided*
Clinical recommendations on ischemic stroke	• Glucose • INR** • Thrombin time**	Timings not provided*
	• General (clinical) hematology panel • Blood biochemistry panel • Blood testing for evaluating the lipid metabolism disorders • Coagulation tests • Clinical urinalysis	Within 3 hours from the moment of admission
Directive issued by the Ministry of Health on the criteria for evaluating the quality	• Platelet count • Glucose • INR • APTT	20 min from the admission to the in-patient department

Note. * — tests are carried out at the diagnostics stage; ** — all the patients that are considered candidates for reperfusion therapy. CVA — cerebrovascular accident; INR — international normalized ratio; APTT — activated partial thromboplastin time.

METHODS

In order to understand and to process the logistics of all the processes related to the hospitalization of acute ischemic stroke patients, the in-house drills were arranged with the participation of the employees as volunteers.

The admission ward with intensive therapy units under the Federal State Budgetary Institution FCBRN of the Russian Federal Medical-Biological Agency is located at the 2nd floor and it is involved into registering the patients and issuing the referrals for testing, drawing and labeling the biomaterial, sending the test tubes to the express-laboratory by means of pneumatic transportation system. The express-laboratory is situated at the 10th floor with the pneumatic transportation system receiving terminal being located at a distance of 80m from the entrance to the laboratory. The laboratory testing request is compiled in the medical information system (MIS) and imported to the laboratory information system (LIS), where the express-laboratory staff member activates it, inputs the results and approves it. Later on, within half an hour, the result form is automatically uploaded into the MIS.

The time tracking was conducted at the admission ward and at the express-laboratory after mastering of all the processes of the pre-analytical stage. The clinical-laboratory diagnostics physician and the Quality Control Department staff member were measuring the time required for compiling the request in the MIS, for labeling the test tubes, for drawing the blood sample, for delivering it to the pneumatic transportation system terminal, for its further transportation by means of the pneumatic system, for the transfer from the pneumatic transportation system terminal to the express-laboratory, for importing the samples to the LIS, placing them into the centrifuge and for centrifugating, for performing the clinical hematology panel for assessing the platelet concentration by means of the Nihon Kohden MEK-6500K hematology analyzer, for transferring the test tubes from the centrifuge to the analyzers, for measuring the activated partial thromboplastin time (APTT) and the international normalized ratio (INR) at the Sysmex CA-660 coagulometer, for measuring the glucose level by means of the Spotchem biochemistry express-analyzer and for approving the results by the clinical laboratory diagnostics physician.

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RESULTS

Problems, revealed based on the results of the drills

As a result of conducting the in-house drills, certain problems were revealed which may increase the time of issuing the result. Thus, at the admission ward stage, referrals were compiled and blood samples were drawn not only for emergency testing for platelet count, glucose, INR and APTT, but also for the tests which should be carried out both in the emergency and in the scheduled order (biochemistry panel, lipid profile, electrolytes, blood group and rhesus-factor, blood-transmitted infections), which was increasing the time of registration and drawing blood samples, on the one hand, while on the other — it was resulting in an over-consumption of test tubes in cases when the diagnosis was not confirmed, and the patient was not hospitalized or he (she) was transferred to another in-patient department. Compiling separate referrals for clinical hematology panel, INR/APTT and glucose was extending the compilation process: each referral required printing its own barcode via the MIS, which was only possible after pressing the "Send request to laboratory" button.

Upon sending the capsule with the test tubes by means of pneumatic transportation system, additional notice had to be given to the express-laboratory, for the pneumatic transportation system terminal was located remotely at a certain distance from the express-laboratory and its staff members could not immediately notice the delivery of the biomaterial.

Upon admission of the biomaterial to the express-laboratory, there could be a situation in which the required analyzers were in process of calibrating or measuring the reference samples, which was also causing a delay in issuing the results. The biochemistry analyzer, which was used to measure the glucose levels, could be currently in process of analyzing the blood samples from the patients admitted on a scheduled basis, due to which, certain time was required for stopping the operation and testing the emergency samples.

The neurologist could receive the results of laboratory tests with a delay caused by its uploading from the LIS to MIS once in 30 minutes.

Solving the revealed problems

In order to solve the detected issues, the following was proposed and implemented:

An in-house directive "On the provision of emergency medical aid to the patients with acute disorders of the cerebral circulation at the FSBI "FCBRN" under the Russian Federal Medical-Biological Agency" was approved, in which, a clear sequence of actions was established for implementation by the medical staff along with the methods of communication/notification on compiling the results with setting the specific housephone numbers.

Upon the patient's presenting to the admission ward, only 3 test tubes had to be filled in for performing the required test profile: the one containing gel and the clot activator, the one with sodium citrate and the one with EDTA (ethylenediaminetetraacetic acid). Blood samples for all the other tests are now drawn after the patient's transfer to the intensive care unit, where the referrals for these tests are compiled in the MIS.

A "CVA profile" was created in the LIS, the results of which are printed on a single sheet and which includes the general (clinical) hematology panel, the glucose level, the APTT and the INR. The profile testing request should be compiled in the MIS with bearing a single number and, respectively, a single barcode.

Changes were also introduced into the algorithm of compiling the request for laboratory tests in the MIS: it became possible to initially print the barcode, to attach it to the test tubes, to draw the blood sample and then, after the completion of all the procedures with the patient at the level of admission department, to send the request from the MIS to the LIS. Thus, the LIS is now showing the real time of sending the samples to the laboratory.

The express-laboratory was equipped with a sound alarm notifying about the receipt (by means of the pneumatic transportation system) of the capsule containing the biomaterial tubes.

The staff of the admission department uses the telephone to notify the express-laboratory personnel about the planning admission (by means of the ambulance crew) in case of a stroke patient (the data used are taken from the "Stacionar" automated information system): this allows for preparing the analyzers and, if necessary, for delaying the scheduled rinsing, calibration and quality control procedures.

For the purpose of measuring the serum glucose concentration, a "dry chemistry" express-analyzer is now being used.

For the purpose of rapid obtaining the results, now the Neurology physician is not waiting for the results to be uploaded to the MIS, he immediately calls the express-laboratory. The reverse approach of notifying a neurologist by the laboratory personnel is not deemed rational, for the neurologist could go to the medical procedure room, to the magnetic resonance or computed tomography office, while searching for his (her) exact location could take a certain time.

The next stage included a time tracking of the procedures at the pre-analytical, analytical and post-analytical stages of laboratory testing for patients presenting with ischemic stroke.

The phase of registering a request in the MIS together with labeling the tubes took 8 minutes. Transportation of test tubes from floor 2 to floor 10 took 2.07 minutes, activation in the LIS — 0.15 minutes, placing into the centrifuge — 0.3 minutes, centrifugation — 10.28 minutes (taking into consideration the time of stopping the centrifuge). The clinical hematology panel was done in 1.12 minutes during the centrifugation of the other test tubes. The placement of the test tube into the coagulometer and the coagulation testing itself took 10.24 minutes. During the coagulation testing, glucose level was measured using the "dry chemistry" analyzer, which took 6.47 minutes (for comparison — the measurements performed using the "Sapfir 400" takes 14.2 minutes). Approval of the results — 0.15 minutes; total TAT — 32 minutes, laboratory TAT (from the moment of sample admission to the laboratory) — 24 minutes, with the 2/3 of the total TAT taken by the non-laboratory pre-analytical (compilation of the request, drawing the blood and transportation — 9.12 minutes) and by the intra-laboratory pre-analytical (centrifugation — 10.58 minutes) stages. The minimal time of performing the laboratory tests is limited to the operating speed of the coagulometer — 10.24 minutes. The measurements of the duration of performing only the APTT as more time-consuming test comparing to the INR, has shown the result of 9.09 minutes. The possible solutions here can include the use of test tubes with the clot activator and thrombin for performing the biochemistry tests (thrombin shortens blood clotting time, which allows for avoiding repeated centrifugation) and for lowering the centrifugation time down to 5 minutes. Shortening the time required for measuring the APTT and the INR can be aided by using the semi-automatic coagulometers with manual addition of reagents. Measuring the APTT in that case takes up to 5 minutes, while the INR requires up to 4 minutes. The hemostasis analyzers recently introduced into the market, capable of, in particular, measuring the INR in whole blood, as well as the "dry chemistry" principle-based analyzers, according to our own experience, do not comply to the criteria of recommending them for usage: the comparison of the results obtained using 22 plasma samples with the data from ACL Top 300 coagulometer, has revealed a mean overestimation of 23%. Such a distribution is unacceptable, especially when dealing with the patients that are candidates for reperfusion therapy.

Within the framework of the general activities directed at increasing the quality of laboratory tests, in accordance with the national standard [5] and practical recommendations from the Federal Service for Surveillance in Healthcare on the internal quality control at the medical laboratory [6], standard operations procedures were developed and approved on the rules of rejecting the biomaterial, on the archivation of referrals and of the biomaterial, on the critical values for the laboratory results, as well as on the rules of operating the pneumatic transportation systems. The LIS allows for selecting the type of defect for rejection, which facilitates the analytical operations and the determination of the corrective actions. The critical values shall be marked in the LIS using flags, upon seeing which, the clinical-laboratory diagnostics physician immediately calls the attending physician and registers the result in the Critical Result Report Log.

A certain part of patients presenting with suspected ischemic stroke, required differential diagnostics with alcohol or narcotic poisoning. For such cases, an agreement for performing the chemical-toxicological testing was signed with the external laboratory related to the Department of Healthcare of Moscow City. The biomaterial intended for defining the levels of ethanol and narcotic/psychoactive drugs, is drawn from the patient on admission and later transferred for further testing. Due to the fact that chemical-toxicological tests are regulated by the separate regulatory documents [7], a specific standard operation procedure was developed on drawing, labeling and transportation of the biomaterial for performing such tests, with the SOP being provided for familiarization to all the staff members of the express-laboratory and of the clinical departments, which has accelerated the process of drawing and preparing the biomaterial for transportation and which has decreased the probability of rejecting it by the chemical-toxicological laboratory.

Separate attention should be paid to the blood group testing in patients during the most acute period of ischemic stroke. Initially, for CVA patients, the planned prescriptions included a complete immunohematology profile — blood group (AB0 system) and rhesus-factor, phenotyping of Rhesus-antigens and antierythrocytic antibodies. The justification of this was the possible necessity of blood transfusion at the intensive care unit, but performing a full set of the tests mentioned above to all the patients with suspected CVA is unjustifiably cost-intensive, for the immunohematological tests at the FSBI "FCBRN" under the Russian Federal Medical-Biological Agency are carried out using the gel

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cards, the net cost of which is quite high. The analysis of the regulatory basis has shown that the requirements for performing the immunohematological tests in the given groups of patients are controversial. Thus, in the Procedure of providing medical aid to CVA patients, in the Directive on the establishing the criteria for evaluating the quality of medical aid, as well as in the Clinical recommendations on ischemic stroke, the testing for blood group and rhesus-factor are not included into the list of necessary laboratory tests. The Standard of medical aid for stroke patients (upon providing specialized medical aid) states only the detection of the main blood group antigens (A, B, 0) and the testing for rhesus-status. The detection of K (Kell) antigen and of the antierythrocytic antibodies, in accordance with the Decree issued by the Government of the RF on June 22, 2019 No. 797 [8], is indicated to the patients requiring blood transfusion, while the detection of C, c, E, e antigens in red blood cells — to female patients aged under 18 years and to the women of child-bearing age; to the recipients that have indications for repeated blood transfusions; to the recipients which were ever diagnosed as having alloimmune antibodies, as well as to the recipients with a history of incompatible blood transfusions. Thus, for decreasing the costs of reagents and expendable materials, as well as for decreasing the load of the laboratory personnel, the decision drawn was to detect only the blood group (AB0) and the rhesus-factor among the presenting CVA patients and, if blood transfusion is necessary, to perform additional testing of the phenotype and antibody profile.

Based on the conducted research, we can propose our algorithm of actions upon the admission of CVA patients for the purpose of decreasing the TAT (Fig. 1).

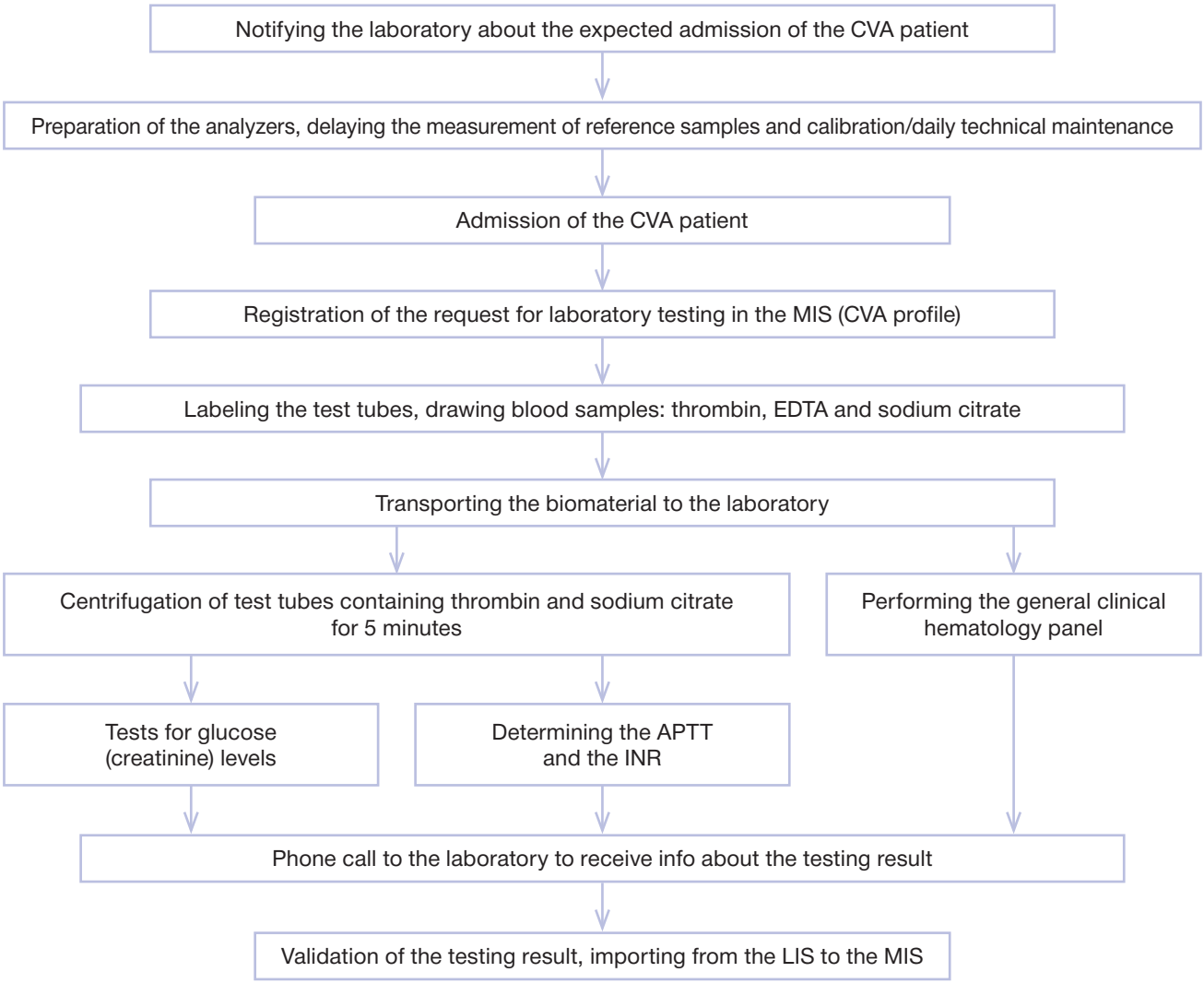

Fig. 1. Operation algorithm upon the admission of the patient with an acute disorder of the cerebral circulation. CVA — cerebrovascular accident; MIS/LIS — medical and laboratory information systems; APTT — activated partial thromboplastin time; INR — international normalized ratio; EDTA — ethylenediaminetetraacetic acid.

DISCUSSION

In order to decrease the total TAT for conforming the quality criteria, shortening the time of pre-analytical and analytical stages is required. Shortening the duration of pre-analytical stage can be achieved by training the medium-level medical personnel of admission department on maximally rapid algorithms of compiling the request in the MIS, as well as by decreasing the time of sample centrifugation down to 5 minutes with the setting of using the vacuum test tubes containing the clot activator and thrombin for faster clot formation. Shortening the analytical stage is possible by means of using the portable express-coagulometer, capable of testing the whole blood samples (though requiring the procedure of measuring the repeatability of the result with comparing them to the classic clot-method), or a semi-automated coagulometer, which should allow for shortening the time of testing. In case of a large number of presenting CVA patients, it is more practicable to locate the express-laboratory, equipped with a centrifuge, hematology analyzer, express-biochemistry analyzer and express-coagulometer, at the admission ward, which shall allow for decreasing the time of biomaterial transportation.

CONCLUSION

The high quality of laboratory tests for patients with ischemic stroke is assured by operating in accordance with the standard operation procedures, which strictly regulate the sequence of operations, as well as by the coordinated interactions between the laboratory and clinical department personnel, as well as by using the optimized MIS/LIS operations at the medical organizations.

ADDITIONAL INFORMATION

Author contribution. *O.V. Lyang* — conducting research, making recommendations, writing the text and final editing of the article; *Yu.V. Novozhenova* — conducting timekeeping in the laboratory, writing the text of the article; *I.A. Zhirova* — search and analytical work, writing the text of the article. 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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ACUTE MACULAR NEURORETINOPATHY: CLINICAL CASES

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ABSTRACT

BACKGROUND: *Acute macular neuroretinopathy is a rare disease of the central retinal zone.* ***CLINICAL CASES DESCRIPTION:*** *The first clinical case represents a male patient aged 47 years with the complaints of a decreased vision acuity and developing a spot in the vision fields of the left eye. He was treated at the ophthalmology clinic due to acute central serous chorioretinopathy with no effect. At the moment of examination, his vision acuity in the left eye was 1.0, with the anterior segment showing no abnormalities, the ophthalmoscopy has not revealed any changes. According to the data from the optical coherence tomography of the macular zone, the findings included the changes in the reflectivity at the level of the external plexiform and the external nuclear layers. The diagnosis set was «Acute macular neuroretinopathy in the left eye», the recommendations included dynamic follow-up. The second description is a case of female patient aged 39 years, undergoing dynamic checkups due to the operated squamous carcinoma in the lower orbital wall on the right side and in the maxilla, s/p radiation therapy. The patient had no vision-related complaints, but the ophthalmoscopy of the right eye (at the macular zone para- and perifoveally) has revealed three «cotton-wool-like» exudates. According to the data from the optical coherence tomography, in the right eye, there were foci of hyperreflectivity at the level of the neural layer of retinal fibers along with the corresponding «cotton-wool-like» exudates, as well as juxtafoveally at the level of the external nuclear layer, which is characteristic for acute macular neuroretinopathy.* ***CONCLUSION:*** *The first clinical case shows the importance of multimodal diagnostics in cases of complaints of a decreased vision acuity and spots in the vision fields, despite the high acuity of central vision. The second clinical case demonstrates that radiation therapy, conducted in the areas adjacent to the eyeball, is capable of resulting in an impaired circulation in the capillary plexuses of the retina, including the superficial vascular complex and in the deep capillary plexus with the development of ischemic retinal manifestations.*

Keywords: *acute macular neuroretinopathy; retina; optical coherence tomography.*

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BACKGROUND

One of the relatively recently discovered retinal diseases is the acute macular neuroretinopathy, the description of which was provided by P.J. Bos and A.F. Deutman in 1975 [1]. The modern name was proposed by S. Yeh et al. in 2011 [2]. Acute macular neuroretinopathy manifests by the development of single or multiple dark-reddish, wedge-shaped or drop-shaped foci in the macular zone of the retina with a background of complaints of veiling of vision, distortion and deformation of the visual perception of objects along with developing dark spots in the vision fields [3, 4]. The disease more often manifests in younger women, developing in a background of viral diseases of the airways, after episodes of stress, after an intake of oral contraceptive pills and in cases of previous trauma or systemic shock [5, 6]. Beginning from 2020, a growth has been observed in the number of cases of developing acute macular neuroretinopathy, which can be related to the Pandemic of the novel coronaviral infection (COVID-19) [7].

Several theories exist on the pathogenesis of acute macular neuroretinopathy, however, the main one supposes the formation of retinal ischemia at the level of the deep capillary plexus of the retina due to the primary vascular insufficiency or as a result of inflammation, causing the occlusion of small retinal vessels [5, 8].

For establishing the diagnosis of acute macular neuroretinopathy, besides standard ophthalmology examination, including visometry, biomicroscopy and ophthalmoscopy, it is necessary to arrange an obligatory optical coherence tomography (OCT) of the macular zone of retina. According to the data from various investigators, there are several OCT-patterns of retinal impairment in case of acute

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ОСТРАЯ МАКУЛЯРНАЯ НЕЙРОРЕТИНОПАТИЯ: КЛИНИЧЕСКИЕ СЛУЧАИ

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АННОТАЦИЯ

Обоснование. *Острая макулярная нейроретинопатия является редким заболеванием центральной зоны сетчатки.* ***Описание клинических случаев.*** *В первом клиническом случае представлен мужчина 47 лет с жалобами на снижение зрения и появление пятна в поле зрения левого глаза. Лечился в глазной клинике по поводу острой центральной серозной хориоретинопатии, но безрезультатно. На момент осмотра острота зрения левого глаза 1,0, передний отрезок без особенностей, офтальмоскопически без изменений. По данным оптической когерентной томографии макулярной зоны обнаружены изменения рефлективности на уровне наружного плексиформного и наружного ядерного слоёв. Установлен диагноз «Острая макулярная нейроретинопатия левого глаза», рекомендовано динамическое наблюдение. Во втором описании представлен случай женщины 39 лет, проходившей динамический осмотр по поводу оперированного плоскоклеточного рака нижней стенки орбиты справа и верхней челюсти, состояние после лучевой терапии. Жалоб на зрение не предъявляла, но при офтальмоскопии правого глаза в макулярной зоне пара- и перифовеально определялись три «ватных» экссудата. По данным оптической когерентной томографии, на правом глазу обнаружены участки гиперрефлективности на уровне слоя нервных волокон сетчатки, соответствующие «ватным» экссудатам, а также юкстафовеально на уровне наружного ядерного слоя, что характерно для острой макулярной нейроретинопатии.* ***Заключение.*** *Первый клинический случай свидетельствует о важности мультимодальной диагностики при наличии жалоб на снижение зрения и пятна в поле зрения, несмотря на высокую остроту центрального зрения. Второй клинический случай демонстрирует, что лучевая терапия, проводимая в близости от глазного яблока, способна приводить к нарушению кровотока в капиллярных сплетениях сетчатки, в том числе в поверхностном сосудистом комплексе и глубоком капиллярном сплетении с формированием ишемических ретинальных проявлений.*

Ключевые слова: *острая макулярная нейроретинопатия; сетчатка; оптическая когерентная томография.*

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macular neuroretinopathy: the abnormalities can be localized either at the level of photoreceptor segments coupling or within the “external nuclear layer — external plexiform layer” complex, or even at the level of the external limiting membrane, the internal contour of the pigmented retinal epithelium [9–11]. When examining the fields of vision using the computed static perimetry with the threshold detection software, scotomas can be found in the central or paracentral vision fields. Fluorescent angiography usually does not detect any changes, the indocyanine green angiography in a number of cases demonstrates areas of focal parafoveal hypofluorescence [12].

The differential diagnostics of acute macular neuroretinopathy shall include a wide range of retinal impairments: the acute posterior multifocal placoid pigment epitheliopathy, the acute retinal pigment epitheliitis, the central serous chorioretinopathy etc. [13, 14]. In the vast majority of cases, acute macular neuroretinopathy has a favorable prognosis in terms of restoring the vision, for it resolves spontaneously, not requiring special therapy [15].

In the research work, two different clinical cases of acute macular neuroretinopathy were demonstrated, each one being diagnosed by means of multimodal diagnostics methods.

DESCRIPTION OF THE CASES

Clinical observation 1

Patient info. The patient G., 47 years old male, in January 2023 has presented with the complaints of a decreased vision acuity and developing a spot in the vision fields of his left eye. According to oral information provided by the patient, the spot has appeared approximately 2.5 months ago (from November 2022), with the complaints not being related by the patient to anything. Due to this, in November-December 2022 he was receiving an in-patient treatment in one of the ophthalmology clinics of Khabarovsk city, where, besides standard ophthalmology examination, he underwent OCT of the macular zone of the retina in the left eye. In the same clinic, he was diagnosed with «Acute central serous chorioretinopathy of the left eye». However, according to the data from OCT of the macula in the left eye, signs of acute central serous retinopathy at the moment of hospitalization were not found (Fig. 1). The conducted treatment, namely the parabulbar injections of 12.5% Etamsylate solution (0.5 ml, No. 10), intravenous bolus infusions of 12.5% Etamsylate solution (No. 10), the intravenous push of 5.0% ascorbic acid solution (5.0 ml, No. 10), the intramuscular injections of vitamin B12 (1.0 ml, No. 10) and the orally administered 25 mg of Chloropyramine before going to bed (No. 10) did not provide any effect: the vision did not improve, the spot in the central field of vision did not resolve.

Ophthalmology status. At the moment of examination: the right eye shows no abnormalities,

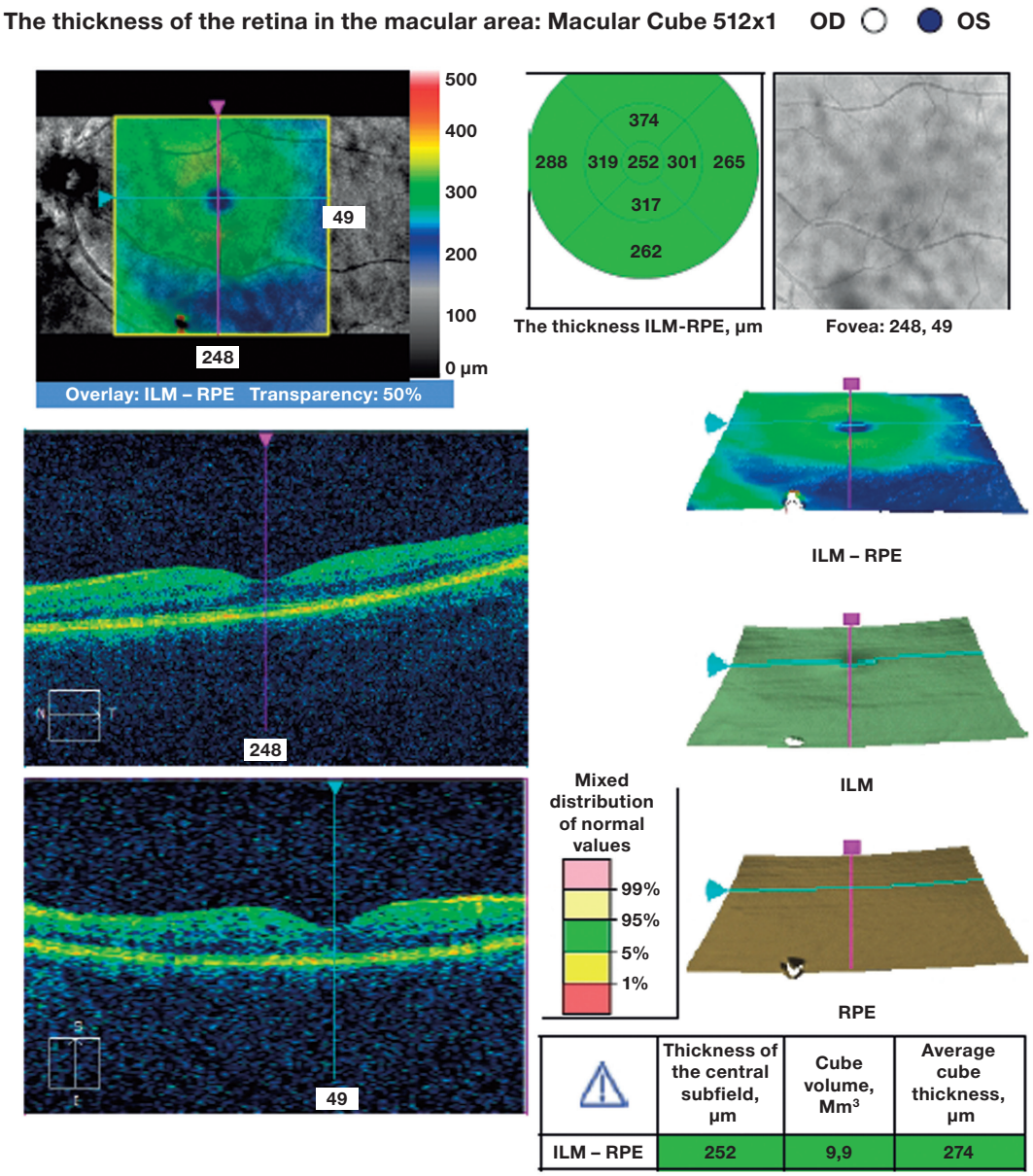

Fig. 1. A photo of the optical coherence tomography protocol of the macular zone of the retina in the left eye: no data confirming the presence of acute central serous chorioretinopathy.

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the vision acuity is 1.0; the vision acuity in the left eye is 1.0. Upon external visual examination of the left eye, the appendages of the eye are unremarkable. The palpebral fissure is of usual shape. Biomicroscopic findings: no signs of inflammation or irritation, the cornea is transparent, the anterior chamber is of medium depth, homogeneous, the aqueous humour is transparent, the iris is structurally intact, the pupil has a correct shape (round), active photoreaction is present, other findings include an induration of the eye lens nucleus, the vitreous body is transparent. Upon ophthalmoscopy: the optic nerve disc is pale-pink, contoured, the neuroretinal rim is unremarkable, the macular zone and the peripheral areas show no signs of abnormalities (Fig. 2).

Instrumental diagnostics. Taking into consideration the absence of clear and ophthalmoscopically detectable abnormalities in left eye, which could deteriorate the vision, OCT of the macular zone of the left eye was carried out (equipment: Solix Optovue, USA, Macula Cube protocol): the findings included pathological changes expressed as the para- and perifoveally located reflectivity abnormalities at the level of the external plexiform and external nuclear layers, predominantly on the nasal side (Fig. 3). According to the data from fundus-microperimetry of the left eye, a diffuse decrease of light-sensitivity was found — up to 22.5 dB (fundus-microperimetry equipment — MAIA, iCare, Finland, strategy 4-2). The right eye shows no abnormalities — 28.2 dB (Fig. 4, 5).

Diagnosis. Based on the disease history data (developing a spot in the field of vision 2.5 months ago), the data from the OCT of the macular zone of retina, the decreased microperimetry values in the left eye, the diagnosis set was the «Acute macular neuroretinopathy in the left eye».

Prognosis and recommendations. Taking into consideration the favorable prognosis of the disease, the patient has received recommendations on undergoing dynamic checkups with controlling the status of the macula by means of OCT control every 6 months. No further follow-up was arranged for the patient, for he did not visit us to undergo the control examinations.

Clinical example 2

Patient info. Female patient K., aged 39 years, has presented in May 2023 for the purpose of undergoing a scheduled medical checkup due to being previously operated for the reason of having a squamous carcinoma in the lower orbital wall on the right side

Fig. 2. A photo of the ocular fundus in the left eye (equipment: Solix Optovue, USA, Fundus Photo): no abnormalities.

and in the maxilla with a status post radiation therapy. She had no active complaints. In 2020 (within the premises of our clinic), she underwent a resection of the malignant tumor located in the lower-medial wall of the right orbit with the destruction of the lacrimal bone and partially — of the frontal process of maxilla (squamous carcinoma). In 2021, within the premises of the National Medical Research Center of Oncology named after N.N. Blokhin (Moscow), a medial resection of maxilla was carried out with the exenteration of the ethmoid labyrinth cells, with a defect plastics using the dermal-muscle flap. In the same year, at the Regional Clinical Oncology Center (Khabarovsk), the patient was receiving external beam radiotherapy applied to the area of the right orbit. According to the data from discharge epicrises, in 2021 in her right eye she had a vision acuity of 0.3, when corrected — sph-0.50 cyl-0.75 ax102 = 1.0.

Ophthalmology status. At the moment of examination, the vision acuity in the right eye is 0.3, sph-0.5 cyl-0.75 ax105 = 0.5. Upon the external visual examination, there are deformations in the skin of the internal third of the lower eyelid with the formation of fistula (connected to the maxillary sinus), with a retraction of the lower eyelid, predominantly in its internal third, the eyelid closure is complete. Upon biomicroscopy: the right eye has no signs of irritation or inflammation, the cornea is transparent, the anterior chamber is of medium depth, the aqueous humour is transparent, the iris is structurally unremarkable, the pupil has a correct shape, active photoreaction

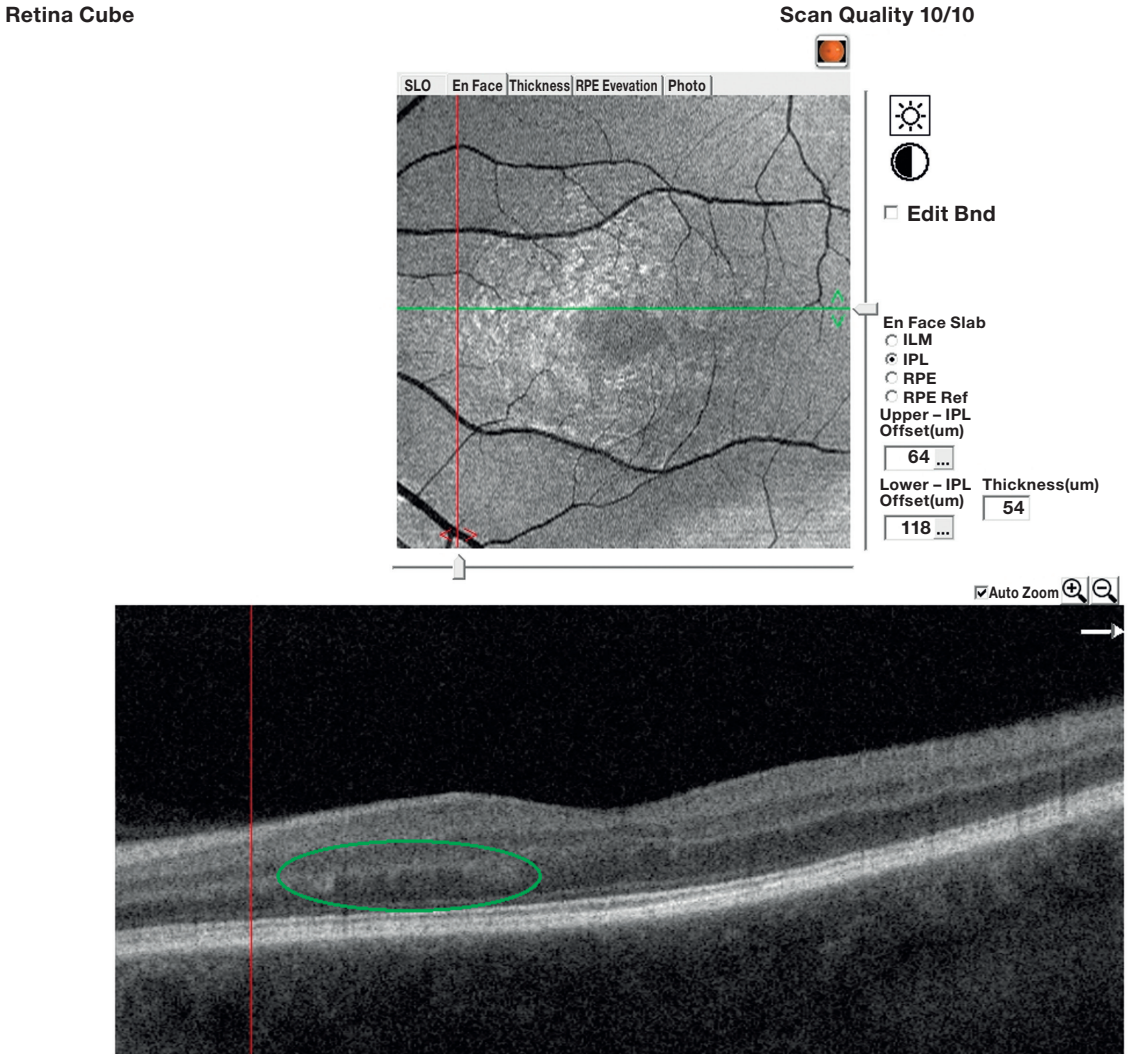

Fig. 3. Optical coherence tomography of the retina (equipment: Solix Optovue, USA, Macula Cube protocol): top — En Face image, bottom — transverse scan. Para- and perifoveally, predominantly from the nasal side, showing changes at the level of the external plexiform and the external nuclear layers (green oval).

is present, the eye lens is transparent, moderate destruction was found in the vitreous body. Upon ophthalmoscopy: the optic nerve disc is pale-pink, contoured, the neuroretinal rim is unremarkable, the retinal arteries and veins show no abnormalities, in the macular zone, the para- and perifoveal findings include three "cotton-wool-like" exudates (Fig. 6). The left eye shows no abnormalities: the vision acuity is 0.4, when corrected — cyl-1.5 ax11 = 1.0.

Instrumental diagnostics. Taking into consideration the decreased vision acuity in the right eye, the presence of signs of retinal ischemia in the superficial vascular plexus, expressed as the developing "cotton-wool-like" exudates, the OCT procedure of the macular zone of the right eye was carried out (equipment: Solix Optovue, USA, Macula Cube protocol): the detected findings included foci of hyperreflectivity with the location at the level of the retinal nerve fiber layer, located para- and perifoveally, the corresponding "cotton-wool-like" exudates, as well as juxtafoveally at the level of the external nuclear layer (Fig. 7, 8).

Diagnosis. Based on the obtained data, a conclusion was drawn that the reason of decreased vision in the right eye was the impaired blood perfusion at the level of the deep capillary retinal plexus, which indicates the presence of acute macular neuroretinopathy.

Prognosis and recommendations. The female patient has received the recommendations of undergoing periodic checkups by the ophthalmologist with dynamic OCT control of the macula in the right eye every 6 months. The female patient did not come to undergo the control examination.

DISCUSSION

Acute macular neuroretinopathy is one of the four macular ischemic syndromes (infarction of the nerve fiber

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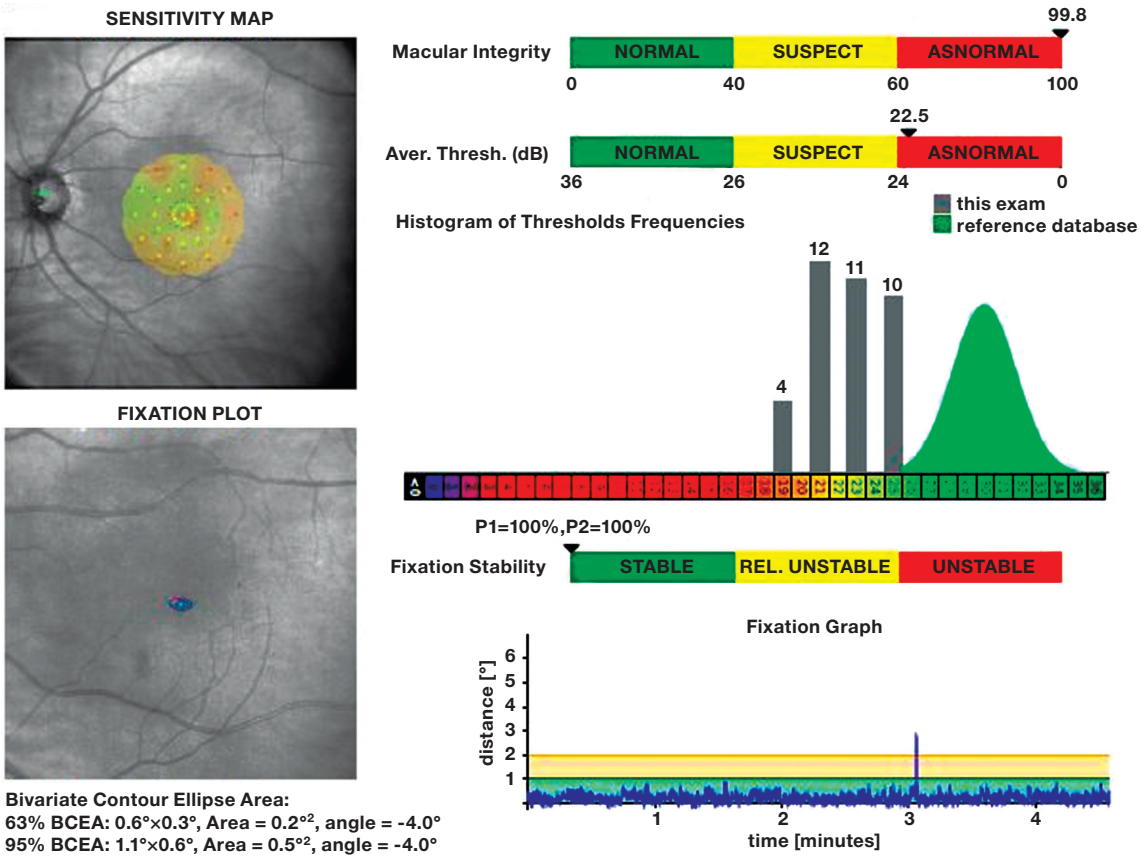

Fig. 4. Fundus-microperimetry of the left eye (equipment: MAIA fundus-microperimeter, iCare, Finland, threshold strategy 4-2): decreased mean threshold of light sensitivity.

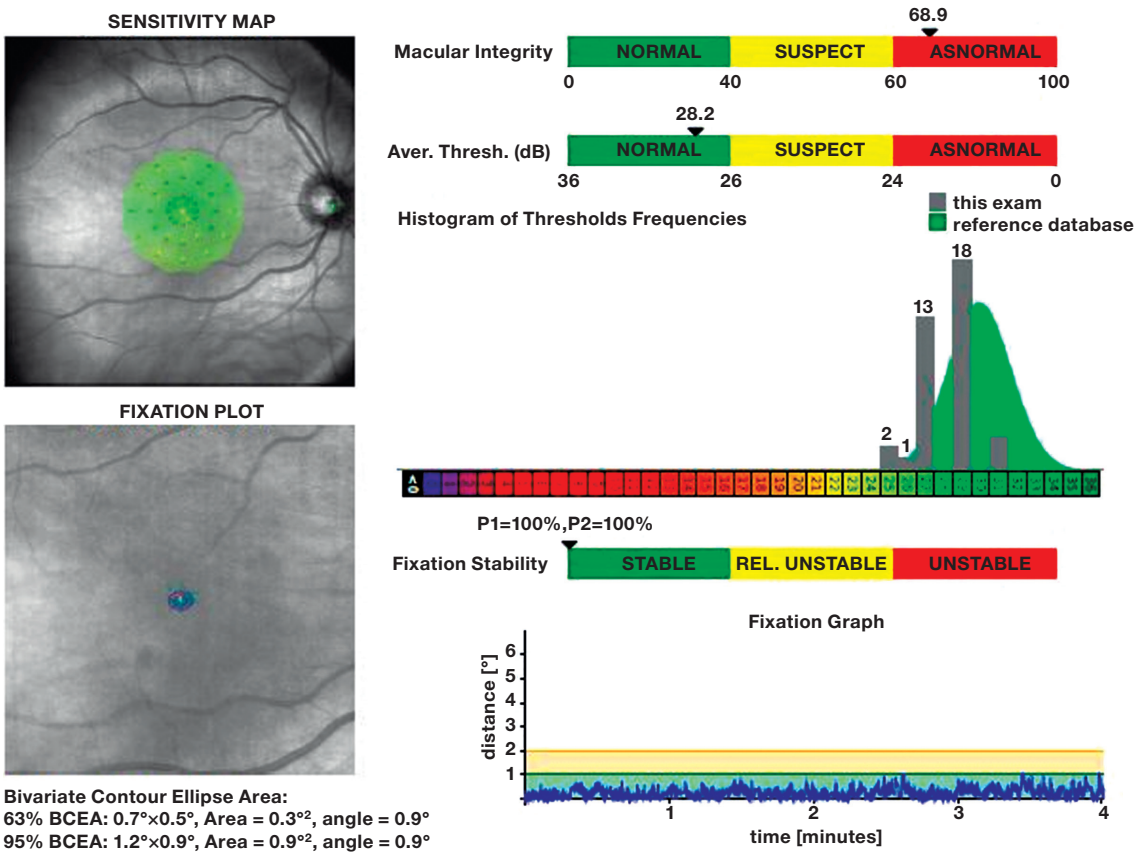

Fig. 5. Fundus-microperimetry of the right eye (equipment: MAIA fundus-microperimeter, iCare, Finland, threshold strategy 4-2): the mean threshold of light sensitivity is within the normal ranges.

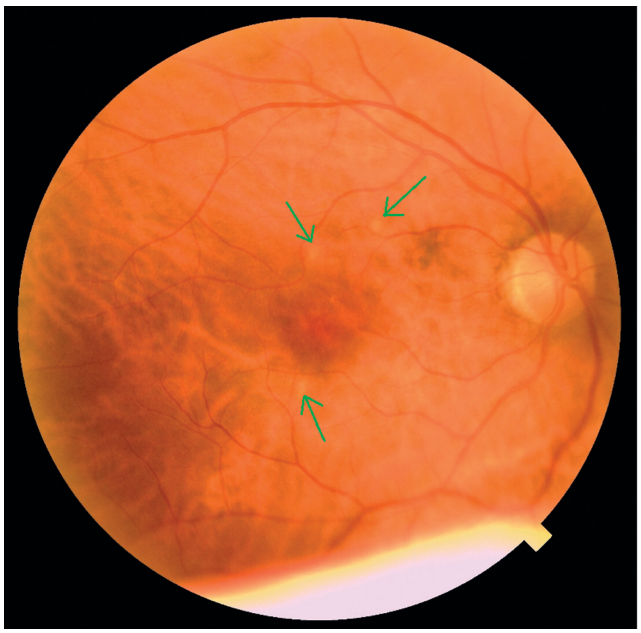

Fig. 6. A photo of the ocular fundus in the right eye (equipment: Solix Optovue, USA, Fundus Photo): para- and perifoveally visualized “cotton-wool-like” exudates (green arrows).

layer, the disorganization of the inner retinal layers, the paracentral acute middle maculopathy and, particularly, the acute macular neuroretinopathy). This disease is characterized by impaired circulation at the level of the deep capillary retinal plexus. Despite the presence of modern examination methods, such as OCT, including the angiography function, allowing for a detailed evaluation of the retinal structure at the micron level, the manifestations of acute macular neuroretinopathy often remain undetected. The potential reasons for this can be the relatively expressionless manifestation of retinal ischemia, especially in its outcome stage, as well as the low awareness of the ophthalmologists in terms of the possible presence of this disease, due to which we decided to share our own experience in the diagnostics of acute macular neuroretinopathy.

The first clinical case has shown that, in a patient with high acuity of central vision (1.0), in case of complaints of sudden and painless decreased vision acuity in the absence of clear ophthalmological abnormalities, the

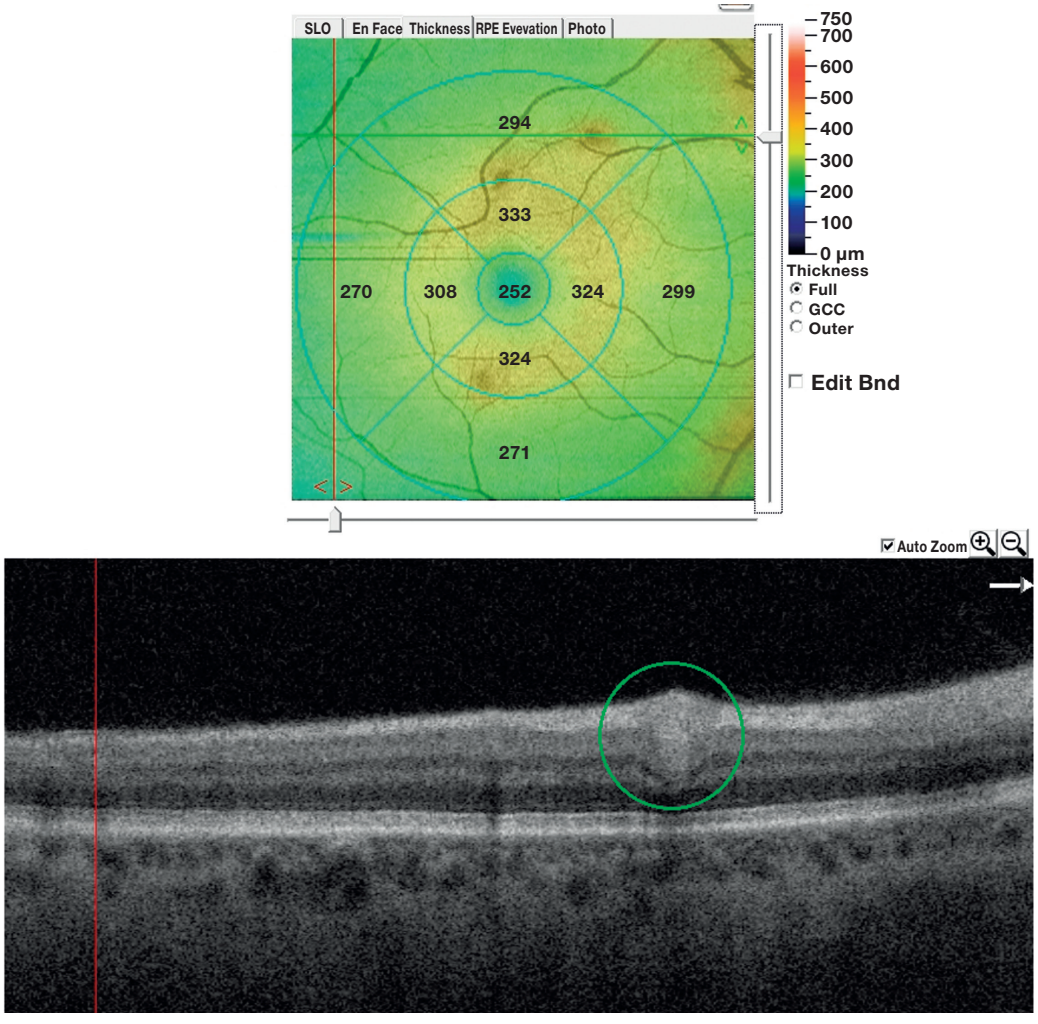

Fig. 7. Optical coherence tomography of the retina, the scan reveals the “cotton-wool-like” exudate (equipment Solix Optovue, USA, Macula Cube protocol): top — thickness map, bottom — transverse scan. The visualized findings include an area of hyperreflectivity at the level of nerve fiber layer of the retina (green oval).

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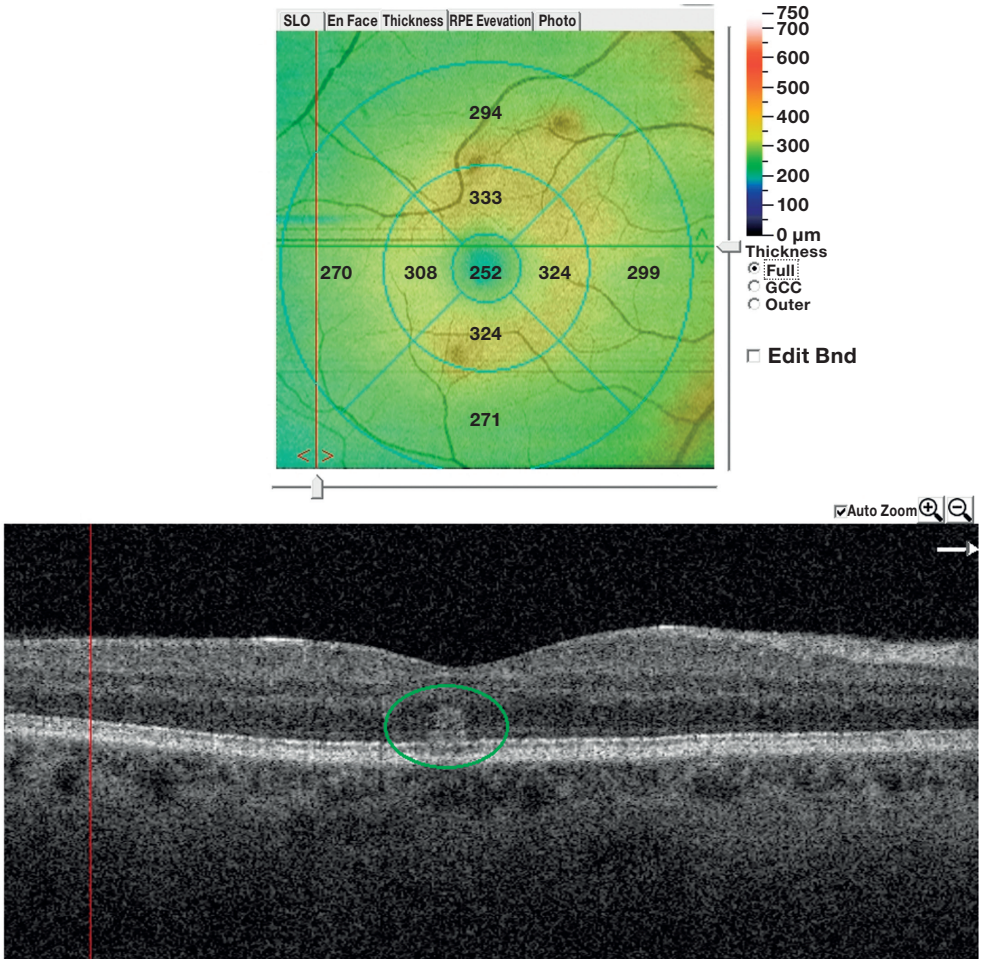

Fig. 8. Optical coherence tomography of the retina (equipment Solix Optovue, USA, Macula Cube protocol): juxtafoveally at the 12 o'clock position, the visualized findings include an area of hyperreflectivity at the level of the external nuclear layer of retina (green oval).

multimodal diagnostics methods can be efficient, in particular, the OCT of the macular zone of retina and the microperimetry, which helped to reveal the zones of retinal ischemia in the deep capillary plexus of the retina, which is characteristic for the clinical signs of acute macular neuroretinopathy. The second clinical case is an indication of the fact that radiation therapy, applied to the zone closely adjacent to the eyeball, is capable of resulting in an impairment of retinal circulation in the capillary plexuses of the retina, including the superficial vascular complex and the deep capillary plexus (a part of the deep vascular complex), with the development of ischemic retinal manifestations expressed as the acute macular neuroretinopathy. Due to this, in case the patient has complaints of decreased vision acuity, despite the absence of clear intraocular abnormalities, it is necessary to use the multimodal diagnostics methods for defining the haemodynamic parameters in the capillary plexuses of the retina. Due to the fact that in the literature sources we did not find similar cases of developing acute macular neuroretinopathy after radiation therapy, the issue of the cause-and-effect relation between them remains discussible.

CONCLUSION

We have demonstrated two different clinical cases of acute macular neuroretinopathy. Despite the rareness of this disease, the ophthalmologist must keep it in mind, for the acute macular neuroretinopathy in the majority of cases is a self-resolving disease with a favorable prognosis in terms of restoring the visual functions, while the incorrectly defined diagnosis may lead to the prescribing incorrect or excessive treatment.

ADDITIONAL INFORMATION

Author contribution. *R.S. Zhazybaev* — analysis of literature and data, manuscript writing; *E.L. Sorokin* — concept development, editing, approval of the final version of the article; *A.L. Zhirov*, *O.V. Danilov* — data collection and processing. 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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Competing interests. The authors declare that they have no competing interests.

Consent for publication. The authors received the written informed voluntary consent of the patient to publish personal data, including photographs (with face covering), in a scientific journal, including its electronic version (signed on 06/03/2024). The amount of published data is agreed with the patient.

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