ISSN 2500-1388 (Print)
ISSN 2618-754X (Online)

НАУКА и ИННОВАЦИИ в медицине

2025
Том 10
Volume
Выпуск 1
Issue

SCIENCE and INNOVATIONS in medicine

www.innoscience.ru

САМАРСКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ

НАУКА И ИННОВАЦИИ В МЕДИЦИНЕ
SCIENCE AND INNOVATIONS IN MEDICINE

Том 10 | Выпуск 1 | 2025 | Издается с 2016 г.

НАУЧНО-ПРАКТИЧЕСКИЙ РЕЦЕНЗИРУЕМЫЙ ЖУРНАЛ

Учредитель и издатель
ФГБОУ ВО СамГМУ Минздрава России

Зарегистрирован Федеральной службой по надзору в сфере связи, информационных технологий и массовых коммуникаций (Роскомнадзор) 06.06.2016. Регистрационный № ФС 77-65957

ISSN 2500-1388 (Print)
ISSN 2618-754X (Online)

Периодичность: 4 номера в год.

Журнал включен в Перечень ведущих научных журналов и изданий ВАК (К2)

Индексация
DOAJ
Российский Индекс Научного Цитирования (eLibrary.ru)
Cyberleninka
Google Scholar
Ulrich's Periodicals Directory
Dimensions
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Прием статей в журнал:
https://innoscience.ru/2500-1388/author/submit/1
Правила публикации авторских материалов:
https://innoscience.ru/2500-1388/about/submissions

Адрес издателя и редакции:
ул. Чапаевская, 89, г. Самара, Россия, 443099.
Тел.: + 7 (846) 374 10 04.
E-mail: edition@innoscience.ru

Зав. редакцией: Стефанская А.В. (e-mail: a.v.stefanskaya@samsmu.ru)
Переводчик: Калинин К.М.
Корректор: Чайникова И.Н.
Верстка: Овчинникова Т.И.

Подписано в печать: 03.03.2025
Выход в свет 15.03.2025
Отпечатано: ООО «Прайм».
Байкальский пер., 12, г. Самара, Россия, 443079.
Тел.: +7 (846) 922 62 90.
Формат 60 × 90⅛. Печать офсетная.
Заказ №0079.
Усл. печ. л. 9.
Тираж 250 экз.

SAMARA STATE MEDICAL UNIVERSITY

SCIENCE & INNOVATIONS IN MEDICINE

NAUKA I INNOVATSII V MEDITSINE

Volume 10 | Issue 1 | 2025 | Founded in 2016

QUARTERLY PEER-REVIEWED MEDICAL JOURNAL

Founder and Publisher
Samara State Medical University

Registered by the Federal Service for Supervision of Communications, Information Technology and Mass Media (Roskomnadzor) 06.06.2016. Registration number FS 77-65957

ISSN 2500-1388 (Print)
ISSN 2618-754X (Online)

Publication frequency: quarterly.

Indexation
DOAJ
Russian Science Citation Index (eLibrary.ru)
Cyberleninka
Google Scholar
Ulrich's Periodicals Directory
Dimensions
Crossref

Journal archive:
www.innoscience.ru
Archive and current issues are in open access.

Articles submission:
https://innoscience.ru/2500-1388/author/submit/1
Author Guidelines:
https://innoscience.ru/2500-1388/about/submissions

Publisher and editorial office address:
89 Chapaevskaya st., Samara, Russia, 443099.
Tel.: + 7 (846) 374 10 04.
E-mail: edition@innoscience.ru

Executive editor: Alla V. Stefanskaya (e-mail: a.v.stefanskaya@samsmu.ru)
Translator: Konstantin M. Kalinin
Proofreader: Inna N. Chainikova
Layout editor: Tat'yana I. Ovchinnikova

Signed for printing: 03.03.2025
Publication 15.03.2025
Printed by: LLC "Prime"
12 Baikalsky lane,
Samara, Russia, 443079.
Tel.: +7 (846) 922 62 90.
Order: No0079.

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DOI: https://doi.org/10.35693/SIM643217

Functional features of anatomical structures affecting the process of endotracheal intubation

Natalya V. Zharova[1], Vladimir N. Nikolenko[1, 2], Yurii O. Zharikov[1], Nikolai A. Zharov[3], Aleksei V. Zharov[4], Tatyana S. Zharikova[1, 2]

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Abstract

The study of the morphofunctional features of various structures of the head and the neck, as well as their congenital and acquired changes, enables a better understanding of conditions that influence performance of endotracheal intubation. Knowledge of the patient's individual anatomy enables one to forecast and to minimize incidence of intubation failure that might lead to adverse consequences, including dental trauma, damage to respiratory tract, hypoxic brain damage, and even death. As early as on the stage of collecting the patient's history, the anesthesiologist has to anticipate possible complications and identify the factors that might lead to complicated intubation and provision of anesthetic support.

This study analyzes the functional peculiarities of the anatomical structures influencing the process of endotracheal intubation, that are considered in the scales for the assessment of difficult airways and that cause complications for the visibility of the glottis. The article also dwells on various diseases that could cause difficult intubation of the trachea. The generalized results of these studies may be instrumental in the development of new methods and approaches towards the tracheal intubation procedure.

Keywords: endotracheal intubation, determination of patency of airways, head tilt, opening of the mouth, obstruction of airways.
Conflict of interest: nothing to disclose.

Citation
Zharova NV, Nikolenko VN, Zharikov YuO, Zharov NA, Zharov AV, Zharikova TS. **Functional features of anatomical structures affecting the process of endotracheal intubation.** *Science and Innovations in Medicine.* 2025;10(1):4-9.
DOI: https://doi.org/10.35693/SIM643217

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Received: 19.12.2024
Received: 01.02.2025
Published: 05.02.2025

Функциональные особенности анатомических структур, влияющих на процесс эндотрахеальной интубации

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Аннотация

Изучение морфофункциональных особенностей различных структур головы и шеи, а также их врожденных и приобретенных изменений позволяет более глубоко понять условия, которые оказывают влияние на проведение эндотрахеальной интубации. Знание индивидуальных анатомических особенностей пациента позволяет спрогнозировать и минимизировать количество случаев неудачной интубации, приводящей к серьезным последствиям, включая травму зубов, повреждение дыхательных путей, гипоксическое повреждение головного мозга и даже смерть пациента. Анестезиолог уже на этапе сбора анамнеза должен предусмотреть возможные осложнения и распознать факторы, которые могут привести к трудной интубации и осложнить оказание анестезиологического пособия.

В настоящем обзоре проведен анализ функциональных особенностей анатомических структур, влияющих на процесс эндотрахеальной интубации, учтенных в шкалах для оценки трудных дыхательных путей и являющихся причиной затруднения видимости голосовой щели. Также в статье рассматриваются различные нозологии, которые могут быть причиной трудной интубации трахеи. Обобщенные результаты этих исследований могут помочь в разработке новых методов и подходов к процедуре интубации трахеи.

Ключевые слова: эндотрахеальная интубация, оценка проходимости дыхательных путей, запрокидывание шеи, открывание рта, обструкция дыхательных путей.

Конфликт интересов: не заявлен.

Для цитирования:
Жарова Н.В., Николенко В.Н., Жариков Ю.О., Жаров Н.А., Жаров А.В., Жарикова Т.С. **Функциональные особенности анатомических структур, влияющих на процесс эндотрахеальной интубации.** *Наука и инновации в медицине.* 2025;10(1):4-9.
DOI: https://doi.org/10.35693/SIM643217

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Список сокращений
ШОТИ – шкала оценки трудностей интубации.

Получено: 19.12.2024
Одобрено: 01.02.2025
Опубликовано: 05.02.2025

INTRODUCTION

In the practical anesthesiology, the incidence of difficult airways is 2-5% from the total number of cases of tracheal intubation. Difficult airways might cause complications hazardous to the patient's life [1]. This situation occurs in the event the visibility of the glottis is obstructed. As early as on the stage of collecting the patient's history, the anesthesiologist has to anticipate possible complications and identify the factors that might lead to complicated intubation and provision of anesthetic support.

The study of the morphofunctional features of various structures of the head and the neck, as well as their congenital and acquired changes, enables a better understanding of conditions that influence performance of endotracheal intubation.

This study analyzes the functional peculiarities of the anatomical structures influencing the process of endotracheal intubation, that are considered in the scales for the assessment of difficult airways and that cause complications for the visibility of the glottis.

SCALES USED TO EVALUATE AIRWAY PATENCY

The following scales for the airway patency assessment are used in clinical practice: LEMON, El-Ganzouri, and Intubation Difficulty Score (IDS).

The LEMON score includes evaluation of the facial injuries, large incisors, mustache or beard, large tongue [1, 2]. In 2018, S. Ji confirmed the efficacy of the LEMON score having shown that it correlated with intubation difficulties in 114 adult patients with injuries who underwent urgent operation under general anesthesia. This means that the LEMON score may be instrumental in the prediction of difficulty of intubation of patients [3].

Mallampati described 4 classes of visualization of mouth cavity structures that can be used to predict difficult intubation. In Class I patients, the soft palate, the uvula, the palatoglossal and the palatopharyngeal are completely visible; in Class II, palatal arches and the soft palate are visible, but the uvula is obstructed by the tongue; in Class III, only the frontal section of the soft palate is visible; and in Class IV, the soft palate is not visible at all [4].

According to the El-Ganzouri index, the risk of difficult intubation increases if the oral opening expands by less than 4 cm between the lips, the thyromental distance is less than 6.5 cm, Mallampati Class II or III, amplitude of the neck mobility is below 90°, the jaw thrust is not possible, the body weight is over 90 kg, and there is a history of difficult intubation.

In contrast to the El-Ganzouri risk index, the LEMON scale primarily assesses the patient's appearance and the geniohyoid and thyrohyoid distances, and the presence of airway obstruction and protrusion of the lower jaw are taken into account, which is not considered in other scales.

The IDS distinguishes such criteria as sternomental distance and short neck [5]. Using the stereotopometric method, the location of the anatomical structures of the thyroid cartilage relative to three mutually perpendicular planes was determined, taking into account sexual dimorphism and the body type of the subjects. Using the data obtained, it is possible to predict the width of the glottis [6].

It is also worth considering the upper lip bite test developed by Z.H. Khan in 2003 to replace the Mallampati scale. To perform the test, the patient is asked to protrude the jaw and bit the upper lip with lower incisors. The test allows

evaluation of the movement range of the jaw and the work of the temporomandibular joint. The specificity of the upper lip bite test is considered to be considerably higher than the measurement of the tiromental, sternomental, and the interincisal distance separately [2, 7].

All three scales consider such factors as degree of mobility of the neck, mobility of the jaw: the degree of oral opening directly depends on these. In the process of tracheal intubation, the patient's head tilted back, and any problems of neck mobility might complicate the intubation. The sternomental distance, i.e. distance between the chin and the episternim, that is the indicator of the mobility of the head and the neck, is also to be taken into consideration: according to the IDS, it has to be at least 12.5 cm. If this value is below 12.5 cm, it is a case of difficult intubation [8].

CAUSES OF MOBILITY DISORDERS OF THE CERVICAL SPINE

We shall now look into the causes that impede normal back tilting of the head: the short neck, disruption of the biomechanics of the atlanto-occipital and atlanto-axial joints, hernias and injuries, and other diseases of the cervical section of the spine. The abnormally short neck is one of the causes of difficult intubation. The shorn neck may be seen in the Klippel-Feil deformity (congenital fusion of the cervical vertebrae) characterized by the distortion of the segmentation and differentiation of the cervical somite in the embryogenesis, where the second and third, fifth and sixth cervical segments are most frequently involved [9]. Usually people with dolichomorphic body type have a long and narrow neck, and people with brachymorphic body type, a short and broad neck [10]. The shape of the neck is identified individually by the specific features of the structure of cervical vertebrae, specific features of the upper aperture of the thorax and the external base of skull [11]. There are no national or international standards of the neck length. In their study, P.V. Mahajan, B.A. Bharucha (1994) attempted at compiling standards and percentile diagrams and calculate the correlations of the neck length with linear dimensions such as height in the standing and seating position that would be independent from the age. The neck length was, on average, 12.7±4.58% of the height and 20.1±6.73%, respectively. The linear regression equations independent from the age: neck length = 10 + (0.035 × height) and neck length = 9.65 + (0.07 × height in the seated position), were highly significant ($p < 0.001$) [12].

The range of flexion of the atlanto-occipital joint is approx. 13°. If the range is below this value, there may occur difficulties in the back tilting of the head, which, in its turn, may obstruct the visibility of the glottis [13].

Stability disorders in the cervical region of the spine may be caused by degenerative disk diseases, which result in the replacement of the fibrous ring tissue with scar tissue with much lower strength; therefore, the intervertebral disk becomes weak, and, with increased pressure, the fibrous ring might rupture. The mobility of the neck may be affected by the invagination (indrawal) of the odontoid [14]. In the operations in the region of the medial atlanto-axial articulation there may occur difficulties in choosing the intubation method due to close passage of the upper respiratory tract [15, 16].

Bekhterev's disease (ankylosing spondylitis of the neck) that involves both the vertebral body and the anular epiphysis and is characterized with progressive pathological kyphosis and scoliosis, presence of tendonitis, tendovaginitis and enthesitis, leads to a complete ankylosing of the joints, also affects the biomechanics of the cervical region of the spine [17]. The difficulty in the back tilting of the head may be accounted for by the rigidity of the occipitalis muscle in meningitis [18].

The mobility of the neck depends directly on the fractures of the cervical spine. Tracheal intubation for this category of patients is reasonably difficult due to a high probability of iatrogenic damage during the manipulation [19].

The hernias in the cervical spine are characterized with clinical polymorphism and lead to disorders in the static condition of this region, to displacement of the vertebral pulp, and pinching of the spinal nerves. The rate of incidence of herniation of the cervical disk increases with age and comprises up to 60% of cases, among patients of either sex it was diagnosed most frequently in the age group of 51-60 years [20]. The damage of the cervical region of the spine is seen in patients with rheumatoid arthritis in 86% of cases [21].

Limited mobility of the neck is seen in cases of obesity that created additional burden on the cervical spine [22].

This emphasizes the necessity of taking into account of the individual features of the patient, their somatotype and length of the neck in order to choose the best approach and ensure safety of the procedure.

DEGREE OF ORAL OPENING

The degree of oral opening directly depends on the mobility of the jaw and the proper biomechanics of the temporomandibular joint. The average value and the range of maximum oral opening was identified at 50.3±6.26 mm for men and 49.9±6.74 mm for women, which correlated to the width of three fingers. The maximum average oral opening was registered in the younger age group, and the minimum in the senior age group of either sex [23].

Micrognathia and abnormal bite directly affect the mobility of the mandible. Micrognathia may be the cause of the short tiromental distance, which is considered an indicator of the mandibular space. It was found that successful intubation needs more than 6.5 cm of tiromental distance. If this distance is less than 6.5 cm, it is a case of difficult intubation [1]. Micrognathia may be congenital and acquired. Congenital micrognathia is rooted in disorders of the embryogenesis (first arch syndrome), damage of the growth plate of the mandible, lack of or damage of primordia of the primary and secondary teeth, Down's syndrome and Pierre Robin syndrome [24]. Micrognathia may be the cause of abnormal bite. The formation of the abnormal bite may also be based on the infants' habit of suckling (long-term breast-feeding, bottle feeding, habit of sucking a pacifier or a finger), as well as on night-time open-mouth breathing [25].

Another reason of poor oral opening may be the pathology of the temporomandibular articulation. According to results of epidemiological studies, muscle and joint dysfunction of this articulation is found in 5-12% of the population, much more frequently in women (70-82%), than in men [26]. The pathologies of the organ may include several conditions: arthritis, arthrosis, ankyloses, and others. The causes of

development of the arthritis of the joint may be as follows: local infection (paradontosis, gingivitis, stomatitis, otitis, tonsillitis, osteomyelitis of the jaw), general infectious diseases (acute respiratory infections, influenza, pneumonia, dysentery, tuberculosis, syphilis), allergic diseases, outcomes of trauma [27]. Osteoarthritis of the temporomandibular joint is characterized with synovitis, cartilage destruction and remodeling of the subchondral bone [28]. Ankyloses develops due to fibrous or osseous fusion of the articular surface of the temporomandibular joint [29]. In the case of hyperplasia of the coronoid process, there are clinical observations of progressive reduction of the amplitude of oral opening, usually bilateral and painless [30]. The fracture of the condylar process causes loss of integrity of the mandible, which results in disorders of the joint biomechanics, ankyloses, loss of balance in the growth of the lower jaw (in children), which is detrimental to its function [31].

Tumors of the head and neck region may also restrict oral opening. Radiotherapy assigned to patients with malignant tumors of the head and the neck causes microvascular and lymphatic changes, tissue fibrosis, edema, and reduced salivations. It is related to an increased risk of development of trismus, or a masticatory spasm, limiting the mobility in the temporomandibular joint (5-38%), which directly influences the capability of normal opening of the mouth [32].

MACROGLOSSIA

Large tongue may also cause difficult intubation. The length and the width of the organ are placed within the range of 70-120 mm and 45-75 mm, respectively. Macroglossia may be congenital and acquired. Congenital macroglossia either had genetic background or is due to harm to the fetus in the course of pregnancy: Beckwith-Wiedemann syndrome, Down's syndrome, Pompe's disease, mucopolysaccharidosis [33-35]. Among the causes of acquired macroglossia, there are various injuries (mechanical, physical, or combined), endocrine dysfunction, and tumor masses [36]. In the cases of misplacement of the thyroid gland, tongue size was also observed, and this may complicate the endotracheal intubation [37]. Cancer of the tongue accounts for 65% in the incidence rate of malignant neoplasms of the mouth cavity; it develops from the elements of squamous epithelium. The disease is found 5-7 times more frequently in men than in women, usually in advanced age, after 50 [38].

CAUSES OF OBSTRUCTION OF RESPIRATORY TRACT

Laryngomalacia may cause obstruction of the airways due to changes in the position of the epiglottic cartilage, arytenoepiglottic and interarytenoid folds. The assessment of entry into the larynx in such patients sometimes reveals the collapse of the epiglottic cartilage, dense arytenoepiglottic folds, omega epiglottis, retroflexed epiglottis, prolapse of the interarytenoid fold. The distance from the laryngeal ventricle to the vocal process of the arytenoid cartilage varied from 7.8±0.2 to 12.4±0.33 mm [39].

In tracheomalacia, weakness is observed in tracheal rings that perform the carcass function of the airways, which causes its anterior inclination. Thus, the patency of airways is impeded and the positioning of the endotracheal tube is complicated. Clinical practice has seen lots of cases, in which patients with tracheomalacia developed tracheal diverticulae caused by congenital or acquired weakness of the tracheal wall. In emergency situations, the presence of large tracheal diverticula can complicate the process of inserting a tube into the airway, since diverticula are benign cystic formations that obstruct the lumen of the airway [40].

Gastroesophageal reflux disease may cause abnormal laryngostenosis due to the effect of chemical components [41]. Chronic inflammation of the laryngeal mucosa leads to its swelling and disruption of the normal structure of the organ tissues, replacing them with scar tissue and causing a narrowing of its lumen, which makes it difficult to visualize the glottis [42].

Angioedema can make intubation more difficult because the airway becomes narrower, making the glottis invisible [43].

Descending purulent mediastinitis, which causes swelling of the soft tissues surrounding the upper and lower airways, can make it difficult to open the oral slit and complicate tracheal intubation due to narrowing of the airways and a decrease in the angle of view of the glottis [44].

Securing the airway in patients requiring surgery due to deep infectious involvement of the neck poses a significant challenge for anesthesiologists because of alterations in airway anatomy, limited mouth opening, tissue edema, and restricted range of motion of the cervical spine. It is crucial to assess the risk of potential airway passage issues and select the most appropriate intubation method. Studies among patients with neck infections have shown that in cases of mucosal infections of the oral cavity or pharynx, intubation requires more extensive equipment preparation. The choice of intubation method depends on the extent to which the infection affects the airway anatomy, particularly at the level of the epiglottis and aryepiglottic folds [45].

Epidemic parotitis can also lead to airway obstruction due to the enlargement of the salivary glands, venous stasis, and excessive salivation [46].

CONCLUSION

The study of the morphofunctional characteristics of various structures of the head and neck, as well as their congenital and acquired changes, allows for a deeper understanding of the conditions that affect the performance of endotracheal intubation.

Causes of difficult intubation may include a short neck, diseases of the cervical spine, conditions associated with biomechanical joint disorders (atlanto-occipital, atlantoaxial, temporomandibular), macroglossia, micrognathia, malocclusion, as well as the presence of diseases in the patient that lead to airway obstruction.

Understanding anatomical peculiarities and their association with pathologies during the history-taking stage will help anesthesiologists and resuscitation specialists prepare more effectively for tracheal intubation and minimize potential complications.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Study funding. The study was the authors' initiative without external funding.	***Источник финансирования.*** Работа выполнена по инициативе авторов без привлечения финансирования.
Conflict of Interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	***Конфликт интересов.*** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Contribution of individual authors. N.V. Zharova: concept and writing of the article, literature search and analysis. T.S. Zharikova, N.A. Zharov, A.V. Zharov: literature search and analysis. V.N. Nikolenko, Yu.O. Zharikov: editing of the article. All authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	***Участие авторов.*** Н.В. Жарова – концепция и написание текста статьи, поиск и анализ литературы. Т.С. Жарикова, Н.А. Жаров, А.В. Жаров – поиск и анализ литературы. В.Н. Николенко, Ю.О. Жариков – редактирование статьи. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.

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Оригинальное исследование | Original study article
DOI: https://doi.org/10.35693/SIM642560

Macromicroscopic anatomy of the placenta after *in vitro* fertilization

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Abstract

Aim – to obtain new data on the macromicroscopic anatomy of the placenta in pregnancy after in vitro fertilization.

Material and methods. The work was performed on 60 placentas after in vitro fertilization. Morphologic study was performed on 30 placentas after IVF. Two fragments were isolated from each placenta – from the marginal and central zone. Serial histotopograms stained according to the Van Gieson method were made. Ultrasound examinations were performed at 20.4-21.1 weeks of gestation. The slice size of the marginal sinus and the area of the placenta were studied.

Results. The median thickness of the choroidal lamina was 250 μm in the central zone and 166.5 μm in the marginal zone; the median vascular diameter was 1653 μm in the central zone and 1040 μm at the edge of the placenta. The median basal lamina thickness was 300 μm in the central zone and 210 μm at the margin. The median length of septa in the central and marginal zones of the placenta was 19893.5 μm and 16007 μm, respectively, and the width of septa was 300 μm in the central zone and 240 μm in the marginal zone. At 20-22 weeks, ultrasound scans can reveal the marginal sinus. The slice shape of the marginal sinus varied from triangular to irregular: the frequency of triangular shape was 40%, arrow-shaped – 30%, irregular shape – 30%.

Conclusion. Thus, it is possible to distinguish three zones in the placenta after IVF at the macromicroscopic level: subchorionic, middle and suprabasal, which have their own histotopographic picture.Quantitative characteristics of placental structures are connected to the place of umbilical cord attachment and have differences in the marginal and central zones.

The shape of the marginal sinus when assessed by ultrasound scanning is different (triangular, arrow-shaped, irregular), with the largest area sizes noted for the irregularly shaped marginal sinus.

Keywords: placenta; macromicroscopic anatomy, *in vitro* fertilization.

Conflict of Interest: nothing to disclose.

Citation
Mitrofanova IV, Lutsay ED. **Macromicroscopic anatomy of the placenta after *in vitro* fertilization.** *Science and Innovations in Medicine*. 2025;10(1):10-16.
DOI: https://doi.org/10.35693/SIM642560

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Abbreviations
IFV – *in vitro* fertilization; ART – assisted reproductive technologies.

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Received: 04.12.2024
Accepted: 15.01.2025
Published: 22.01.2025

Макромикроскопическая анатомия плаценты после экстракорпорального оплодотворения

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Аннотация

Цель – получить новые данные по макромикроскопической анатомии плаценты при беременности после экстракорпорального оплодотворения (ЭКО).

Материал и методы. Работа выполнена на 60 плацентах после ЭКО. Морфологическое исследование проведено на 30 плацентах после ЭКО. Из каждой выделяли два фрагмента – из краевой и центральной зоны. Изготавливались серийные гистотопограммы, окрашенные по методу ван Гизона. Ультразвуковые исследования проводились в сроке беременности 20,4–21,1 недели. Изучались размеры среза краевого синуса и площадь плаценты.

Результаты. Медиана толщины хориальной пластинки составила 250 мкм в центральной зоне и 166,5 мкм в краевой зоне; медиана диаметра сосудов – 1653 мкм в центральной зоне и 1040 мкм у края плаценты. Медиана толщины базальной пластинки составила 300 мкм в центральной зоне и 210 мкм у края. Медиана протяженности септ в центральной и краевой зонах плаценты составила 19893,5 мкм и 16007 мкм соответственно, а ширина септ – 300 мкм в центральной зоне и 240 мкм в краевой зоне. В сроке 20–22 недели при ультразвуковом сканировании можно выявить краевой синус. Форма среза краевого синуса варьировала от треугольной до неправильной: частота встречаемости треугольной формы – 40%, стреловидной формы – 30%, неправильной формы – 30%.

Заключение. В плаценте после ЭКО на макромикроскопическом уровне возможно выделить три зоны: подхориальную, среднюю и надбазальную, которые имеют свою гистотопографическую картину. Количественные характеристики структур плаценты имеют связь с местом прикрепления пуповины и различия в краевой и центральной зонах. Форма краевого синуса при оценке ее методом ультразвукового сканирования различна (треугольная, стреловидная, неправильная), при этом наибольшие размеры площади отмечены для краевого синуса неправильной формы.

Ключевые слова: плацента, макромикроскопическая анатомия, экстракорпоральное оплодотворение.

Конфликт интересов: не заявлен.

Для цитирования:
Митрофанова И.В., Луцай Е.Д. **Макромикроскопическая анатомия плаценты после экстракорпорального оплодотворения.** *Наука и инновации в медицине.* 2025;10(1):10-16.
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Получено: 04.12.2024
Одобрено: 15.01.2025
Опубликовано: 22.01.2025

INTRODUCTION

Considering the increasing need in the in-vitro fertilization (IVF) and the respective necessity of studying the pregnancy and childbirth after the IVF, the formation of the feto-placental complex in the pregnancy after *in vitro* fertilization remain some of the most important questions. The studies of the placenta structure after the IVF usually consider its histology and pathomorphology [1–4]. It was proven, however, that the changes in the macromicroscopic anatomy of the placenta are instrumental in the development of feto-placental blood circulation disorders and complications of pregnancy (gestational toxicosis and intrauterine growth retardation). Maintenance of such pregnancy and prenatal care are more than a medical problem being important social and psycho-emotional aspects of life of families expecting childbirth against reproductive problems [5–8].

The ultrasound scanning method has made it possible to conduct screening tests on pregnant women, which includes diagnostics of placental development pathology[1]. Currently, antenatal ultrasonic examination is used generally to study such a pathology of the placenta as its growing into the uterine wall [9, 10]. Given that the protocol of the second ultrasonic screening includes descriptions of placenta position in the uterine cavity, measurement of its thickness and study of specifics of its structure, as well as measurement of the blood flow velocity in the umbilical arteries and the uterine arteries [11–13], it is important to elaborate the data on its macromicroscopic anatomy. Starting from the second trimester of pregnancy, it is possible to identify the marginal sinus, so important in the utero-placental blood flow [14].

AIM

To obtain new data on the macromicroscopic anatomy of the placenta in pregnancy after in vitro fertilization.

MATERIAL AND METHODS

The object of the study was 60 placentas after IVF, of which 30 were subjected to morphological examination. Inclusion criteria: urgent delivery in case of singleton pregnancy after IVF, absence of severe extragenital pathology and pregnancy complications in women. Exclusion criteria: premature birth, multiple pregnancy.

To study the macromicroscopic anatomy of the placenta, fragments were isolated from the marginal and central zones. After passing through alcohols of increasing concentration and pouring into celloidin, serial histotopograms were made. The sections were stained using the standard van Gieson method. The histotopograms were studied under the MBS-10 and MicroOptix MX-1150 T microscopes, digital eyepiece camera ToupCam DCM 500 at 8×, 20×, and 30× magnification with photographing of each specimen.

Ultrasonic examinations were performed using the Voluson S10 unit with the RAB6-RS and Samsung HS 70 (A) probes, and with the 5-9 MHz microconvex probe at the gestational age of 20.4–21.1 weeks. The following criteria were studied: longitudinal and transverse dimensions of the cross-section of the marginal sinus, the area of the cross-section of the placenta and the area of the cross-section of the marginal sinus by tracing.

The obtained data were subjected to variational statistical processing on a personal computer (operating system: Windows XP, Microsoft Word Excel 2010 and IBM SPSS Statistics 20.0 software suites). Descriptive statistics of quantitative data were carried out after analyzing them for the nature of distribution by calculating the Kolmogorov-Smirnov criterion. All variation series had a distribution different from normal, due to this the central tendency was described using the median with the diversity of quantitative features using the interquartile range, presented in the work in the Me format [Q_1-Q_3]. The level of statistical significance of differences between the compared groups was determined using the Kruskal-Wallis test. In the statistical analysis procedures, the level of statistical significance (p) was calculated, the critical value of which in the study was 0.05.

The work was carried out at the Department of Human Anatomy of the Orenburg State Medical University, in the departments of the Orenburg Regional Clinical Hospital No. 2. The study was approved by the local ethics committee of the Orenburg State Medical University (protocol dated November 28, 2022, No. 308).

RESULTS

The macromicroscopic structure of the placenta is the chorionic plate, stained red using the van Gieson method. Above it are the blood vessels significantly varying in diameter from 540 μm to 1939.5 μm. From the choroidal plate, large supporting villi extend to the depth of the placental tissue. The cross-section of the villi below the choroidal plate varies in the wide range from 250 μm to 1470 μm. Inside the stem villi, numerous arterial and venous vessels are located. Close to the center of the section, the number of large villi decreases and the variations in their cross-section sizes diminish coming to 70–150 μm. On the surface of the placenta adjacent to the uterine wall, the uneven surface of the placental wall

[1]Order of the Ministry of Health dated October 20, 2020 No. 1130n "On approval of the Procedure for the provision of medical care in the field of obstetrics and gynecology". Available online: https://base.garant.ru/74840123/

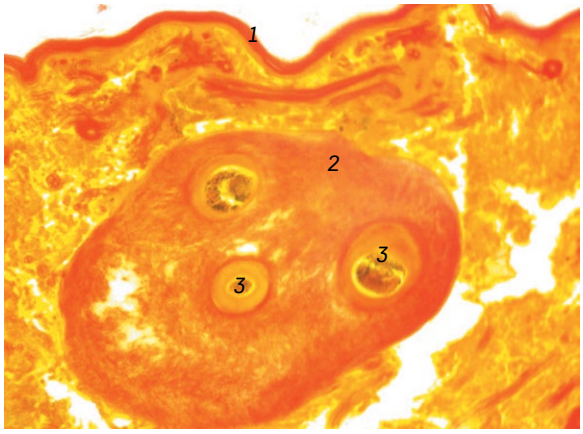

Figure 1. *Transverse section of the villus. Subchorionic zone of the placenta in the central part. Histotopogram. Photos under the microscope MX-1150 (T). Magnification: lens 2.0, eyepiece 10. Van Gieson staining. 1 – choroidal plate; 2 – supporting villi; 3 – villous vessels.*

Рисунок 1. *Поперечный срез ворсины. Подхориальная зона плаценты в центральной части. Гистотопограмма. Фотографии под микроскопом МХ-1150 (Т). Увеличение: объектив 2,0, окуляр10. Окраска по ван Гизону. 1 – хориальная пластинка; 2 – опорная ворсина; 3 – сосуды ворсины.*

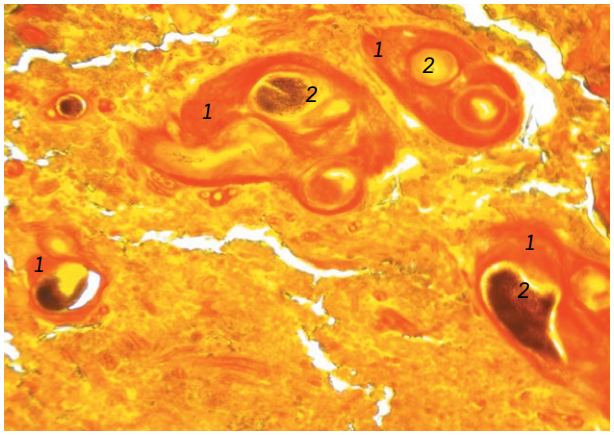

Figure 2. *Group arrangement of villi. Middle zone of the placenta in the central part. Histotopogram. Photos under the microscope MX-1150 (T). Magnification: lens 2.0, eyepiece 10. Van Gieson staining. 1 – intermediate villi; 2 – villous vessels.*

Рисунок 2. *Групповое расположение ворсин. Средняя зона плаценты в центральной части. Гистотопограмма. Фотографии под микроскопом МХ-1150 (Т). Увеличение: объектив 2,0, окуляр 10. Окраска по ван Гизону. 1 – промежуточные ворсины; 2 – сосуды ворсины.*

is clearly detectable, and the boundaries between the two placental cotyledons are seen. These cotyledons are divided by septa. The placental septa are characterized by a manifested polymorphism of shapes and sizes. The depth of their extension to the placental tissue varies from 13350 μm to 30160 μm. Over the basal plate are the terminal villi with smaller cross-sections varying between 45 to 75 μm.

The histotopographic approach towards assessment of the structural elements of the placenta allowed for the identification of three zones in the sections that are different in their macro-microscopic characteristics: the subchorionic, the middle, and the suprabasal zones.

In the subchorionic zone (**Fig. 1**), located below the chorionic plate, large villi with many vessels inside are usually located.

The majority of villi and blood vessels in this area were circular or oval in section. Between the villi of this zone, there were areas where the density of placental tissue was lower.

In the middle zone (**Fig. 2**), the number of intermediate villi and the density of their distribution were grouped. Inside the villi, the blood vessels could be arranged in groups or in pairs. The section of villi and blood vessels was polymorphous, and irregularly shaped structures prevailed.

In the suprabasal zone, located above the basal plate, smaller villi were situated. Their number in this area was lower, and the area of intervillary space was larger.

The macro-microscopy of placenta allows identification of all three zones, there are no stem villi, the number of smaller villi is higher and the area of intervillary space is larger.

The quantitative characteristics of different anatomic structures of the placenta were assessed specifically for placentas with different types of the umbilical cord attachment (**Fig. 3**).

The quantitative characteristic of structural elements of the placenta depending on the umbilical cord attachment location follows in **Table 1**.

In the case of central attachment of the umbilical cord, the quantitative characteristics of the two zones had differences. The medians of all values in the central zone were higher than those for the marginal zone: placenta thickness, by 23.5%; choroidal plate thickness, by 36.4%; diameter of vessels in the choroidal plate, by 75.8%; length of septa, by 27.2%; width of septa, by на 25%; and basal plate thickness, by 42.9%.

In the case of marginal attachment of the umbilical cord, the difference in median values for the similar indicators in the central zone of the placenta were as follows: 28.1% for the placenta thickness; 39.8% for the choroidal plate thickness; 51.5% for the diameter of vessels in the choroidal plate; 25.6% for the length of placental septa; 38.5% for the width of placental septa; 20% for the basal plate thickness.

In the case of sheathed attachment of the umbilical cord, the values tended to be higher in the central zone: 20% for the placenta thickness; 42.9% for the choroidal plate thickness;

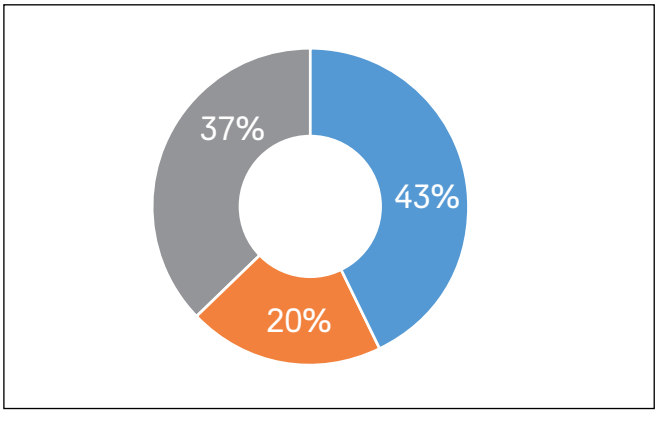

Figure 3. *Options for attaching the umbilical cord to the placenta: central (43%), marginal (20%), sheathed (37%) umbilical cord attachment.*

Рисунок 3. *Варианты прикрепления пуповины к плаценте: центральное (43%), краевое (20%), оболочечное (37%) прикрепление пуповины.*

Parameter		Central attachment	Marginal attachment	Sheathed attachment	P
Central zone					
Placenta thickness, μm	Me	21 000	20 500	24 000	0.458
	$[Q_1-Q_3]$	20 000–25 000	17 750–26 000	20 000–26 000	
Choroidal plate thickness, μm	Me	300	295	303	0.128
	$[Q_1-Q_3]$	245–300	264.8–430.5	250–400	
Diameter of vessels on the choroidal plate, μm	Me	1 600	1 591	1 700	0.458
	$[Q_1-Q_3]$	1 281–1 919.5	1 184.3–1 896.3	1 500–2 151	
Length of septa, μm	Me	20 596	19 725	19 620	0.624
	$[Q_1-Q_3]$	19 365–23 624.5	17 408.5–22 537.8	18 620–25 096	
Width of septa, μm	Me	300	332.5	210	0.163
	$[Q_1-Q_3]$	278–410	200–375	200–364	
Basal plate thickness, μm	Me	300	270	300	0.65
		229–300	200–398.5	212–300	
Marginal zone					
Placenta thickness, μm	Me	17 000	16 000	20 000	0.147
	$[Q_1-Q_3]$	15 000–18 000	14 750–18 500	16 000–25000	
Choroidal plate thickness, μm	Me	220	211	212	0.31
	$[Q_1-Q_3]$	152.5–259	207.5–234	170–300	
Diameter of vessels on the choroidal plate, μm	Me	910	1050	1 212	0.123
	$[Q_1-Q_3]$	750–1 075	920–1 370.8	900–1 400	
Length of septa, μm	Me	16 190	15 700	17 120	0.555
	$[Q_1-Q_3]$	14 737.5–17 742.5	14 247.5–17 435	14 520–20 660	
Width of septa, μm	Me	240	240	300	0.722
	$[Q_1-Q_3]$	200–300	200–355	151–350	
Basal plate thickness, μm	Me	210	225	200	0.835
	$[Q_1-Q_3]$	161–259.5	200–274.5	200–273	

Table 1. *Quantitative characterization of placenta structural elements after IVF depending on the place of umbilical cord attachment*
Таблица 1. *Количественная характеристика структурных элементов плаценты после ЭКО в зависимости от места прикрепления пуповины*

40.3% for the diameter of vessels in the choroidal plate; 14.6% for the length of placental septa, 50% for the basal plate thickness. At the same time, the median width of placental septa was higher in the marginal zone of the placenta by 42.9%.

Thus, the quantitative values for placentas with central and marginal attachment of the umbilical cord have the largest differences between the central and the marginal zones in the vessel diameter in the choroidal plate; in the case of sheathed attachment of the umbilical cord, the largest difference is found in the basal plate thickness.

The comparison of quantitative characteristics of placental elements in the central zone with different types of umbilical cord attachment revealed the following: the median values of the placenta thickness, choroidal and basal plate thickness, diameter of the vessels of the choroidal plate tended to decrease from the central attachment group towards the marginal attachment, and to increase from the marginal attachment group to the sheathed attachment group.

The median length values of placental septa decreased from the group with central attachment to the group with marginal attachment, and from the group with marginal attachment to the group with sheathed attachment.

The median width of placental septa increased from the group with central attachment to the group with marginal attachment, and decreased from the group with marginal attachment to the group with sheathed attachment.

In the case of the marginal zone of the placenta, similar differences were noticed for the median values of placenta

Parameter		Triangular shape	Swept shape	Irregular shape	p
Longitudinal size of marginal sinus section, cm	Me	1.6	1.7	2.7	0.248
	$[Q_1-Q_3]$	1.3–2.0	1.3–2.2	1.3–3.8	
Transversal size of marginal sinus section, cm	Me	0.8	1.0	1.2	0.298
	$[Q_1-Q_3]$	0.6–1.0	0.8–1.4	0.7–1.7	
Area of marginal sinus section, cm^2	Me	0.7	1.1	1.9	0.147
	$[Q_1-Q_3]$	0.4–1.0	0.7–1.3	0.5–3.0	
Area of placenta cross- section, cm^2	Me	33.2	29.5	32.3	0.147
		28.6–35.7	26.3–37.4	29.8–38.4	

Table 2. *Quantitative characterization of the size of the marginal sinus of the placenta*
Таблица 2. *Количественная характеристика размеров краевого синуса плаценты*

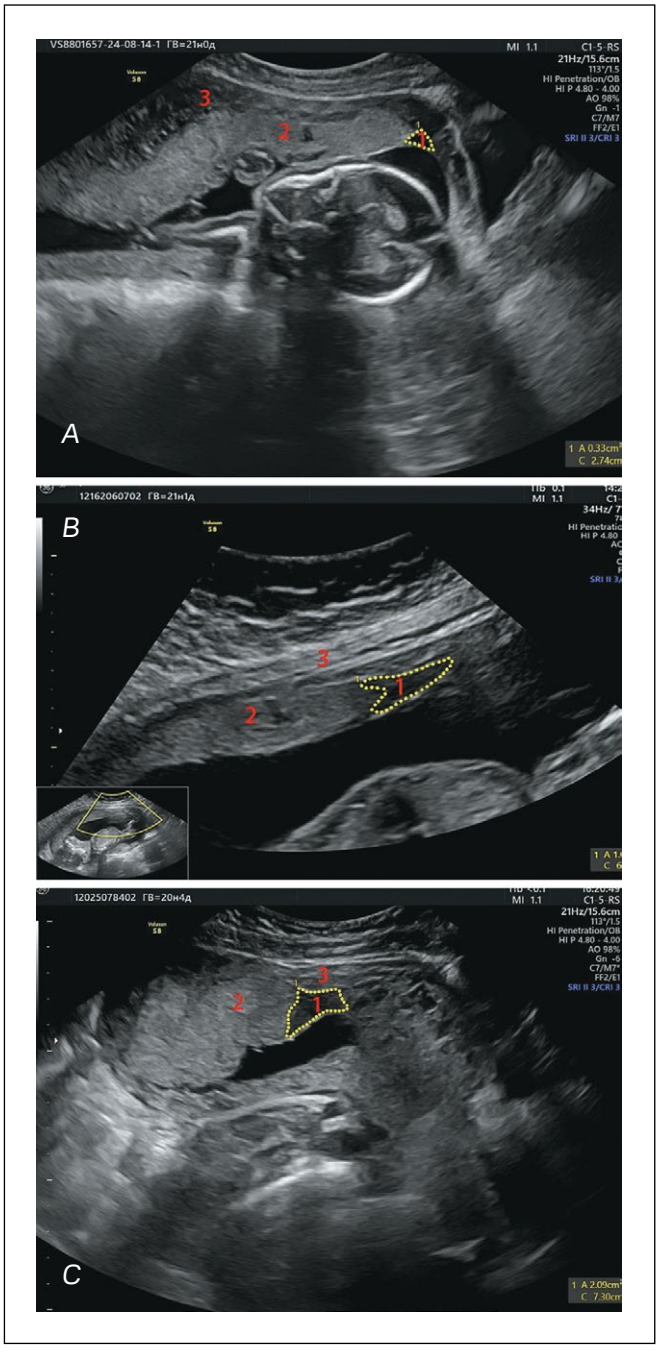

Figure 4. *Various shapes of the edge sine slice. Ultrasound scan of the placenta in the B-mode. A – triangular, gestational age 20 weeks 6 days; B – swept, gestational age 21 weeks 1 day, C – incorrect, gestational age 20 weeks 4 days. 1 – marginal sinus; 2 – placenta; 3 – uterine wall.*

Рисунок 4. *Различные формы среза краевого синуса. Ультразвуковая сканограмма плаценты в В-режиме. А – треугольный, гестационный возраст 20 недель 6 дней; В – стреловидный, гестационный возраст 21 неделя 1 день, С – неправильный, гестационный возраст 20 недель 4 дня. 1 – краевой синус; 2 – плацента; 3 – стенка матки.*

thickness and choroidal plate thickness, diameter of the vessels of the choroidal plate and the length of placental septa; at the same time, the median width of placental septa was similar in the groups with central and marginal attachment of the umbilical cord, yet the same value increased from the marginal attachment to the group with sheathed attachment. The median value of basal plate thickness increased from the central attachment group to the marginal attachment group, and decreased from the marginal attachment group to the sheathed attachment group.

In addition, ultrasonic scanning allows for the description of the marginal sinus at the gestational age of 20–22 weeks; it is located on the periphery of the placenta and limits the intervillary space.

In the ultrasonic scans, the marginal sinus is shown as a space of varied shaped. The section form of the marginal sinus is closer to triangular (**Fig. 4A**) in 40% of the cases; the swept (**Fig. 4B**) and irregular (**Fig. 4C**) shapes being registered in 30% of the cases each, respectively (**Fig. 4**).

The quantitative characteristics of the dimensions of the marginal sinus follow in **Table 2**.

It is seen from the table that the largest longitudinal size is characteristic for the irregular-shaped marginal sinus, and the smallest, for the triangular-shaped. At the same time, it increases by 5.9 and 37% from the triangular-shaped towards irregular shaped marginal sinus, respectively. The transversal size of the swept-shaped marginal sinus for all studied shapes increases from the triangular towards irregular shape by 20% and 20%, respectively. The difference in the area between the triangular and irregular shapes of marginal sinus is 2.7 times.

All the quantitative values of the irregular-shaped marginal sinus prevail in the triangular and swept-shaped forms.

DISCUSSION

According to the literature [15, 16], the fetal surface of the placenta is smooth and glossy; it is covered with the amniotic sac, below which branched blood vessels of various diameter are clearly seen. This confirms the data of this study to the effect that the diameter of vessels of the choroidal plate is highly variable. The intervillary space on the fetal side is formed by the choroidal plate and villi attached to it, and on the maternal side, it is restricted by the basal plate, decidual membrane and partitions (septa) branching from it. It is found that the septa are of varying shape and length, which, in its turn, depends on the location of the umbilical cord location, and on the zone of placenta (central or marginal).

The structure of the fetal part of the placenta is represented by numerous chorionic villi, which are united into structural formations, i.e. cotyledons.

According to A.P. Milovanov and S.V. Savelieva (2006) [17], the villous tree presents three levels of branching. Supporting villi of levels 1, 2, and 3 form the fetal part of the placenta, i.e. they are found in the subchorionic zone and comprise the anatomical framework of the cotyledon. The intermediate differentiated villi branch from Level 2 and 3 supporting villi and range in sizes from 75 to 150 μm, i.e. are found in the middle zone of the placenta. The terminal villi branch from intermediate villi, their diameter is 40–80 μm. This data found its confirmation in the findings of this study.

Foreign researchers [18–20] note that placenta previa is detected more often after the IVF, as is, respectively, marginal and sheathed attachment of the umbilical cord; however, differences in the macro-microscopic anatomy are minor and statistically insignificant as compared to placentas after in vivo fertilization.

According to M.V. Medvedev (2016) [14], the ultrasonic scanning allows the detection of the marginal sinus, starting from the second trimester. It lies on the periphery of the placenta and has the exterior of an uneven slit sized from 0.5 to 1.5 cm. The same is supported by this study; besides, the latter

identified the shapes of the marginal sinus (triangular, swept, and irregular) and describes variations in its size depending on the shape.

The fundamental research in the 'mother-placenta-fetus' system in the post-IVF pregnancies are quite prospective for a variety of reasons. Firstly, the state policy focuses on tackling the demographic situation and entails increased financing of the number of IVF cycles. Secondly, the 'mother-placenta-fetus' system has its proper morphological and clinical peculiarities in the pregnancies achieved by assisted reproductive technologies and requires special attention from the obstetricians-gynecologists and neonatology physicians in terms of maternity and neonatal care. Thirdly, numerous studies have found that there is a regional component both in the fetometry and in the morphology of placenta in the normal conditions (without assisted reproductive technologies), therefore, a promising line of research is the development of the 'morphological profile' of the 'mother-placenta-fetus' system for women after IVF in various administrative units of the Russian Federation.

CONCLUSION

It is possible to identify three zones in the placenta after the IFV: the subchorionic, middle and suprabasal zones, each with a histotopography of its own.

The quantitative characteristics of the placental structures are related to the location of the umbilical cord attachment, and differences in the marginal and central zones.

The shape of the marginal sinus, as inspected by ultrasonic scanning, is different (triangular, swept, and irregular), the largest area sizes detected in the irregularly shaped marginal sinus.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Ethical review. The study was approved by the local ethics committee of Orenburg State Medical University (protocol dated 28.11.2022, No. 308).	***Этическая экспертиза.*** Исследование одобрено локальным этическим комитетом ОрГМУ (протокол от 28.11.2022 года №308).
Study funding. The study was the authors' initiative without external funding.	***Источник финансирования.*** Работа выполнена по инициативе авторов без привлечения финансирования.
Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	***Конфликт интересов.*** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Contribution of individual authors. I.V. Mitrofanova: concept and design of the study, collection, analysis and interpretation of data, preparation of the text. E.D. Lutsay: concept and design of the study; editing of the manuscript. All authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	***Участие авторов.*** И.В. Митрофанова – концепция и дизайн исследования, получение, анализ и интерпретация данных, подготовка текста. Е.Д. Луцай – концепция и дизайн исследования; редактирование рукописи. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.

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Оригинальное исследование | Original study article
DOI: https://doi.org/10.35693/SIM643582

The possibilities of ultrasound diagnostics in assessing the structural variants of the bifurcation of the common carotid artery

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Abstract

Aim – to identify various structural variants of the bifurcation of the common carotid artery using the ultrasound imaging method, taking into account the age characteristics of patients.

Material and methods. We examined 1,061 patients (the average age was 57.0±10.7 years). Using ultrasound imaging, the anatomical variant of the bifurcation of the common carotid artery was determined, taking into account the location of the external and internal carotid arteries at the visualization level. The results were grouped according to the age and gender of the patients, statistically processed.

Results. 2,122 vascular complexes were studied (1,396 in women and 726 in men). Five main types of bifurcation structure of the common carotid artery (types A – E) were identified. Type A was the most common among all participants (up to 42%). Type B was detected in up to 35% of men and 27% of women. Type C accounted for 15%-19% of cases. Other options were estimated at 4-7%. Taking into account the age, four groups were formed for men and women. At the same time, type A was 41-43% for women, regardless of age, and 31-40% for men. Type B in men in the age group 1 was detected in 48%. Type C was 2-4% more common among women in the age groups 2 and 3. In the older age group of men, type C was 31% and type E was 12% (the most common). In other age groups, D and E types accounted for 4-7%.

Conclusion. The results obtained contribute to the development of personalized directions in the treatment of vascular diseases and help to improve minimally invasive surgical interventions.

Keywords: variant anatomy, carotid arteries, ultrasound imaging.
Conflict of Interest: nothing to disclose.

Citation
Moshkin AS, Nikolenko VN, Khalilov MA, Gavryushova LV, Moshkina LV, Li Zhi. **The possibilities of ultrasound diagnostics in assessing the structural variants of the bifurcation of the common carotid artery.** *Science and Innovations in Medicine*. 2025;10(1):17-23. DOI: https://doi.org/10.35693/SIM643582

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Received: 03.01.2025
Accepted: 20.01.2025
Published: 24.01.2025

Возможности ультразвуковой диагностики в оценке вариантов строения бифуркации общей сонной артерии

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Аннотация

Цель – используя метод ультразвуковой визуализации, выявить различия вариантов строения бифуркации общей сонной артерии с учетом возрастных особенностей пациентов.

Материал и методы. Нами обследован 1061 пациент (средний возраст составил 57,0±10,7 года). С использованием ультразвуковой визуализации определялся анатомический вариант строения бифуркации общей сонной артерии с учетом расположения наружной и внутренней сонных артерий на уровне визуализации. Полученные результаты были сгруппированы с учетом возраста и пола пациентов и статистически обработаны.

Результаты. Всего изучено 2122 сосудистых комплекса (у женщин 1396, у мужчин 726). Определены 5 основных типов строения бифуркации общей сонной артерии (типы А – Д). Тип А наиболее часто встречался среди всех участников (до 42%). Тип Б выявлялся до 35% у мужчин и 27% среди женщин. Тип В составлял 15–19% случаев. Другие варианты определялись в 4–7%. С учетом возраста были сформированы по 4 группы для мужчин и женщин. При этом у женщин независимо от возраста тип А составлял 41–43%, а для мужчин 31–40%. Тип Б у мужчин в первой возрастной группе выявлен в 48%. Тип В на 2–4% определялся чаще среди женщин в первой – третьей возрастных группах. В старшей возрастной группе мужчин тип В составил – 31% и тип Д – 12%. В других возрастных группах типы Г и Д составляли 4–7%.

Заключение. Полученные результаты способствуют развитию персонифицированных направлений в лечении сосудистых заболеваний и помогают совершенствовать малоинвазивные хирургические вмешательства.

Ключевые слова: вариантная анатомия, сонные артерии, ультразвуковая визуализация.

Конфликт интересов: не заявлен.

Для цитирования:
Мошкин А.С., Николенко В.Н., Халилов М.А., Гаврюшова Л.В., Мошкина Л.В., Ли Чжи. **Возможности ультразвуковой диагностики в оценке вариантов строения бифуркации общей сонной артерии.** *Наука и инновации в медицине.* 2025;10(1):17-23. DOI: https://doi.org/10.35693/SIM643582

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Получено: 03.01.2024
Одобрено: 20.01.2025
Опубликовано: 24.01.2025

INTRODUCTION

Variable anatomy of the vascular bed demonstrates the importance of systematization of knowledge for subsequent successful implementation of results into clinical practice [1, 2]. The active development of methods of intravital diagnostics and modern data processing technologies make it possible to find many new features in the structure of the vascular system [3–5]. The development of minimally invasive surgical interventions and the expansion of personalized approaches in medicine require a more in-depth and detailed assessment of the main vessels [6–8]. The neck area contains the most important main arteries, which are often the site of development of dangerous hemodynamic disorders [9, 10]. Ultrasound diagnostics at the current stage of its development allows not only to evaluate the structure of the vascular wall and hemodynamic parameters, but also to obtain extensive information about the anatomy in the field of visualization [11], and the risk of developing cardiovascular diseases [12–14].

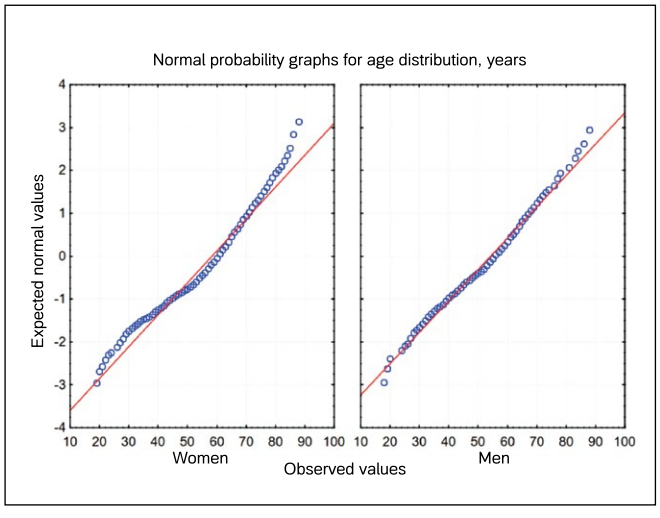

Figure 1. *Graphs of the normal probability distribution of participants by age, taking into account the gender in the observation (the Shapiro – Wilk W test for women w=0.9674, p=0.0000; for men w=0.9893, p=0.00004).*

Рисунок 1. *Графики нормального вероятностного распределения участников по возрасту с учетом пола в наблюдении (критерий Шапиро – Уилка для женщин w=0,9674, p=0,0000; для мужчин w=0,9893, p=0,00004).*

AIM

Using the ultrasound imaging method, taking into account the age characteristics of patients, to identify various structural variants of the bifurcation of the common carotid artery.

MATERIAL AND METHODS

The study was conducted using the SonoAce R7 and Logiq F6 ultrasound diagnostic systems in an outpatient setting. Linear multifrequency sensors were used for visualization.

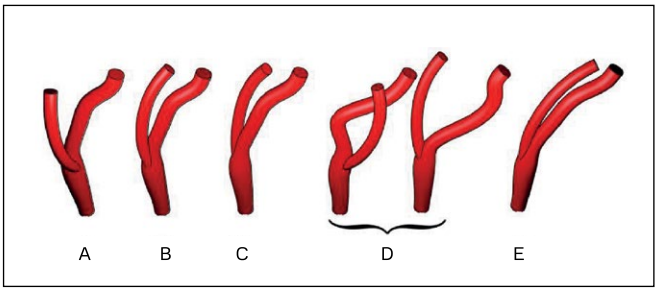

Figure 2. *Structural variants of the bifurcation region of the common carotid artery in the observation.*

Рисунок 2. *Варианты строения области бифуркации общей сонной артерии в наблюдении.*

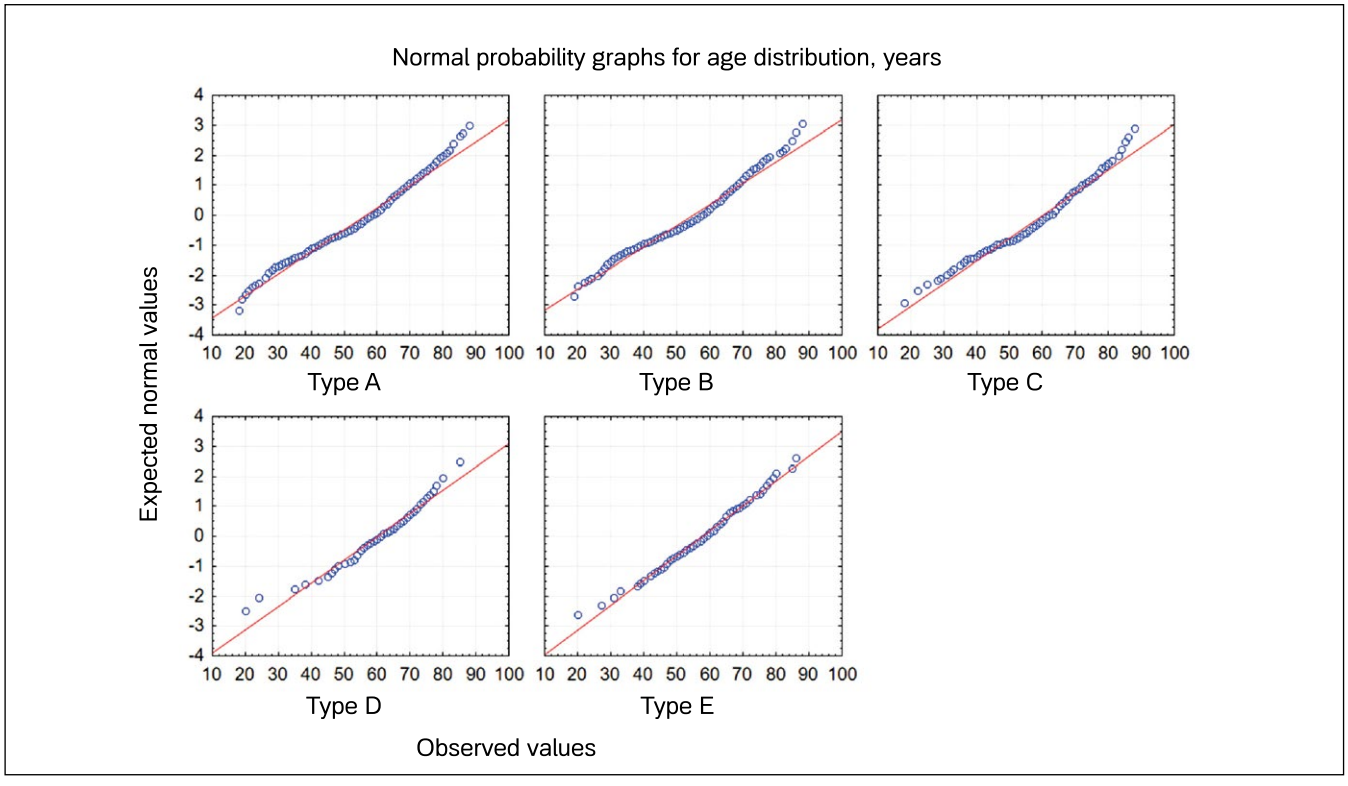

Figure 3. *Graphs of the normal probability distribution of participants by age, taking into account the type of structure of the bifurcation of the common carotid artery (Shapiro – Wilk W test: type A w=0.9787, p=0.0000; type B w=0.9729, p=0.0000; type C w=0.9701, p=0.0000; type D w=0.9622, p=0.0044; type E w=0.9913, p=0.4966).*

Рисунок 3. *Графики нормального вероятностного распределения участников по возрасту с учетом типа строения бифуркации общей сонной артерии (критерий Шапиро – Уилка: тип А w=0,9787, p=0,0000; тип Б w=0,9729, p=0,0000; тип В w=0,9701, p=0,0000; тип Г w=0,9622, p=0,0044; тип Д w=0,9913, p=0,4966).*

A total of 1061 people (698 women and 363 men) were examined. The age of the study participants ranged from 18 to 88 years, with an average of 57.0±10.7 years.

We determined the anatomical variant of the structure of the bifurcation of the common carotid artery, taking into account the location of the external and internal carotid arteries at the level of visualization. The data were summarized in Microsoft Excel 2007 tables. Statistical data processing was performed in StatSoft Statistica 10 and IBM SPSS Statistics 20 software suites.

Type of bifurcation structure	Kolmogorov-Smirnov test with Lilliefors significance correction		
	Statistics	Degree of freedom	Significance
1.00	0.080	867	0.000
2.00	0.090	626	0.000
3.00	0.090	375	0.000
4.00	0.081	105	0.089
5.00	0.054	149	0.200

Table 1. *Normality tests for age with respect to the type of structure of the bifurcation of the common carotid artery*

Таблица 1. *Критерии нормальности для возраста с учетом типа строения бифуркации общей сонной артерии*

RESULTS

By combining data from both sides of the entire visualization, 2122 carotid bifurcations were analyzed. Among women, 1396 vascular structures were assessed, and 726 among men. A visual representation of the normal age distribution among men and women in the work is presented in **Figure 1**.

In our study, we used the original system of determining the structure of the region of carotid bifurcation [3] that comprises 5 types (Fig. 2): A – median position of the external carotid artery; B – ventral position of the internal carotid; C – lateral position of the external carotid artery; D – divergence or intersection of vessels in the bifurcation region; E – medial inclination of carotid arteries.

The general data on normal distribution of participants according to age between men and women is shown in **Fig. 3** and **Table 1**.

Type of bifurcation structure	Total number of cases			% among participants		
	Women	Men	Total	Women	Men	Total
A	586	281	867	42	39	40
B	375	251	626	27	35	30
C	266	109	375	19	15	18
D	73	32	105	5	4	5
E	96	53	149	7	7	7

Table 2. *Information on the prevalence of various vascular structural variants among all participants in the observation*

Таблица 2. *Сведения о распространенности различных вариантов строения сосудов среди всех участников наблюдения*

Parameter	Type of relative position of vessels				
	A	B	C	D	E
Number, people	207	126	63	12	12
Proportion in the group, %	49	30	15	3	3

Table 3. *Distribution of the same structural variants of the common carotid artery bifurcation on both sides among the participants in the observation*

Таблица 3. *Распределение одинаковых вариантов строения бифуркации общей сонной артерии с обеих сторон среди участников наблюдения*

General data on the occurrence of structural variants of bifurcation of the common carotid artery among participants in absolute and relative values are shown in **Table 2**.

The most frequent structural variants of bifurcation are types A and B. Type A comprises up to 40% of all observed cases, reaching 42% in women and 38% in men. Type B comprises up to one third of cases: 35% among men and 27% among women. Type C is found in one fifth of cases: 19% among women and 15% among men. Other variants of the relative position of vessels (D and E), depending on the sex of patients, were found in 4-7%.

In 420 participants of the study (164 men and 256 women) similar structural variants of bifurcation of the common carotid arteries on either side were identified, which comprises 39.6% of the total data in the observation; the general data follows in **Table 3**.

We then analyzed the results obtained taking into account the gender and age of the patients. The following groups of study participants were formed as per age periods: Group 1,

Type of bifurcation structure	Kolmogorov-Smirnov test with Lilliefors significance correction			Shapiro-Wilk W test		
	Statistics	Degree of freedom	Significance	Statistics	Degree of freedom	Significance
A	0.280	867	0.000	0.844	867	0.000
B	0.263	626	0.000	0.846	626	0.000
C	0.303	375	0.000	0.834	375	0.000
D	0.291	105	0.000	0.837	105	0.000
E	0.264	149	0.000	0.826	149	0.000

Table 4. *Normality test for the type of structure of the bifurcation of the common carotid artery with respect to the age group*

Таблица 4. *Критерии нормальности для типа строения бифуркации общей сонной артерии с учетом возрастной группы*

Age group	Kolmogorov-Smirnov test with Lilliefors significance correction			Shapiro-Wilk W test		
	Statistics	Degree of freedom	Statistics	Degree of freedom	Statistics	Degree of freedom
1	0.273	178	0.000	0.770	178	0.000
2	0.253	770	0.000	0.794	770	0.000
3	0.232	1010	0.000	0.818	1010	0.000
4	0.234	164	0.000	0.837	164	0.000

Table 5. *Normality test for the age group with respect to the type of structure of the bifurcation of the common carotid artery*

Таблица 5. *Критерии нормальности для возрастной группы с учетом типа строения бифуркации общей сонной артерии*

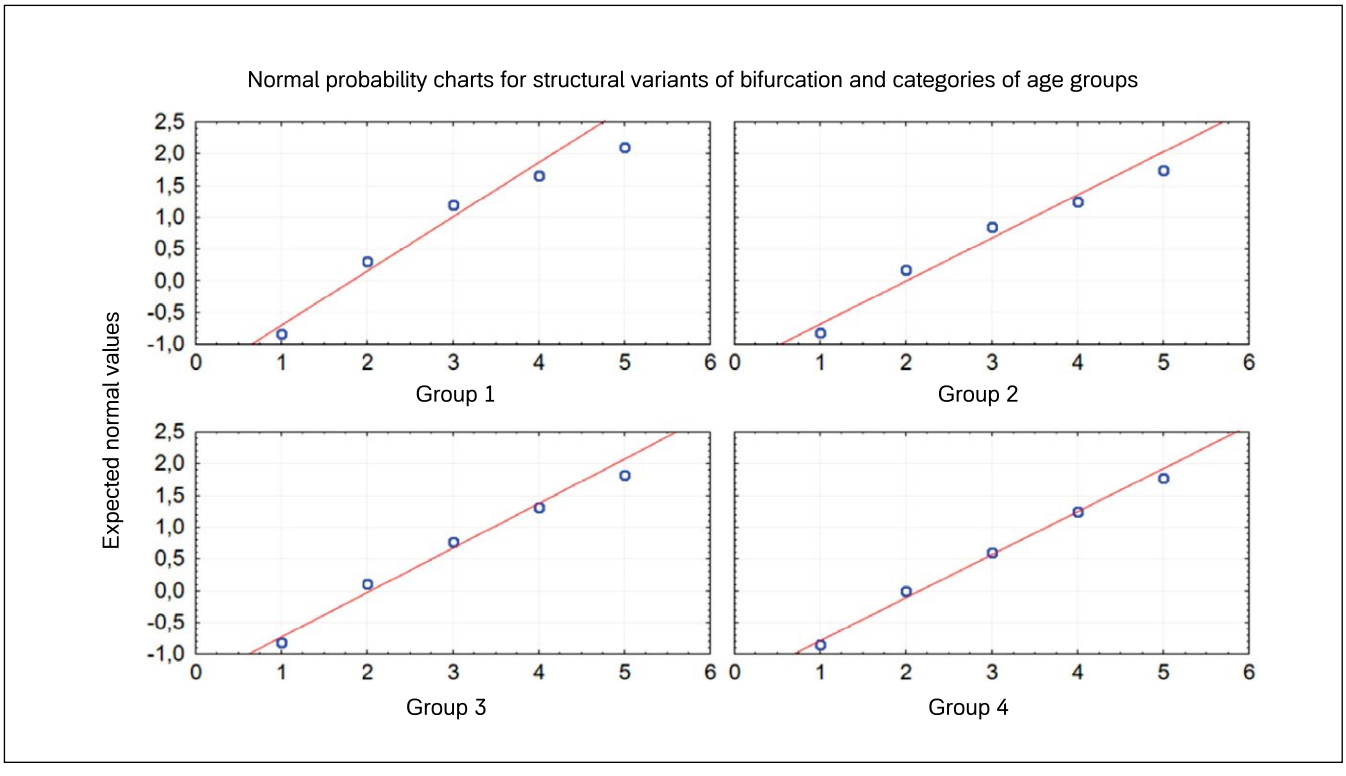

Figure 4. *Diagram of the distribution of participants, taking into account the type of structure of the common carotid artery bifurcation and age group (Shapiro – Wilk W test: group 1, w=0.7703, p=0.0000; group 2, w=0.794, p=0.0000; group 3, w=0.8183, p=0.0000; group 4, w=0.8368, p=0.0000).*

Рисунок 4. *Диаграмма распределения участников с учетом типа строения бифуркации общей сонной артерии и возрастной группы (критерий Шапиро – Уилка: первая группа w=0,7703, p=0,0000; вторая группа w=0,794, p=0,0000; третья группа w=0,8183, p=0,0000; четвертая группа w=0,8368, p=0,0000).*

Type of relative position of vessels	Women				Men			
	G 1 n=100	G 2 n=372	G 3 n=802	G 4 n=122	G 5 n=78	G 6 n=398	G 7 n=208	G 8 n=42
A	44 (44%)	159 (43%)	279 (41%)	51 (43%)	28 (36%)	157 (39%)	83 (40%)	13 (31%)
B	39 (39%)	106 (28%)	172 (26%)	22 (18%)	37 (48%)	140 (35%)	64 (31%)	10 (24%)
C	12 (12%)	60 (16%)	137 (20%)	31 (25%)	7 (9%)	50 (13%)	39 (18%)	13 (31%)
D	-	19 (5%)	32 (6%)	10 (8%)	5 (6%)	16 (4%)	10 (5%)	1 (2%)
E	5 (5%)	28 (8%)	42 (7%)	7 (6%)	1 (1%)	35 (9%)	12 (6%)	5 (12%)

Table 6. *Distribution of structural variants of the bifurcation of the common carotid artery, taking into account gender and age group*
Таблица 6. *Распределение вариантов строения бифуркации общей сонной артерии с учетом пола и возрастной группы*

youth and I adult period (men and women aged below 35); Group 2, II adult period (men over 35 and below 60, and women below 55 years of age); Group 3, elderly people (men over 60 years of age and women over 55 and below 74 years of age); Group 4, old people (above 75 years of age).

The distribution of structural variants of main vessels in the region of the common carotid artery bifurcation among participants from various age groups regardless of their sex is shown in **Fig. 4** and **Tables 4** and **5**.

The data on the number of identified types of relative position of vessels in the region of the common carotid artery bifurcation among women and men are shown in **Table 6**.

Most frequently, Type A was found among women, comprising 41-43% of the cases in all age groups. Among men, this type of relative position of vessels was found least frequently, in 31% of the cases, in Group 4.

In the male group, Type B was identified more frequently than in the female group. The largest number of cases was found in Group 1 of men (48%), and the least number in Group 4 (24%). Among women, this variant of relative position of vessels in the region of the common carotid artery bifurcation was 39% of the cases in Group 1, whereas the least number of cases, 18%, was found in age Group 4.

Type C in Groups 1, 2 and 3 was mound 2-4% more frequently in women. In Group 4 among men, Type C was found most frequently comprising 31%.

The remaining types of relative position of vessels (D and E) made up to 4–7% of the cases across the age groups. The greatest value for Type E was found in the among men reaching 12% in Group 4. Type D was not found in women in age Group 1.

DISCUSSION

The study of the variable anatomy of the main arteries of the neck is performed by different teams of specialists. Morphological studies based on pathological examinations are of special interest. P.A. Samptesov et al. (2012) report the data of morphological examination of the main arteries considering individual specifics of the shape of the neck based on examination of bodies of 97 men [15]. F. Hojaij et al. (2019) uses the data of 50 pathological examination to study anatomic peculiarities in the relative position of the carotid arteries, jugular vein and the vagal nerve [16]. The undisputed advantage of pathological examination is its unbiased nature, the possibility of detailed documentation of the study process, and the possibility of append the results of studies with histological specimens. Unfortunately, autopsy data do not always allow for a full assessment of the functional relationships that are most relevant in clinical practice.

Great attention is paid to descriptions of dimensional characteristics of the main arteries of the neck [1]. Many clinical studies dwell, in much detail, on questions of diagnosing [2] or specifics of surgical treatment [4, 6]. The variable anatomy of the main arteries is of particular importance when planning high-tech and minimally invasive surgical interventions [17–19].

The classification of relative position of vessels, presented by us, was originally developed to assess the variability of the main arteries when studying images obtained by magnetic resonance tomography [3], however, in the process of practical work it proved well in performing ultrasonic visualization.

In vascular surgery, the area of intravascular interventions is rapidly developing [9], allowing for the individual characteristics of the anatomy of the main arteries to be taken into account directly at the operating table. Methods of minimally invasive surgery require refined knowledge of individual variability of the bloodstream. The region of the bifurcation of the common carotid artery includes one of the most important reflexogenic zones of vegetative innervation, and is the location of the most frequent diagnostic of significant atherosclerotic changes at the level of the vessel wall. Contemporary methods of processing of diagnostic information using computers enable the use of methods of computer analysis, create realistic three-dimensional models facilitating surgery planning [20, 21].

The data on age and sex factors associated with varying anatomy of the main arteries in the region of bifurcation presented in this paper, combined with ultrasonic visualization, enable improvement of personalized approach in medicine [11].

Our study demonstrates the possibility of practical implementation if a simple, straightforward and effective method to determine anatomic variants of the structure of the common carotid artery bifurcation. The relatively large scope of research allowed for a precise identification of the rare types (D and E) and formation of participant groups with respect to their age.

CONCLUSION

Our study presents the possibilities of ultrasonic visualization of the anatomical variations in the structure of the common carotid artery bifurcation. The considerable size of

our sampling allowed showing the correlations of prevalence of the different anatomic variants among men and women, and taking into account the factor of the patients' age.

In general, typical variants of relative position of the vessels (types A and B) are most frequent with Type A being prevalent among women. Type B variant of the vessel relative position is seen more often in young men. Type C, in its turn, is more often identified in both men and women, as the age progresses. Rare types of vessel position (D and E) are identified in 4-7% of the cases; and only in men of II adult period type E comprised 12% cases.

The presented data are relevant for assessing the variable anatomy of the main arteries of the neck, allowing development of personalized directions in the treatment of vascular diseases and improvement of minimally invasive surgical interventions.

ADDITIONAL INFORMATION

Study funding. The work was carried out at Orel State University named after I.S. Turgenev within the framework of the state assignment No. 075-00196-24-08 for 2024 and for the planning period of 2025 and 2026 dated August 23, 2024, project No. FSGN-2024-0014 (1024041900023-6-1.2.1; 2.6.2; 3.1.3; 3.2.12; 3.2.4).

Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.

Compliance with Ethical Standards

The authors confirm that the rights of the people who participated in the study were respected, including obtaining informed consent where necessary. The study protocol was approved by the local Ethics Committee of the Orel State University named after I.S. Turgenev (protocol No. 25 dated November 16, 2022).

Contribution of individual authors. A.S. Moshkin – organization of the theoretical and clinical part of the research, conducting the research, editing of the manuscript. V.N. Nikolenko – design of the research; interpretation of the research results. M.A. Khalilov – statistical data processing; editing of the manuscript. L.V. Gavryushova – coordination of the clinical part of the research, interpretation of the research results. L.V. Moshkina – statistical processing, editing the manuscript. Zhi Li – statistical data processing; interpretation of research results.

All authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Источник финансирования. Работа выполнена в ФГБОУ ВО «Орловский государственный университет имени И.С. Тургенева» в рамках государственного задания № 075-00196-24-08 на 2024 год и на плановый период 2025 и 2026 годов от 23.08.2024 г., проект № FSGN-2024-0014 (1024041900023-6-1.2.1;2.6.2;3.1.3;3.2.12;3.2.4).

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.

Соответствие нормам этики

Авторы подтверждают, что соблюдены права людей, принимавших участие в исследовании, включая получение информированного согласия в тех случаях, когда оно необходимо. Протокол исследования был одобрен локальным этическим комитетом ФГБОУ ВО «Орловский государственный университет имени И.С. Тургенева» Министерства науки и высшего образования РФ (протокол № 25 от 16 ноября 2022 г.).

Участие авторов. А.С. Мошкин – организация теоретической и клинической части исследований, проведение исследования, редактирование рукописи. В.Н. Николенко – оформление дизайна исследования; интерпретация результатов исследования. М.А. Халилов – статистическая обработка данных; редактирование рукописи. Л.В. Гаврюшова – координация клинической части исследования, интерпретация результатов исследования. Л.В. Мошкина – статистическая обработка, редактирование рукописи. Чжи Ли – статистическая обработка данных; интерпретация результатов исследования.

Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.

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Оригинальное исследование | Original study article
DOI: https://doi.org/10.35693/SIM626840

Age, disease duration and multimorbidity as predictors of hypoglycemia in elderly women with type 2 diabetes mellitus

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Abstract

Aim – to study the correlations between age, disease duration, concomitant chronic non-infectious pathology and the risk of developing hypoglycemia in patients with type 2 diabetes mellitus (T2DM).

Material and methods. The study involved 90 elderly women (mean age 70.5 ± 6.2 years) with T2DM. The medical history of all study participants collected during the interviews was supported by the following analysis of their medical documentation. Additionally, we analyzed the results of clinical and biochemical blood tests and calculated the Charlson comorbidity index for all participants.

Results. The prevalence of hypoglycemia among patients with T2DM was: 47% in patients aged 65–74 years, and 75% in older patients (75–85 years). The significant correlation was found between the indicators "Patient's age" and "Presence of hypoglycemia" r = 0.2489 (p = 0.018). When calculating χ^2 (chi-square), the value obtained was $\chi 2 = 5.513$ (p = 0.018). One-way analysis of variance of these values resulted in F-ratio = 5.811 at the significance level p = 0.018, which confirmed a significant relationship between the two variables. The significant correlation was found for the indicators "Existing cases of hypoglycemia" and "Duration of diabetes mellitus" (r = 0.3512 with a significance level of p = 0.0007). The data allowed us to draw a conclusion about the statistical dependence of these values. The result of the χ^2 test for the trend was χ^2 (trend) = 10.982 (p = 0.0009). The data obtained might indicate the relationship between these variables. The correlation between the indicators "Existing cases of hypoglycemia" and "Charlson Comorbidity Index score" was confirmed by the value r = 0.4020 (p = 0.0001). The relationship between these variables was revealed by calculating $\chi^2 = 16.336$ (p = 0.0059). Based on the χ^2 test for the trend, the value χ^2 (trend) = 14.544 (p = 0.0001) was obtained. One-way analysis of variance for these indicators presented F-ratio = 3.734 (p = 0.004).

Conclusion. The patient's age, duration of T2DM and multimorbidity were significantly associated with the risk of hypoglycemia in patients with T2DM.

Keywords: type 2 diabetes mellitus, hypoglycemia, risk factors of hypoglycemia, multimorbidity, Charlson Comorbidity Index, CCI, gerontology.

Conflict of interest: nothing to disclose.

Citation
Merzlova PYa, Bulgakova SV, Kurmaev DP, Treneva EV. **Age, disease duration and multimorbidity as predictors of hypoglycemia in elderly women with type 2 diabetes mellitus.** *Science and Innovations in Medicine.* 2025;10(1)::24-29. https://doi.org/10.35693/SIM626840

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Abbreviations
DM – Diabetes Mellitus; T2DM – Type 2 Diabetes Mellitus; CVDs – cardiovascular diseases; CCI –Charlson Comorbidity Index; ESR – erythrocyte sedimentation rate; HDL – high-density lipoproteins; LDL – low-density lipoproteins; ALT – alanine aminotransferase; AST – aspartate aminotransferase.

Received: 13.02.2024
Accepted: 16.03.2024
Published: 15.05.2024

Возраст, длительность заболевания и полиморбидность как предикторы гипогликемии у женщин пожилого и старческого возраста с сахарным диабетом 2 типа

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Аннотация

Цель – изучить взаимосвязь возраста, длительности заболевания и сопутствующей хронической неинфекционной патологии с риском развития гипогликемии у женщин с сахарным диабетом 2 типа (СД2).

Материал и методы. В исследовании участвовали 90 пациенток пожилого и старческого возраста (средний возраст 70,5 ± 6,2 года) с СД2. У всех участников исследования собран анамнез заболевания, изучена медицинская документация. Исследованы показатели клинического анализа крови и биохимического анализа крови, а также вычислен индекс коморбидности Charlson.

Результаты. Распространенность гипогликемии среди пациенток с СД2 составила 47% у пожилых и 75% у пациенток старческого возраста. Индекс корреляции между показателями «возраст пациента» и «наличие случая гипогликемии» составил r = 0,2489 (p = 0,018), что свидетельствует о статистической зависимости данных величин. При вычислении χ^2 (хи-квадрат) получено значение χ^2 = 5,513 (p = 0,018). Однофакторный дисперсионный анализ данных величин демонстрирует результат F-отношения = 5,811 при уровне значимости (p = 0,018), что подтверждает значительную связь между двумя переменными. Был вычислен индекс корреляции по показателям «наличие случаев гипогликемии» и «стаж сахарного диабета» (r = 0,3512 при уровне значимости p = 0,0007). Данные позволяют сделать вывод о статистической зависимости данных величин. Результат теста χ^2 для тренда получено значение χ^2 (тренд) = 10,982 (p = 0,0009). Приведенные данные свидетельствуют о взаимосвязи данных переменных. Корреляция между показателями «наличие случая гипогликемии» и «индекс коморбидности Charlson (баллы)» подтверждается значением r = 0,4020 (p=0,0001). Связь между данными переменными выявлена вычислением χ^2 = 16,336 (p = 0,0059). На основании теста χ^2 для тренда получено значение χ^2 (тренд) = 14,544 (p = 0,0001). Однофакторный дисперсионный анализ данных показателей демонстрирует результат F-отношения = 3,734 (p = 0,004).

Заключение. Возраст пациента, стаж СД2 и полиморбидность достоверно связаны с риском гипогликемии у пациенток с СД2.

Ключевые слова: сахарный диабет 2 типа, гипогликемия, факторы риска гипогликемии, полиморбидность, индекс коморбидности Charlson, CCI, геронтология.

Конфликт интересов: не заявлен.

Для цитирования
Мерзлова П.Я., Булгакова С.В., Курмаев Д.П., Тренева Е.В. **Возраст, длительность заболевания и полиморбидность как предикторы гипогликемии у женщин пожилого и старческого возраста с сахарным диабетом 2 типа.** *Наука и инновации в медицине.* 2025;10(1):24-29.
DOI: https://doi.org/10.35693/SIM626840

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Список сокращений
СД – сахарный диабет; СД2 – сахарный диабет 2 типа; ССЗ – сердечно-сосудистые заболевания; СКФ – скорость клубочковой фильтрации.

Получено: 13.02.2024
Одобрено: 16.03.2024
Опубликовано: 15.05.2024

INTRODUCTION

Diabetes Mellitus (DM) is one of the most prevalent non-infectious pathologies and a global problem of healthcare worldwide. Over 500 million people internationally and almost 5 million Russians have Diabetes Mellitus [1, 2]. More than 90% of all cases of the disease are Type 2 Diabetes Mellitus (T2DM) diagnosed in 4.58 million people in Russia [2]. Vital importance of T2DM problem is related to the overall trend of population aging resulting from combined increased expectancy of life and decreasing birth rate [3]. More than a half of all cases of T2DM are found in patients over 65, and the greater prevalence of the pathology is observed in the cohort of 65–70 years olds [4]. The pathogenesis of T2DM is related to insulin resistance combined with dysfunction of beta cells of the pancreas and reduced synthesis of insulin resulting in a persistent hypoglycemia, which, in its turn, affects the vascular endothelium and causes damage to various organs and systems [5]. With advancing age, the tissue sensitivity to insulin decreases on the post-receptor level. Loss of muscle mass and development of sarcopenia result in the decreased glucose consumption by muscles, increase of insulin resistance, and increase of hypoglycemia [6–8]. Sedentary lifestyle, high-calorie processed foods and intake of some medications additionally assist increased insulin resistance. Elderly and old patients demonstrate an involution of the pancreatic beta cells and a decrease of their sensitivity to incretins, which leads to insulin secretion disorder [7, 8]. Thus, the T2DM is an age-associated disease.

Elderly patients with T2DM often take antihyperglycemic agents of such groups as sulfonyl urea and insulin [2, 9]. Being effective and available to patients under reimbursement programs, these agents are also characterized with a higher frequency of hypoglycemia occurrence versus other groups of antihyperglycemic agents [10, 11]. Glycaemia values of 3 to <3.9 mmol/l in DM patients receiving antihyperglycemic therapy are predictors of hypoglycemia development and require measures to manage this condition regardless of the presence or absence of symptoms. The blood glucose below 3 mmol/l points at clinically significant hypoglycemia. In cases of severe hypoglycemia, depression of consciousness and cognitive functions is observed, the management of which requires assistance from third persons or medical professionals [10]. The hazard of hypoglycemia, especially for patients of advanced age, lies in the increased risk of adverse cardiovascular events and death [12, 13]. Hypoglycemia initiates a cascade of reactions forming a counter-regulatory response. One of components of this response is the activation of the sympathoadrenal system whereby adrenalin is released; under hypoglycemia, it reduces glucose consumption by muscles and stimulates its production by the liver [14]. The activation of the sympathoadrenal system result in the patient developing adrenergic effects such as increased sweating, tremor of the upper extremities; these symptoms allow for a timely identification of a hypoglycemic event and prevention of development of severe hypoglycemia by the patient. Changes in the hemodynamics related to hypoglycemia and reactive increased secretion of adrenaline are manifested in an increased heart rate and systolic blood pressure, increased myocardial contractility, stroke and ejection volume [15]. Hypoglycemia also causes changes in the hemostasis shown in the increase of activity of platelets and blood coagulation factors, viz. Factor VII and von Willebrand Factor. Increased

concentration of C-reactive protein and proinflammatory cytokines under hypoglycemia may lead to damage of vascular endothelium [16]. The above mentioned changes in the hemostasis and hemodynamics contribute to the ischemia of the myocardium, especially in elderly and old patients, in the presence of atherosclerotic coronary disease. In the structure of mortality of T2DM patients in the Russian Federation, cardiovascular diseases (CVDs) are leading [2]. The patient's age and presence of CVDs are the factors determining the individual targets of glycemic control [10, 17]. Hypoglycemia elevates the risk of development of dementia and, respectively, functional dependence of advanced age patients with T2DM, whereas the existing cognitive deficiency increases the risk of the onset of severe hypoglycemic events [17, 18].

The primary physiological reaction to hypoglycemia is reduction of insulin secretion by pancreatic beta cells. Possibly, due to paracrine interrelation between the cells of the pancreatic islets, the alpha cells then release the glucagon, an insulin counter-regulatory hormone stimulating development of hypoglycemia by activating breakdown of glycogen in the liver. As the duration of DM increases, chronic hypoglycemia leads to damage and loss of beta cells, and cross-reactions between alpha and beta cells are disrupted as well as glucagon secretion in response to decrease of glycaemia [19, 20]. This results in an elevated risk of the onset of a severe hypoglycemic event. It may be suggested that a long duration of DM may be a risk factor of severe hypoglycemia.

Geriatric practices are closely related to the problem of polymorbidity or two or more chronic conditions found in the same patient [21]. Among patients aged over 65, the prevalence of polymorbidity reaches 95.1%. Some scientists believe that the processes of aging and development of chronic diseases are based on similar mechanisms, and polymorbidity may be viewed as a marker of accelerated aging [22]. To assess stratification of patients against the level of comorbidity and to ensure individual approaches to treatment and follow-up various indices and scales are used [23]. One of such widely used indices is the Charlson Comorbidity Index (CCI) developed in 1987. It is expressed in points and allows identification of the patient's comorbidity and to predict the probability of 10-year mortality [23, 24].

Considering the aforementioned adverse outcomes of hypoglycemia on T2DM patients of advanced age groups, the evaluation of the patient's age, duration of T2DM and the value on the Charlson comorbidity index as predictors of a hypoglycemic event is of interest.

AIM

To determine the significance of age, duration of T2DM and polymorbidity as predictors of hypoglycemia in elderly and old women with T2DM.

MATERIAL AND METHODS

The cross-sectional study included 90 elderly and old female patients. The minimum age of the participant was 60 years, the maximum was 85 years, and the average age was 70.5 ± 6.2 years.

Inclusion Criteria: female sex, age of 60 and above, history of T2DM, signing of informed voluntary consent by the patient to participate in the study.

Exclusion Criteria: history of T1DM, presence of diabetic ketoacidosis at the time of examination, acute infectious diseases, severe cognitive impairment that makes it difficult to collect complaints and anamnesis, a history of cancer, severe renal impairment (GFR below 15 ml/min/1.73m2 calculated using the CKD-EPI equation), severe liver failure (increase in liver transaminase activity by more than 5 times the upper limit of reference values). The participants of the study were divided into two groups. The first group were the patients who experienced a hypoglycemic event within the past year (49 people, 54.4%), average age of 72.1 ± 5.9 years. The second group were patients without history of hypoglycemia (41 people, 45.6%), average age of 68.5 ± 6.1 years.

Hypoglycemia was determined by the glucose level in the blood below 3.9 mmol/l [10], registered within the past year in the biochemical blood assay or in the patient's self-measurement of glucose in the capillary blood using a glucometer, which is registered in the glycaemia control diary. A detailed history of T2DM was collected from patients: age at the onset of the disease, glycaemia and glycated hemoglobin levels over time, adjustment of antihyperglycemic therapy, history and frequency of hypoglycemic events. The medical histories and electronic outpatient cards of patients in the Unified Medical Information and Analytical System of the Samara Region (EMIAS) were studied in detail. The following laboratory parameters were studied: red blood cell count, mean cell value, hemoglobin, hematocrit, white blood cell count, platelet count, erythrocyte sedimentation rate (ESR), glucose, glycated hemoglobin, creatinine, total protein, total cholesterol, triglycerides, high-density lipoproteins (HDL), low-density lipoproteins (LDL), alanine aminotransferase (ALT) и aspartate aminotransferase (AST). The calculation of GFR was done using the CKD-EPI and MDRD equations widely used in medical practice (KDIGO 2012). Charlson comorbidity index was calculated for all the patients.

The statistical analysis of the obtained data was performed with the MedCalc 20.009 software suite (MedCalc Software Ltd, Belgium). The variables are presented as the average mean (M) with a standard deviation (SD). The normality of the sample distribution was checked using the Kolmogorov-Smirnov criterion. The linear dependence between the indicators was determined using the r-Pearson correlation coefficient. The chi-square ($\chi 2$) criterion was used to analyze the presence of a relationship between categorical variables. One-way ANOVA was used to determine statistically significant intergroup differences. The results were considered statistically significant at $p < 0.05$.

RESULTS

Depending on the age, the patients were divided into groups according to the WHO classification. Out of the 90 participants of the study, the elderly cohort (60–74 years) of patients included 66 people, and the group of old/senile patients (75–85 years) was 24 people. Among the elderly patients, 31 (47%) people had a history of a hypoglycemic event within the past year; in 35 (53%) patients, there was no history of hypoglycemia. In the group of old patients, hypoglycemia was found in 18 (75%) people, the number of patients without hypoglycemic events was only 6 (25%) people. That is, among old patients hypoglycemia is more prevalent than among elderly patients (**Table 1**).

Age category	Group 1 (n=49)		Group 2 (n=41)		p-value
	Number of people, abs.	Percentage from total number in this category	Number of people, abs.	Percentage from total number in this category	
Elderly	31	47%	35	53%	0.0180
Old	18	75%	6	25%	

Table 1. *The prevalence of hypoglycemia in two groups of elderly patients divided by age*
Таблица 1. *Сравнение распространенности гипогликемии среди пациентов пожилого и старческого возраста*

T2DM duration	Group 1 (n=49)		Group 2 (n=41)		p-value
	Number of people, abs.	Percentage from total number in this category	Number of people, abs.	Percentage from total number in this category	
0–10 years	10	33.3%	20	66.7%	0.0007
11–20 years	25	62.5%	15	37.5%	
Over 21 years	14	70%	6	30%	

Table 2. *The prevalence of hypoglycemia in T2DM patients depending on disease duration*
Таблица 2. *Распространенность гипогликемии в зависимости от длительности СД2*

When calculating the correlation coefficient between the indicators "History of a hypoglycemic event" and "Patient age (age group)", a direct correlation was revealed (r=0.2489; p=0.018). These values indicate a statistical dependence of the indicators under consideration. Based on the chi-square criterion, the value of $\chi2 = 5.513$ ($p = 0.018$) was obtained. The one-way ANOVA shows the F ratio = 5.811 ($p = 0.018$). The calculations performed confirm the relationship between two categorical variables.

Depending on the duration of the T2DM, the participants of the study were also divided into groups shown in **Table 2**. It may be pointed out that hypoglycemic events are more frequently observed in patients with the duration of T2DM of 21 years and more (70%). The prevalence of hypoglycemia in patients with disease duration of 11–20 years was 62.5%, and in patients with disease duration of 0–10 years, 33.3%.

The statistic correlation between the parameters under consideration is confirmed by the correlation index ($r = 0.3512$; $p = 0.0007$). In the calculation of the $\chi2$ value, the $\chi2$ (trend) = 10.982 ($p = 0.0009$) value was obtained, which also confirms a significant correlation between these variables.

We collected the history of concomitant non-infectious pathologies (**Table 3**).

According to Table 3, the following chronic non-infectious diseases were most prevalent in the patients of Group 1: arterial hypertension (100% patients), stable angina (65.31%), chronic heart failure (75.51%), osteoarthritis (40.82%), and carotid artery atherosclerosis (32.65%).

In the patients of Group 2, the following picture may be observed: arterial hypertension (100% patients), stable angina (51.22%), chronic heart failure (51.22%), osteoarthritis (43.9%), and carotid artery atherosclerosis (21.95%).

In the process of comparative analysis of morbidity between patients of Groups 1 and 2, we calculated the Charlson comorbidity index, depending on the value of which the patients were distributed as follows (**Table 4**).

The correlation index for the indicators "History of hypoglycemic events" and "Charlson comorbidity index (points)" was $r = 0.4020$ ($p = 0.0001$), which shows the statistic dependence of these variables.

Based on the $\chi2$ test, the $\chi2 = 16.336$ ($p = 0.0059$) was obtained. When calculating the $\chi2$ for the trend, the $\chi2$ (trend)

Disease	Group 1 (n=49)		Group 2 (n=41)		Dynamic (n1%/n2%)	p-value
	No. of people, abs.	No. of people, %	No. of people, abs.	No. of people, %		
Arterial hypertension	49	100.00%	41	100.00%	1,0	1.0000
Stable angina	32	65.31%	21	51.22%	1,28	0.1801
Myocardial vascularization surgery	7	14.29%	7	17.07%	0,84	0.7200
Chronic heart failure	37	75.51%	21	51.22%	1,47	**0.0163**
Atrial fibrillation	5	10.20%	0	0.00%	0,0	**0.0356**
Carotid artery atherosclerosis	16	32.65%	9	21.95%	1,49	0.1190
Bronchial asthma	4	8.16%	3	7.32%	1,11	**0.8830**
Chronic anemia	12	24.49%	3	7.32%	3,35	0.0296
Deep vein thrombosis	1	2.04%	0	0.00%	0,0	0.3633
Pulmonary artery thromboembolia	1	2.04%	0	0.00%	0,0	0.3633
Osteoarthritis	20	40.82%	18	43.90%	0,93	0.7709
Knee arthroplasty	2	4.08%	0	0.00%	0,0	0.1949
Parkinson's disease	0	0.00%	1	2.44%	0,0	0.2768
Alzheimer's disease	0	0.00%	0	0.00%	0,0	1.0000
Trophic ulcers and pressure sores	2	4.08%	2	4.88%	0,84	0.8571
Gouty arthritis	1	2.04%	1	2.44%	0,84	0.8998

Table 3. *Comparison of the prevalence of chronic noncommunicable diseases between patient groups*
Таблица 3. *Сравнение распространенности хронических неинфекционных заболеваний между группами пациентов*

Charlson comorbidity index (points)	Group 1 (n=49)		Group 2 (n=41)		p-value
	No. of people	No. of people, %	No. of people	No. of people, %	
3	1	2.04%	4	9.75%	0.0001
4	2	4.08%	11	26.83%	
5	12	24.48%	10	24.39%	
6	20	40.81%	13	31.71%	
7	13	26.53%	3	7.32%	
8	1	2.04%	0	0%	

Table 4. *Distribution of patients depending on the Charlson comorbidity index*
Таблица 4. *Распределение пациентов в зависимости от индекса коморбидности Charlson*

= 14.544 (p = 0.0001) value was obtained. One-way ANOVA shows the F ratio = 3.734 (p = 0.004). The calculations performed confirm the relationship between two categorical variables.

DISCUSSION

In the course of the study, we analyzed the correlation between the patient's age, duration of the T2DM and polymorbidity with the risk of the onset of hypoglycemia. The results show that the age and the duration of the disease are predictors of the onset of hypoglycemia. Old patients experienced this condition more often than the elderly. We already mentioned that with advancing age the insulin resistance is increasing and the functional reserve of the pancreas is decreasing as the number of beta cells grows lower. This leads to glycaemia levels in elderly patients to go higher, respectively, the antihyperglycemic treatment is intensified, which may lead to the development of hypoglycemia. A large study demonstrated an increase in mortality from CVDs among T2DM patients in the group with intensive glycaemia control as compared to the group in which individual targets of carbohydrate metabolism were observed [25]. Besides, as the age and the duration of the disease advance, the vegetative symptoms of hypoglycemia appear with lower values of hypoglycemia, and the cognitive dysfunction, with higher levels as compared to younger patients. Thus, both the adrenergic symptoms that allow for a timely identification and management of hypoglycemia and the neurology deficiency appear simultaneously in elderly patient. Recurrent hypoglycemic events lead to a further lowering of the threshold of activation of the sypmathoadrenal system. This phenomenon is referred to as 'hypoglycemia unawareness syndrome'. Some authors regard it as a manifestation of autonomous diabetic neuropathy, and some view is as a temporary functional disorder that is potentially reversible with compensation of carbohydrate metabolism and prevention of further hypoglycemia [19, 26].

As per results of our study, patients had differences of prevalence of chronic non-infectious diseases between groups. Among patients with history of hypoglycemia, the increase of atrial fibrillation occurrence was statistically significant (p = 0.0356), as well as chronic heart failure (p = 0.0163) and chronic anemia (p = 0.0296). Contrary to our expectations, the differences in prevalence of stable angina and myocardial vascularization surgery were not statistically significant between the studied groups (p > 0.05), which may be explained by a small sample of patients.

The Charlson comorbidity index is used within the framework of complex geriatric evaluation to assess the risks of negative outcome in patients with polymorbidity from advanced age groups. We found a direct correlation between the score on the Charlson comorbidity index and hypoglycemia. In the group of patients with history of hypoglycemic events, higher scores on the Charlson comorbidity index were found, which is associated with a worse long-term prognosis and lower chance of 10-year survivability. In calculating this index, the following factors are considered: complications of T2DM, history of CVDs, significant decrease of GFR and impairment of the liver function; those are the factors that influence glucose metabolism and pharmacokinetics of antihyperglycemic agents that potentially contribute to the development of a hypoglycemic event.

CONCLUSION

Older patients experienced hypoglycemia more often than the elderly ones. Age of patients and duration of the T2DM are risk factors for the development of hypoglycemia. The choice of antihyperglycemic therapy for patients of advanced age groups requires an assessment of concomitant geriatric syndromes and comorbid conditions increasing the risk of hypoglycemia. The results of our study emphasize, once again, the importance of reaching individual targets of carbohydrate metabolism in elderly patients with T2DM. The targets of treatment of T2DM in such patients should be the maintenance of quality of life and minimization of side effects of antihyperglycemic agents including hypoglycemia.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Study funding. The study was the authors' initiative without external funding.	***Источник финансирования.*** Работа выполнена по инициативе авторов без привлечения финансирования.
Conflict of Interest. The author declares that there are no obvious or potential conflicts of interest associated with the content of this article.	***Конфликт интересов.*** Автор декларирует отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Contribution of individual authors. P.Ya. Merzlova – was responsible for clinical data collection, its systematization and statistical analysis, wrote the first draft of the manuscript. S.V. Bulgakova – developed the study concept, goals and plan. D.P. Kurmaev – provided final manuscript editing. E.V. Treneva – provided the study design and text revision. All authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	***Участие авторов.*** П.Я. Мерзлова – сбор и обработка клинического материала, написание текста, статистическая обработка данных. С.В. Булгакова – постановка задачи, планирование концепции исследования. Д.П. Курмаев – финальное редактирование текста научной статьи. Е.В. Тренева – дизайн исследования, верстка текста. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.

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Оригинальное исследование | Original study article
DOI: https://doi.org/10.35693/SIM623623

A multivariate weighted assessment model for the course of ischemic stroke accompanied by carotid stenosis of varying severity

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Abstract

Aim – to develop a multivariate weighted assessment model for analyzing the influence of individual risk factors for acute ischemic cerebrovascular accidents on the course of ischemic stroke with concurrent carotid stenosis of varying severity.

Material and methods. The study involved 606 in-patients receiving treatment for the acute ischemic stroke. The patients were divided into three groups according to the NASCET scale for severity of carotid stenosis. In all patients, we identified the risk factors for the stroke development, the size of the ischemic locus according to the CT imaging, the patient's condition at admission and discharge from the hospital using the NIHSS, Rankin, and Rivermead scales.

Results. The estimated indicators were represented by different measurement scales, so there was a need to bring them to the universal basis. A weighted assessment model required assigning weights for each component of the new index. A multivariate weighted assessment was modeled in order to identify the main factors influencing its variation. We selected the risk factors for acute ischemic cerebrovascular accidents, built the regression models, performed the statistical analysis and assessed their quality.

Conclusion. The regression models are helpful in covering a wide range of factors and mathematically expressing their relationship with performance indicators. The developed logistic regression models demonstrated the degree of positive or negative influence of various risk factors on the course of ischemic stroke in the studied groups of patients.

Keywords: carotid stenosis, ischemic stroke, risk factors, logistic regression analysis, multivariate weighted assessment.

Conflict of interest: nothing to disclose.

Citation
Tkachenko AS, Poverennova IE, Romanova TV, Persteneva NP. A **multivariate weighted assessment model for the course of ischemic stroke accompanied by carotid stenosis of varying severity.** *Science and Innovations in Medicine.* 2025;10(1):30-36.
DOI: https://doi.org/10.35693/SIM623623

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Abbreviations
ACVA – acute cardiovascular accident; IS – ischemic stroke; RS – Rankin Scale; RMI – Rivermead Mobility Index; MWA – multivariate weighted assessment.

Received: 20.11.2023
Accepted: 24.03.2024
Published: 10.04.2024

Многомерная взвешенная оценка в анализе течения ишемического инсульта на фоне каротидного стеноза различной степени выраженности

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Аннотация

Цель – разработать многомерную взвешенную оценку влияния факторов риска острого нарушения мозгового кровообращения (ОНМК) на течение ишемического инсульта, развившегося на фоне каротидного стеноза различной степени выраженности.

Материал и методы. Исследовано 606 больных, находившихся в отделении для больных с ОНМК в остром периоде ишемического инсульта, которые были разделены на три группы по степени выраженности каротидного стеноза согласно NASCET. У всех больных выявляли факторы риска развития ОНМК, определяли размер очага ишемии по КТ головного мозга, оценивали состояние пациента и его изменения по шкалам NIHSS, Рэнкина, Ривермид.

Результаты. Оценочные показатели представлены различными измерительными шкалами, поэтому их необходимо привести к одному основанию. Методика построения взвешенной оценки предполагает формирование весовых коэффициентов для каждого компонента нового индекса. Произведено моделирование многомерной взвешенной оценки для выявления основных факторов, влияющих на ее вариацию. Был проведен отбор факторов риска ОНМК у исследованных больных, построены регрессионные модели, выполнен их статистический анализ и оценено их качество.

Выводы. Регрессионные модели позволяют охватить большой круг факторов и математически выразить их связь с результативными показателями. Разработанные логистические модели показывают степень положительного или отрицательного влияния различных факторов риска на течение ишемического инсульта в исследованных группах больных.

Ключевые слова: каротидный стеноз, ишемический инсульт, факторы риска, логистический регрессионный анализ, многомерная взвешенная оценка.

Конфликт интересов: не заявлен.

Для цитирования:
Ткаченко А.С., Повереннова И.Е., Романова Т.В., Перстенева Н.П. **Многомерная взвешенная оценка в анализе течения ишемического инсульта на фоне каротидного стеноза различной степени выраженности.** *Наука и инновации в медицине.* 2025;10(1):30-36. DOI: https://doi.org/10.35693/SIM623623

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Список сокращений
ИИ – ишемический инсульт; КТ – компьютерная томография; МВО – многомерная взвешенная оценка; ОНМК – острые нарушения мозгового кровообращения; NASCET – North American Symptomatic Carotid Endarterectomy Trial; NIHSS – National Institutes of Health Stroke Scale; RS – Rankin Scale, шкала Рэнкина; RMI – Rivermead Mobility Index, индекс мобильности Ривермид.

Получено: 20.11.2023
Одобрено: 24.03.2024
Опубликовано: 10.04.2024

INTRODUCTION

Among the causes of death and disability worldwide, cardiovascular diseases are leading. With every decade, the frequency of strokes among patients aged 50–55 increases by 1.8–2.0 times [1]. Loss of working capacity after an acute cardiovascular accident (ACVA) reaches 3.2 per 10000 adults and leads among the causes of disability. A great number of patients with ACVA are people of productive age: 23.6% from 41 up to 50 years, and 12.3% of the total number of patients are below 40 [2]. After the vascular accident, 40-45% patients die within 12 months, and every fifth patient develops a second stroke in the subsequent years [3]. It is for that reason that contemporary neurology focuses on prevention of ischemic stroke (IS) and post-stroke patient rehabilitation.

Constrictive lesion of the major arteries of the head and the neck are one of the principal causes for development of the brain ischemia [4, 5]. There is a classification of carotid stenosis depending on the degree of vessel constriction, which identified mild (0–29%), mild to moderate (30–49%), moderate (50–69%) and severe stenosis (70–99%), and full occlusion of the vessel (100%) [6, 7]. In the recent years, there were published many papers on the assessment of the major factor of risk of IS development [8, 9]. Thus, important roles in the onset and progress of ACVA belong to arterial hypertension – like the carotid stenosis, it is a type of a macrovascular disease [10], – and the decrease of just the diastolic arterial blood pressure by 5 mmHg leads to the decrease of risk of cerebral stroke by 34% [11]. Atrial fibrillation is the supraventricular tachycardia. According to several sources, in 15–20% of patients it is the atrial fibrillation that is the major reason of vascular accidents [12]. Studying the influence of these factors on the progress and prognosis of the acute period of ischemic stroke may open a possibility of lowering the risk of development of recurrent ACVAs and reduce the severity of the neurological deficiency in the acute period of ischemic stroke [13, 14]. In this regard, the analysis of the impact of risk factors on the progress of IS with concurrent carotid stenosis, seems an important task.

AIM

To develop a multivariate weighted assessment model for analyzing the influence of individual risk factors for acute ischemic cerebrovascular accidents on the course of ischemic stroke with concurrent carotid stenosis of varying severity.

MATERIAL AND METHODS

The paper is based on the results of an open prospective observation study involving 606 in-patients receiving treatment for the acute ischemic stroke. The studies patients included 292 women (48.2%) and 314 men (51.8%) aged between 39 and 89. The median age of the patients was 67.4 (81.75; 52.9) years.

Depending on the severity of stenosis of the major arteries of the head and the neck measured by duplex Doppler ultrasound inspection of the brachiocephalic trunk upon admission for ACVA treatment as per the NASCET (North American Symptomatic Carotid Endarterectomy Trial) classification, the patients were divided into three groups. The first group of hemodynamically mild/mild to moderate stenosis (below 49%) included 446 patients (73.6%). The second group (moderate stenosis of 50–69%) included 85 (14.0%) patients. The third group (hemodynamically severe stenosis of 70–100%) included 75 patients (12.4%).

In all of the examined patients, risk factors for the ACVA development were identified: degree of arterial hypertension, cardiac pathology, history of acute vascular accidents, diabetes mellitus, dyslipidemia, etc. The size of IS lesion was measured by the data of brain CT performed upon patient admission for treatment: lacunar, up to 10 mm, mini, up to 15 mm, medium, 20–50 mm, and large, over 50 mm. To ensure a complex evaluation of changes in the patient's condition from admission to (examination 1) to discharge from the in-patient facility (examination 2), three evaluation scales were used: National Institutes of Health Stroke Scale (NIHSS), Rankin Scale (RS), and Rivermead Mobility Index (RMI).

RESULTS

The results of examination of patients from the three groups on admission to (examination 1) and on discharge (examination 2) from the ACVA in-patient facility are shown in **Table 1**.

The initial data array consists of scores registered under each scale and every examination. The greater the difference (delta) between the scores of the same patient under both examination, the greater is the change in their condition during in-patient treatment. Undoubtedly, scores under separate indices provide vital information for the planning of therapy and control of its efficiency, yet the greatest prognostic value lies in the combination of all three separate indices represented in the single multivariate assessment. Since

Group / Scale	Group I (n = 446)		Group II (n = 85)		Group III (n = 75)	
	Ex. 1	Ex. 2	Ex. 1	Ex. 2	Ex. 1	Ex. 2
Lacunar stroke						
NIHSS	7.2 (4; 8)	3.0 (1; 3)	9.2 (6; 12)	3.1 (1; 6)	9.1 (5; 12)	6.9 (2; 8)
p-value	p < 0.001		0.001		0.142	
Rankin	3.0 (2; 3)	2.0 (1; 2)	4.0 (3; 5)	2.0 (1; 2)	3.0 (3; 4)	2.5 (2; 4)
p-value	p < 0.001		0.002		0.091	
Rivermead	6.2 (2: 7)	12.3 (9; 13)	2.0 (1; 4)	10.0 (9; 12)	3.0 (1; 6)	8.0 (5; 12)
p-value	p < 0.001		0,001		0.013	
Mini stroke						
NIHSS	10.0 (7.5; 12.5)	4.0 (3; 5)	8.5 (5.0; 8.0)	4.6 (2.0; 6.0)	10.2 (5; 15)	8.4 (3; 11)
p-value	p < 0.001		0.011		0.075	
Rankin	4.0 (3.0; 4.5)	2.0 (1; 3)	3.0 (3; 3)	2.0 (1; 3)	3.0 (3; 4)	3.0 (2; 3)
p-value	p < 0.001		0.028		0.310	
Rivermead	3.0 (1; 6)	8.0 (6; 12)	4.5 (1.0; 6.0)	9.5 (7.0; 13.0)	2.0 (1; 6)	6.0 (3; 10)
p-value	p < 0.001		0.005		0.043	
Medium stroke						
NIHSS	7.0 (4; 11)	3.5 (3.0; 8.0)	9.5 (6.0; 15.0)	6.0 (2; 9)	11.5 (7.0; 18.0)	9.0 (3; 10)
p-value	p < 0.001		p < 0.001		p < 0.001	
Rankin	3.0 (3; 4)	2.0 (2; 4)	4.0 (3; 5)	3.0 (2; 4)	4.0 (3.0; 4.0)	3.0 (1.0; 4.0)
p-value	p < 0.001		p < 0.001		0.002	
Rivermead	3.0 (1; 6)	8.0 (4; 12)	2.5 (1.0; 5.0)	7.0 (4; 12)	2.0 (1; 6)	4.5 (3; 11)
p-value	p < 0.001		p < 0.001		0.001	
Large stroke						
NIHSS	10.0 (8.5; 13.0)	5.5 (5.0; 11.0)	11.0 (10; 16)	6.5 (5; 6)	13.0 (5; 16)	10.0 (4; 11)
p-value	p < 0.001		0.043		0.176	
Rankin	4.2 (4; 5)	3.4 (3; 4)	4.1 (4; 5)	3.0 (2; 4)	4.3 (3; 5)	4.0 (3; 4)
p-value	0.002		0.109		0.178	
Rivermead	2.0 (1.0; 3.5)	4.8 (2.5; 6.5)	1.8 (1; 2)	5.0 (3; 8)	1.0 (1; 1)	3.0 (3; 8)
p-value	p < 0.001		0.068		0.028	

Table 1. *Indicators of neurological deficit at the admission (Study 1) and at the discharge from the hospital (Study 2) depending on the degree of atherosclerotic lesions and the volume of the stroke lesion (median, quartile 1; quartile 3)*

Таблица 1. *Показатели неврологического дефицита при поступлении (исследование 1) и при выписке из стационара (исследование 2) в зависимости от степени атеросклеротического поражения и объема очага инсульта (медиана, квартиль 1; квартиль 3)*

the evaluation indicators (components) of the multivariate assessment are represented by different evaluation scales, there arises a need of bringing them together to a universal basis. Each scale has its own specifics related not only to the nature of the assessed phenomenon, but to the difference in the evaluated parameters as well:

– The NIHSS scale evaluates the neurological status; it has an interval from 0 to 42, the "0" meaning "No stroke symptoms", and "42" meaning "Severe stroke";

– The Rankin scale measures degree of disability, i.e. to what extent the patient depends on assistance. The scale runs from 0 to 6, where "0" means "No symptoms", and "5" means "Severe disability";

– The Rivermead mobility index assesses functional mobility in gait and transfers. The range of scores is from "0" ("inability to independently perform any arbitrary movements") to "15" ("ability to run 10 meters in 4 seconds").

While forming the data array, it is very important to meet two requirements: single direction and normalization of scales. Single direction implies unified interpretation of all three specific indices, i.e. the increase of values of each index is to be interpreted in the same way: only either as 'improvement' or only as 'impairment'. Normalization means that all three indices are to have the same range of values.

In order to meet these requirements, we based our research on the Rivermead index. Its scale is 'ascending', i.e. the increase of its values represents improvement of the patient's mobility. Such a scale is intuitively perceived as a logical and adequate. The maximum score is 15 (the range of values being larger than that of the Rankin scale and smaller than that of the NIHSS scale). It is in the range of the Rivermead index that we will normalize the values of the other two scales that are 'descending', i.e. the increase of values represents the decline in the patient's condition.

To address the task of normalization, we will introduce correction factors, based on which we will recalculate all the scores obtained. For the NIHSS scale, all scores will be proportionately decreased with respect to the factor 15/42 = 0.357. E.g., the score of 12 will decrease after recalculation to 4.284 (12*0.357), however, in its essence the normalized score will remain the same: prior to normalization, it was 12 out of 42, after normalization it became 4.284 out of 15, i.e. it decreased proportionately. At the same time, the scale will still remain 'descending'; therefore, to 'turn over' the scale, to make it 'ascending', we will subtract each obtained normalized score from the maximum possible score of 15:

$$NIHSS_{norm} = 15 - NIHSS_{act},$$

where $NIHSS_{norm}$ – is the normalized score; $NIHSS_{act}$ – is the actual score.

Next, we will calculate the score difference (Δ_{NIHSS}):

$$\Delta_{NIHSS} = NIHSS_{norm2} - NIHSS_{norm1},$$

where $NIHSS_{norm1}$ and $NIHSS_{norm2}$ – are the scores after the first and the second examinations, respectively.

Index / Scale	Scale type	Value range
Specific indices (non-normalized scales)		
NIHSS Scale	'descending' – from better to worse	0 … 42
Rankin Scale	'descending' – from better to worse	0 … 5
Mobility Index	'ascending' – from worse to better	0 … 15
MWA		
Normalized scale	'ascending' – from worse to better	0 … 15

Table 2. *Scales of private MWA indices*
Таблица 2. *Шкалы частных индексов МВО*

Now, the plus sign "+" of the difference will mean the positive change in the neurological status, and the minus sign "–", the negative change.

We will apply the same procedure to the Rankin scale. All scores will be proportionately increased with the factor of 15/5 = 3. For example, the score of 2 after normalization will become greater: 6 (2*3). Transferring to the 'ascending' scale, we will subtract each obtained score from the maximum possible score of 15:

$$RS_{norm}=15–RS_{act},$$

where RSnorm – is the normalized score; RS_{act} – actual score.

Next, we will calculate the score difference (Δ_{RS})

$$\Delta RS=RS_{norm2}–RS_{norm1},$$

where RS_{norm1} and RS_{norm2} – are the scores after the first and the second examinations, respectively.

Thus, we are turning to the 'ascending' scale. Now, the plus sign "+" of the difference will mean the positive change in the total disability, and the minus sign "–", the negative change. The Rivermead index, taken as the reference, will remain unchanged. The difference in scores after the first and the second examination of the patient will provide information about the changes in the patient's mobility. The «+» plus sign "+" of the difference will mean the positive change in the mobility, and the minus sign "–", the negative change.

Number	Variable	Scale
X_1	Sex	nominal, binary
X_2	Age (years)	Quantitative
X_3	Arterial hypertension (140–160 mmHg)	nominal, binary
X_4	Arterial hypertension (161–180 mmHg)	nominal, binary
X_5	Arterial hypertension (181 mmHg and higher)	nominal, binary
X_6	Arrhythmia	nominal, binary
X_7	Ischemic changes on the ECG	nominal, binary
X_8	Stage 1 chronic heart failure	nominal, binary
X_9	Stage 2a chronic heart failure	nominal, binary
X_{10}	Stage 2b chronic heart failure	nominal, binary
X_{11}	Stage 3 chronic heart failure	nominal, binary
X_{12}	Second stroke in the same territory	nominal, binary
X_{13}	Second stroke in a different territory	nominal, binary
X_{14}	Stroke history	nominal, binary
X_{15}	Lacunar ischemic stroke	nominal, binary
X_{16}	Mini ischemic stroke	nominal, binary
X_{17}	Medium ischemic stroke	nominal, binary
X_{18}	Large ischemic stroke	nominal, binary
X_{19}	Acute cerebrovascular accident in the territory of the left middle cerebral artery	nominal, binary

Table 3. *Composition of factor variables for MWA modeling*
Таблица 3. *Состав факторных переменных для моделирования МВО*

The next stage will be the calculation of the multivariate weighted assessment (MWA) of the changes in the patient's condition. The multivariate array comprises a complex of differences (delta) of the abovementioned indices. The method of calculation of the weighted assessment implies formation of weight factors for each component of the new scale. There exist different approaches to the selection of weights, and the simples and most effective of these is the expert approach. The weight factors are assigned based on an intuitive recognition of comparative importance of components. In our case, it is suggested to determine the weights as follows (with the fixed sum of 1):

$\Delta NIHSS – 0,6;$
$\Delta RS – 0,2;$
$\Delta RMI – 0,2.$

We believe that the NIHSS is the universal tool to assess the patient's condition, whereas the two other factors serve auxiliary, albeit quite important, roles. The equation for the calculation of the MWA of the changes in the condition of a specific patient is as follows:

$$MBO = \Delta NIHSS_{norm}*0,6+\Delta RS_{norm}*0,2+\Delta RMI*0,2.$$

We will consider the proposed method on an example. Let patient A have 10 and 13 points (respectively in the first and second examinations) on the normalized NIHSS scale, 9 and 10 points on the normalized RS index, 13 and 15 points on the RMI index. Thus, the differences (deltas) will have the following values: 3 points on the normalized NIHSS scale, 1 point on the normalized RS index, 2 points on the RMI scale. Below is the calculation of the MWA for patient A:

$$MBO = 3*0.6+1*0.2+2*0.2 =2,4.$$

The MWA was calculated for each patient. We will provide brief data for all private indices (MWA components) and for the normalized scale (**Table 2**).

The algorithm for building the MWA is as follows: selection of components (private indices) for the MWA; normalization of private indices (bringing to the unified scale); recalculation of scores of each private index to normalized scores; calculation of normalized differences (deltas) of assessments for each private index; selection and assignment of weight factors; calculation of MWA.

The next stage of the research was the modeling of the multivariate weighted assessment to identify the major factors influencing its variation. Regression models allow for encompassing a vast variety of factors and for a mathematical expression of their correlation with resultative indicators. We selected the ACVA risk factors in the studied patients, constructed regression models, performed their statistical analysis and evaluated their quality. The models were built specifically for each patient group. The multivariate weighted assessment served as the dependent variable Y. The

Groups	Better condition	Worse condition
Group I	Lacunar ischemic stroke	Stage 2a chronic heart failure Large ischemic stroke
Group II	Mini stroke	Medium stroke
Group III	Stage 1 chronic heart failure	Second stroke in the same territory

Table 4. *The results of multivariate weighted assessment modelling*
Таблица 4. *Результаты моделирования с использованием многомерной взвешенной оценки*

numbering of factored variables was single for all models. The list of cardiovascular risk factors for the modeling is given in **Table 3**.

The major array of factors is represented by nominal binary variables that are included in the models as dummies if needed. For each group of patients, a minimum of two coupled regression models of comparable quality were built with the aim of identifying and qualitatively expressing the multi-directional impact increasing the multivariate assessment or decreasing it, respectively. All models are significant by the F-test, and their parameters are significant by the t-test. The regression model 1 for the Group I is as follows:

$$\hat{Y}_1 = 2{,}678 - 0{,}422X_9.$$
$$(0{,}114) \quad (0{,}182)$$

Explanation of the regression factor. Patients with Stage 2a chronic heart failure have a multivariate weighted assessment approx. 0.422 points lower than that of patients without chronic heart failure.

Regression model 2 for Group I is as follows:

$$\hat{Y}_1 = 2{,}575 - 0{,}571X_{18}.$$
$$(0{,}095) \quad (0{,}287)$$

The diagnosis of 'large ischemic stroke' is a factor aggravating the patient's condition; its multivariate weighted assessment will be 0.571 points lower, on average, than that of patients with less severe forms of stroke.

Regression model 3 for Group I is as follows:

$$\hat{Y}_1 = 2{,}388 + 0{,}466X_{15}.$$
$$(0{,}104) \quad (0{,}201)$$

If the patient had a lacunar ischemic stroke, their multivariate weighted assessment will be approx. 0.466 points higher, on average, than that of patients with more severe forms of stroke.

Thus, from the perspective of a more favorable condition of a patient from Group I, the presence of lacunar ischemic stroke is significant, and adverse effects on the patient's condition will be expected from Stage 2a chronic heart failure and history of a large ischemic stroke.

Regression model 1 for the Group II is as follows:

$$\hat{Y}_1 2 = 3.065 - 0.572X_{17}.$$
$$(0.239) \quad (0.263)$$

Patients with a medium ischemic stroke have a multivariate weighted assessment that is 0.572 points lower, on average, than that of patients with other types of stroke.

Regression model 2 for the Group II is as follows:

$$Y_2 = 2.530 + 1.115X_{16}.$$
$$(0.200) \quad (0.393)$$

Patients diagnosed with mini ischemic stroke, when compares to patients with other types of stroke, have a multivariate weighted assessment that is on average 1.115 points higher. It can be concluded that for the patients of Group II two types of stroke have a varied impact on their overall condition: medium stroke in the decline of their condition, mini stroke in the improvement.

Regression model 1 for the Group III is as follows:

$$Y_3 = 2.206 - 3.235X_{12}.$$
$$(0.274) \quad (1.858)$$

Second stroke in the same territory reduces the patient's multivariate weighted assessment by approx. 3.235 versus patients without the second stroke or with the second stroke in a different territory.

Regression model 2 for the Group III is as follows:

$$Y_3 = 1.852 + 1.305X_8.$$
$$(0.303) \quad (0.650)$$

The diagnosis of Stage 1 chronic heart failure was a factor of a better condition of a patient by an average of 1.305 points (vs. patients with other stages of CHF). In this way, the modeling results showed that for the patients from Group III the most negative influence on their condition was caused by the second stroke in the same territory, and the favorable influence, by Stage 1 chronic heart failure as compared to more severe stages of CHF. The results of our modeling follow in **Table 4**.

DISCUSSION

Constrictive lesion of the major arteries of the head and the neck per se is a significant risk factor of ACVA development [15, 16]. The risk increases depending on the decree of vessel constriction [6]. The onset and progress of ischemic strokes are influenced by other adverse risk factors of ACVA, mainly of vascular nature: arterial hypertension of various severity, chronic heart failure of various severity, cardiac arrhythmia, history of ACVA, etc. [8, 10, 12]. In analyzing the problem of interrelation of carotid stenosis and ischemic stroke, contemporary studies mainly focus on the surgical aspect only, viz. carotid endarterectomy and its role in the post-stroke prognosis and rehabilitation [17, 18].

To evaluate the condition of a stroke patient, clinical scales (indices) are used and changes of their values over time are considered; without doubt, this provides information for the planning of treatment and control of its efficiency. Much interest lies in the combination of all three private indices in a single multivariate assessment and in the analysis of its values for the selected groups of patients. Regression models enable involvement of a wide variety of factors and mathematical representation of their connection with resultative values. When analyzing the available literature, we could not find similar studies. At the same time, this aspect of studying the results and prognosis of the progress of ischemic stroke with concurrent carotid stenosis of various severity seems vital and requiring more effort.

CONCLUSION

Mathematical modeling involving development of a multivariate weighted assessment facilitates the determination of the influence of one or another risk factor for stroke on the course of ischemic stroke in patients with varying degrees of carotid stenosis.

Regression models enable involvement of a wide variety of factors and a mathematical representation of their connection with resultative values. The developed logistic models show the degree of positive or negative impact of various risk factors on the course of ischemic stroke in the studies groups of patients.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Ethical expertise. Minutes No. 202 of the meeting of the Committee on Bioethics at SamSMU dated October 09, 2019.	***Этическая экспертиза.*** Протокол №202 заседания комитета по биоэтике при СамГМУ от 09 октября 2019 г.
Study funding. The study was the authors' initiative without external funding.	***Источник финансирования.*** Работа выполнена по инициативе авторов без привлечения финансирования.
Conflict of Interest. The author declares that there are no obvious or potential conflicts of interest associated with the content of this article.	***Конфликт интересов.*** Автор декларирует отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Contribution of individual authors. I.E. Poverennova, T.V. Romanova – developed the study concept, performed detailed manuscript editing and revision; A.S. Tkachenko, N.P. Persteneva – has been responsible for scientific data collection, its systematization and analysis, wrote the first draft of the manuscript; manuscript editing. All authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	***Участие авторов.*** И.Е. Повереннова, Т.В. Романова – разработка концепции исследования, редактирование текста. А.С. Ткаченко, Н.П. Перстенева – сбор и обработка научного материала, написание текста, редактирование текста. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.

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Клинический случай | Case report
DOI: https://doi.org/10.35693/SIM642748

Possibilities of laparoscopic simultaneous surgery in the treatment of rectal cancer

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Abstract

Colorectal cancer (CRC) with synchronous liver metastases remains a complex problem in modern oncology. Minimally invasive simultaneous surgeries are increasingly considered as an effective approach to treating this category of patients.

The article describes a clinical case in which laparoscopic simultaneous surgery was performed for rectal cancer with solitary liver metastasis. The patient successfully underwent simultaneous laparoscopic-assisted intra-abdominal rectal resection, with left hemihepatectomy, with resection of SV and SVIII of the right lobe of the liver.

The presented case demonstrates the effectiveness of laparoscopic access in performing simultaneous surgeries in patients with CRC and synchronous liver metastases. Further work in this direction will allow us to define more clearly the place of laparoscopy in performing simultaneous operations in surgical oncology.

Keywords: colorectal cancer, liver metastases, simultaneous operations, laparoscopic access.

Conflict of Interest: nothing to disclose.

Citation
Valiev AA, Gataullin BI, Zankina AP, Gataullin IG, Khasanov RSh, Valitov BR. **Possibilities of laparoscopic simultaneous surgery in the treatment of rectal cancer.** *Science and Innovations in Medicine.* 2025;10(1):37-43.
DOI: https://doi.org/10.35693/SIM642748

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Abbreviations
CRC – colorectal cancer; BMI – body mass index; CEA – carcinoembryonic antigen; MRI – magnetic resonance imaging; CT –computed tomography; ALT – alanine aminotransferase; AST – aspartate aminotransferase.

Received: 10.12.2024
Accepted: 08.01.2025
Published: 17.01.2025

Возможности лапароскопической симультанной хирургии в лечении рака прямой кишки

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Аннотация

Колоректальный рак (КРР) с синхронными метастазами в печень остается сложной задачей современной онкологии. Минимально инвазивные симультанные хирургические вмешательства все чаще рассматриваются как эффективный подход к лечению данной категории пациентов.

В статье описан клинический случай, в котором было выполнено лапароскопическое симультанное оперативное вмешательство по поводу рака прямой кишки с солитарным метастазом в печень. Пациенту была успешно произведена симультанная лапароскопически-ассистированная внутрибрюшная резекция прямой кишки, с гемигепатэктомией слева, с резекцией SV и SVIII правой доли печени.

Представленный случай демонстрирует эффективность лапароскопического доступа при выполнении симультанных операций у пациентов

с КРР и синхронными метастазами в печень. Дальнейшая работа в данном направлении позволит более четко обозначить место лапароскопии при выполнения симультанных операций в онкохирургии.

Ключевые слова: колоректальный рак, метастазы печени, симультанные операции, лапароскопический доступ.
Конфликт интересов: не заявлен.

Для цитирования:
Валиев А.А., Гатауллин Б.И., Занькина А.П., Гатауллин И.Г., Хасанов Р.Ш., Валитов Б.Р. **Возможности лапароскопической симультанной хирургии в лечении рака прямой кишки.** *Наука и инновации в медицине.* 2025;10(1):37-43.
DOI: https://doi.org/10.35693/SIM642748

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Список сокращений
КРР – колоректальный рак; ИМТ – индекс массы тела; РЭА – раковый эмбриональный антиген; МРТ – магнитно-резонансная томография; S – сегмент; ЧКН – частичная кишечная непроходимость; ECOG – Eastern Cooperative Oncology Group; АЛТ – аланинаминотрансфераза; АСТ – аспартатаминотрансфераза; КТ – компьютерная томография.

Получено: 10.12.2024
Одобрено: 08.01.2025
Опубликовано: 17.01.2025

BACKGROUND

Oncological diseases remain the leading cause of morbidity and mortality worldwide. As per assessments of Globocan 2022, there were 20 new cases of the disease registered in the world in 2022, and 9.7 million deaths from cancer [1].

According to A.D. Kaprin, V.V. Starinsky et al. (2024), in Russia, in the structure of overall cancer morbidity the rate of cancer of the rectum, recto-sigmoid junction and the anus (C19-21) in 2023 was 128.1 people per 100,000 population, and the rate of the malignant neoplasm of the colon (C18) was 172.0 people per 100,000 population.

One-year mortality in patients with colorectal cancer (CRC) was 20.6% (C19-21) and 18.2% (C18) [2].

At the moment of diagnosis, 20% to 30% CRC patients have synchronous distant metastases. In 30-50% patients who had undergone surgical treatment of CRC, during the follow-up progression of the malignant process is identified in the form of liver metastases [3]. The resectability of metastatic lesions in the liver is 15-20% [4].

As long as 30 ago, the overall survival rate of patients with metastatic CRC was low, but the development and implementation of new strategies of combined therapy allowed an increase of the number of patients eligible for radical treatment [5-7].

According to M.G. Efavon et al. (2019), the comparison of laparoscopic and open methods of liver resection to remove CRC metastases shows the following: performance of the least invasive resection surgery of the liver does not affect the long-term outcome, but improves relapse-free survival and enables a decrease of the operational trauma, which requires less time of in-patient care [8].

Today, one of the leading methods of radical treatment of CRC patients with metastases to the liver remains the surgery, i.e. liver resection of some extent. Lately, there have been more references to the advisability of performing combined treatment for this group of patients [3-10].

The article presents a case study of laparoscopic simultaneous surgery in the treatment of the rectal cancer with a solitary metastasis to the liver. The work was performed in the Republican Clinical Oncologic Dispensary named after Prof. M.Z Sigal.

CLINICAL CASE

Patient X, 53-year-old male, body mass index (BMI) of 24.1 was admitted to the hospital with complaints of constipation, abdominal tympany, episodic blood in the stool, and abnormal urination (sense of incomplete emptying of the bladder).

Preoperative Examination

Following the results of the videocolonoscopy and biopsy, a circular obstructive tumor was identified 11 cm from the sphincter ani externum, obstructing 3/4 of the bowel lumen. Preoperative histology: moderately differentiated adenocarcinoma.

Findings of laboratory examinations: the level of carcinoembryonic antigen (CEA) was 26.07 ng/ml, and the level of cA 19-9 was 3.7 units/ml. Findings of magnetic resonance imaging (MRI) of the pelvic organs with contrasting (**Fig. 1**): in the rectum, at the height of 95 mm from the anus and higher, at a length of approx. 80 mm, there is a deformation and an uneven infiltrative thickening of the walls up to 20 mm that affected all layers, with a moderate obstruction of the bowel lumen; with intravenous contract administration, it accumulated the contrast in an unevenly intensive way. In the affected area, the outer contours of the bowel are uneven and indistinct, with signs of invasion to the mesorectal fascia. Pelvic vessels have no pathological changes. Enlarged mesorectal lymph nodes up to 11×7 mm are visualized. Conclusion: locally advanced rectum cancer, metastases to mesorectal lymph nodes; benign hyperplasia of the prostate.

Findings of contrast-assisted computed tomography (CT) of the abdomen: the liver is of regular size, shape and position. Hepatic veins and branches of the portal vein are differentiated distinctly with no abnormalities. Density is without abnormalities. In the Segment IV (SIV) of the liver, there was identified an 86×84 mm hypovascular segment accumulating contrast (**Fig. 2**). On the border between SVIII and SVII, a 6×5 mm cyst is identified. Conclusion: solitary focus of metastasis to the liver.

Preliminary diagnosis: C20, cancer of the rectum complicated by partial obstruction of the bowel. Solitary metastasis to the liver cT3N1M1 stage 4, clinical group II. Condition is after an event of intestinal bleeding.

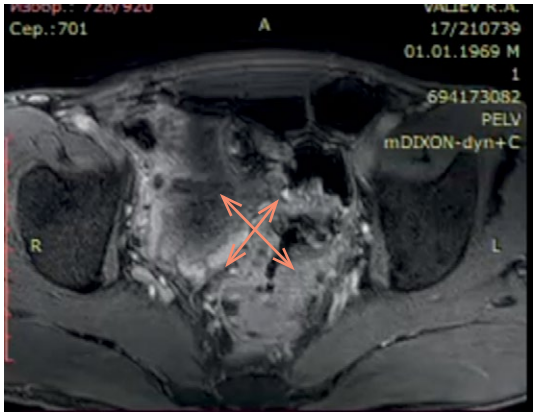

Figure 1. *MRI of the pelvis. Picture of locally advanced rectal cancer (indicated by arrows).*

Рисунок 1. *МРТ малого таза. Картина местнораспространенного рака прямой кишки (указано стрелками).*

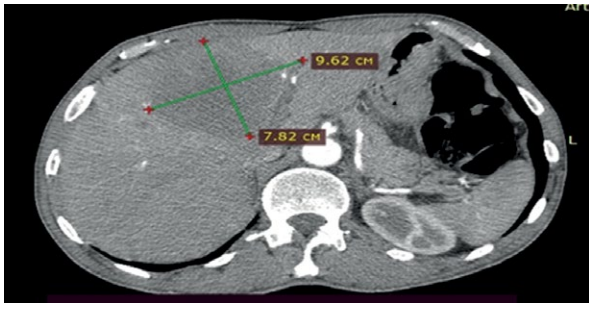

Figure 2. *Computed tomography. Metastasis focus in the left lobe of the liver (indicated by arrows).*

Рисунок 2. *Компьютерная томография. Очаг метастазирования в левой доле печени (указано стрелками).*

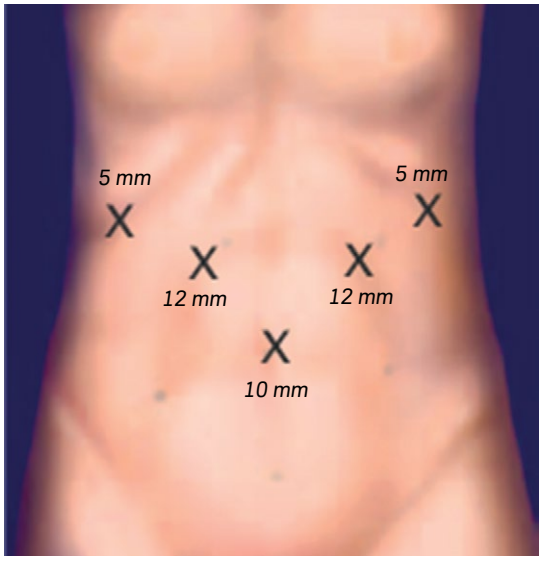

Figure 3. *Trocar placement points. Liver resection stage.*

Рисунок 3. *Точки установки троакаров. Этап резекции печени.*

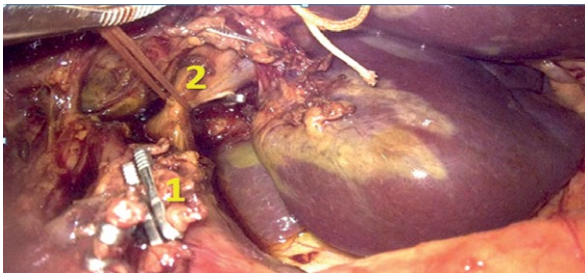

Figure 4. *1 – stump of the left lobar hepatic artery, 2 – left lobar branch of the portal vein on the tourniquet.*

Рисунок 4. *1 – культя левой долевой печеночной артерии, 2 – левая долевая ветвь воротной вены на турникете.*

Figure 5. *Dissection of the liver parenchyma with clipping of intraparenchymal vessels.*

Рисунок 5. *Рассечение паренхимы печени с клипированием интрапаренхиматозных сосудов.*

Following the results of the oncological interdisciplinary consultation, the decision was made to carry out surgical treatment as the first stage.

Standard preoperative preparation of the patient was carried out in the hospital setting. The detailed assessment of the physical status of the patient included Echo CG, ultrasound examination of the vessels of lower extremities, consultations with the primary care doctor and the anesthesiologist-reanimatologist. No contraindications to this type of surgery were found, ECOG performance status was 0.

Surgical treatment was performed in the following extent: simultaneous nerve-sparing laparoscopic-assisted intra-abdominal rectal resection, with left hemihepatectomy, with resection of SV and SVIII of the right lobe of the liver.

Surgical Technique

Liver Resection Stage

The patient is positioned on the operating table. The patient's lower limbs are spread apart. The surgeon takes a position between the patient's spread legs, the first assistant is on the left side of the patient, the second assistant with a video camera is on the right side of the patient. The monitor is located on the side of the patient's head.

Access with five ports was used. The positioning of the trocars for the resection of the liver (**Fig. 3**) included placement of the optical port in the area of the navel ring, and placement of two 5 mm ports in the right and left subcostal areas 2 cm below the costal arch. Between the 5-mm ports

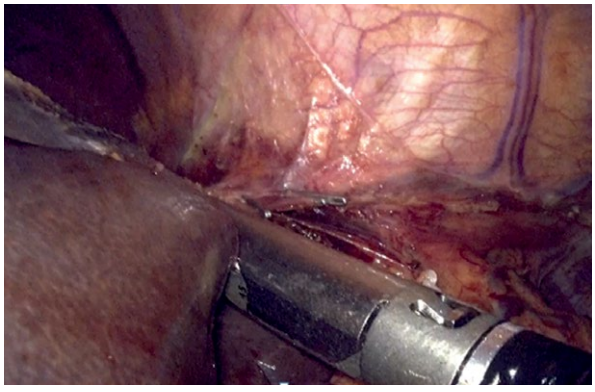

Figure 6. *Crossing of the left and middle hepatic veins.*
Рисунок 6. *Пересечение левой и средней печеночных вен.*

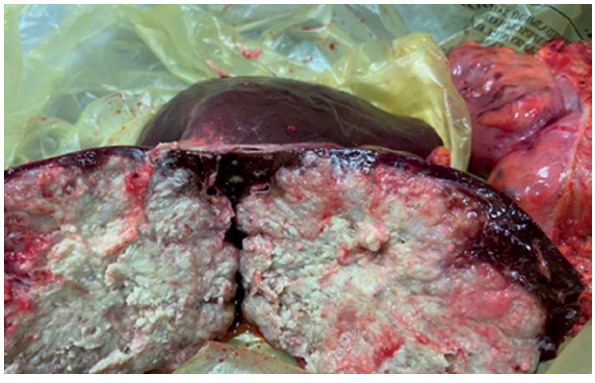

Figure 7. *Sectional liver preparation.*
Рисунок 7. *Препарат печени на срезе.*

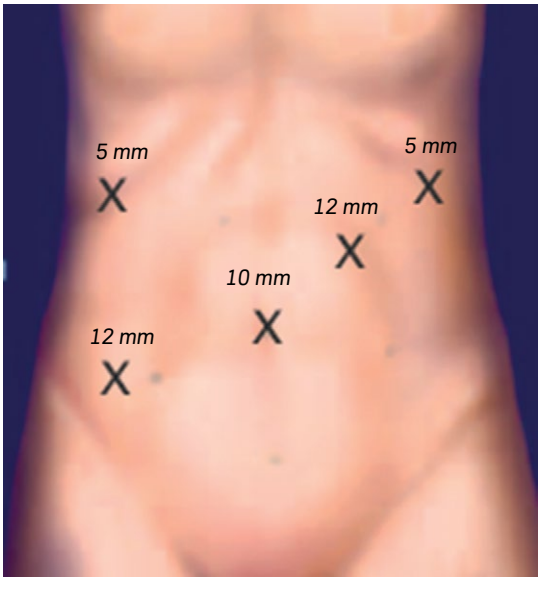

Figure 8. *Trocar placement points. Bowel resection stage.*
Рисунок 8. *Точки установки троакаров. Этап резекции кишечника.*

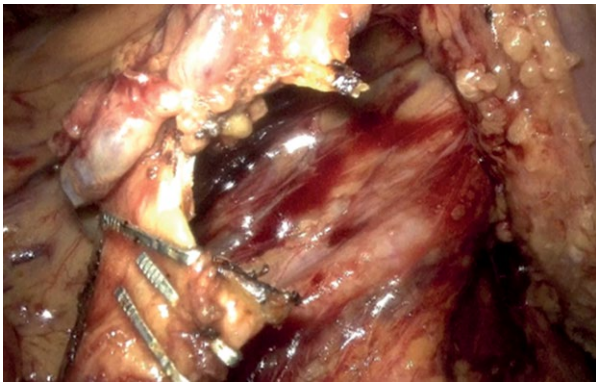

Figure 9. *Clipping of the inferior mesenteric artery.*
Рисунок 9. *Клипирование нижней брыжеечной артерии.*

and the optical port, 2 cm below the median line, two 12-mm ports are located.

During the revision, a solitary metastatic focus is identified that occupies practically the entire SIV of the left lobe spreading to the SV and SVIII of the right lobe, the size is 7×8 cm.

Resection of the liver started with the mobilization of the left lobe. The attachments were dissected using the "Harmonic" ultrasonic dissector: the round ligament, the falciform ligament and the left triangular ligament of the liver were transected. The elements of the hepatoduodenal ligament were skeletonized and lymph node dissection was performed.

The left lobar hepatic artery and, left lobar branch of the portal vein and the left bile duct were isolated and clipped in succession (**Fig. 4**).

While inspecting the parenchyma of the liver, a clear demarcation zone was identified at the blood supply boundary. The liver parenchyma was dissected with the bipolar coagulating tool Aesculap Caiman (**Fig. 5**) along the demarcation line with sequential clipping of isolated intraparenchymal vessels.

Left-side hemohepatectomy was performed with resection of the SV, SVIII. The left and the middle hepatic veins were visualized which were crossed and stapled with the Echelon Stapler (**Fig. 6**).

The preparation was placed in the container (**Fig. 7**). The distance from the edge of resection to the metastatic focus is 1 cm. The wound surface was covered with "TachoComb" hemostatic plates (2 plates). The duration of this stage of the operation was 120 minutes, the intraoperative blood loss was 350 ml.

Rectal Resection Stage

The patient's lower limbs are spread apart and fixed in a flexed position at the hip and knee joints using supports. The surgeon took the position to the right of the patient, the first assistant to the left of the patient, the second assistant with a video camera to the left at the head end of the operating table. The monitor was located at the patient's feet. The position of the trocars for bowel resection was changed (**Fig. 8**).

Figure 10. *View of the postoperative wound after the stitches have been removed.*
Рисунок 10. *Вид послеоперационной раны после снятия швов.*

The patient was placed in the Trendelenburg position (lying on the back at an angle of up to 45°). In the course of the operation, during the revision, 2 cm above the pelvic area of the abdomen the tumor of the rectum is identified. The tumor grows into the serous membrane of the rectum.

Using the "Harmonic" ultrasonic dissector and the unipolar coagulation tool, the descending colon and the sigmoid colon were mobilized. The rectum is mobilized to the diaphragm of the pelvis with total mesorectumectomy. The inferior mesenteric artery was mobilized with lymph nodes attached to the preparation; then it was clipped and transected at the mouth (**Fig. 9**).

Lymph node dissection in the D2 volume was performed. With an offset of 5 cm below the tumor edge, the rectum was transected with the linear cutter stapler "Echelon 60". To remove the gross specimen, minilaparotomy access was performed in the hypogastrium. The mobilized colon was taken to the wound; the colon was transected 20 cm above the tumor. The specimen was removed en bloc. Also the specimen of the left love of the liver with the metastatic lesion was removed. Using the circular stapler, 'end to end' descendo-recto anastomosis was constructed. A retroperitoneal drainage was installed in the small pelvis area. Peritonization of the pelvic peritoneum was performed. Drainages to the small pelvis and subhepatic space were installed. The duration of this stage was 70 minutes; the blood loss was 30 ml.

Post-operative Period

This period proceeded without complications. One day after the operation, the patient was transferred from the intensive care unit to a common ward. The post-surgery follow-up included daily examinations with change of dressing, control of vital signs and clinical analyses of blood. During the first 48 hours, pain was managed with narcotic and non-narcotic analgesics. Also, the post-operative period included thromboprophylaxis, infusion therapy, antibiotic therapy, and administration of hepatoprotective agents (Ademetionine).

The vital signs monitored included arterial blood pressure, heart rate, breathing, and body temperature.

In the first day, 200 ml of hemorrhagic drainage was drained, in the second day, 50 ml of serous drainage, on the third day, trace amounts of serous drainage. The drainages were removed on the fourth day after the surgery. The early activation of the patient started 24 hours after the operation. The bowel movement restored on the second day, and full mobility restored 30 hours after the operation. The first intake of liquid food was performed one day after the operation. On the fifth day, a control ultrasonic inspection of the abdominal organs was performed. Following the inspections, no free fluid and pathological changes were identified.

On the fifth day of the postoperative period, the levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in the blood decreased and came back to normal. The blood values were normal.

The data of post-operative histology were as follows: highly differentiated adenocarcinoma of the rectum, the tumor grows into the submucosal and muscular layers with invasion to the fatty tissue (pT3). In the 14 examined regional lymph nodes, no tumor elements were found. In the liver, there was the metastasis of the enteric adenocarcinome. No signs of tumor growth were identified in the edges of resection lines (pT3 N0 M1 Stage 4).

Genetic studies of the KRAS, NRAS, BRAF genes were performed and found no mutations (wild type). Microsatellite instability (MSI) was also not found. The surgical wound has no signs of inflammation (**Fig. 10**).

On the 11th day, the patient was discharged in satisfactory condition to be followed up by the local oncologist. Furthermore, adjuvant chemotherapy under the XELOX regimen was prescribed (6 cycles) that the patient tolerated fairly well. As the patient was followed up (10 months after the surgery), there were no findings of progression or relapse.

DISCUSSION

The case reviewed above demonstrated the efficiency of laparoscopic access in the performance of simultaneous surgeries in patients with colorectal cancer and synchronous metastases into the liver. With the proper selection of patients, availability of required equipment, trained and sufficiently experienced specialists, it is possible to secure acceptable immediate results in the performance of such surgeries with a low-invasive access.

It is to be noted, that the use of the laparoscopic access allowed for the restoration of the patient's mobility and possibility of adequate nutrition within the first week of the post-operative period [10].

The use of laparoscopic methods in simultaneous surgeries allows for a reduced time of patients' staying in the surgical department and prepare them for the subsequent specialized therapy in the minimal time possible.

The latest developments in the laparoscopic surgery, anesthesiology and intensive therapy have rendered simultaneous colorectal cancer resections with resections of the liver more safe and efficient, and comparable in terms of hospitalization time and post-surgery complications with open surgery [11,12].

We performed similar surgical interventions in 11 patients with colorectal cancer with synchronous metastases to the liver in the period from 2021 to 2024. The operations also demonstrated positive outcomes with reduced hospital time and thus were an efficient and safe component of the complex therapy for this category of patients.

Simultaneous radical interventions combined with other treatment methods (systemic anti-cancer drug therapy) allow achievement of 42% overall five-year survival rate [13].

In the opinion of S.V. Gorchakov et al., there have been more and more reports as to the possibility and practicability of synchronous surgeries in patients of this category [14].

The majority of foreign studies found no significant difference in the rate of complications in simultaneous laparoscopic surgery as compared to the open surgery [15].

CONCLUSION

Laparoscopic simultaneous surgeries of the colorectal cancer with synchronous metastases have their proper specifics. The question of the optimal type of surgical treatment for a patient leaves room for argument. Further work in this area will allow a better understanding of the place of laparoscopy in the performance of simultaneous operations in surgical oncology.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Study funding. The study was the authors' initiative without external funding.	***Источник финансирования.*** Работа выполнена по инициативе авторов без привлечения финансирования.
Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	***Конфликт интересов.*** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Информированное согласие на публикацию. Авторы получили письменное согласие пациента на публикацию в журнале медицинских данных и фотографий в обезличенной форме.	***Consent for publication.*** Written consent was obtained from the patient for the depersonalized publication of relevant medical information and all of accompanying images in the journal.
Contribution of individual authors. Valiev A.A., Khasanov R.Sh., Gataullin I.G. – concept and design of the study, editing the text of the article. Valiev A.A., Gataullin B.I. – statistical processing of materials, writing the text of the article. Zankina A.P., Valitov B.R. – collection and processing of materials. All authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	***Участие авторов.*** Валиев А.А., Хасанов Р.Ш., Гатауллин И.Г. – концепция и дизайн исследования, редактирование текста статьи. Валиев А.А., Гатауллин Б.И. – статистическая обработка материалов, написание текста статьи. Занькина А.П., Валитов Б.Р. – сбор и обработка материалов. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.

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Научный обзор | Review
DOI: https://doi.org/10.35693/SIM501769

Delayed reconstruction of pharyngeal and pharyngoesophageal defects in patients with malignant neoplasms of the larynx and laryngopharynx after laryngectomy

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Abstract

Aim of the review – to investigate the current surgical approaches and complications of delayed reconstruction of pharyngeal and pharyngoesophageal defects in patients with malignant neoplasms of the larynx and laryngopharynx after laryngectomy using different reconstructive materials.

The most frequent complication after delayed reconstructive surgery was anastomosis incompetence with subsequent formation of fistula and stricture. The causes of this complication in the presence of viability of reconstructive plastic material included postradiation changes, inflammatory process in the tissues in the defect area, weakened nutritional status of the patient and a number of other reasons.

When planning delayed reconstruction of pharyngeal defects, a personalized approach is necessary in each clinical case in choosing the timing and type of plastic material.

Keywords: greater pectoral muscle flap; radial forearm flap; plastic material; anterolateral thigh flap.

Conflict of interest: nothing to disclose.

Citation
Kaganov OI, Sidorenko AO, Orlov AE, Makhonin AA, Gabrielyan AG. **Delayed reconstruction of pharyngeal and pharyngoesophageal defects in patients with malignant neoplasms of the larynx and laryngopharynx after laryngectomy.** *Science and Innovations in Medicine*. 2025;10(1):44-49.
DOI: https://doi.org/10.35693/SIM501769

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Abbreviations
PM – plastic material; PMCC flap – pectoralis major myocutaneous flap. RFFF – radial forearm free flap; ALT flap – anterolateral thigh flap.

Received: 20.06.2023
Accepted: 22.08.2023
Published: 07.02.2024

Отсроченные реконструкции фарингеальных и фарингоэзофагеальных дефектов у пациентов со злокачественными новообразованиями гортани и гортаноглотки после ларингэктомии

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Аннотация

Цель обзора – изучить существующие хирургические подходы и осложнения при отсроченной реконструкции фарингеальных и фарингоэзофагеальных дефектов у пациентов со злокачественными новообразованиями гортани и гортаноглотки после ларингэктомии с применением различного реконструктивного материала.

Наиболее частыми осложнениями после отсроченных реконструктивных операций являются несостоятельность анастомоза с последующим формированием свища и стриктуры. К причинам возникновения данных осложнений при наличии жизнеспособности реконструктивного пластического материала можно отнести постлучевые изменения, наличие воспалительного процесса в тканях в области дефекта, ослабленный нутритивный статус пациента и ряд других причин.

Таким образом, при планировании отсроченной реконструкции дефектов глотки в выборе сроков и вида пластического материала необходим персонифицированный подход в каждом клиническом случае.

Ключевые слова: лоскут большой грудной мышцы; лучевой лоскут предплечья; пластический материал; переднелатеральный лоскут бедра.

Конфликт интересов: не заявлен.

Для цитирования:
Каганов О.И., Сидоренко А.О., Орлов А.Е., Махонин А.А., Габриелян А.Г. **Отсроченные реконструкции фарингеальных и фарингоэзофагеальных дефектов у пациентов со злокачественными новообразованиями гортани и гортаноглотки после ларингэктомии.** *Наука и инновации в медицине.* 2025;10(1):44-49. DOI: https://doi.org/10.35693/SIM501769

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БГМ – большая грудная мышца; ЛЛП – лучевой лоскут предплечья; ПМ – пластический материал; ПЛБ – переднелатеральный лоскут бедра.

Получено: 20.06.2023
Одобрено: 22.08.2023
Опубликовано: 07.02.2024

BACKGROUND

Laryngeal cancer is the most common localization among malignant neoplasms of the head and neck organs. The incidence of malignant growths of the larynx and laryngeal section of the pharynx is growing over time in Russia; e.g., in 2021 it was 29.1 and 12.8 per 100,000 population [1]. The detection rate of laryngeal and hypopharyngeal cancer at stages three and four in 2021 was 58% and 83%, respectively [2]. Unfortunately, failure to seek medical help in a timely manner leads to advanced stages of laryngeal and hypopharyngeal cancer. In cases of localized cancer of the larynx and hypopharynx, clinical recommendations entail chemo- or chemoradiation therapy. In cases of regional cancer of the larynx and hypopharynx, the presence of constriction and dysphagia requires extensive combined surgeries that include removal of the larynx with resection of the pharynx, esophagus and tissues of the oropharyngeal region [3]. Patients with localized cancer of the larynx and hypopharynx after combined and combined extensive surgeries are not always recommended single-stage grafting of the formed defects of the pharynx and the esophagus die to the weakened nutritive status; quite often thin may lead to formation of pharyngeal or pharyngo-esophageal defects in the post-surgery period [3]. These defects may include a pharyngostoma, pharyngo-esophagostoma, tracheostoma, constant salivation, feeding through a nasogastric tube, and significantly deteriorate the quality of the patient's life contributing to a psychological trauma. This necessitates a search of new approaches towards surgical rehabilitation and treatment of such patients. One of the major tasks to restore the lost or weakened functions in patients is the reconstruction of the digestive tract [4]. There are numerous plastic methods of reconstructing the pharyngeal and pharyngo-esophageal defects; unfortunately, post-radiation complications and the aggressive environment of the mouth cavity and the pharynx concurrent with suppression of reparative processes in the weakened cancer patients significantly exacerbate the post-surgery period and result in anastomotic leakage and formation of pharyngostoma or pharyngo-esophagostoma. Therefore, the process of selection of the plastic material (PM) for each patient requiring the defect reconstruction, should be personalized to avoid complications [4, 5].

AIM

To investigate the current surgical approaches and complications of delayed reconstruction of pharyngeal and pharyngo-esophageal defects in patients with malignant neoplasms of the larynx and laryngopharynx after laryngectomy using different reconstructive materials.

TYPES OF DEFECTS

In modern literature, there are various classifications of pharyngo-esophageal defects, in which it is necessary to focus on the shape, size and structure of the pharyngeal defect. The classification that is most frequently used in the selection of plastic materials for the reconstruction of pharynx defects is the Blackwell and Urken classification. It identifies the following types of pharyngo-esophageal defects: type 0 – small defects closed primarily without the introduction of tissue; type 1 – non-circumferential defects that preserve a viable strip of mucosa from the hypopharynx to the cervical esophagus; type 2 – circumferential defects extending from the vallecula, i.e. the depression between the root of the tongue and the lingual surface of the epiglottis, to the thoracic inlet; type 3 – circumferential defects that extend from the level of the vallecula cranially to the oropharynx; type 4 – extensive defects that extend below the clavicles to the thoracic esophagus [5, 6]. In the work of M.V. Ratushny, this classification was systematized, and three types of defects were proposed. The first type is formed after

laryngectomy with the wall of the hypopharynx preserved. The second type is formed after laryngectomy without preservation of the hypopharynx walls. The third type is formed after multi-organ resections [6–8].

METHODS OF DELAYED RECONSTRUCTION OF PHARYNGEAL AND PHARYNGO-ESOPHAGEAL DEFECTS

In case of Blackwell and Urken Type 0 defects, local plastic material is used, i.e. tissues near the defect. This is a simple yet efficient technique available to majority of surgeons; it may be performed in a smaller less sophisticated operating room. Nevertheless, this type of plasty entails frequent formation of post-operative fistulae and strictures. Besides, this method is applicable to close only minor defects due to small quantities of plastic material [8, 9]. However, N. Süslü et al. (2016) showed in 602 patients that the early enteral feeding may be started even if local tissue is used as plastic material. In these patients, early enteral feeding was started within three days after the operation, and the incidence of fistulae was approx. 11% [9]. With this type of defect, complications are usually related with radiotherapy or severe concurrent pathologies.

In case of Blackwell and Urken Type 1 defects, it is possible to use deltopectoral, pectoral, thoracodorsal and radial flaps [5, 6, 9–11].

The 10-year "Swee Keong Kang" study included 73 patients (80% males) who had undergone the reconstruction of pharyngeal and pharyngo-esophageal defects with the use of the deltopectoral flap. 13 patients developed minor complications, such as leakages of anastomotic sutures, of which 10 were treated conservatively and 3 required additional reconstruction. In 13 patients, a pharynx to skin fistula developed, and in 6 patients, constriction of the 'neopharynx' [12]. The advantages of the deltopectoral flap include the technical simplicity of forming the large-size flap; thin and flexible structure that fits well the cover tissue of the head and the neck in texture and color; no muscular structures of the chest and the shoulder are affected in harvesting the flap; the donor area is not located in the open parts of the body and may be concealed under clothing. The disadvantages include deformation of cover tissue in the donor area, specifically, in women this may result is cicatrical deformation of the breast and the nipple, and in men, in an increased hairiness: growth of hairs in the reconstruction area might bring discomfort [13, 14].

Some authors used the thoracodorsal flap involving the latissimus dorsi, predominantly in women, to eliminate deformation of the breast and formation of cicatrical tissue in the thoracic wall that occur after the plasty with the pectoral flap. This method, however, involves a major disadvantage: the harvesting of the material requires changing of the patient's position on the surgical table [15, 16].

One of the most frequently used flaps is the pectoralis major myocutaneous flap (PMCC flap). The study by G. Montemari et al. (2012) involved a retrospective analysis of 45 reconstructions of pharyngeal defects with the use of PMCC flap performed from February 1995 to February 2008. Post-surgery complications related to the use of the flap were seen in 6.7% of the cases. The frequency of complications that required surgical revision was 2.2%. Two minor complications were found: constriction of the 'neopharynx' and formation of the fistula, both of these were rectified without surgical intervention. No complete or partial necrosis occurred in any of the cases. In the rest of the cases, the X-ray examination of the esophagus showed absence of fistulae and an adequate bore of the digestive tract. Eating through the mouth started on day 10–12 after the operation with no problems of swallowing of liquid or solid food. Post-surgery radiation therapy performed in 30 patients was accepted well [17, 18].

PMCC flap is a safe, reliable and often used material providing a good volume of tissue. It does not entail microvascular technique and significantly reduces the surgical intervention time as compared to free flap reconstruction. Significant disadvantages, however, include the bulkiness of the donor site and unsatisfactory functional results compared to free flaps, both in terms of speech and swallowing. Besides, there complications were reported in the donor site that could affect the movement amplitude in the upper extremity [18, 19]. An alternative method of tissue replacement in the pharyngeal and pharyngo-esophageal defects is the use of the radial forearm free flap (RFFF). It is considered to be safe, relatively easy to handle among other free flaps, flexible and reliable, with a rather long pedicle. The major drawback of this method of tissue reconstruction is the delicate nature of the donor site that requires a very careful elevation of the flap and that might result in post-surgery complications: these may seriously affect the function of the arm and, therefore, the quality of life. Besides, the RFFF requires a proper technical training on part of the surgeon, a large surgical crew, and a considerably long time of the surgery [20, 21].

In their study, Jerry W. Chao et al. (2015) reviewed the literature on delayed reconstruction of pharyngeal and pharyngo-esophageal defects with the use of PMCC and RFF flaps. The analysis of integrated data showed that in 301 patients after the restoration with PMCC flap, fistulae were found in 24.7% of the cases, and reintervention was required in 11.3% of the cases. In 605 patients for whom RFF flap as used as restorative material, fistulae were found in 8.9% of the cases, and reintervention was needed in 5.5% of the cases. The was no difference in the incidence of strictures and in the transition to normal diet when these flaps were used [22].

Patients with Blackwell and Urken Type 1 defects may experience complications with any kind of restorative material. The structure of complications has no visible differences. The onset of complications may be related to a number of factors, e.g. post-radiation changes in the tissue, severe concurrent conditions, weakened nutritive status, presence of inflammation and intoxication of the organism. However, there are no publications that assess the causes of post-surgery complications related to restorative material [23, 24].

In cases of Blackwell and Urken Types 2, 3 and 4 defects after the circumferential resection of the hypopharynx and the cervical esophagus, a more radical approach towards reconstructive surgery is needed. Restoration of these kinds of defects widely involve visceral flaps, viz. jejunal flap, and gastroepiploic flap [25, 26]. Rachel J. Walker et al. (2014) performed a retrospective analysis of complications in 104 patients after reconstruction of pharyngo-esophageal defects with the use of the jejunal flap. Out of the 104 patients, early complications involving the use of the flap were identified in 14 (13%) patients, but the survival of the flap was 97%. 11 (11%)

patients developed a fistula on average in 15 days following the surgery, and 11 (11%) patients had minor complications in the donor site. A total of 95 (91%) patients were able to resume oral alimentation at the time of discharge [27]. The jejunal flap has a long vascular pedicle of an adequate diameter that allows for the use of the flap in case of large defects while providing low complication rate. The flap also retains some peristaltic action; however, it does not coordinate with other tissues, which might cause problems with swallowing.

In their study, J.M. Viñals Viñals et al. (2017) performed a retrospective analysis of clinical cases of patients who had undergone pharynx and esophagus reconstruction with the use of the gastroepiploic free flap after laryngopharyngectomy for pharynx or larynx cancer in the period from 1992 to 2012. In two cases, abdominal evisceration was observed, whereas other patients experienced no abdominal complications. In 3 (11.5%) of patients, total necrosis of the flap was observed. In 20 patients, the post-surgery period had no complications [28].

The gastroepiploic flap contains quite a bit of vascularized omentum by means of which it is possible to cover the anastomosis and the major blood vessels of the area. It has a long vascular pedicle, which allows for a wider area of usage of mircrosurgical anastomoses. However, it requires a longer operation, which may increase surgical risks. Last, but not least is that the flap is susceptible to the same abdominal complications as the jejunal flap [29].

The RFF flap and the anterolateral thigh flap (ALT flap) are the two of the most frequently used free flaps that are harvested circumferentially to cover the defect. The RFF flap is considered a safe, relatively easy, flexible and reliable flap with a rather long vascular pedicle hat can be used to reconstruct the circumferential defect of the pharynx. However, the incidence rate of fistulae and constrictions is higher when compared to the ALT flap. Other downsides of using the RFF flap include worse functional outcomes, presence of hair, mismatch of skin color and complications in the donor site. The ALT flap is a widely used flap that has become an alternative to the radial forearm flap in the reconstruction of the pharyngeal area. It may be used in various forms, as can be the forearm flap, to reconstruct both the extensive and partial defects. Just as the radial forearm flap, it is a reliable and safe flap with a similarly low perioperative mortality and flap necrosis occurrence. The incidence rate of transcutaneous fistulae and constrictions is also lower than is the case with the radial forearm flap [30–32].

The study of N.C. Tan et al. (2015) analyzed complications and compared the incidence rate of fistulae and strictures among ALT and RFF flaps, and flaps from the tissue of the jejunum in cases of circumferential reconstruction of the pharynx and the esophagus. In 40 patients, only one leakage of the ALT was found. The incidence of fistulae was 33%, 50% and 30% in the ALT, RFF, and jujunal flap groups, respectively. The incidence of strictures was 38.1%, 57.1% and 0% in the ALT, RFF, and jujunal flap groups, respectively [33].

Thus, the use of visceral and free flaps in defects of types 2, 3 and 4 also entails the risk of complications in the post-surgery period [34]. Various factors associated with the weakened status of the patient, post-radiation and inflammatory changes can lead to a complicated course of the postoperative period [35].

CONCLUSION

Delayed reconstruction of pharyngeal and pharyngo-esophageal defects in oncology patients involves the use of various reconstructive tissues: covering tissues, tissues on axial blood supply (deltopectoral, pectoral, thoracodorsal material), free flaps (RFF, ALT) and visceral flaps from the gastro0intestinal tract allowing for restoration of the integrity and the slit of the pharynx [36, 37]. With all types of plastic surgery, complications may develop in the postoperative period.

As the analysis of scientific literature has shown, the most frequent complications after delayed reconstructive surgeries are anastomotic failure with subsequent formation of fistula and stricture [38]. The causes of these complications, given the viability of the reconstructive material, may be the post-radiation changes, presence of an inflammatory process in the tissues in the defect area, weakened nutritive status of the patient, and some others [39, 40]. Therefore, planning of delayed reconstruction of pharyngeal defects, as far as time frame and type of reconstructive material are concerned, necessitate a personalized approach in each clinical case.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Study funding. The study was the authors' initiative without external funding.	***Источник финансирования.*** Работа выполнена по инициативе авторов без привлечения финансирования.
Conflict of Interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	***Конфликт интересов.*** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Contribution of individual authors. A.O. Sidorenko – wrote the first draft of the manuscript. O.I. Kaganov, A.G. Gabrielyan – edited the manuscript. A.A. Makhonin – was responsible for scientific data collection. A.E. Orlov – provided scientific data processing. The authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	***Участие авторов.*** А.О. Сидоренко – написание текста. О.И. Каганов, А.Г. Габриелян – редактирование. А.А. Махонин – сбор литературы. А.Е. Орлов – обработка материала. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.

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Оригинальное исследование | Original study article
DOI: https://doi.org/10.35693/SIM642579

Long-term results of comprehensive treatment of patients with locally advanced tongue cancer using selective intraarterial and systemic polychemotherapy

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Abstract

Aim – to evaluate the long-term results of complex treatment of patients with locally advanced tongue cancer (T3-4N0-3M0) using modified selective intra-arterial polychemotherapy and systemic polychemotherapy.

Material and methods. Depending on the polychemotherapy regimen, taking into account the designated classifications, all patients were divided into two groups. The study group included 51 patients who received intra-arterial polychemotherapy according to the PF regimen, followed by radiation therapy. The control group included 50 patients who received intravenous polychemotherapy according to the PF regimen, followed by radiation therapy. With positive dynamics in the study group and the control group (partial tumor regression), surgical treatment was performed in the amount of hemiglossectomy. In case of complete tumor regression, the 2nd stage of the telegammatherapy course on the tongue was performed up to a total dose of 60 Gy. In case of oncological process stabilization, the 2nd stage of the telegammatherapy course on the tongue was performed up to a total dose of 60 Gy, followed by palliative courses of systemic polychemotherapy. In case of disease progression, palliative courses of systemic polychemotherapy were performed.

Results. Three-year survival in the study group was 80.1±6%, while in the control group it was 56.6±7% ($p<0.05$). Five-year survival among patients in the study group was 39.4±7%, while in the control group it was 2 times lower – 18.9±5% ($p<0.05$). About 7% of patients in the study group survived for more than 8 years.

Conclusions. The treatment regimen we developed for patients with locally advanced tongue cancer, which includes selective intra-arterial polychemotherapy followed by radiation therapy to the primary tumor and areas of regional metastasis, increased the median survival, three- and five-year survival.

Keywords: locally advanced tongue cancer, selective intra-arterial polychemotherapy, radiation therapy.

Conflict of Interest: nothing to disclose.

Citation
Sedakov IE, Polzikov GN, Koktyshev IV. **Long-term results of comprehensive treatment of patients with locally advanced tongue cancer using selective intraarterial and systemic polychemotherapy.** *Science and Innovations in Medicine*. 2025;10(1):50-55.
DOI: https://doi.org/10.35693/SIM642579

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Received: 05.12.2024
Accepted: 15.01.2025
Published: 22.01.2025

Отдаленные результаты комплексного лечения больных с местнораспространенным раком языка с использованием селективной внутриартериальной и системной полихимиотерапии

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Аннотация

Цель – оценить отдаленные результаты комплексного лечения больных с местнораспространенным раком языка (Т3-4N0-3M0) с использованием модифицированной селективной внутриартериальной полихимиотерапии и системной полихимиотерапии.

Материал и методы. В зависимости от режима проведения полихимиотерапии с учетом обозначенных классификаций все пациенты были распределены на две группы. В исследуемую группу вошли пациенты (51 человек), которые получили внутриартериальную полихимиотерапию по схеме PF с последующим проведением лучевой терапии. В контрольную группу вошли пациенты (50 человек), которые получили внутривенную полихимиотерапию по схеме PF с последующим проведением лучевой терапии. При положительной динамике в группах (частичная регрессия опухоли) выполняли оперативное лечение в объеме гемиглоссэктомии. При полной регрессии опухоли проводили второй этап курса телегаммматерапии на язык до СОД – 60 Гр. При стабилизации онкологического процесса проводили второй этап курса телегаммматерапии на язык до СОД – 60 Гр, а после – паллиативные курсы системной полихимиотерапии. При прогрессии заболевания – паллиативные курсы системной полихимиотерапии.

Результаты. Трехлетняя выживаемость в исследуемой группе равна 80,1±6%, а в контрольной группе – 56,6±7% (p<0,05). Пятилетняя выживаемость среди пациентов исследуемой группы – 39,4±7%, а в контрольной группе в два раза ниже – 18,9±5% (p<0,05). Около 7% больных в исследуемой группе прожили более 8 лет.

Заключение. Разработанная нами схема лечения больных с местнораспространенным раком языка, которая включает проведение селективной внутриартериальной полихимиотерапии с последующей лучевой терапией на первичную опухоль и зоны регионарного метастазирования, позволила увеличить медиану выживаемости, трех- и пятилетнюю выживаемость.

Ключевые слова: местнораспространенный рак языка, селективная внутриартериальная полихимиотерапии, лучевая терапия.

Конфликт интересов: не заявлен.

Для цитирования:
Седаков И.Е., Ползиков Г.Н., Коктышев И.В. **Отдаленные результаты комплексного лечения больных с местнораспространенным раком языка с использованием селективной внутриартериальной и системной полихимиотерапии.** *Наука и инновации в медицине*. 2025;10(1):50-55. DOI: https://doi.org/10.35693/SIM642579

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ОГШ – опухоли головы и шеи; ЗНО – злокачественное новообразование; РПР – рак полости рта; СОД – суммарная очаговая доза; РОД – разовая очаговая доза.

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Получено: 05.12.2024
Одобрено: 15.01.2025

INTRODUCTION

Carcinomas of the head and the neck make up a substantial group of the entire oncopathology, an 18-20% group of malignant tumors characterized with a progressing morbidity [1].

Following the national and worldwide statistics, cancer of the oral organs and the oropharyngeal cavity accounts for 2% to 10% of all human malignant tumors and for up to 15-20% among head and neck tumors. The incidence rate of cancer of the oral organs in Russia in 2013 was 24.4 per 100 thousand people, whereas in 2023, 31.9 per 100 thousand people. The amount of patients with malignant tumors of the oral cavity under regular check-up in the cancer care facilities was 48.2% in 2013, whereas in the year 2023 it was 53.9%. The proportion of malignant tumors of the oral cavity identified in the advanced stages (Stage III-IV) in 2013 in Russia was 28.4%, and in 2023, it was 39.5%. The mortality rate in patients with this pathology in the course of one year after the diagnosis in Russia was 35.0% in 2013 vs. 27.0% in 2023 [2].

The cancer of the tongue and of the oral cavity, according to many authors, ranks first among other malignant tumors of the oral mucosa [3]. Whereas in the year 2011 in Russia, 7674 cases of primary diagnoses of tongue cancer were identified, in the year 2023 the occurrence reached 8681 cases including 25.6% cases in stage III, and 39.5% cases with stage IV [1]. In the USA, the number of patients with identified oral cavity cancer was 47010, making it 1.2% of all malignant neoplasms. Oral cavity and pharynx cancer most often occurs in men aged 55–64 years, with a five-year survival rate of 63.2% [4].

In the treatment of locally advanced cancer of the oral cavity, the combined method prevails that brings together surgical intervention and radiation therapy in various combinations. [5].

Oral cavity cancer is characterized with high mortality rates. This is accounted for by the low disease identification rate at early stages, highly malignant progression of the disease, fast expansion of the tumor process to nearby vital organs, frequent metastases to regional lymph nodes, high resistance to chemo- and radiotherapy, and limited availability of contemporary molecular and biological methods of examination and treatment in some clinics [6]. Specific tumor markers of the oral cavity cancer (SCC, S100A8, IL-6, IL-8, KI-67, Gli1, etc.) in the patient's saliva, blood serum, and tumor biopsy material may be instrumental in choosing the treatment methods [7, 8].

Radiotherapy is considered the main method of treatment of patients with oral cavity cancer. Regretfully, the efficiency of radiotherapy alone is not satisfactory: relapses and metastasis develop in 60-70% of observations, thus limiting the 5-year survival to 15-20%. Therefore, in order to improve efficiency of radiotherapy new regimens are developed; and some authors insist on increasing the exposure dose to 70 Gy [9].

Some research has focused on augmentation of effects of exposure by radiation-induced hyperthermia and magnetothermia, induction chemotherapy, and performance of simultaneous chemoradiotherapy [10–12].

Combination of intra-arterial multidrug chemotherapy using the Seldinger technique and retrograde superselective intra-arterial multidrug chemotherapy using the PF regimen with the radiotherapy has played a highly important role in the treatment of locally advanced squamous-cell carcinoma of the oral cavity: it resulted in the reduction of the malignant

Study Group	Control Group
2 neoadjuvant courses using modified PF regimen: - Cisplatin, 10 mg/m2, continuous 6-hour intra-arterial infusion: 10 days; - Fluoruracil, 250 mg/m2, continuous 6-hour intra-arterial infusion: 10 days. Interval between courses: 21 days. 21 days after two courses of intra-arterial polychemotherapy, irradiation of the primary tumor and regional metastasis zones was performed using the "Rokus" and "Agat" gamma-therapy units in the classical dose fractionation mode to the tongue - SBD - 2 Gy, TBD - 40 Gy, to the submandibular, cervical, supraclavicular regions on both sides - SBD - 2 Gy, TBD - 40 Gy per single stage.	**2 neoadjuvant courses of systemic multidrug chemotherapy using modified PF regimen:** - Cisplatin, 100 mg/m2, intravenous drip-feed: 1 day; - Fluoruracil, 1000 mg/m2, intravenous drip-feed, continuous 96-hour infusion: days 1-4. Interval between courses: 21 days. 21 days after two courses of systemic multidrug chemotherapy, irradiation of the primary tumor and regional metastasis zones was performed using the "Rokus" and "Agat" gamma-therapy units in the classical dose fractionation mode to the tongue - SBD - 2 Gy, TBD - 40 Gy, to the submandibular, cervical, supraclavicular regions on both sides - SBD - 2 Gy, TBD - 40 Gy per single stage.

Table 1. *Scheme of complex treatment of patients in the control and study groups*
Таблица 1. *Схема комплексного лечения больных в контрольной и исследуемой группах*

tumor of the oral cavity, and had the least number of side effects [13, 14].

AIM

To evaluate the long-term results of complex treatment of patients with locally advanced tongue cancer (T3-4N0-3M0) using modified selective intra-arterial polychemotherapy and systemic polychemotherapy.

MATERIAL AND METHODS

Case histories and outpatient cards of 323 patients with tongue cancer were studied. They had been treated at the G.V. Bondar Republican Cancer Center from 1995 to 2018. We excluded patients with intolerance to chemotherapeutic drugs, HIV infection, hepatitis B and C; clinically relevant cardiovascular disease, pregnancy or lactation, gastric or duodenal ulcer in the acute phase, diabetes mellitus. Thus, the retrospective controlled study included 101 patients.

In determining the stage of the disease, we adhered to AJCC-TNM Classification of Malignant Tumors, 8th Edition (American Joint Committee on Cancer) (2017).

Depending on the regimen of the multidrug chemotherapy and with regard to the said classifications, the patients were divided into two groups.

The study group included patients (51 persons) who had received intra-arterial polychemotherapy under the PF regimen with subsequent radiotherapy.

The control group included patients (50 persons) who had received intravenous polychemotherapy under the PF regimen with subsequent radiotherapy. The groups were comparable in the sex, age, and stage of the tumor process.

The scheme of complex treatment of patients in the control and the study groups follows in **Table 1**.

In cases of positive changes in the groups (partial regression of the tumor), surgical treatment was performed (hemiglossectomy). In cases of complete regression of the tumor, the second stage of gamma-ray therapy was performed to the tongue up to TBD=60 Gy. In cases of stabilization of the tumor process, the second stage of gamma-ray therapy was performed to the tongue up to TBD=60 Gy followed by palliative curses of systemic polychemotherapy. In cases of disease progression, palliative curses of systemic polychemotherapy were performed.

The statistical analysis of the obtained research results and indicators of remote effectiveness of treatment using the proposed methods of complex therapy for locally advanced tongue cancer was carried out in the Statistica 10 software suite.

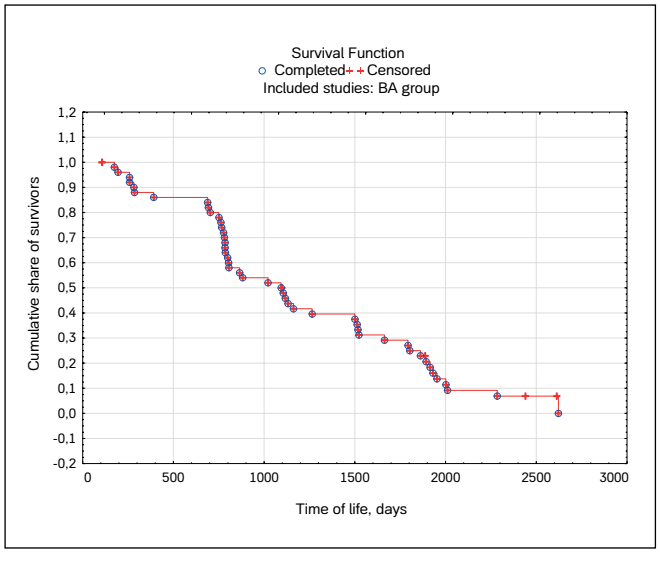

Figure 1. *Estimation of the survival function in the study group using the Kaplan-Meier maximum likelihood method.*
Рисунок 1. *Оценка функции выживаемости в исследуемой группе методом максимального правдоподобия Каплана – Майера.*

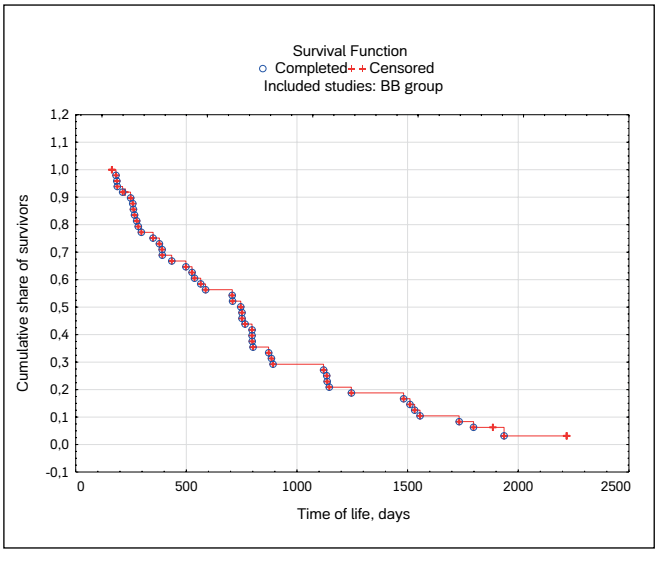

Figure 2. *Estimation of the survival function in the control group using the Kaplan-Meier maximum likelihood method.*
Рисунок 2. *Оценка функции выживаемости в контрольной группе методом максимального правдоподобия Каплана – Майера.*

Interval	Initial number	Proportion of diseased	Proportion of survivors	Total proportion of survivors	Relative risk	Median t_survival
1 year	51	11.9	88.1	100.0	0.03	1076
2 year	44	9.1	90.9	88.1	0.02	844
3 year	40	43.0	56.96	80.1	0.2	710
4 year	22	13.6	86.4	45.6	0.04	749
5 year	19	42.1	57.9	39.4	0.1	464
6 year	11	57.1	42.9	22.8	0.2	328
7 year	4	33.3	66.7	9.8	0.1	375
8 year	1	50.0	50.0	6.5		

Table 2. *Table of patient survival in the study group*
Таблица 2. *Таблица дожития пациентов в исследуемой группе*

Interval	Initial number	Proportion of diseased	Proportion of survivors	Total proportion of survivors	Relative risk	Median t_survival
1 year	50	22.5	77.6	100.0	0.1	711
2 year	37	27.0	72.97	77.6	0.1	524
3 year	27	48.2	51.9	56.6	0.2	349
4 year	14	35.7	64.3	29.3	0.1	476
5 year	9	44.4	55.6	18.9	0.2	388
6 year	5	44.4	55.6	10.5	0.2	380
7 year	2	50.0	50.0	5.8	0.2	159
8 year	1	100.0	0.0	2.9		

Table 3. *Table of patient survival in the control group*
Таблица 3. *Таблица дожития пациентов в контрольной группе*

For qualitative indicators, incidence rate was calculated (P, in %). In all cases, the discrepancies were deemed statistically significant at $p<0.05$.

In the calculation of survival and average life expectancy, the survival curve method was used. For a more detailed analysis of the degree of difference in survival curves, several tests were used: log-rank, Gehan-Wilcoxon, Cox, Cox-Mentel, Wilcoxon-Peto.

RESULTS

The specific feature of survival analysis is the presence of subjects who did not experience the event of interest during the study (death).

The time of life may be described mathematically by the survival function and the risk function. The survival function (St) characterizes the percentage of individuals surviving for more than t units of time, where t is measured from the start of the therapy (**Fig. 1, 2**).

Difference assessment test	Test assessment	Level of statistical significance (p=)
Gehan-Wilcoxon	-2.96	0.003
Cox F-test	1.55	0.018
Cox-Mentel	-2.91	0.004
Wilcoxon-Peto	2.96	0.003
Log-rank	2.77	0.006

Table 4. *Criteria for assessing the similarity of survival curves*
Таблица 4. *Критерии оценки одинаковости кривых выживаемости*

Comparing the amount of survivors in the two groups from the moment of the start of the therapy, the following conclusions can be made. On the 500th day from the start of treatment the proportion of survivors was 86±5%, and in the control group, 65±6% ($p<0.05$). On the 1000th day from the start of treatment, the proportion of survivors in the study group was 55±7%, and in the control group, 30±6% ($p<0.05$). On the 1500th day from the start of treatment, the proportion of survivors in the study group was 40±7%, and in the control group, 18±5% ($p<0.05$). On the 2000th day from the start of treatment, the proportion of survivors in the study group was 11±5%, and in the control group, 4±3% ($p>0.05$). On the 2500th day from the start of treatment, the proportion of survivors in the study group was 8±4%, and there were no survivors in the control group. Therefore, in all periods from the start of the treatment, the proportion of survivors in the study group was significantly higher than that in the control group; on the 1500th day it was more than 2.2 times higher ($t=2.6$, $p<0.05$).

To evaluate the survival of patients, tables of patient survival were calculated (**Tables 2, 3**).

It is seen from the tables, the cumulative proportions of survivors in the study group in all time intervals are higher than those in the control group of patients. Three-year survival in the study group was 80.1±6%, and in the control group, 56.6±7% ($p<0.05$). Five-year survival among patients in the study group was 39.4±7%, and in the control group it was twice as low: 18.9±5% ($p<0.05$). Eight-year survival in the study group is also two times higher than that in the control group, 6.5% vs. 2.9±2% ($p>0.05$). The median survival in the study group in practically all time intervals is higher than that in the control group. In the first year, median survival in the study group was 36 months vs. 23.7 months in the study group. In the second year, median survival in the study group was 28.1 months vs. 17.5 months in the control group. In the third year, median survival in the study

group was 23.7 months vs. 11.6 months in the control group. In the fourth year, median survival in the study group was 25 months vs. 15.9 months in the control group. In the fifth year, median survival in the study group was 15.5 months vs. 12.9 months in the control group. In the sixth year, median survival in the study group was 10.9 months vs. 12.6 months in the control group. In the seventh year, 12.5 months vs. 5.3 months in the control group. It is seen that the median survival in the sixth year in the study group was lower than that in the control group. Following the table data it is seen that the median survival was decreasing every year in both groups, but it increased in both groups in the fourth year.

The median survival in the study group was reached for 36.5 months, whereas in the control group it was only 24.9 months.

It is seen from **Table 4** that all known non-parametric tests of assessing the similarity of survival curves have high levels of statistical significance ($p<0.05$), therefore, survival curves are not similar in the two groups: in the study group, survival was higher than in the control group.

CONCLUSION

The median survival in the study group is 36.5 months and it is 24.9 months in the control group. Cumulative proportions of survivors in the study group in all time intervals are higher than those in the control group. Three-year survival in the study group is 80.1±6%, and it is 56.6±7% in the control group ($p<0.05$). Five-year survival among the patients of the study group is 39.4±7%, and in the control group it is twice as low: 18.9±5% ($p<0.05$). About 7% of patients in the study group survived for over 8 years.

The regimen of treatment of patients with locally advanced tongue cancer developed by us included selective intra-arterial multidrug chemotherapy with subsequent radiotherapy to the primary tumor and zones of regional metastasis. It increased the median survival, three- and five-year survival.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ	ADDITIONAL INFORMATION
Источник финансирования. Работа выполнена по инициативе авторов без привлечения финансирования.	***Study funding.*** The study was the authors' initiative without external funding.
Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.	***Conflict of interest.*** The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.
Участие авторов. Седаков И.Е. – сбор научного материала, редактирование статьи. Ползиков Г.Н. – формулировка цели исследования, оформление дизайна исследования, распределение пациентов в исследуемую и контрольную группы. Коктышев И.В. – расчет статистических показателей, анализ выживаемости больных в исследуемой и контрольной группе. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.	***Contribution of individual authors.*** Sedakov I.E.: collection of scientific material, editing of the article. Polzikov G.N.: formulation of the study objective, design of the study, distribution of patients into the study and control groups. Koktyshev I.V.: calculation of statistical indicators, analysis of survival of patients in the study and control groups. The authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.

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Оригинальное исследование | Original study article
DOI: https://doi.org/10.35693/SIM643504

Prognosis of distal diffuse gastric cancer depending on the extent of surgical procedure

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Abstract

Aim – to study the clinical and morphological characteristics and conduct a comparative assessment of the survival of patients with locally advanced distal diffuse gastric cancer depending on the type of the surgical procedure.

Material and methods. We performed a retrospective review of the impact of the extent of surgery in the prognosis of 125 patients with diffuse gastric cancer of distal localization, who underwent total gastrectomy or distal subtotal gastrectomy at the N.N. Blokhin National Medical Research Center of Oncology in the period from 2005 to 2022.

Results. The depth of tumor invasion (T4), the lymph node status, and the tumor stage had a significant negative prognostic value in the univariate analysis. Resection margin (R1) tended to significantly affect the overall survival (p=0.082). The extent of the surgical procedure did not affect overall survival in the univariate analysis (p=0.75). The multivariate analysis revealed that only the tumor stage had a relative effect on the overall survival. In the distal gastrectomy group, the median overall survival and the 5-year OS rates were 85.0 months, 58.8% (95% CI: 0.487-0.711). In the total gastrectomy group, the median overall survival, 5-year OS rates were 89.0 months, 60.3% (95% CI: 0.460-0.791). However, the differences were statistically insignificant (p=0.75). In patients in the distal subtotal gastrectomy group, the recurrence was detected in 12.7% of all cases of recurrence (8/63): 6 of them with intramural recurrence and 2 of them with intramural and distant recurrence of the disease. In patients in the total gastrectomy group, intramural recurrence was found only in one patient (4.8%) in the esophago-enteroanastomosis.

Conclusions. Overall survival and relapse-free survival rates in patients with diffuse cancer of distal localization after total and distal subtotal gastrectomy do not have significant differences. However, distal subtotal gastrectomy in this category of patients is associated with a higher risk of local recurrence (12.7%) and can not be recommended as an alternative to total gastrectomy in patients with satisfactory functional status.

Keywords: diffuse gastric cancer, distal subtotal gastrectomy, gastrectomy, prognosis.

Conflict of Interest: nothing to disclose.

Citation
Torosyan RO, Nered SN, Kozlov NA, Sun Henian, Kononets PV, Stilidi IS. **Prognosis of distal diffuse gastric cancer depending on the extent of surgical procedure.** *Science and Innovations in Medicine*. 2025;10(1):56-62.
DOI: https://doi.org/10.35693/SIM643504

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Received: 27.12.2024
Accepted: 10.01.2025
Published: 19.01.2025

Прогноз при диффузном раке желудка дистальной локализации в зависимости от объема хирургического вмешательства

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Аннотация

Цель – изучить клинико-морфологические характеристики, провести сравнительную оценку выживаемости и частоты интрамурального рецидива опухоли у больных диффузным раком желудка дистальной локализации в зависимости от объема хирургического вмешательства.

Материал и методы. Проведен анализ влияния объема хирургического вмешательства на прогноз у 125 больных диффузным раком желудка дистальной локализации, которым в НМИЦ онкологии имени Н.Н. Блохина в период 2005-2022 гг. выполнена радикальная гастрэктомия (ГЭ) или дистальная субтотальная резекция желудка (ДСРЖ).

Результаты. При однофакторном анализе достоверное влияние на выживаемость имели глубина опухолевой инвазии (Т4), статус пораженных лимфатических узлов, стадия опухолевого процесса. Тенденцию к статистически значимому влиянию на общую выживаемость имел край резекции (p=0,082). Объем выполненного хирургического вмешательства на общую выживаемость при однофакторном анализе влияния не оказывал (p=0,753). При многофакторном анализе было выявлено, что статистически значимое влияние на общую выживаемость имела только стадия опухолевого процесса. Медиана общей выживаемости, 5-летняя выживаемость в группе ДСРЖ составили 85,0 месяца, 58,8% (95% ДИ: 0,487-0,711). Медиана общей выживаемости, 5-летняя выживаемость в группе ГЭ составили 89,0 месяца, 60,3% (95% ДИ: 0,460-0,791). Различия в общей выживаемости статистически недостоверны (p=0,75). У пациентов в группе ДСРЖ интрамуральный рецидив выявлен в 12,7% случаев всех рецидивов (8/63): у 6 пациентов выявлен только интрамуральный рецидив в зоне гастроэнтероанастомоза, а у двоих пациентов – интрамуральный рецидив и отдаленные метастазы. В группе пациентов, которым провели ГЭ, выявлен лишь 1 случай (4,8%) интрамурального рецидива заболевания в эзофагоэнтероанастомозе.

Заключение. Показатели общей выживаемости и безрецидивной выживаемости у больных диффузным раком дистальной локализации после ГЭ и ДСРЖ достоверных различий не имеют. Однако выполнение ДСРЖ у данной категории пациентов сопряжено с более высоким риском интрамурального рецидива опухоли (12,7%) и не может быть рекомендовано в качестве альтернативы ГЭ у больных с удовлетворительным функциональным статусом.

Ключевые слова: диффузный рак желудка, дистальная субтотальная резекция желудка, гастрэктомия, прогноз.

Конфликт интересов: не заявлен.

Для цитирования:
Торосян Р.О., Неред С.Н., Козлов Н.А., Сунь Хэнянь, Кононец П.В., Стилиди И.С.
Прогноз при диффузном раке желудка дистальной локализации в зависимости от объема хирургического вмешательства.
Наука и инновации в медицине. 2025;10(1):56-62.
DOI: https://doi.org/10.35693/SIM643504

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Список сокращений
РЖ – рак желудка; ПКР – перстневидноклеточный рак; ДСРЖ – дистальная субтотальная резекция желудка; ГЭ – гастрэктомия; БРВ – безрецидивная выживаемость; ОВ – общая выживаемость; ОР – отношение рисков; ДИ – доверительный интервал.

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Получено: 27.12.2024
Одобрено: 10.01.2025
Опубликовано: 19.01.2025

INTRODUCTION

Morphologically diffuse gastric cancer (GC) is characterized with disorders in the intercellular adhesion without formation of glandular tissue, diffused spreading of the tumor cells in the walls of the stomach, more aggressive course of the neoplastic process and adverse survival outcomes as compared to the intestinal subtype of cancer. In the group of diffuse gastric cancer, the predominant histologic form is the signet ring cell carcinoma (SRCC) represented by isolated cells with a characteristic signet cell morphology and diffused growth pattern, which allows its reference to the diffuse GC (P. Lauren) [1-6]. According to the SEER register, in the period from 1975 to 2016 proportion of patients with SRCC is 16.8%. The diffuse subtype is more incident in women and young people, it is characterized with a more frequent dissemination in the peritoneum, resistance to chemotherapy, and locally advanced tumor course by the moment of disease diagnosis [5, 7-9].

In the Japanese classification of gastric carcinoma, it is customary to refer to three sections of the stomach approximately similar in size: the upper third (proximal section), the middle third (corpus) and the lower part [10]. This conventional division of the stomach into three parts in surgical practice is only used to describe the tumor localization. It is to be emphasized that the sections of the stomach in the surgical classifications do not match those in the anatomical classifications. In Russia, distal GC is identified as a tumor involving only the antrum or the pylorus, in which, according to the clinical recommendations of the Russian Oncology Association, distal subtotal gastrectomy (DSG) is indicated. It is interesting to note that the involvement of the lower third

of the corpus in distal cancer may necessitate an extensive instead of a preserving surgery [11].

In Russia, in the cases of antrum diffuse GC, gastrectomy with D2 lymph node dissection is preferred as a standard surgical procedure, especially in young patients, since in this category of patients the possibility of recurrent cancer in the remaining part of the stomach remains high [8, 9, 12], and the lymph node dissection is less extensive in the preserving surgery as compared to the conventional gastrectomy. According to the data from 62 hospitals of Europe, in the cases of antrum diffuse GC, 44% of surgeons prefer the gastrectomy [12].

Lesser surgical trauma and more favorable outcomes of the restoration of nutritive status of patients after DSG raise no doubts and are used actively in the cases of intestinal adenocarcinoma of distal localization [13, 14].

According to the ESMO clinical recommendations, the major condition of the radically performed DSG is the absence of cancer cells along all margins of resection (R0). The margin for the proximal edge of resection in the diffuse GC is to be at least 5 cm, for the diffuse cancer is characterized with submucosal growth, which might be a technical difficulty to achieve 'clear' margins of resection. Thus, performance of DSG in the cases of distal GC may only be justified if the radical principles are met and there are no cancer cells along the resection margin [15].

As of today, there is no definitive consensus as to the extent of surgical intervention in cases of distal gastric cancer. The extent of surgery in distal gastric cancers is usually determined by the surgeon's preference and personal experience, as well as the patient's total physical condition [11, 12]. Thus, the effect of the extent of surgery on the prognosis of patients with diffuse distal gastric cancer remains a disputable and understudied problem.

Factors	DSG (N=87)	TG (N=38)	P
Age (years) <55 >55	 32 (36.8%) 55 (63.2%)	 23 (60.5%) 15 (39.5%)	0.014
Sex M F	 35 (40.3%) 52 (59.7%)	 18 (47.4%) 20 (52.6%)	0.0002
Invasion depth T1 - T2 T3 - T4	 29 (33.3%) 58 (66.7%)	 14 (36.8%) 24 (63.2%)	0.704
Borrmann type I - II III – IV	 17 (19.5%) 70 (80.5%)	 5 (13.2%) 33 (86.8%)	0.388
Lymph node status pN0 pN+	 47 (54.0%) 40 (46.0%)	 22 (57.9%) 16 (42.1%)	0.688
Localization - antrum section - lower third of corpus and antrum section border - lower third of corpus and antrum section	 78 (89.7%) 7 (8.0%) 2 (2.3%)	 21 (55.2%) 9 (23.7%) 8 (21.1%)	<0.001
Stage IA/B IIA/B IIIA/B/C IV	 27 (31.0%) 31 (35.6%) 18 (20.7%) 11 (12.7%)	 11 (28.9%) 15 (39.5%) 10 (26.3%) 2 (5.3%)	0.592
Resection margin R0 R+	 81 (93.1%) 6 (6.9%)	 37 (97.4%) 1 (2.6%)	0.340
Lymphovascular invasion Yes No	 6 (6.9%) 81 (93.1%)	 4 (10.5%) 34 (89.5%)	0.491
Perineural invasion Yes No	 4 (4.6%) 83 (95.4%)	 5 (13.2%) 33 (86.8%)	0.088
Relapse Yes No	 8 (9.2%) 79 (90.8%)	 1 (2.6%) 37 (97.4%)	0.191

Table 1. *Clinical and morphological characteristics of patients depending on the surgical intervention performed*

Таблица 1. *Клинико-морфологические характеристики больных в зависимости от выполненного хирургического вмешательства*

MATERIAL AND METHODS

The study included 125 patients with diffuse gastric cancer of distal localization who had undergone radical or palliative total gastrectomy or distal subtotal gastrectomy at the N.N. Blokhin National Medical Research Center of Oncology in the period from 2005 to 2022. Distal localization of GC was identified as the tumor localized in the antrum of the stomach with or without spreading to the lower third of the stomach corpus. Such clinical and morphological factors as sex, age, tumor localization, depth of tumor invasion, macroscopic form of the tumor, number of affected lymphatic basins, lymphovascular or perineural invasion, and resection margins were identified and compared among the patient groups that were formed depending on the extent of the surgery performed. Pathomorphological staging was performed in accordance with TNM Classification of Malignant Tumors, 8th Edition.

Statistical Analysis. In the analysis of long-term outcomes, the relapse-free survival (RFS) was considered the period from the beginning of treatment to the emergence of signs of progression of the disease, death, or the last follow-up of the patient. The overall survival (OS) was considered the period from the beginning of treatment to all-cause death or the last follow-up. The statistical analysis included the Chi-square criterion used to test the hypotheses. Survival analysis was carried out by Kaplan-Meyer method and compared by log-rank tests. The statistical analysis was carried out in the RStudio Version 2023.09.0+463 software suite by Posit Software PBC. Two-sided significance levels of research used to test the hypotheses are 5%. Univariate and multivariate analysis between dependent and independent variables (determination of the independent influence of potential risk factors on the rate of occurrence of the studied event over the studied time period) was performed using the Cox proportional hazards (regression) model.

RESULTS

The following surgeries were performed to the following extents: total gastrectomy, 38 (30.4%); distal subtotal gastrectomy, 87 (69.6%). Of the 125 patients, 27 (21.6%) had early gastric cancer, 85 (68.0%) had locally advanced cancer, and 13 (10.4%), metastatic cancer. The age of patients was between 26 and 81 years (median age was 53.5 years). Tumor type according to P. Lauren in all patients was considered diffuse (100%). Among all patients, pN0, pN1, pN2 and pN3 was identified in 69 (55.2%), 23 (18.4%), 15 (12.0%) and 18 (14.4%) patients, respectively. Stages I, II, III, IV were identified in 38 (30.4%), 46 (36.8%), 28 (22.4%) and 13 (10.4%) patients, respectively. Patients with multiple primary tumors and neuroendocrine tumors were excluded from the study.

Correlation was studied between the extent of the surgery performed and age, sex, depth of tumor invasion, status of lymph nodes, Borrmann tumor classification, tumor staging, resection margin, presence of lymphovascular or perineural invasion, and incidence rate of intramural relapse of the disease. In our study, the group of patients who had undergone

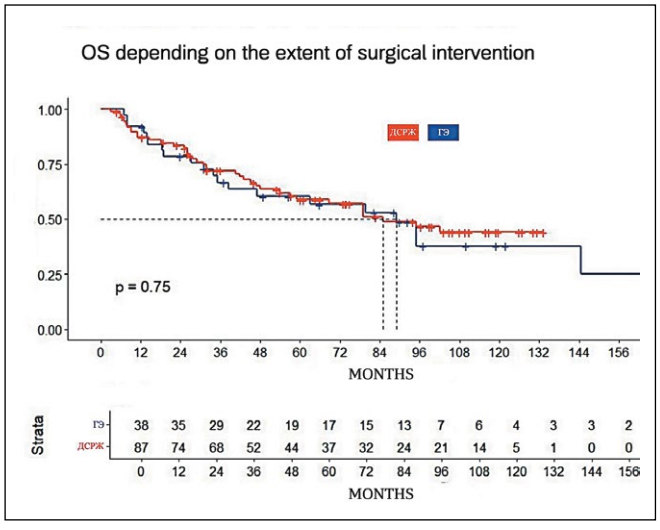

Figure 1. *Overall survival depending on the extent of surgical intervention.*

Рисунок 1. *Общая выживаемость в зависимости от объема оперативного вмешательства.*

DSG, had more females (59.7% vs. 52.6%; p=0.0002) and older persons (>55 years of age; 63.2% vs. 39.5%; p=0,014), than in the total gastrectomy group. It was also found that the tumor was more frequently localized only within the antrum section of the stomach in the DSG group vs. the TG group (89.7% vs. 55.2%; p<0.001). Perineural invasion had a tendency towards statistically significant difference between the two groups (4.6% vs. 13.2%; p=0.088). Other statistically significant differences were not identified. It is interesting to note that the patients of the DSG group had cancer cells along the resection margins more frequently (6.9% vs. 2.6%; p=0.340), and relapse was identified in them more often as well (9.2% vs. 2.6%; p=0.191). The data follows below in **Table 1**.

The median OS and 5-year survival in the DSG group were 85.0 months, 58.8% (95% CI: 0.487-0.711). The median OS and 5-year survival in the TG group were 89.0 months, 60.3% (95% CI: 0.460-0.791). The differences in overall survival are statistically unreliable (p=0.75) (**Fig 1**).

Univariate analysis was performed to assess the impact of clinical and morphological factors on overall survival. As shown in Table 1, the reliable prognostic value in the univariate analysis was in the depth of tumor invasion, status of affected lymph nodes, and stage of the tumor process. The margin of resection tended to be statistically significant on OS (p=0.082). The extent of the surgery performed had no impact on OS in the univariate analysis (p=0.753).

Next, a multivariate analysis was performed to determine the prognostic significance of clinical and morphological factors. Multivariate analysis revealed that only the stage of the tumor process had a statistically significant effect on OS. The results follow in **Table 2**.

In our study, only 84 (67.2%) patients showed up for follow-up at the N.N. Blokhin National Medical Research Center of Oncology after the surgery. Among the patients who showed up for the follow-up, 63 (75%) had undergone DSG, and 21 (25%), TG. In 89.3% (75/84) of the patients, no relapse of the disease was identified at the moment of the examination. In 10.7% (9/84) of the patients, relapse was identified: 7 patients (77.8%) with intramural recurrence in the esophago- or gastro-enteroanastomosis, and 2 patients (22.2%) with intramural recurrence and distant metastasis. On average, the relapse of disease was identified 33 months after the surgery.

In the patients in the DSG group who showed for a follow-up, the intramural recurrence was identified in 12.7% cases of all relapses (8/63): in 6 patients, only the intramural recurrence in the gastro-enteroanastomosis was identified, and in two patients, the intramural recurrence and remote metastases. In 9% (7/78) of the patients in the DSG group with intramural recurrence, the primary tumor was initially localized within the antrum of the stomach. At the same time, only in two patients after the primary surgery (distal subtotal gastrectomy) positive resection margins were found along the stomach line (R1).

In the TG group, the patients who showed for the control follow-up, only one case (4.8%) of the intramural recurrence of the disease in the esophago-enteroanastomosis was identified, however, in this specific case the tumor was transferring from the antrum to the lower third of the stomach corpus. Of all the cases of the disease relapse, only two patients (25%) with intramural relapse were able to undergo repeated surgery. At the moment of the follow-up, six (66.7%) relapsing patients were dead from disease progression.

DISCUSSION

Diffuse gastric cancer according to P. Lauren, which includes the signet cell gastric cancer with characteristic morphology, had adverse prognosis, aggressive course, and resistance to chemotherapy [3-5, 16].

TG with D2 lymph node dissection is the preferred treatment approach for diffuse gastric cancer. However, it is related to lower quality of life of patients, unsatisfactory nutritive status and higher lethality as compared to DSG [12-14]. In the clinical recommendations of ESMO (2016), DSG was regarded as an alternative to the total gastrectomy for diffuse gastric cancer with at least 5 cm margin from the visual border of the proximal edge of the tumor [15].

The multi-center LOGICA study compared the immediate and long-terms results of surgical treatment of 211 patients with gastric cancer who had undergone total (n=89) or distal subtotal (n=122) gastrectomy with perioperative chemotherapy in the period from 2015 to 2018. The comparison of the two groups showed that diffuse tumors (51% vs. 31%; p=0.005) and lower rate of R0-resections (91% vs. 98%; p=0.019) were reliably more frequent in the TG rather than in the DSG group respectively. Positive resection margins in the TG group (n=8) in 88% of the cases were due to the diffuse type of the tumor. Both cases of positive resection margins in the DSG group were due to the diffuse type of the tumor. In the multivariate analysis, the diffuse type of the tumor is reliably associated with positive resection margins (RR 10.04; p=0.035). Also, in the DSG group lower rate of post-surgery complications was found (34% vs. 57%; p<0.001), such as leakage of anastomosis (3% vs. 19%), pneumonia (4% vs. 22%), atrial fibrillation (3% vs. 14%) as compared to the TG group (p<0.05). The overall survival showed a trend towards reliable difference (p=0.084). The only prognosis factor to affect overall survival was the neoadjuvant chemotherapy (RR 0.41; 95% CI: 0.20 – 0.87; p=0.020) [17].

The meta-analysis performed by J. Qi et al. (2016) compared patients depending on the surgery performed. The subgroup

	Univariate analysis of OS		Multivariate analysis of OS	
Factor	P-value	Risk ratio (95% CI)	P-value	Risk ratio (95% CI)
Age (years) <55 >55	 1 0.191	 1 1.417 (0.841-2.387)	 - -	 - -
Sex M F	 1 0.115	 1 0.660 (0.394-1.106)	 - -	 - -
Invasion depth T1 T2 T3 T4	 1 0.144 0.187 0.002	 1 2.171 (0.767-6.146) 1.912 (0.730-5.009) 3.240 (1.551-6.767)	 1 0.673 0.345 0.363	 1 1.303 (0.381-4.451) 0.460 (0.092-2.308) 0.456 (0.084-2.479)
Lymph node status N0 N1 N2 N3	 1 0.265 <0.001 <0.001	 1 1.559 (0.714-3.401) 3.818 (1.852-7.873) 5.394 (2.726-10.673)	 1 0.338 0.942 0.973	 1 0.527 (0.143-1.951) 1.056 (0.245-4.544) 1.027 (0.217-4.850)
Tumor stage IA/B IIA/B IIIA/B/C IV	 1 0.026 <0.001 <0.001	 1 2.442 (1.113-5.359) 4.670 (2.061-10.580) 15.170 (6.084-37.826)	 1 0.055 0.078 0.010	 1 5.099 (0.968-26.858) 11.321 (0.762-168.153) 40.073 (2.380-674.606)
Borrmann type Type I Type II Type III Type IV	 1 0.891 0.882 0.785	 1 0.865 (0.108-6.898) 0.860 (0.117-6.318) 1.371 (0.141-13.302)	 - - - -	 - - - -
Tumor localization - antrum section - lower third of corpus and antrum section border - lower third of corpus and antrum section	 1 0.496 0.613	 1 0.753 (0.333-1.703) 0.774 (0.287-2.088)	 - - -	 - - -
Resection margin R0 R1	 1 0.082	 1 2.280 (0.900-5.776)	 1 0.313	 1 1.745 (0.592-5.139)
Lymphovascular invasion Yes No	 1 0.677	 1 1.216 (0.485-3.047)	 - -	 - -
Perineural invasion Yes No	 1 0.772	 1 1.189 (0.369-3.829)	 - -	 - -
Preoperative chemotherapy No Yes	 1 0.586	 1 0.723 (0.226-2.317)	 - -	 - -
Extent of surgery TG DSG	 1 0.753	 1 0.915 (0.529-1.585)	 - -	 - -

Table 2. *Results of uni- and multivariate analysis of the prognostic significance of clinical and morphological factors*
Таблица 2. *Результаты одно- и многофакторного анализа прогностической значимости клинико-морфологических факторов*

analysis revealed that in the cases of total gastrectomy the incidence rate of intabdominal apostasies was reliably higher (RR = 3.41; 95% CI: 1.21 – 9.63; p<0.05). Five-year survival in the total and subtotal gastrectomy groups was 49.6% and 55.9% (RR = 0.91; 95% CI: 0.85 – 0.97; p=0.006), respectively [18].

Performing distal subtotal gastrectomy in cases of distal diffuse gastric cancer may only be justified if the principles of radical surgery are respected and if there are no cancer cells along the resection margin (R0). S. Gaspar-Figueiredo el at. (2023) demonstrated in their study the negative influence of R1-resection on overall survival in cases of diffuse gastric cancer in 20 patients who had undergone total gastrectomy. The OS median in the patient group with R0N0 was 102 (95% CI: 1-207) months versus the groups with R1N+ and R1N0, where the OS median was 7 (95% CI: 1-13; p<0.001) and 36 (95% CI: 13-59) months, respectively. Median RFS in the R0N0 group was 41 (95% CI: 32-50) months vs. R1N+ and R1N0 groups, where the median RFS was 4 (95% CI: 1-7) and 25 (95% CI: 17-33) months, respectively (p<0.001). The multivariate analysis revealed that the resection margin was an independent factor for the adverse prognosis (RR 4.1; 95% CI: 3.4-12.3) [19].

M. Boubaddi et al. (2024) ran a retrospective multicenter analysis in which they compared two groups of patients with poorly cohesive gastric carcinoma: 140 patients (52%) underwent total gastrectomy and 129 (48%) underwent distal subtotal gastrectomy. The patients were similar in pTNM and major clinical characteristics. In terms of long-term outcomes of 5-year OS and RFS no reliable differences were found: in the TG group, 46% (95% CI: 35.9% – 55.5%); in the DSG group, 45.3% (95% CI: 34.3% - 55.6%). In the TG group, 5-year OS was 53.8% (95% CI: 43.2% – 63.3%); in the DSG group, 53% (95% CI: 41.4 – 63.3%) (RR 0.94; 95% CI: 0.68 – 1.29); 5-year RFS in the TG group was 46% (95% CI: 35.9% – 55.5%) vs. DSG group with 45.3% (95% CI: 34.3% – 55.6%) (RR 0.97; 95% CI: 0.70 – 1.34). The incidence rate of post-surgery complications according to Clavien-Dindo was reliably higher in the TG group in comparison with the DSG group (p<0.001). At the same time, in the DSG group the positive resection margins (R1) were found more often than in the TG group (20.3% vs. 11.4%; p=0.046). The factor analysis revealed that the R1-resection (p=0.08) and the poorly cohesive morphological form with over 50% of signed-shaped cells (p=0.31) do not reliably influence OS [20].

J.A. Gajardo et al. (2024) performed a retrospective analysis where two groups of patients with diffuse/mixed cancer according to P. Lauren: 62 patients underwent total gastrectomy (48%), and 68 underwent distal subtotal gastrectomy (52%). The distal cancer was identified as a tumor involving the lower third of the stomach corpus, or the antrum, or the pylorus. R0 resection was made in all of the patients. The post-surgery complication rate was similar in both groups (4.4% vs. 8.1%; p=0.387). The survival median in the TG group was 69 months, whereas in the DSG group, the median had not been reached (p=0.097); five-year OS in the TG group was 51%, and it was 63% in the DSG group. No reliable differences in RFS were found (p=0.392) [21]. M.A. Moslim et al. (2021) made a comparative study of 17,086 patients with gastric cancer. The study included patients with squamous cell carcinoma (SCC) and non-squamous cell carcinoma (non-SCC) who underwent DSG (25.5% vs. 20.9%) and TG (74.5% vs. 79.1%), respectively. The patients with SCC underwent TG more frequently (p<0.001). The patients in the SCC group, who had undergone distal subtotal gastrectomy, had better values of 5-year OS (RR = 0.67, 95% CI: 0.60-0.75; p <0.0001) [22].

In our study, we were able to demonstrate that the 5-year survival in the DSG group was comparable to that of the group of patients who had undergone total gastrectomy (58.8% and 60.3%, respectively). Such high values of OS are related to the fact that the examination of 67.2% identified stages I-II of the tumor process. The patients in the DSG group were reliably older than those in the TG group. The ag and the presence of concomitant diseases may have a certain impact on the choice of the surgery, viz. choice of DSG to decrease risk of mortality. It is likely that it was in this regard that stomach resection was performed (87/125) rather than total gastrectomy.

It must be noted, though, that in the DSG group the incidence rate of R1-resections was somewhat higher than in the TG group (6.9% vs. 2.6%, respectively), which might be the cause for more frequent relapse cases in this group of patients. The univariate analysis revealed that the resection margin (R1) has a tendency towards a statistically significant adverse impact on overall survival (p=0.082). In two out of eight patients with relapsing disease from the DSG group, the planned histological examination identified tumor cells along the proximal line of resection. Presence of tumor cells in the proximal margin of resection could have been an indication towards surgery before total gastrectomy in the event the same had been identified intraoperatively.

We were able to establish that during the follow-up the patients in the DSG group showed relapses of the disease in 12.7% of all relapse cases (8/63), and in seven patients of those the tumor was localized in the antrum of the stomach. In the group of patients who had undergone total gastrectomy, one case (4.8%) of intramural reoccurrence (1/21) was found, which, again, testifies to the aggressive biology of diffuse cancer and its potential towards development of intramural relapse in the esophago-enteroanastomosis area despite the surgical intervention. Notwithstanding the similar outcomes of overall survival between the two groups, the incidence rate of relapse is higher in the DSG group vs. the TG group. It may be concluded that in patients with distal localization of diffuse gastric cancer, total gastrectomy is the safer and more radical method of surgery, whereas distal subtotal gastrectomy is to be considered only in specific cases, where total gastrectomy entails high operative risk for the patient. Nevertheless, the choice of surgical intervention is to be carefully weighed.

CONCLUSION

Distal subtotal gastrectomy with D2 lymph node dissection in cases of distal gastric cancer does not have any reliable adverse effect on survival values (p=0.75). Performing the DSG for this category of patients entails higher risks of intramural recurrence of the disease in comparison with total gastrectomy, where the relapse risk is significantly lower.

Thus, today we cannot recommend DSG in distal diffuse gastric cancer as the alternative to the total gastrectomy, especially in the cases of the tumor transferring to the lower third of the stomach corpus due to higher incidence of intramural relapses. This may exclude patients of advanced age with manifested concomitant pathology.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Study funding. The study was the authors' initiative without external funding.	***Источник финансирования.*** Работа выполнена по инициативе авторов без привлечения финансирования.
Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	***Конфликт интересов.*** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Consent for publication. Written consent was obtained from the patient for the depersonalized publication of relevant medical information and all of accompanying images in the journal.	***Информированное согласие на публикацию.*** Авторы получили письменное согласие пациента на публикацию в журнале медицинских данных и фотографий в обезличенной форме.
Contribution of individual authors. R.O. Torosyan – data collection, analysis and interpretation, preparation of the text of the article, determination of the patient's treatment tactics, planning and execution of surgical intervention. S.N. Nered, N.A. Kozlov, Sun H. – study concept and design, approval of the final version of the article. I.S. Stilidi. P.V. Kononets – editing of the article. All authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	***Участие авторов.*** Р.О. Торосян – сбор, анализ и интерпретация данных, подготовка текста статьи. С.Н. Неред, Н.А. Козлов, Сунь Х. – концепция и дизайн работы, утверждение окончательного варианта статьи. И.С. Стилиди, П.В. Кононец – редактирование статьи. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.

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Оригинальное исследование | Original study article
DOI: https://doi.org/10.35693/SIM646475

Predictors of successful molecularly targeted therapy based on comprehensive genomic profiling data

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Abstract

Aim – to study predictors of successful performance of comprehensive genomic profiling and prescription of molecular targeted therapy for patients with advanced solid tumors.

Material and methods. We performed a retrospective single-center study of data of 104 patients who underwent comprehensive genomic profiling by targeted sequencing in the period of 2019 to 2023. The assessment of clinical significance of the identified genome alterations was performed using the scale for clinical actionability of molecular targets of the European Society for Medical Oncology (ESCAT). Analysis were performed of the mutation spectrum, efficiency of molecular targeted therapy, and its effect on survivability. Methods of logistical regression were used for the statistical analysis.

Results. Comprehensive genomic profiling was successfully performed in 87 patients (83.7%). Potentially targeted alterations were found in 44.8% patients, of which 11 persons received molecular targeted therapy. The main predictors of successful performance of comprehensive genomic profiling were the sufficient volume of tumors and lower number of revisions of biological material. Among the patients who received molecular targeted therapy, the overall median survival in the groups was 58 weeks as compared to the 35 weeks in the group of patients without molecular targeted therapy (p=0.097). In three patients, extraordinary response was noted.

Conclusion. The findings show clinical relevance of comprehensive genomic profiling in personalized treatment of solid tumors. The obtained data emphasize the need for careful selection of patients for comprehensive genomic profiling to improve its efficiency and availability.

Keywords: predictors, comprehensive genomic profiling, solid tumors, next generation sequencing, molecularly targeted therapy.

Conflict of interest: nothing to disclose.

Citation
Shilo PS, Makarkina ML, Zakharenko AA. **Predictors of successful molecularly targeted therapy based on comprehensive genomic profiling data.** *Science and Innovations in Medicine*. 2025;10(1):63-68.
DOI: https://doi.org/10.35693/SIM646475

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Received: 03.01.2025
Accepted: 06.02.2025
Published: 12.02.2025

Предикторы успешной молекулярно-направленной терапии на основании данных комплексного геномного профилирования

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Аннотация

Цель – изучить предикторы успешного выполнения комплексного геномного профилирования и назначения молекулярно-направленной терапии у пациентов с распространенными солидными опухолями.

Материалы и методы. Проведено ретроспективное одноцентровое исследование данных 104 пациентов, которым с 2019 по 2023 годы выполнено комплексное геномное профилирование методом таргетного секвенирования. Для оценки клинической значимости выявленных геномных альтераций использована классификация ESCAT. Проведен анализ спектра мутаций, эффективности молекулярно-направленной терапии и ее влияния на выживаемость. Для статистического анализа применялись методы логистической регрессии.

Результаты. Комплексное геномное профилирование было успешно выполнено у 87 пациентов (83,7%). Потенциально таргетируемые альтерации выявлены у 44,8% пациентов, из которых 11 человек полу-

чили молекулярно-направленную терапию. Основными предикторами успешного выполнения комплексного геномного профилирования стали достаточный объем опухолевой ткани и меньшее количество пересмотров биоматериала. У пациентов, получивших молекулярно-направленную терапию, медиана общей выживаемости в группах составила 58 недель в сравнении с 35 неделями в группе пациентов без молекулярно-направленной терапии (p=0,097). Экстраординарный ответ наблюдался у 3 пациентов.

Заключение. Результаты исследования демонстрируют клиническую значимость комплексного геномного профилирования в персонализированном лечении солидных опухолей. Полученные данные подчеркивают необходимость тщательного отбора пациентов для комплексного геномного профилирования, что позволит повысить его эффективность и доступность.

Ключевые слова: предикторы, комплексное геномное профилирование, солидные опухоли, секвенирование нового поколения, молекулярно-направленная терапия.

Конфликт интересов: не заявлен.

Для цитирования:
Шило П.С., Макаркина М.Л., Захаренко А.А. **Предикторы успешной молекулярно-направленной терапии на основании данных комплексного геномного профилирования.** *Наука и инновации в медицине.* 2025;10(1):63-68.
DOI: https://doi.org/10.35693/SIM646475

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КПГ – комплексное геномное профилирование;
МНТ – молекулярно-направленная терапия.

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Получено: 03.01.2025
Одобрено: 06.02.2025
Опубликовано: 12.02.2025

INTRODUCTION

Despite today's achievements in the sphere of oncology, the prognosis of patients with advanced forms of malignant tumors remains negative. Five-year survival in pancreatic cancer with remote metastases is approx. 3%, for patients with colonic carcinoma it is 13%, and for female patients with breast cancer, approx. 30% [1, 2].

The high incidence rate of solid tumors identified in the locally disseminated and metastatic stages, and poor outcomes of treatment account for the necessity of search for additional therapeutic options for this category of patients.

One of prospective approaches is the comprehensive genomic profiling (CGP) and prescription of molecular targeted therapy (MTT) based on the results of this diagnostic test. CGP allows to increase the number of potentially targeted alterations, i.e. biological events that may be the targets of the respective targeted therapy. In 51.7-99% of patients with disseminated forms of tumors who undergo such profiling, changes are identified that may be aligned with a registered targeted therapy or a clinical trial focusing on MTT [3-7].

The advent of such technologies makes oncologists face numerous new diagnostic and clinical tasks: high cost of diagnostics, difficulty of interpretation of results account for the necessity of finding a group of patients who would receive the maximum benefit from profiling.

AIM

To find predictors of targeted alterations by using comprehensive genomic profiling and predictors of successful molecular targeted therapy.

MATERIAL AND METHODS

In the single-center retrospective study, data were analyzed from 104 patients who underwent tumor tissue CGP using technologies of tumor genome sequencing. The patients were under observation in the oncology department of the "Lakhta" (formerly "Luch") clinic from 2019 to 2023. The decision of performing the new generation sequencing (NGS) and prescription of MTT was made jointly within the framework of oncology consultations. CGP was performed my method of targeted sequencing using large size (>300 genes) commercially available panels (OncoAtlas, FoundationOne). The identified genome alterations were classified using the ESCAT criteria to assess the level of their clinical significance [8].

The study included the analysis of the range of mutations, prescription of targeted therapy based on molecular data, evaluation of the clinical response of the tumor, and study of patient survival rates on the background of treatment. To identify predictors of successfully performed CGP, as well as predictors of successful MTT, statistical analysis was performed with multivariate logistic regression.

RESULTS

General characteristics of the cohort

CGP was performed for 104 patients, and successful results were obtained for 87 people (83.7%). The baseline parameters of this cohort of patients are shown in **Table 1**.

The following are identified as the prevalent oncological diseases: breast cancer (n=20, 23%), colorectal cancer (n=19, 21.8%) and pancreatic cancer (n=7, 8%). The average age of patients at the moment of profiling was 57 years. All patients included in the study had either the primary diagnosed metastatic stage of the disease, or the progression of the earlier localized process.

The data on the number of lines of previous therapy were available for 79 patients. 33 patients (41.8%) had received three and more lines of therapy. Atlas Solo (n=43, 49.4%) and FoundationOne (n=39, 44.8%) were the most frequently used diagnostic panels.

Characteristics of identified alterations

The CGP method revealed alterations in 74/87 patients (85.1%). These alterations were potentially targetable in

		Number	%
Diagnosis	Pulmonary adenocarcinoma	5	5.7%
	Colorectal cancer	19	21.8%
	Melanoma	3	3.4%
	Tumor metastasis from unknown primary site	1	1.1%
	Bile duct tumor	3	3.4%
	Tumor of the central nervous system	2	2.3%
	Head and neck cancer	1	1.1%
	Gastric cancer	6	6.9%
	Breast cancer	20	23.0%
	Pancreatic cancer	7	8.0%
	Salivary gland cancer	1	1.1%
	Cervical cancer	1	1.1%
	Ovarian cancer	4	4.6%
	Rare subtypes of cancer	8	9.2%
	Soft tissue sarcoma	5	5.7%
	Squamous cell lung cancer	1	1.1%
Number of lines of therapy prior to comprehensive genomic profiling	0-2 lines of therapy	46	58.2%
	3 and more lines of therapy	33	41.8%
ECOG status	0-1	29	44.6%
	2-3	36	55.4%
Name of diagnostic test	Atlas Solo	43	49.4%
	FoundationOne	39	44.8%
	Other	5	5.7%
Year of performance of diagnostic test	2020	26	29.9%
	2021	20	23.0%
	2022	19	21.8%
	2023	22	25.3%

Table 1. *Baseline characteristics of patients included in the study*
Таблица 1. *Базовые характеристики пациентов, включенных в исследование*

39 patients (44.8%). In 25 (29.1%) patients, one targeted alteration was found, in 9 (10.5%) patients, two, in 4 (4.7%) patients, three targeted alterations. A detailed distribution of alterations is shown in **Table 2**. In 39/87 (46.4%) cases the targeted alterations detected by CGP could not be detected with conventional diagnostic methods.

Analysis of predictors of unsatisfactory results of comprehensive genomic profiling

CGP was unsatisfactory for 17 patients (16.3% cases). The main reasons for unsatisfactory testing were the insufficient amount of tumor in the block for the analysis and lack of intact DNA for analysis. Among patients with unsatisfactory results, the majority were patients with lung tumors (n=6, 35.3%) and pancreatic tumors (n=5, 29.4%).

Univariate and multivariate logistic regressions were performed to analyze predictors of unsatisfactory results of the testing. The following parameters were assessed: localization of primary tumor, diagnostic panel, number of reviews of biomaterial, availability of only the biopsy material for analysis.

The following were predictors of unsatisfactory results of testing as identified by univariate logistic regression: number of preceding lines of therapy (OR = 2.01, 95% CI [1.10-3.04], p=0.041), number of performed revisions of biomaterial (OR = 3.96, 95% CI [2.42-5.59], p=0.003) and availability of only the biopsy material for analysis (OR=4.31, 95% CI [2.09-6.38], p<0.001). The multivariate analysis showed that the number of preceding lines of therapy was mutually correlated with the number of material revisions. The number of biomaterial revisions

		Number	% for sub-table
Distribution of alterations and medications according to ESCAT	1	38	22.4%
	2	7	4.1%
	3	58	34.1%
	4	67	39.4%

Table 2. *Distribution of detected alterations according to ESCAT*
Таблица 2. *Распределение обнаруженных альтераций по шкале ESCAT*

(OR=3.71, 95% CI [2.19-5.47], p=0.002) and availability of only the biopsy material for analysis (OR=5.32, 95% CI [3.01-7.45], p<0.001) were independent predictors. No statistically significant results in the number of unsatisfactory results depending on the diagnostic panel and diagnosis were found. Detailed information on predictors of unsatisfactory results of CGP are shown in **Table 3**.

Predictors for the prescription of molecularly targeted therapy

Univariate analysis of potential predictors for the prescription of MTT following the results of CGP was performed. It analyzed such parameters as reference to various groups of biomarkers as per ESCAT classification, sex and age of patients, number of preceding lines of therapy and ECOG status at the moment of CGP, and the diagnosis.

The predictors for the prescription of MTT were as follows: biomarker of ESCAT Tier I and II, female sex, age below 40 years (**Table 4**).

It is to be noted that this type of analysis may include more unaccounted factors, e.g., patient's financial and

Parameter		Univariate logistic regression, OR [95% CI]	p-value	Multivariate logistic regression, OR [95% CI]	p-value
Number of preceding lines of therapy	0-2	1 (reference)	0.041	1 (reference)	0.14
	>2	2.01 [1.10-3.04]		1.81 [0.83-2.99]	
Number of performed revisions of biomaterial	1	1 (reference)	0.003	1 (reference)	0.002
	>1	3.96 [2.42-5.59]		3.71 [2.19-5.47]	
Availability of only the biopsy material for analysis	Да	1 (reference)	<0.001	1 (reference)	<0.001
		4.31 [2.09-6.38]			

Table 3. *Predictors of unsatisfactory results in comprehensive genomic profiling*
Таблица 3. *Предикторы неудовлетворительных результатов комплексного геномного профилирования*

Parameter		Univariate logistic regression, OR [95% CI]	p-value
ESCAT scale biomarker reference	III, IV	1 (reference)	0.044
	I, II	1.92 [1.03-3.12]	
Sex	Male	1 (reference)	0.002
	Female	4.08 [2.11-6.39]	
Age	Above 40 years	1 (reference)	0.023
	Below 40 years	3.24 [1.87-5.02]	

Table 4. *Analysis of predictors for the prescription of molecularly targeted therapy*
Таблица 4. *Анализ предикторов назначения молекулярно-направленной терапии*

social status. The multivariate analysis was not possible due to mosaic omission of data and small size of sampling.

Analysis of survival in the mixed cohort of patients

The median overall survival in the mixed cohort of patients after CGP was 42 weeks (95% CI [28.6-55.4]). The medians of overall survival in the groups with and without MTT were 58 weeks and 35 weeks, respectively (**Fig. 1**). At the same time, no statistically significant differences were found, likely due to low number of participants in groups (p=0.097).

It is to be noted that the observed difference of absolute values in the survival between the groups is likely accounted for by single cases of extraordinary response in the group of patients who received MTT.

Cohort of patients receiving MTT

Among the 87 patients, for which the CGP was performed successfully, MTT was prescribed in 11 cases. Detailed clinical characteristics of patients follow in **Table 5**. Based on the results of genomic profiling, molecularly targeted therapy was prescribed to two female patients with breast cancer, two female patients with serous highly differentiated ovarian carcinoma, two male patients with lung adenocarcinoma, one male patient with colorectal cancer, one female patient with ovarian granulosa cell tumor, one female patient with glioblastoma, one female patient with soft tissue sarcoma, and one female patient with gall bladder cancer.

Most frequently, Alpelisib (n=3), Pembrolizumab (n=3) and Olaparib (n=3) were prescribed as medications. In singular cases, Erlotinib (n=1) and Sunitinib (n=1) were prescribed.

In two cases, the full clinical response was achieved: the patient with lung adenocarcinoma and high mutational burden after treatment with pembrolizumab, and the patient with POLE mutation and high mutational burden after a preceding course of treatment. In one case, the patient with colorectal cancer, long-term remission was achieved for over two years, with no signs of disease progression. This case was considered one of extraordinary response to MTT.

DISCUSSION

There are numerous publications assessing the efficiency of CGP. Many non-randomized trials demonstrate better outcomes in patients with disseminated forms of solid tumors with implementation of approaches based on molecular profiling [9-13].

The results of prospective trials are contradictive. For example, in the MOSCATO 01 study, out of 1035 adult patients planned for NGS, only 199 (19%) tested patients received genomic targeted therapy. This percentage is comparable with the highest evaluations obtained in

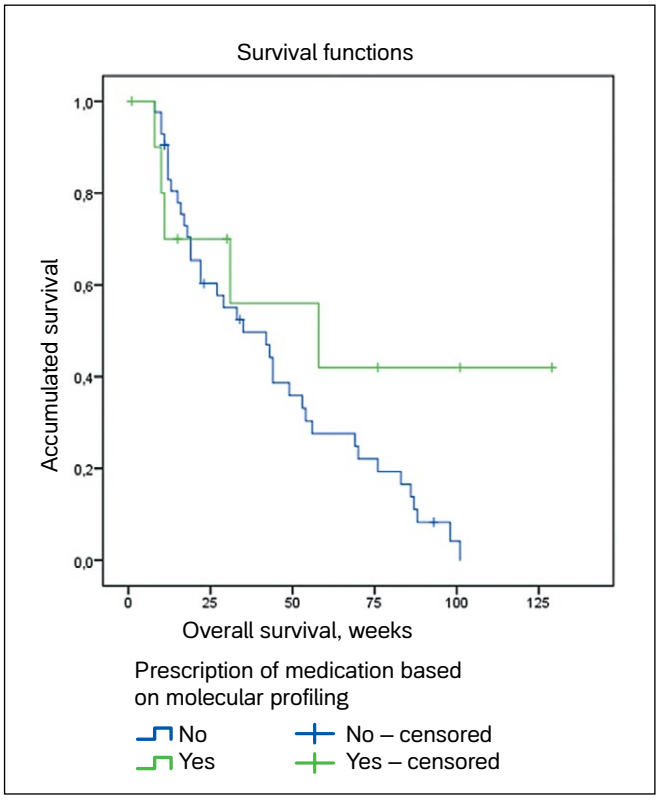

Рисунок 1. *Общая выживаемость в зависимости от факта назначения молекулярно-направленной терапии.*
Figure 1. *Overall survival depending on the administration of molecularly targeted therapy.*

Diagnosis, group	Brief clinical characteristics	Identified alteration	Medication prescribed	Maximum effect of therapy
Breast cancer	39 year old female patient. Triple negative breast cancer (metaplastic carcinoma), after 8 lines of drug therapy	PIK3CA	Alpelisib	Stabilization
Breast cancer	27 year old female patient. Triple negative breast cancer, after 4 lines of drug therapy	High mutational burden (12 mut/Mb)	Pembrolizumab	Progression
Ovarian cancer	42 year old female patient. Serous high-grade ovarian carcinoma.	ATM	Olaparib	Stabilization
Ovarian cancer	38 year old female patient. Serous high-grade ovarian carcinoma.	BRCA2	Olaparib	Partial regression
Lung adenocarcinoma	82 year old female patient. Adenocarcinoma of the upper lobe of the right lung	EGFR	Erlotinib	Partial regression
Lung adenocarcinoma	56 year old male patient. Adenocarcinoma of the upper lobe of the left lung	High mutational burden (12 mut/Mb)	Pembrolizumab	Full clinical response
Colorectal cancer	34 year old male patient. Adenocarcinoma	POLE, TMB	Pembrolizumab	Full clinical response
Ovarian granulosa cell cancer	29 year old female patient. Ovarian granulosa cell tumor, progression against background of 3 lines of drug therapy	CGHCH	Sunitinib	Progression
CNS tumor	55 year old female patient. Glioblastoma of the left parietal lobe, Grade IV, progression against background of 3 lines of drug therapy	PIK3CA	Alpelisib	Progression
Soft tissue sarcoma	28 year old female patient. Leiomyosarcoma of the soft tissue of the face, after 4 lines of drug therapy	BRCA1	Olaparib	Progression
Gall bladder cancer	59 year old female patient. Gall bladder cancer, after 3 lines of drug therapy	PIK3CA	Alpelisib	Stabilization

Table 5. *Clinical characteristics of patients receiving the drug based on molecular profiling data*
Таблица 5. *Клиническая характеристика пациентов, получивших молекулярно-направленную терапию*

specific centers [13]. However, only 22 patients (2.1 %) from the original cohort were able to receive an objective response [14]. Their mOS was 11.9 months. This study also evaluated the PFS2:PFS1 ratio; it was found that this correlation is over 1.3 in 33% of patients. The PFS2:PFS1 ratio >1.3 indicates the advantages of treatment based on CGP, considering that the progression-free time decreases with each line of therapy in the natural progress of the disease.

Another large-scale prospective study (ProfiLER) showed that based on the results of CGP, molecularly targeted therapy was prescribed to 699/2579 patients (27%), and only 163 patients (6%) received at least one target medication based on profiling. Of the 182 implemented lines of therapy based on CGP, partial response was observed in 23 (13 %) patients. At the same time, the full response was observed only in 0.9% from the total cohort [15].

The only multicenter randomized study SHIVA, phase 2 [16], included only patients with disseminated cancer, obstinate to conventional therapy, in which changes were observed in one of the three molecular pathways (hormone receptors, PI3K/AKT/mTOR, RAF/MEK); a total of 11 medications were available. The median PFS was 2.3 months in the experiment group (n=99) vs. 2.0 in the control group (n=96) (HR 0.88, 95% CI 0.65-1.19, p=0.41).

The NCI MATCH (Molecular Analysis for Therapy of Choice) trial [17] included over 40 arms, matching the number of molecular alterations based on the results of profiling using extended panels. The partial response rate (PRR) in the majority of arms was not over 10%, however, 7/27 (25.9%) sub-trials of NCI-MATCH that ended, were positive.

The results of our study are comparable with global data. They confirm the importance of application of CGP in clinical practice to improve results of treatment of patients with disseminated solid tumors. Successful performance of CGP and use of its results for the prescription of MTT assist identification of clinically significant genetic alterations, which fosters customization of therapeutic approaches.

The following turned out to be the predictors of successful performance of CGP: lower number of preceding therapy lines, lower number of revisions of biomaterial, and availability of sufficient amount of tumor tissue for the analysis. These factors require special attention when selecting the patients for the study.

Although no statistically significant differences in overall survival were found (p=0.097), some cases of extraordinary response were registered. They emphasize the potential of MTT in the achievement of positive outcomes of treatment in individual patients.

CONCLUSION

The obtained data complement the necessity of further study of factors influencing efficiency and availability of CGP, as well as implementation of new molecularly targeted medications in the clinical practices. This may help to expand the range of therapeutic options for patients with poor prognosis.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Study funding. The study was the authors' initiative without external funding.	***Источник финансирования.*** Работа выполнена по инициативе авторов без привлечения финансирования.
Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	***Конфликт интересов***. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Contribution of individual authors. Shilo P.S.: development of the research concept, performance of the research, data collection, statistical calculations, preparation, creation and design of the manuscript. Makarkina M.L.: performance of the research, data collection, manuscript editing. Zakharenko A.A.: development of the research concept, manuscript editing, management. The authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	***Участие авторов.*** Шило П.С. – разработка концепции исследования, непосредственное проведение исследования, сбор данных, статистические расчеты, подготовка, создание и оформление рукописи. Макаркина М.Л. – непосредственное проведение исследования, сбор данных, редакция рукописи. Захаренко А.А. – разработка концепции исследования, редакция рукописи, руководство. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.

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Оригинальное исследование | Original study article
DOI: https://doi.org/10.35693/SIM653486

Characteristics of complications after surgical treatment of deformities of the forefoot in patients with rheumatoid arthritis

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Abstract

Aim – to evaluate and analyze postoperative complications that occurred after joint-preserving operations and arthrodesis of the 1st metatarsophalangeal joint in combination with resection of the small ray heads on the forefoot in patients with rheumatoid arthritis.

Material and methods. Patients with rheumatoid arthritis (n-143) were divided into 2 groups depending on the surgical technique. 63 patients were included in group 1 (main group), 80 patients were included in group 2 (control group). Joint-preserving surgical techniques were used in group 1, and arthrodesis of the 1st metatarsophalangeal joint and resection of small rays were performed in the second group. The number of postoperative complications and their types in both groups were assessed, as well as the parameters influencing the occurrence of complications.

Results. There were 25 cases of complications in both groups, 13 cases (20.58%) in group 1, 12 cases (15%) in group 2. The distribution in groups 1 and 2 was as follows: recurrence of deformities of 1 finger (9.52% and 0%), recurrence of deformities of 2-5 fingers (3.17% and 5%), pain in VAS ≥ 60 mm (4.76% and 5%), formation of pseudoarthrosis (0% and 1.25%), instability of metal structures (3.17% and 2.50%), trophic disorders (0% and 1.25%), respectively. A correlation was found between the activity of rheumatoid arthritis ≥ 3.98 points on the DAS28 scale and an increased incidence of postoperative complications.

Conclusion. The results obtained in both groups indicate that joint-preserving techniques for surgical correction of deformities of the forefoot in patients with rheumatoid arthritis, as well as standard ones, are recommended for use in compliance with indications and contraindications.

Keywords: rheumatoid arthritis, rheumatoid forefoot, forefoot deformity, rheumoorthopedics.

Conflict of interest: nothing to disclose.

Citation
Kapitonov DV, Byalik EI, Alekseeva LI, Makarov SA, Byalik VE. **Characteristics of complications after surgical treatment of deformities of the forefoot in patients with rheumatoid arthritis.** *Science and Innovations in Medicine.* 2025;10(1):69-74.
DOI: https://doi.org/10.35693/SIM653486

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Received: 03.01.2025
Accepted: 05.02.2025
Published: 08.02.2025

Характеристика осложнений после хирургического лечения деформаций переднего отдела стопы у пациентов с ревматоидным артритом

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Аннотация

Цель – оценить и проанализировать послеоперационные осложнения, возникшие после проведения суставосберегающих операций и артродеза первого плюснефалангового сустава в комбинации с резекцией головок малых лучей на переднем отделе стопы у пациентов с ревматоидным артритом.

Материал и методы. Пациенты с ревматоидным артритом (n-143) были разделены на две группы в зависимости от хирургической техники. В основную группу включены 63 пациента, в контрольную группу – 80 пациентов. В основной группе использовались суставосберегающие техники операций, пациентам контрольной группы выполняли артродез первого плюснефалангового сустава и резекцию головок малых лучей. Производилась оценка количества послеоперационных осложнений и их видов в обеих группах, а также параметров, влияющих на возникновение осложнений.

Результаты. Выявлено 25 случаев возникновения осложнений в обеих группах: в основной группе 13 случаев (20,58%), в контрольной – 12 случаев (15%). Распределение осложнений в группах было следующим: рецидив деформаций первого пальца (9,52% и 0%), рецидив деформаций 2–5 пальцев (3,17% и 5%), боль по ВАШ ≥ 60 мм (4,76% и 5%), образование ложного сустава (0% и 1,25%), нестабильность металлоконструкций (3,17% и 2,50%), трофические нарушения (0% и 1,25%) соответственно. Выявлена корреляция между активностью ревматоидного артрита ≥ 3,98 балла по шкале DAS28 и повышением частоты возникновения послеоперационных осложнений.

Выводы. Полученные в обеих группах результаты свидетельствуют о том, что суставосберегающие техники хирургической коррекции деформаций переднего отдела стопы у пациентов с ревматоидным артритом, как и стандартные, рекомендованы к использованию с соблюдением показаний и противопоказаний.

Ключевые слова: ревматоидный артрит, ревматоидный передний отдел стопы, деформация переднего отдела стопы, ревмоортопедия.

Конфликт интересов: не заявлен.

Для цитирования:
Капитонов Д.В., Бялик Е.И., Алексеева Л.И., Макаров С.А., Бялик В.Е.
Характеристика осложнений после хирургического лечения деформаций переднего отдела стопы у пациентов с ревматоидным артритом.
Наука и инновации в медицине. 2025;10(1):69-74.
DOI: https://doi.org/10.35693/SIM653486

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Список сокращений
РА – ревматоидный артрит; ПОС – передний отдел стопы; ПФС – плюснефаланговый сустав; ГРО – глобальная реконструктивная операция; ГИПБ – генно-инженерный биологический препарат; ССО – суставосберегающая операция; МК – металлоконструкция.

Получено: 03.01.2025
Одобрено: 05.02.2025
Опубликовано: 08.02.2025

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory disease; in 65-90% of the cases it affects the joints and paraarticular joints of the forefoot. In the vast majority of cases, metatarsophalangeal joints (MTPJ) are involved [1, 2]. Chronic inflammation and synovitis in the MTPJ area cause various deformations such as hallux valgus, hammer deformations of small rays, and other pathological changes on various levels including damage of periarticular structures (muscles, tendons, juxta-joint capsules), which require surgical treatment in the majority of cases [3-5].

The generally recognized standard of surgical correction of MTPJ deformation in RA patients worldwide is arthrodesis of the first MTPJ and resection of metatarsal heads (the Hoffmann-Clayton procedure or global reconstructive surgery, GRS) [6]. The choice of this method is accounted for by the great prevalence of a severe deformation with a high degree of joint degeneration, and positive surgical outcomes.

Pharmacological treatment of RA has now reached quite good results. In 10-20% of patients receiving genetically engineered biological agents (GEBA), complications are observed in the treatment of RA. At the same time, the majority of patients may benefit from of shifting the paradigm of surgical treatment from radical operations to joint-preserving surgeries (JPS). Properly selected and regularly used, the medications may slow down the degeneration of joints and periarticular structures, and improve the patients' general condition [3].

According to international data, JPS in RA patients have positive outcomes [6, 7]. At the same time, our own and international practice shows the increased risk of postoperative complications in joint-preserving surgeries for RA patients. Various sources report the rate of complications in RA patients varying in the range of 27% to 30% after joint-preserving surgeries [8-11].

AIM

Analyze results after joint-preserving surgeries and global reconstructive surgeries in patients with rheumatoid arthritis, and identify causes of postoperative complications.

MATERIAL AND METHODS

We conducted a retrospective study of 143 patients (139 women and 4 men), who had undergone surgical treatment of MTPJ deformations at the Department of Traumatology and Orthopedics of the V.A. Nasonova Research Institute of Rheumatology from 2018 to 2022.

All patients had rheumatoid arthritis of varying activity as per DAS28 (Disease Activity Score-28) scale. The study included 3 patients in remission (<2.6 points), 32 patients with low (2.6-3.2 points) activity or rheumatoid arthritis, and 108 patients with moderate (3.3-5.1 балла) activity.

The average age of patients at the moment of surgical treatment was 55.1±11.7 years (from 26 to 75 years), and the average activity of the disease as per DAS28 was 3.5±0.5 (1.3-4.9) points. In the treatment of rheumatoid arthritis, the patients received basic anti-inflammatory agents and genetically engineered biological agents.

The assessment of outcomes also included the valgus angle of the great toe as per classification of M.J. Coughlin and R.A. Mann, where the deformity angle in Grade I is HVA < 20°, in Grade II, HVA 20°-40°, in Grade III, HVA > 40°.

The group of patients with RA (n=143) was divided into two subgroups by method of surgery. In the main group (n=63) the deformity of the forefoot was treated with joint-preserving surgery, and in the control group (n=80) the global reconstructive surgery was performed.

The joint-preserving surgery included the Scarf lateralising shortening diaphyseal osteotomy of the first metatarsal bone, Akin osteotomy of the base of the proximal phalanx of the first toe, and Weil osteotomy of the heads of the 2nd-5th metatarsal bones. All osteotomies were performed in compliance with the Lelièvre arc and fixed with cannulated Herbert screws of various diameters and lengths. The global reconstructive surgery included arthrodesis of the first metatarsophalangeal joint and resection of heads of the 2nd-5th metatarsal bones.

The observation period was 36 months with follow-up examinations 3 months, 1 and 3 years after the surgery. In cases of patients' complaints, unscheduled examinations in various periods were performed to ensure ongoing evaluation of treatment outcomes and their correction as needed.

The information about the methods of surgical treatment and their outcomes, including patient satisfaction and availability of complications, was obtained from patient charts, and during follow-up examinations after the surgery. Clinical results were evaluated using the functional scale of the American Orthopaedic Foot & Ankle Society (AOFAS), visual analog score of pain, post-surgery X-ray data and patient reports during follow-ups.

Statistical processing of data was performed in Microsoft Excel (Microsoft Corp., USA) and statistical data analysis software suite Statistica 10 for Windows (StatSoft Inc., USA).

RESULTS

In the course of the study, we registered 25 cases of complications among patients with rheumatoid arthritis: 13 in the joint-preservation surgeries and 12 in the global reconstructive surgeries. The complications were distributed according to patient complaints and the clinical evidence as follows: recurrence of deformity of the great toe, recurrence of deformity of the 2nd-5th fingers, formation of the false joint, instability of metal structure, pain score of VAS ≥ 60 mm, trophic disorders (**Table 1**).

Complication \ Surgery	JPS	GRS
Recurrent deformity of the great toe	6 (9.52%)	0 (0%)
Recurrent deformity of the 2nd-5th fingers	2 (3.17%)	4 (5%)
False joint formation	0 (0%)	1 (1.25%)
Instability of metal structure	2 (3.17%)	2 (2.5%)
VAS pain ≥ 60 mm	3 (4.76%)	4 (5%)
Trophic disorders	0 (0%)	1 (1.25%)

Table 1. *Distribution of postoperative complications in the group of patients with rheumatoid arthritis during JPS and GRS and the percentage of the total number of each group (in parentheses)*

Таблица 1. *Распределение послеоперационных осложнений в группе пациентов с ревматоидным артритом при выполнении ССО и ГРО и процентное соотношение от общего числа каждой группы (в скобках)*

Recurrent deformations were seen in 8 cases of JPS and in 4 cases of GRS. The pain in the forefoot was registered in 3 cases after JPS and in 4 cases after GRS. In one case in the GRS group, a false joint formed. Instability of metal structures was identified in 2 cases in the JPS group as well as in the GRS group. Trophic disorders occurred in one patient after GRS.

As far as isolated recurrent deformations are concerned, it is to be noted that the patients after the GRS (n=4) reported recurrent deformation of the small fingers, whereas the great toe, after the arthrodesis of the metatarsophalangeal joint and its complete consolidation, remained in the correct position. The patients who had undergone JPS, in 6 out of 8 cases reported recurrent

Figure 1. *X-ray image before the JPS; immediately after the deformity was eliminated; 3 months after the JPS (recurrence of the deformity); the appearance of the foot 3 months after the operation.*

Рисунок 1. *Рентгенограмма до проведения ССО; сразу после устраненной деформации; через 3 месяца после ССО (рецидив деформации); внешний вид стопы через 3 месяца после операции.*

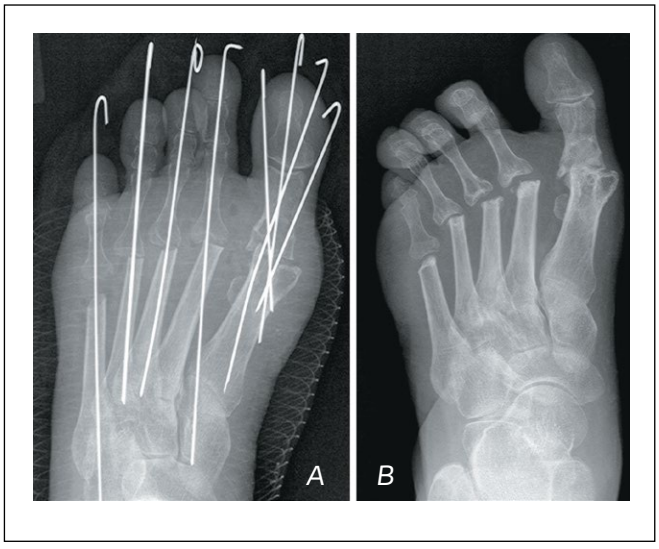

Figure 2. *A – postoperative X-ray; B – X-ray 8 weeks after GRS (false joint 1 MTP).*

Рисунок 2. *А – послеоперационная рентгенограмма; В – рентгенограмма через 8 недель после ГРО (ложный сустав 1 ПФС).*

hallux valgus (**Fig. 1**), the remaining two cases being characterized with deformity of small fingers. This group of patients did not report pain and complications in everyday life related to the recurrent condition.

Complaints of severe pain (≥60 mm VAS) in the surgery site came from 7 patients, 4 after GRS and 2 after JPS. The pain was reported during axial load on the operated limb, predominantly in the transverse arch of the foot and the surgery site. No recurrent deformities were found in these patients.

The formation of the false joint of the great toe was registered in one case, where we observed lack of consolidation in the site or arthrodesis after the removal of Kirschner's wires 8 weeks after the surgery (**Fig. 2**). We need to consider the intraoperative complications that the surgeons faced: they were associated with pronounced cystic reorganization of the head of the first metatarsal bone and the proximal phalanx of the first toe and the poor quality of bone tissue, which made it difficult to fix the achieved correction. Despite the complication, the female patient reported no pain or restrictions in her everyday life after the surgery. After JPS, no formation of false joints was observed.

In four cases, instability of metal structures occurred. Two cases were noted in patients after arthrodesis of the first MTP joint with fixation with two Herbert's cannulated screws. Two more cases were noted in patients after the Scarf and Akin osteotomies with the same type of fixation (**Fig. 3**). It is to be mentioned that the identified instability of metal structures did not affect the function of the foot, but in order to prevent more severe complications it was resolved to perform revision surgeries and remove the unstable metal structures. Following that, there were no complaints from the patients.

Trophic disorders emerged in one case after the GRS: there was disruption in the blood circulation in the distal sections of small fingers, most likely due to the presence of Kirschner's wires. Once these were removed, the female patient reported gradual restoration of microcirculation in the small fingers, and complaints regressed.

Before the surgery, the hallux valgus angle (HVA) in patients with emerged complications was, on average, 50°(±8.51) in the main group and 54° (±11.3) in the control group, which matches Grade III of hallux valgus.

Considering the foregoing, among the rheumatoid arthritis patients there occurred 12 complications after the GRS and 13 complications after the JPS. The total rate of complications in the RA group is 17.48%. After GRS (n-80), the rate of complications was 15%, and after JPS (n-63), 20.58%.

In 23 out of 25 cases of complications, patients received therapy as of the time of surgery and after the surgery. Of this number, 19 patients received basic anti-inflammatory therapy, 4 patients received GEBA; in 13 cases, patients received hormone treatment. In 2 cases, the patients canceled the therapy of their own accord. There was no statistically significant relationship between the risk of postoperative complications and the therapy received by patients.

In the subgroup of patients with RA experiencing complications (n-25), the average score of activity was 3.98±0.6 points; in patients with RA who had no complications, the average score of activity was 3.5±0.5 points. Statistical processing of the indicators revealed a correlation (r = 0.314284) between an increased RA activity index and an increased risk of postoperative complications.

DISCUSSION

Given the progress in the development and implementation of medications for the treatment of RA, the

Figure 3. *A – X-ray immediately after JPS (Scarf, Akin, Weil osteotomy); B – X-ray 6 months after JPS (aseptic necrosis of the head of the 2nd MB, instability of the Herbert screw, recurrence of the hallux valgus deformity of the 1st finger).*

Рисунок 3. *А – рентгенограмма сразу после ССО (остеотомии Scarf, Akin, Weil); В – рентгенограмма через 6 месяцев после ССО (асептический некроз головки второго ПК, нестабильность винта Герберта, рецидив вальгусной деформации первого пальца).*

relevance of joint-preserving surgery is increasing among surgeons [12-15]. These methods of deformity correction help to maintain the normal functional status of the foot for as long as possible, and this in turn improves the quality of life and activity of patients with RA. The obvious advantage of the JPS is, without doubt, the preservation of the scope of movement in the foot articulations and normal biomechanics of motion (during performance of phases of the step).

The data obtained by us shows that patient satisfaction, lack of deformities and complications after surgical treatment depend on timely and regular follow-ups by rheumatologists, and the same is reported by other researchers [2, 3]. This facilitates timely adjustment of RA therapy to maintain acceptable activity of RA (remission and low activity), since the RA activity on the DAS28≥3.98 correlates (r=0.314284) with a more frequent onset of postoperative complications. Kushioka *et al*. (2018) dwell in their study on a significant positive correlation (β=0.44 and p=0.001) between the elevated (3.0±1.0) average value of RA activity before the surgical treatment of DAS28-CRP and the increase of clinical and radiographic complications after the surgery [15].

The complications in the performance of JPS and GRS described above were assessed and statistically analyzed. In the group of patients with RA, who had undergone JPS, recurrent deformities of the great toe were observed in 9.52%, but in the group of patients after the GRS such deformities were not observed, whereas recurrent deformities of the 2nd-5th fingers occurred in 4 cases (5%). These patients complained only of recurrent deformities of the forefoot in different manifestations, but did not complain of pain. In their study, Takakubo *et al*. (2018) also reported a group of patients with RA, who had recurrent deformities of the 1st-5th fingers in the forefoot occurred after JPS in an isolated way, without pain [7]. In another retrospective study, Yano *et al*. (2021) studied JPS in the forefoot of patients with RA. The average observation period was 6 years. The study included 89 people (105 feet), who had various joint-preserving surgeries. The following complications were registered: recurrent hallux valgus, 11 feet (10.5%), recurrent deformities of small rays, 24 joints (7.7%). Revision surgeries were performed for 11 patients with complications (mainly, recurrent HV) [6].

The occurrence of the greater number of recurrent deformities in the JPS group is related to the fact that HVA of the great toe was over 40° at the moment of surgery, and the RA activity tended to be high, ≥3.98 points on the DAS28. This allows to conclude that the correction of grade III hallux valgus of the great toe (≥ 40°) in patients with RA required, apart from standard osteotomy, some interventions into the soft tissue, and to keep the disease activity under control, increase the time of post-surgery patient care, and follow up the operated forefoot at predefined periods. Similar data is reported by Takakubo et al., moreover, they note that there were more recurrent deformities of fingers in patients with the average value of HVA=25° (grade II in the classification of M.J. Coughlin and R.A. Mann) [7] .

The false joint that formed in one case (1.25 %) in the RA group after the GRS was caused by a large defect of the bony mass in the head of the first metatarsal bone before the surgery. Traditionally, in the arthrodesis of the first MTPJ Herbert's screws are used, but, considering the lower quality of bone tissue in RA patients, the arthrodesis of the first MTPJ was fixed with Kirschner's wires with their subsequent removal eight weeks later. Fixation with wires ensures the correct position of the toe, rotational stability and compression required for consolidation. This method provides a positive outcome; considering the single case of formation of the false joint, it is recommended for use in patients with RA.

Problems with metal fixtures occurred in four cases, two in each group (JPS, 3.17%, GRS, 2.50%). In the case of GRS, the instability of screws appeared against the background of slowed consolidation in the zone of arthrodesis of the first MTPJ that were fixed with Herbert's screws. After the JPS, the instability of screws occurred mainly due to the low quality of the bony tissue, which resulted in the early micro-motion and subsequent loosening of the screws. Transition to walking in ordinary footwear with fully bearing on the operated limb in conventional time (6 weeks after the operation) likely affects the stability of fragments and results in the micro-motion of screws. In their study, Zirngibl *et al*. Noted the necessity of adjustment of standard periods of postoperative follow-up of rheumatoid patients, as well as the use of dynamic orthoses, functional bandages, and performance of special exercises to train the motion in the articulations, which may be instrumental in lowering the risk of onset of complications [16].

Such complications as trophic disorders (n=1; 1.25%) after the GRS were caused by ischemia due to compression of blood vessels of the small toe by the wire, following the removal of which the problem was resolved.

CONCLUSION

It follows from the obtained data that the share of surgical treatment of forefoot deformities in patients with RA without complications remains quite high in both groups (JSP, 79.37 %, GRS, 85%). Various authors report that in 74%-89.5% cases positive outcomes are registered after JPS in rheumatoid arthritis patients [6, 17]. This data allow to conclude that with certain indications, viz. grade I and II of hallux valgus of the great toe, preserved articular cartilage of the 1-5 MTPJ, activity of the rheumatoid arthritis below 3.98 points on the DAS28, the joint-preserving technique of correction of deformities of the forefoot in patients with rheumatoid arthritis are recommended with arthrodesis of the first metatarsophalangeal joint and resection of heads of 2nd-5th metatarsal bones.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Study funding. The study was the authors' initiative without external funding.	***Источник финансирования.*** Работа выполнена по инициативе авторов без привлечения финансирования.
Conflict of Interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	***Конфликт интересов.*** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Contribution of individual authors. Kapitonov D.V.: database collection, statistical processing of results, writing of the article, formulating of conclusions. Byalik E.I., Alekseeva L.I.: research idea, article editing. Makarov S.A.: patient selection, operations. Byalik V.E.: statistical processing of the database. The authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work	***Участие авторов.*** Капитонов Д.В. – сбор базы данных, статистическая обработка результатов, написание текста статьи, формулировка выводов. Бялик Е.И., Алексеева Л.И. – идея исследования, редактирование статьи. Макаров С.А. – отбор пациентов, проведение операций. Бялик В.Е. – статистическая обработка базы данных. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.

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DOI: https://doi.org/10.35693/SIM643139

Maxillary reconstruction using the "Autoplan" software suite

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Abstract

Aim – to develop a three-stage algorithm for maxillary reconstruction with the Autoplan software suite to improve the results of surgical treatment.

Material and methods. 110 patients with maxillary defects were included in the study and were divided into the main (60) and control (50) groups. The three-stage algorithm and the Autoplan software suite were used to perform reconstructive procedures only in the main group. All the postoperative results were assessed in a period of six months after the surgery.

Results. Good aesthetic result was noted in 29 (48.33%) cases in the main group and in 17 (34%) cases in the control group (p<0.001). The differences between the main and control groups in functional results are statistically significant (p<0.05): good speech quality: 31 (86.11%) in the main group, 22 (78.57%) in the control group (p=0,047). Diet without limitations: main group, 26 cases (72.22%), control group, 18 cases (64.29%) (p=0,042). The mean time of the reconstructive stage using scapular flap: main group, 210 (35) minutes, control group, 300 (35) minutes (time reduction by 30 (13.4)%; fibular flap: main group, 180 (16) minutes, control group, 260 (36) minutes (time reduction by 30.77 (11.2)%; ALT flap: main group, 175 (17) minutes, control group, 220 (33) minutes (time reduction by 20.45 (13.3)%; radial flap: main group, 130 (12) minutes, control group, 170 (12) minutes (time reduction by 23.53 (8.1)% (p<0,001).

Conclusion. It can be concluded that incorporation of additive technologies, personalized attachment systems, and preoperative planning are crucial components of contemporary reconstructive surgery. This approach not only helps to streamline surgical procedures but also contributes to favorable functional and aesthetic outcomes.

Keywords: maxillary reconstruction, mandible reconstruction, additive technologies, microsurgery, autologous flaps, facial reconstruction.

Conflict of interest: nothing to disclose.

Citation
Ivashkov VYu, Denisenko AS, Kolsanov AV, Verbo EV, Nikolaenko AN, Legonkikh AYu. **Maxillary reconstruction using the "Autoplan" software suite.** *Science and Innovations in Medicine*. 2025;10(1):75-80. DOI: https://doi.org/10.35693/SIM643139

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Received: 17.12.2024
Accepted: 28.01.2025
Published: 05.02.2025

Устранение дефектов верхней челюсти с применением трехэтапного алгоритма и программного комплекса «Автоплан»

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Аннотация

Цель – разработать и внедрить трехэтапный алгоритм устранения дефектов верхней челюсти с программным комплексом «Автоплан» для улучшения результатов хирургического лечения.

Материал и методы. В исследовании приняли участие 110 пациентов с приобретенными дефектами верхней челюсти, которых разделили на основную (60 человек) и контрольную (50 человек) группы. Алгоритм, состоящий из трех этапов, и программный комплекс «Автоплан» применялись для выполнения реконструктивно-пластических операций только в основной группе. Оценка послеоперационных результатов производилась через 6 месяцев после операции и включала следующие параметры: функциональный результат, эстетический результат, временные затраты на оперативное вмешательство.

Результаты. В основной группе хороший эстетический результат был достигнут в 29 (48,33%) случаях, в контрольной – в 17 (34%) случаях (p<0,001). Различия между основной и контрольной группами по функциональным результатам статистически значимы (p<0,05). Хорошее качество речи было получено в основной группе в 31 (86,11%) случае, в контрольной группе – в 22 (78,57%) случаях (p=0,047). Диета без ограничений в основной группе отмечалась в 26 (72,22%) случаях, в контрольной – в 18 (64,29%) случаях (p=0,042). Среднее время реконструктивного этапа с применением лопаточного лоскута в основной группе составило 210 (35) минут, в контрольной – 300 (35) минут (сокращение времени на 30 (13,4)%); с применением малоберцового лоскута в основной группе составило 180 (16) минут, в контрольной – 260 (36) минут (сокращение времени на 30,77 (11,2)%; с применением ALT-лоскута в основной группе 175 (17) минут, в контрольной группе 220 (33) минут (сокращение времени на 20,45 (13,3)%; с применением лучевого лоскута в основной группе составило 130 (12) минут, в контрольной – 170 (12) минут (сокращение времени на 23,53 (8,1)% (p<0,001).

Выводы. Применение аддитивных технологий, индивидуализированных систем фиксации и предоперационного планирования является неотъемлемой частью современной реконструктивной хирургии, что на практике позволяет сократить время операции, а также получать хорошие функциональные и эстетические результаты в большем количестве случаев по сравнению с общепринятыми методиками.

Ключевые слова: реконструкция верхней челюсти, реконструкция нижней челюсти, аддитивные технологии, микрохирургия, аутологичные лоскуты, устранение дефектов лица.

Конфликт интересов: не заявлен.

Для цитирования:
Ивашков В.Ю., Денисенко А.С., Колсанов А.В., Вербо Е.В., Николаенко А.Н., Легоньких А.Ю. **Устранение дефектов верхней челюсти с применением трехэтапного алгоритма и программного комплекса «Автоплан».** *Наука и инновации в медицине.* 2025;10(1):75-80. DOI: https://doi.org/10.35693/SIM643139

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Получено: 17.12.2024
Одобрено: 28.01.2025
Опубликовано: 05.02.2025

INTRODUCTION

Modern facial injuries caused by new types of weapons, increased vehicle speeds, and diagnosed malignancies pose a serious surgical challenge. According to statistics, the number of facial injuries has more than doubled over the past decade[1].

Injuries resulting from a variety of impact mechanisms result in multiple injuries to both soft and hard facial tissues. For example, fractures of the upper jaw are often combined with eye socket injuries and damage to the soft tissues of the face [1]. This requires a comprehensive approach to treatment, including surgical intervention and restorative therapy.

With respect to defects of the maxilla, the main tasks are the elimination of oronasal fistula, restoration of the lower wall of the orbit to ensure the supporting function of the eyeball, restoration of the functions of chewing, swallowing, breathing, speech, as well as the implementation of complete dental rehabilitation.

An important practical area is the customization of surgical interventions based on the patient's anthropometric data. Taking into account the unique anatomical features of the patient ensures good functional and aesthetic results, which opens up new horizons for the successful rehabilitation of patients with complex facial defects [2].

There are numerous classifications of maxillary defects. One of the latest is the classification of J.S. Brown (2010), based on the identification of the vertical and horizontal components of the defect. Depending on the presence of the anastomosis between the oral and the nasal cavity, involvement of the supporting structures of the eye socket in the defect, the scope of damage of the hard palate and some other parameters, the authors suggested six types of defects [3].

Today's clinical practices place more importance on the customized approach, modern systems of visualization, surgery planning combined with involvement of additive technologies. 3D-modeling enables reproduction of precise stereolithographic models on the stage of planning of reconstruction based on the patient's anthropometric data [4]. The use of individual templates provides the possibility of reaching high precision of congruence of the bony surfaces of the flap and recipient wound, reducing surgery time and yielding better functional and aesthetic results of reconstructive plastic surgery [5, 6].

AIM

To develop a three-stage algorithm for maxillary reconstruction with the Autoplan software suite to improve the results of surgical treatment.

[1]Federal Service of State Statistics: traumatism statistics in Russia. Available online: https://rusind.ru/statistika-travmatizma-v-rossii-po-rosstatu.html

MATERIAL AND METHODS

A randomized controlled trial was conducted involving 110 patients with maxillary defects of post-traumatic and post-oncological etiology. The participants of the study were divided into two groups, the main and the control group. The main group included 60 people, average age of 46±11 years, men to women ratio: 46/14. The control group included 50 people, average age of 47±12 years, men to women ratio: 39/11.

In accordance with the J.S. Brown's classification of maxillary defects (2010), four types of defects were identified (Type I-IV).

Type I: lower combined defects of the maxilla, predominantly with a horizontal component, affecting the mucous membrane of the retromolar region, the soft palate region and the lateral wall of the oropharynx (main group: 23 patients; control group: 16 patients).

Type II: defects resulting from total maxillectomy (main group: 13 patients; control group: 12 patients).

Type III: partial defect of the maxilla, predominantly with a vertical component (main group: 15 patients; control group: 13 patients).

Type IV: inclusion of the orbit with its exenteration (main group: 9 patients; control group: 9 patients).

In the main group of patients with combined maxillary defects, the surgery planning, performance and follow-up involved a three-stage algorithm and the Autoplan software suite. In the control group, surgery was performed under conventional methods.

Surgery algorithm. The algorithm used to perform the surgery in the main group consisted of three stages. The first stage is preoperative planning: the patient's head CT data was uploaded to the Autoplan software suite. 3D-model of bony structure and soft tissue is constructed automatically; the defect is visualized and localized, its scope and area were calculated. For plastic material, four types of free surgical flaps were used: maple seed-shaped fasciocutaneous radial flap [7], chimeric scapular flap, ALT-flap (anterolateral thigh), and fibula flap. The selection of the suitable plastic material was performed in the automatic flap selection program[1], based on the following parameters: area, scope and composition of the defect, necessity of cavity plugging. If the selected flap was fibular or scapular, additional CT was performed of the lower leg or the scapular region, respectively. The data was uploaded to the Autoplan software suite, where the 3D model of the flap was constructed with fitting in the defect area. This stage also included construction of 3D models and construction of individual templates for resection, flap modeling and fixation system.

The second stage is the surgery. During the surgery, individual templates for re-resection were used to refresh the bonesaw lines of the recipient area, isolation and modeling of the flap were performed using individual templates and fixation system with retained blood flow in the autogenetic graft.

In the third stage, the modeled flap was repositioned to the recipient area and partially attached to the bonesaw lines of bony structures. Microsurgery was then performed to form the anastomoses with subsequent final fixation of the flap and suture of the wound.

The postoperative results in both groups were assessed six months after the operation. The criteria studied were the results of the functional (binocular vision, dietary restrictions, speech disorders) and aesthetic aspects; the amount of time spent on the surgical stage; the incidence of post-surgery complications. For each of the parameters, the functional result was assessed as 'good', 'satisfactory', or 'poor'. The aesthetic results were assessed using the FACE-Q scales, depending on the score, the 'good' (≥80 points), 'satisfactory' (65-79 points), 'poor' (≤64 points) evaluations were given.

Data processing. Using descriptive statistics, mean values and standard deviations were obtained. Statistical tests were used to determine the statistically significant $\alpha < 0{,}05$ difference between the values in the control and the main groups. To assess the significance of differences between groups, Student's T-test and Pearson's χ^2 were used. IBM SPSS Statistics 23 software suite was used for statistical calculations.

RESULTS

Reconstructive plastic surgeries were performed on 110 patients with defects of the upper jaw (N=60 in the main group, N=50 in the control group). The autogenetic graft used in the main group were distributed as follows: 22 – radial flap, 22 – ALT-flap, 14 – scapular flap, and 2 – fibula flap. The autogenetic graft used in the control group were distributed as follows: 17 – radial flap, 20 – ALT-flap, 12 – scapular flap, and 1 – fibular flap (**Table 1**).

Flap type	Type I		Type II		Type III		Type IV		Total		TOTAL
	O	K	O	K	O	K	O	K	O	K	O+K
Fibular	2 (66.7%)	1 (33.3%)	—	—	—	_	—	_	2 (66.7%)	1 (33.3%)	3 (2.7%)
Scapular	4 (15.4%)	3 (11.5%)	10 (38.5%)	9 (34.6%)	—	_	—	_	14 (53.8%)	12 (46.2%)	26 (23.6%)
ALT-flap	4 (9.5%)	3 (7.1%)	3 (7.1%)	3 (7.1%)	6 (14.3%)	5 (11.9%)	9 (21.4%)	9 (21.4%)	22 (52.4%)	20 (47.6%)	42 (38.2%)
Radial flap	13 (33.3%)	9 (23%)	—	_	9 (23%)	8 (20.5%)	—	_	22 (56.4%)	17 (43.6%)	39 (35.5%)
Total:	23 (20.9%)	16 (14.5%)	13 (11.8%)	12 (10.9%)	15 (13.6%)	13 (11.8%)	9 (8.2%)	9 (8.2%)	60 (54.5%)	50 (45.5%)	110 (100%)

Table 1. *Plastic material used for maxillary reconstruction in the main and control groups. O – main group, K – control group*

Таблица 1. *Аутотрансплантаты, примененные для реконструкции верхней челюсти в основной и контрольной группе. О – основная группа, К – контрольная группа*

[1]Certificate of state registration of the computer program: RUS №2024617819 dated 05.04.2024.
Available online: https://fips.ru/registers-doc-view/fips_servlet?DB=EVM&DocNumber=2024617819&TypeFile=html

Defect Type	TypeI (N=23)	TypeII (N=13)	TypeIII (N=15)	TypeIV (N=9)	TOTAL	P
Speech quality					N=36	p=0.047
Good	21 (91.3%)	10 (76.92%)	-		31 (86.11%)	
satisfactory	2 (8.7%)	1 (7.69%)	-		3 (8.33%)	
Poor	-	2 (15.38%)	-		2 (5.56%)	
Diet			-		N=36	p=0.042
No restrictions	19 (82.61%)	7 (53.85%)	-		26 (72.22%)	
Strained food	4 (17.39%)	5 (38.46%)	-		9 (25%)	
Liquid diet		1 (7.69%)	-		1 (2.78%)	
Aesthetic result					N=60	(p<0.001)
Good	18 (78.26%)	7 (53.85%)	4 (26.67%)		29 (48.33 %)	
satisfactory	4 (17.39%)	3 (23.08%)	9 (60%)	9 (100%)	25 (41.67 %)	
Poor	1 (4.35%)	3 (23.08%)	2 (13.33%)		6 (10%)	
Eyeball position					N=28	p=0.032
symmetrical	-	10 (76.9%)	13 (86.67%)		23 (82%)	
diplopia	-	2 (15.4%)	2 (13.33%)		4 (14%)	
enophthalm	-	1 (7.7%)	0		1 (4%)	

Таблица 2. *Функциональные и эстетические результаты устранения дефектов верхней челюсти у пациентов основной группы*
Table 2. *Functional and aesthetic results of maxillary reconstruction in the main group*

Assessment of aesthetic results. Before the surgery the average score as per the FACE-Q questionnaire was similar in both groups and was 51 points (with quartiles: Q1 - 45, Q2 - 51, Q3 - 57). The assessment 6 months after the surgery yielded the following average scores: in the main group, 79 points (Q1 - 74, Q2 - 79, Q3 - 93); in the control group, 67 points (Q1 - 64, Q2 - 67, Q3 - 80) (p<0.001). God aesthetic results were achieved in 29 (48.33%) patients of the main group and in 17 (34%) patients of the control group. Satisfactory results: 25 (41.67%) patients of the main group;21 (42%) patients of the control group. Poor results: 6 (10%) patients of the main group and 12(24%) patients of the control group.

Assessment of functional results. Speech: good quality of speech was seen in 31 (86.11%) patients of the main group and 22 (78.57%) patients of the control group; satisfactory, in 3 (8.33%) / 3 (10.71%) patients; poor, in 2 (5.56%) / 3 (10.71%) patients, respectively (p<0.05, p=0.047).

Diet. Of the 36 patients of the main group and 28 patients of the control group with maxillary defects of Type I and Type II, for 26 (72.22%) / 18 (64.29%) patients there were no dietary restrictions; 9 (25%) / 8 (28.57%) patients required strained food; 1 (2.78%) / 2 (7.14%) patients required a fluid diet (p<0.05, p=0.042).

Visual acuteness and eye position. Decrease in visual acuteness was not identified at all. In the group of patients with Type II and Type III defects (N=28 / 25) symmetry in the eyeball position was achieved in 23 (82%) / 17 (68%) of the cases; moderate diplopia was seen in 4 (14%) / 7 (28%) of the cases; enophthalmos was seen in 1 (4%) /1 (4%) of the cases, respectively (p<0.05, p=0.032).

Thus, the implementation of the three-stage algorithm allowed achievement of good functional and aesthetic results in the greater number of cases. The differences between the main and the control group are statistically significant (p<0.05) (**Tables 2, 3**).

The time required to perform the reconstructive stage of the surgery, depending on the selected graft, is shown in Table 4. Scapular flap: in the main group, the average time was 210 (35) minutes, in the control group, 300 (35) minutes (time reduced by 30 (13.4)%). Fibular flap: 180 (16) min / 260 (36) min (time reduced by 30.77 (11.2)%).

Defect Type	TypeI (N=16)	TypeII (N=12)	TypeIII (N=13)	TypeIV (N=9)	TOTAL
Speech quality					N=28
Good	13 (81.25%)	9 (75%)	-		22 (78.57%)
satisfactory	2 (12.5%)	1 (8.33%)	-		3 (10.71%)
Poor	1 (6.25%)	2 (16.67%)	-		3 (10.71%)
Diet			-		N=28
No restrictions	12 (75%)	6 (50%)	-		18 (64.29%)
Strained food	4 (75%)	4 (33.33%)	-		8 (28.57%)
Liquid diet		2 (16.67%)	-		2 (7.14%)
Aesthetic result					N=50
Good	10 (62.5%)	5 (41.67%)	2 (5.38%)		17(34%)
satisfactory	4 (25%)	3 (25%)	6 (46.15%)	8 (88.89%)	21 (42%)
Poor	2 (12.5%)	4 (33.33%)	5 (38.46%)	1 (11.11%)	12 (24%)
Eyeball position					N=25
symmetrical	-	7 (58.33%)	10 (76.92%)		17 (68%)
diplopia	-	4 (33.33%)	3 (23.08%)		7 (28%)
enophthalm	-	1 (8.33%)	0		1 (4%)

Table 3. *Results of surgical treatment of patients with maxillary defects in the control group*
Таблица 3. *Функциональные и эстетические результаты устранения дефектов верхней челюсти у пациентов контрольной группы*

	Main group				Control group			
Flap type	Angle of scapula	Fibular	ALT	Radial	Angle of scapula	Fibular	ALT	Radial
Surgery time, min	500 (52)	475 (78)	390 (65)	290 (56)	610 (66)	580 (74)	450 (71)	330 (67)
Flap modeling time, min	90 (12)	75 (13)	85 (8)	30 (4)	180 (57)	160 (24)	120 (8)	70 (6)
Reconstructive stage time, min	210 (33)	180 (15)	175 (16)	130 (12)	300 (33)	260 (34)	220 (32)	170 (11)

Table 4. *Mean surgery time in the main and control groups*
Таблица 4. *Среднее время оперативного вмешательства в основной и контрольной группах*

ALT flap: 175 (17) min / 220 (33) min (time reduced by 20.45 (13.3)%). Radial fasciocutaneous flap: 130 (12) min / 170 (12) min (time reduced by 23.53 (8.1%). The differences both in the average time of reconstructive stage and in the total time of the surgery in the main and the control group are significant ($p<0.001$).

DISCUSSION

The region of the head and the neck is crucial in the functions of chewing, swallowing, breathing, and speech; moreover, it is vital for social interactions. Aesthetic and functional facial defects are detrimental to the patient's quality of life [8], therefore, their repair is required for medical reasons [9-11].

To repair the defects in the middle region of the face and the maxilla, removable exoprostheses are usually used that isolate the oral and the nasal cavities, thus restoring the speech and the swallowing functions. The prosthesis may include dental elements that contribute to a satisfactory aesthetic result. One of the major advantages of this method is fast achievement of the desired result, a shorter and less invasive plan of surgical treatment without the lengthy period of rehabilitation.

In patients undergoing cancer treatment, prostheses provide the possibility of direct visual control, but given the availability of modern imaging techniques, this potential advantage has not been confirmed [12]. In addition, prostheses require daily care and must be removed and cleaned regularly, which can be a major problem for older people or those with visual impairments. In some cases, the exoptostheses may be an acceptable method for the repair of maxillary defects; however, their use can not restore the functions as effectively as the free autogenetic graft can [13].

Scientific literature currently describes a considerable number of microsurgical methods to repair the maxillary defects, including the rib osteo-cutaneous flap [14], latissimus dorsi muscle-cutaneous flap [15], scapular flap [16], rectus abdominis muscle flap [17], osseous radial flap [18], fibular flap [19, 20], and some others [21-23]. The use of the method we propose allows achievement of better functional and aesthetic results in comparison with other methods [24, 25].

Additive technologies allow achieving higher rates of bone surface congruence and reducing surgery time [26].

The three-stage algorithm of reconstructive plastic surgery proposed by us for patients with facial defects allows reducing the surgery time by 17.4% in comparison with conventional techniques. E.g., B. Barton et al. (2022) report that the time for reconstruction of the maxilla with the flap involving the scapular angle is 600 minutes [27]. In fact, this aligns with the time of surgery in the control group of our study (610 minutes), whereas in the main group, where the three-stage algorithm and the Autoplan software suite were used, the average time of surgery was reduced to 500 minutes.

The use of standardized algorithms for constructing a patient's surgical treatment trajectory helps to improve the reproducibility of such complex operations [28, 29].

CONCLUSION

We propose an approach that includes three stages of reconstructive plastic surgeries for patients with facial defects. It allows achieving better results of surgical treatment, reducing the time of surgical intervention and getting fewer complications in comparison with conventional approaches. We also believe that the presented method will reduce the time required for training of surgeons in this area.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Study funding. The study was the authors' initiative without external funding.	***Источник финансирования.*** Работа выполнена по инициативе авторов без привлечения финансирования.
Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	***Конфликт интересов.*** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Compliance with Ethical Standards. The authors confirm that the rights of the people who participated in the study were respected, including obtaining informed consent. The study protocol was approved by the local Ethics Committee (protocol No. 156863 dated 20.10.2024).	***Соответствие нормам этики.*** Авторы подтверждают, что соблюдены права людей, принимавших участие в исследовании, включая получение информированного согласия. Протокол исследования был одобрен ЛЭК (протокол № 156863 от 20.10.2024 г.).
Contribution of individual authors. V.Yu. Ivashkov, A.V. Kolsanov: design of the study, scientific editing. E.V. Verbo, A.N. Nikolaenko: scientific editing. A.S. Denisenko, A.Yu. Legonkikh: review of publications on the article topic, writing of the article, collection and processing of the material. All authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work	***Участие авторов.*** В.Ю. Ивашков, А.В. Колсанов – создание дизайна исследования, научное редактирование; Е.В. Вербо, А.Н. Николаенко – научное редактирование. А.С. Денисенко, А.Ю. Легоньких – обзор публикаций по теме статьи, написание текста статьи, сбор и обработка материала. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.

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