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# GENERAL SURGERY

1 | 2022

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1. Cereda et al, 2009, J am Geriatr Soc. 57:1395–1402

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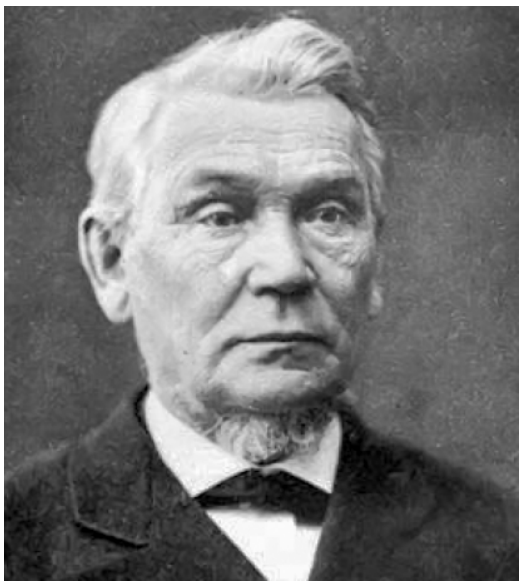
# Professor Volodymyr Opanasovych Karavaiev — surgeon, scientist and innovator

The article presents the professional and scientific path of Professor Volodymyr Opanasovych Karavaiev — the first professor of surgery, first head of the department, first organizer and first dean of the medical faculty of St. Volodymyr University, who worked at the university clinic (now Kyiv City Clinical Hospital No18).

Surgery is the first and leads us to the truth, so we hope
that the passage of time will not take it with us
*M.I. Pirogov*



For many, the life and work of our predecessors became a measure of their own actions and their own lives, an example of dedication to their profession and science.

Volodymyr Opanasovych Karavaiev became the first professor of surgery, the first head of the Department of Surgery, the initiator and the first dean of the Medical Faculty of St. Volodymyr University. He combined not only organizational and managerial qualities, but also, above all, the talent of a scientist, an experimenter, an innovator, and a doctor.

In 1838, under the direction of M. I. Pirogov, V. O. Karavaiev completed a world-renowned experimental clinical study «On Traumatic Inflammation of Veins» («De phlebitide traumatica») devoted to the investigation of causes and mechanisms of purulent complications (pyemia, hospital gangrene). In this scientific work, V. O. Karavaiev made an assumption that did not comply with the scientific views, concepts and ideas of that time. The provision that pus passes through the pulmonary capillaries became a surgical axiom in the treatment of sepsis not so long ago, in spite of the fact that V. O. Karavaiev noted it more than 180 years ago, before Rudolf Virchow began his research on thrombosis and embolism.

The work on the pericardial puncture «On the protocol of the pericardial sac» is particularly noteworthy. V. O. Karavaiev described the surgical techniques for this procedure and their indications, practically implemented many innovative ideas that were groundbreaking in the field of heart surgery. V. O. Karavaiev was the first surgeon to carry out pericardial puncture (access by V. O. Karavaiev) providing its experimental justification.

The era of anesthesia began in 1845. On October 16, 1846, a Boston dentist, Thomas Morton, under the advice of a chemist, Carl Jackson, first used etheric anesthesia. V. O. Karavaiev and A. P. Walter, an anatomist, studied the mechanism of action of ether, and then chloroform, as well as the physiological basis of anesthesia. And importantly, this was the first set of scientific studies that were widely used in national and world medicine. Similarly to M. I. Pirogov V. O. Karavaiev first tried ether on himself, then on volunteers, and only after receiving successful results included patients into the study. It should be noted that V. O. Karavaiev did not observe any fatal complications of anesthesia in his practice. M. I. Pirogov was the only scientist in the world who registered such cases.

V. O. Karavaiev wrote the most accurate and detailed works on the physiological issues of anesthesia and its action. He was the first in the Russian Empire to identify indications and contraindications for the use of inhalation and rectal ether anesthesia, described the stages of anesthesia, and without being familiar with the Charrier apparatus for inhaling ether vapors, designed a device for its use.

V. O. Karavaiev carried out many significant researches in ophthalmology. Thus, in 1841 he was the first in the world, 25 years before Trefe (1865), to use an autopsy of the cornea in its upper part to treat cataracts, proving the feasibility of this procedure in more than 1.5 thousand observations. Out of 897 personally performed cataract surgeries, V. O. Karavaiev achieved good results in 856 patients. Due to V. O. Karavaiev's method, cataract surgery took a few seconds. He developed the technique of tenotomy to eliminate strabismus and was the first to perform this operation. He also invented the original eye instruments: a bayonet catarrhal knife, special tweezers for fixing the eyeball. V. O. Karavaiev was one of the first to teach ophthalmology by combining theory with practice. He is the author of prominent works on certain issues in ophthalmology — «On operations for the formation of an artificial pupil and strabismus» (1842), «On cataracts in practical and surgical terms» (1859) and others.

In the field of facial plastic surgery, V. O. Karavaiev developed several methods of plastic repair of nasal defects, described the original method of straightening of the back of the nose (1838), as well as introduced a suturing technique for hard and soft palate reconstruction that was further used by domestic surgeons (1840). V. O. Karavaiev performed 1215 operations (mortality rate — 3.2 %) on the face, of which 326 were plastic operations.

V. O. Karavaiev was the first to implement a method of amputation of limbs with the formation of skin and skin-muscle flaps with reduced muscle weight to prevent suppuration in the pre-antiseptic period, and widely introduced it into surgical practice. He was one of the first to use subchondral resection, showing that the periosteum is the tissue from which bone tissue is further regenerated. V. O. Karavaiev performed a number of such operations in 1839.

V. O. Karavaiev described the results of his scientific work on rare diseases in «Surgical cases of disease», which was published in Germany in 1843. It should be noted that due to the publications in France and Germany and invitations to the German medical congresses, V. O. Karavaiev became a well-known scientist in Europe.

V. O. Karavaiev participated in the development and implementation of two of the most significant concepts that form the basis of modern world surgery — anesthesia and antiseptics.

V. O. Karavaiev had been using Lister's antiseptic method of treatment («Lister's bandage») in his clinic since 1870, much earlier than surgeons in the European countries (1872). The information about this fact can be found in the «letters of mourning» or today known as case histories. V. O. Karavaiev observed the negative properties of carbolic acid in general, but still began to use it immediately: surgical instruments were washed with a 3 % solution of carbolic acid, and it was used for air disinfection in the operating room. This antiseptic agent significantly increased the success rate of surgical interventions in the clinic.

V. O. Karavaiev suggested an original, and at that time, a radical method for the treatment of rectal prolapse, which in efficiency and simplicity was much better than the methods developed by Diefenbach, Dupuytren and Rust. The work «On the radical cure of prolapse of the anus (prolapsusani)» was published in the journal «Friend of Health» in 1842 N 17, p. 132—134.

Back in the 1870s, V. O. Karavaiev was one of the first to perform skull trepanations. In total, he performed 56 operations indicated for the treatment of skull injuries, inflammatory diseases and tumors.

On March 2, 1863, V. O. Karavaiev became one of the first surgeons in Europe, who successfully performed a resection of the gangrenous bowel resulting from the hernia with a primary anastomosis in the pre-antiseptic period. The surgical treatment of strangulated hernias marked the beginning of the development of this type of surgery not only in the Russian Empire but also in Europe.

V. O. Karavaiev was one of the first surgeons in the world to perform ovariotomy, which was an extremely rare procedure at that time. The operation of ovariotomy was generally condemned in France, Germany and England, where it was not performed at all. He was one of the first to dare to perform ovariectomy. On October 5 (September 23), 1864, the first ovariectomy was carried out by Yu.K. Szymanowski in Kyiv, but the patient developed peritonitis and died on the 6th day of the postoperative period. On February 25, 1865, V. O. Karavaiev performed a similar operation on a 46-year-old patient with a large ovarian cyst. A 24-kilogram cyst led to respiratory and cardiovascular failure. The patient developed peritonitis and died on the 3rd day after surgery. But, after a thorough analysis of this operation, Karavaiev invented a special knife that allowed reducing the operation time and management of the pedicle torsion of the ovarian cyst outside the abdominal cavity. The surgeons used this tool in similar operations.

V. O. Karavaiev and his followers laid foundations for the statistical approach that takes into consideration particular aspects and conditions of work and service arrangement in the surgical clinic. It became the basis for the development of modern evidence-based medicine. Objective reports on surgical activities and their in-depth analysis were made only by the best representatives of the world surgery, including V. O. Karavaiev and his teacher M. I. Pirogov.

From November 1, 1844 to May, 1887, V. O. Karavaiev completed a titanic scientific study, the provisions of which were reported in his work «Surgical Faculty Clinic» that was compiled by Dr. Kutsevol-Artemovsky and later became an integral part of the activities of any clinic or surgical department.

V. O. Karavaiev had encyclopedic knowledge and analytical thinking that resulted in a large number of reviews written by him, published in the scientific journals and kept in the archives. Today, the following provisions of his reviews attract the attention of the world scientific community: firstly, a reviewer's substantial knowledge of the state of the problem and a concept of the peer-reviewed work; secondly, the ability to analyze and give an objective review, to express comments in a polite, delicate and friendly way. Reviews should be presented not as basic and boring reports but as reasonable and useful recommendations and conclusions.

«Operative Surgery (lectures by Professor V. O. Karavaiev)» (1858) was included into the golden fund of domestic medical science and education as it served as a guide for many generations of domestic physicians. In addition to this manual, V. O. Karavaiev compiled the «Atlas of Operative Surgery». Given the artistic presentation of the material, its clarity and comprehensibility, accuracy and completeness, the atlas was unparalleled, as evidenced by the fact that lectures on operative surgery were republished three times: in 1858, 1861, 1873.

All the achievements of national and world surgery were incorporated in this work. V. O. Karavaiev was the first scientist who described the relation of practical surgery to physiology and pathological anatomy.

V. O. Karavaiev was an invaluable member of the medical community. He became an Honorary member of the Universities in Kyiv and Kazan. V. O. Karavaiev was a member of the Russian Surgical Society named after M. I. Pirogov, the medical societies located in Kyiv, Kharkiv, Odesa, Kherson, Arkhangelsk, Vilnius, Vyatka, Ekaterinoslav, the Caucasus, Kamyanets-Podilsky, and Chisinau.

V. O. Karavaiev was highly respected far beyond Ukraine. His achievements were of the utmost importance for national surgery, so he gained recognition and authority from his contemporaries.

Volodymyr Opanasovych Karavaiev was one of the founders of the national medical science as well as an initiator of the scientific surgical school. Based on the numerous data from the literature, there is a reason to believe that such world-famous scientists as M. M. Volkovich, K. M. Sapezhko, O. S. Yatsenko, I. F. Saboneev, O. T. Bogaevsky, and Ya.V. Zilberberg were his students. Many of the students and the faculty members, who worked with V. O. Karavaiev, made a significant contribution to the development of national medicine under the supervision of their teacher.

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Висвітлено професійний та науковий шлях професора Володимира Опанасовича Караваєва — першого професора хірургії, першого керівника кафедри факультетської хірургічної клініки, першого організатора і першого декана медичного факультету університету Св. Володимира в місті Києві. Заснував університетську клініку (нині — Київська міська клінічна лікарня № 18).

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# Transplantation in Turkey and region

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The article provides insight into significant milestones in the history of organ transplantation in Turkey and in region.

In 1975, we were the first in Turkey to perform living-related kidney transplantation and, in 1978, deceased-donor kidney transplantation, using an organ supplied by Eurotransplant. In 1979, the law on harvesting, storage, grafting, and transplantation of organs and tissues was enacted. The first local deceased-donor kidney transplantation was performed by our team in 1979. The first successful deceased-donor liver transplantation, which was a groundbreaking surgery procedure for Turkey, the Middle East and Northern Africa, was carried out by our team in 1988. In 1990, we were the first not only in Turkey but also in the Middle East region as well as Europe to perform pediatric living-related segmental liver transplantation. One month later, an adult-to-adult living-related liver transplant (a left lobe) was successfully performed for the first time in the history of organ transplantation. On May 16, 1992, we carried out the first combined liver-kidney transplantation from a living-related donor, which was the first operation of its kind in the world. Between November 1975 and October 2021, we performed 3,256 kidney transplantations at Hacettepe University Hospitals . Since 1988 to date, we have carried out 695 liver transplantations at Baskent University. According to the registry of the Ministry of Health, from 2002 to 2021, 46,115 kidney transplants were performed nationwide, as compared with 17,868 liver transplants, 1,153 heart transplants and 198 pancreas transplants. In 2001, the Ministry of Health established the National Coordination Center as an umbrella organization to promote transplantation activities, especially deceased-donor organ procurement. Despite constantly increasing overall living-donor transplant rate across the country, overall deceased-donor transplant rate is still far below the desired level.

**KEYWORDS**
organ transplantation, history of transplantation, transplant tourism.

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Transplantation rate may be considered as one of the indicators closely connected with a country's development level. The successful melding of legal, ethical, medical, social, psychological, technological, economical, and religious aspects is mandatory for any transplantation organization. It is nearly impossible to create or run an effective system without regard for all these components. Like all similar programs in the world, transplantation activities in Turkey began with operations that broke new ground [1, 2]. The long journey to an established system was made in baby steps with the initiation of nationwide hemodialysis programs, access to and provision of immunosuppressive drugs, technological improvements in tissue typing, advancements in graft imaging and immunosuppressive drug monitoring, work on legislation, education (including religious aspect of the issue) and coordination of medical staff, legal authorities, media and the Turkish public, establishment of an intercity organ sharing program, and organization of national and international scientific meetings and societies.

## History and development of organ transplantation in Turkey

In Turkey, solid organ transplantation began with two heart transplants in 1969. On November 22,1968, Dr. Kemal Beyazıt attempted the first heart transplant in Turkey at Ankara Yüksek İhtisas Hospital. Just 5 days later, on November 27, 1968, the second attempt was carried out by Dr. Siyami

Ersek in Istanbul. The first patient survived 18 hours, while the second one survived 36 hours.

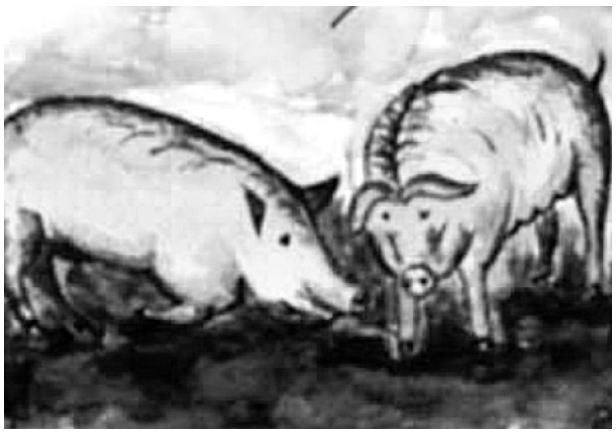
In 1970, a transplantation research program was established at the Department of General Surgery at Hacettepe University Hospitals and, being a third-year resident, I became one of the members of the surgical team. Experimental liver transplantations were performed in pigs and then in dogs [3] (Fig. 1, 2).

On November 3, 1975, we performed the first successful living-related renal transplantation in Turkey, with a kidney donated from a mother to her 12-year-old son [4—6] (Fig. 3). It is important to note that there was no legislation governing organ transplantation in Turkey at that time.

This was followed by the first deceased-donor kidney transplantation, using an organ supplied by Eurotransplant, which was carried out by our team at Hacettepe University Hospitals on October 10, 1978 (Fig. 4, 5). Throughout the 1970s, the only option for the transplant candidates on the national waiting list was to receive a graft from a first-degree living-related donor. There were plenty of patients but not enough organs. In an attempt to make more deceased-donor organs available to the Turkish patients, our team established cooperation with the international networks, including the South Eastern Organ Procurement Foundation (SEOPF) (Richmond, VA, USA) and the Eurotransplant Foundation (Leiden, The Netherlands) [7—9]. Back then, nobody was using deceased kidneys with a cold ischemia time more than 12 hours. The organs received from the organ procurement foundations were delivered to us with a cold ischemia time of more than 24 hours and were also anatomically problematic. However, these kidneys were used with a high success rate. Deceased- donor kidney transplantations with prolonged cold ischemia time, which were performed by our team in the 1970s, added a new dimension to this branch of surgery, and reports about renal transplantations with a cold ischemia time more than 100 hours began to appear in the literature throughout the world [10, 11].


Hacettepe University Hospital

Dr. Mehmet Haberal



First experiment in pigs

Final successful experiment in dogs (post-op 24 hours)

Figure 1. **Experimental animal studies, Hacettepe University Hospitals, 1970s**

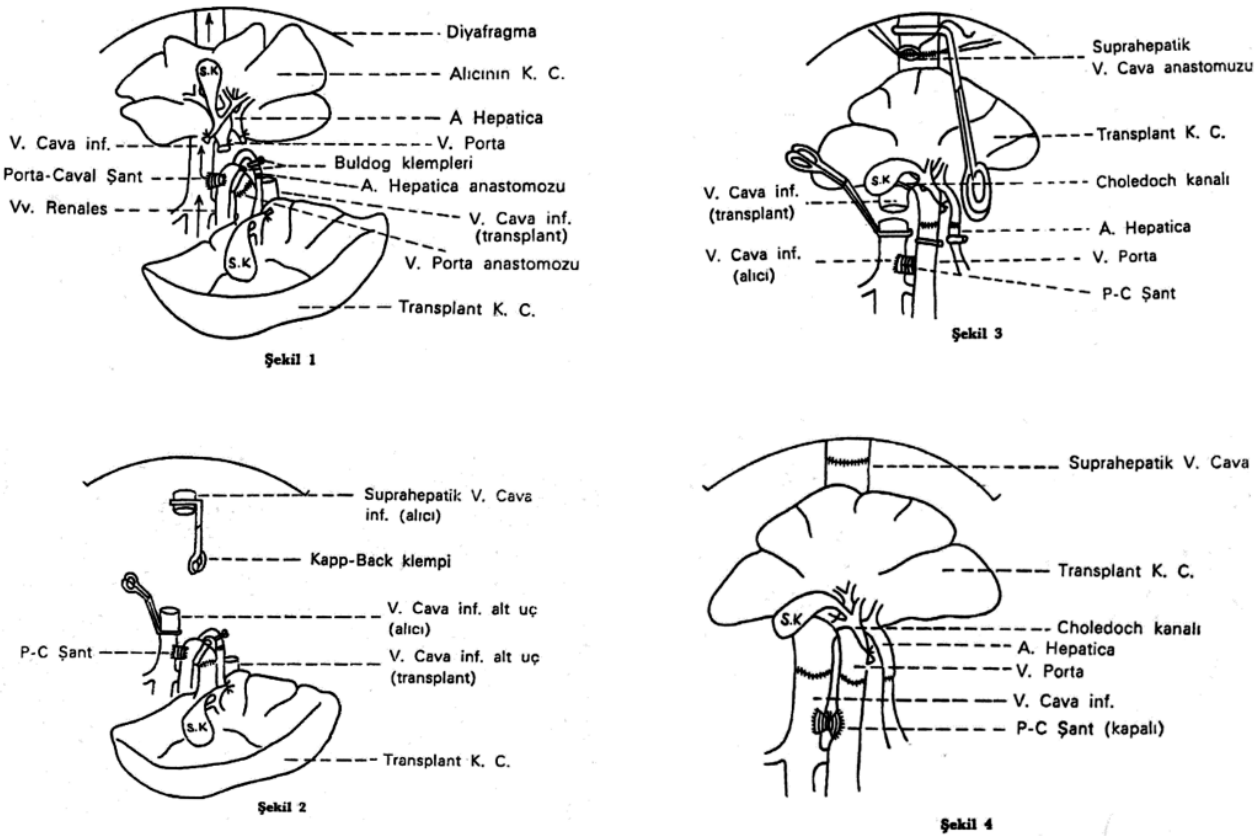



Figure 2. **Experimental orthotopic liver transplantation in dogs**

Senior Surgical Team, Left to Right: Prof. Gülnaz Arslan, Prof. Nevzat Bilgin, Prof. Mehmet Haberal, Prof. Mualla Karamehmetoğlu, Prof. Nebil Büyükpamukçu

Mürvet Çalışkan (mother — donor)

Bahtiyar Çalışkan (son — recipient)

Figure 3. **The first successful living-related renal transplantation in Turkey, Hacettepe University Hospitals**

During the early period in the history of organ transplantation, very few people were aware of organ transplants. The fact that there was no law in Turkey governing organ donation was a major hurdle to be overcome. News and information about deceased-donor kidney transplants were transmitted to the public by means of television, radio, and the press. People were thus able to see the results of the surgeries through images of and interviews with organ recipients who were once again able to lead normal healthy lives. I began working with the government authorities to raise public awareness about the benefits of deceased-donation and the related challenges that health professionals face. In addition, I began to cooperate with the media and various charity organizations as well as with


Erol Emeksizoğlu (recipient)

Figure 4. **The first successful deceased-donor kidney transplantation (the organ supplied by Eurotransplant) in Turkey, Hacettepe University Hospitals**

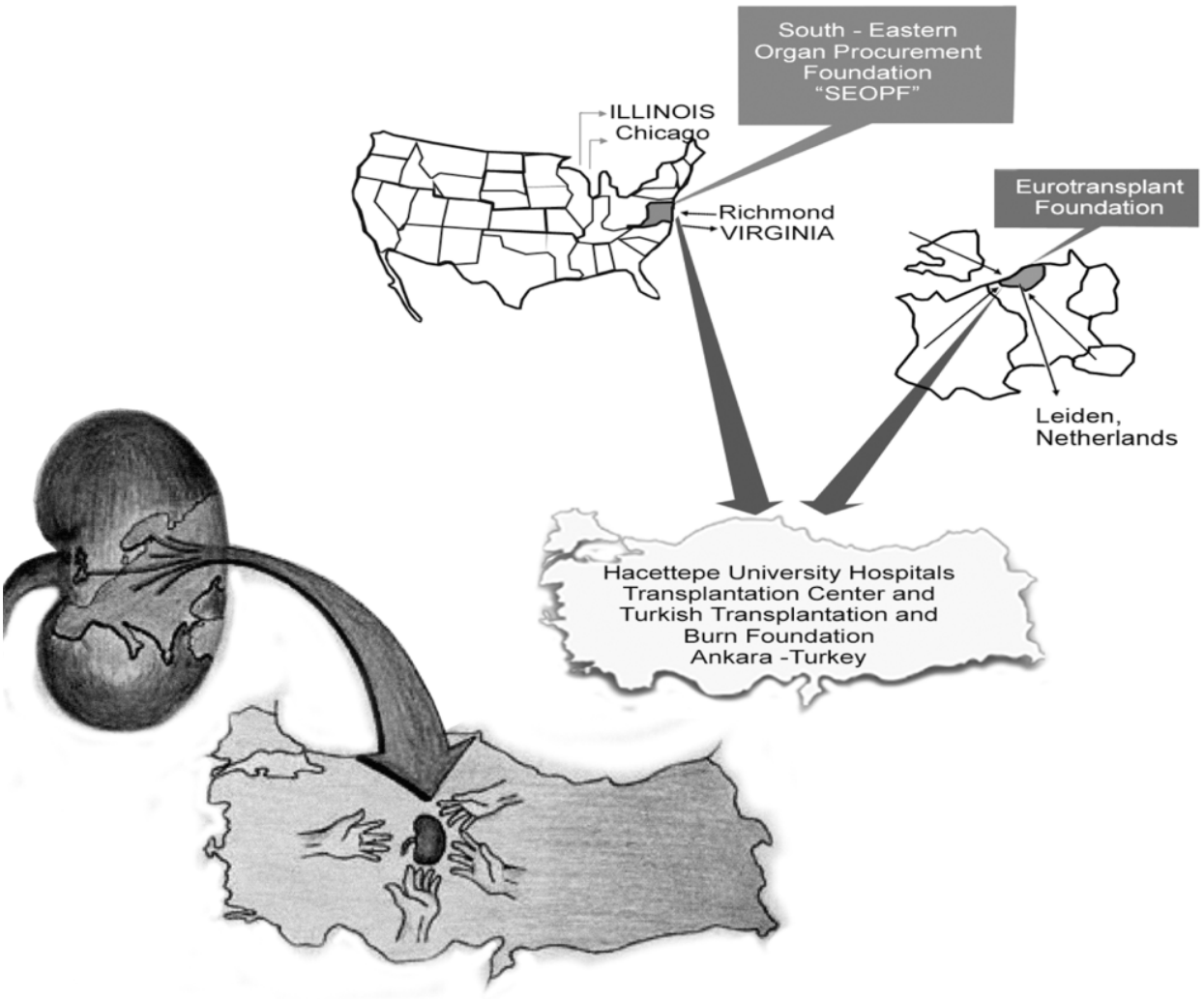



Figure 5. **Donation by Eurotransplant and South-Eastern Organ Procurement Foundation**

**Article 3:** Buying and selling of organs and tissues against a monetary amount or another interest are forbidden.

**Article 4:** Except for the distribution of information having scientific, statistical and new characteristics, all advertisement in connection with the harvesting and donation of organs and tissues is forbidden.

**Article 5:** Harvesting organs and tissues from persons under the age of 18 or from persons who are not sound of mind is forbidden.

**Article 6:** Both verbal and written consent for harvesting an organ must be obtained from a person/persons over 18 years of age and of sound mind in the presence of at least two witnesses and approved by a physician.

**Article 11:** In connection with enforcement of this law, the case of medical death is established unanimously by a committee of 4 physicians consisting of 1cardiologist, 1neurologist, 1 neurosurgeon, and 1anesthesiologist, according to the rules, methods, and practices equivalent to the level of science reached in the country.

**Article 12:** The physicians who will perform the transplant surgery cannot be among the group which pronounced the donor as dead (Article 11).

**Article 15:** Those harvesting, storing, grafting and transplanting organs and tissues in a manner not conforming to this law, and those intermediating in such actions as buying and selling of organs and tissues, and those brokering the same, in the case that it does not require any heavier punishment, shall be sentenced to punishment of two (2) to four (4) years, and of 50,000 to 100,000 Turkish Lira.

Figure 6. **Transplant Legislation: Law No2238, June 3,1979**

the Directorate of Religious Affairs. I highlighted these examples in my efforts to convince the members of the Parliament, governmental institutions, and officials of the Department of Religious Affairs to persuade the public that transplantation is a life-saving procedure and religion is not an obstacle to organ donation. In the meantime, I established the Turkish Dialysis and Transplantation Society to coordinate these activities in 1977.

After all my efforts in that regard with the Parliament, the Board of Religious Affairs, the media and the public, on June 3, 1979, Law No2238 on Harvesting, Storing, Grafting, and Transplanting Organs and Tissues was passed in the Parliament. In fact, the law has been deemed progressive enough to be used as a model by many other countries [1, 2] (Fig. 6). Once Law No2238 was passed, *we were finally enabled to start performing deceased-donor transplants in Turkey, and the first transplantation procedure was carried out on July 27, 1979 at Hacettepe University Hospitals*, a little more than a month after the law was approved [12, 13] (Fig. 7).


Musa Ambarcı (recipient)

Figure 7. **First local deceased-donor kidney transplantation in Turkey, Hacettepe University Hospitals**

**Article 4:** In the case of the aforesaid persons, where the next of kin do not exist or cannot be located, and the termination of life has taken place as a result of accident or natural death, provided that the reason for the death is not in any way related to the reason for harvesting and according to the conditions stated in Article 11, THE SUITABLE ORGANS AND TISSUES CAN BE TRANSPLANTED INTO PERSONS WHOSE LIVES DEPEND ON THIS PROCEDURE WITHOUT PERMISSION FROM THE NEXT OF KIN.

Figure 8. **Transplant Legislation: Law No2594, January 21, 1982 (addendum to Law No2238)**

We continued to educate the Turkish public about the benefits of organ donation and social responsibilities resulting from it. «Organ Donation Cards» were printed to promote organ donation and bring this concept to life by changing people's minds and attitudes. Meanwhile, in 1980, we founded the Turkish Organ Transplantation and Burn Treatment Foundation to advance these ideas. Due to continuous advancements in the field, our efforts were rewarded on January 21, 1982 with the approval of an addendum to Law No2238 and the enactment of Law No2594 (Fig. 8), which allowed the use of deceased-donor organs without consent from next of kin, thus increasing the organ pool for thousands of patients on transplant waiting lists [2].

Despite our kidney transplantation related activities, there were many patients with chronic kidney diseases and not enough hemodialysis centers to treat them. Therefore, we opened the first hemodialysis center in Ankara on March 12, 1982. The Hemodialysis Center eventually grew to become the Turkish Organ Transplantation and Burn Treatment Foundation Hospital in September, 1985 and the Baskent University Ankara Hospital in 1993.

After the enactment of Law No2238 on June 3, 1979 and Law No2594 on January 21, 1982, *the first successful deceased-donor liver transplantation in Turkey, the Middle East and Northern Africa was performed by our team on December 8, 1988 at the Turkish Transplantation and Burn Treatment Foundation Hospital* [14, 15] (Fig. 9). In 1989, our team became the first in Turkey to launch organ harvesting and sharing programs [16, 17].

In 1967, the first successful liver transplantation operation was conducted by Dr. Starzl. The liver was transplanted from a deceased donor. Since then, until the late 1980s, the vast majority of transplantations were performed with the livers from deceased donors. However, many patients were still waiting for the liver transplant. Therefore, partial liver transplantation could become an adequate solution to the problem. Raia S and Associates made the first attempts to carry out the innovative surgical procedure [18]. In 1989, Broelsch's team performed the first living-donor liver transplant in pediatric patients in the United States and it was one of the first successful operations of its kind in the world [19]. Almost simultaneously, on March 15, 1990, *a 10-month-old child received a transplant* from his

Fuat Koç (Recipient)

Figure 9. **The First Successful Deceased-Donor Liver Transplantation in Turkey, the Middle East and Northern Africa, Turkish Organ Transplantation and Burn Treatment Foundation Hospital**

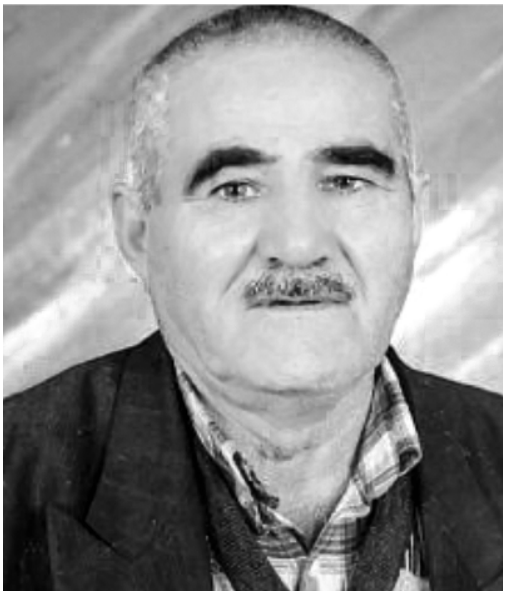
mother *during the first living-related segmental liver transplantation in Turkey, the Middle East and Europe performed by our team* [20—22] (Fig. 10).

The first successful operation in pediatric patients encouraged us to apply the same technique in the treatment of adult patients. *On April 24, 1990, our team was the first in the world to perform successful segmental living-related left lobe liver transplantation in an adult (from a father to his 22-year-old son) at the Turkish Transplantation and Burn Treatment Foundation Hospital* [23] (Fig. 11).

*On May 16, 1992, we performed the first combined liver-kidney transplantation from a living-related donor (from a mother to her 24-year-old daughter) at the Turkish Transplantation and Burn Treatment Foundation Hospital* (Fig. 12). It was the first

Hüseyin Mert (father), Çağdaş Anıl Mert (child), Gül İsmet Mert (mother)

Figure 10. **The first living-related segmental liver transplantation in Turkey, the Middle East and Europe, Turkish Organ Transplantation and Burn Treatment Foundation Hospital**



Hasan Işık (father — donor)

Erdemir ışık (son — recipient)

Figure 11. **The first adult segmental living-related liver transplantation (left lobe) in the world, Turkish Organ Transplantation and Burn Treatment Foundation Hospital**

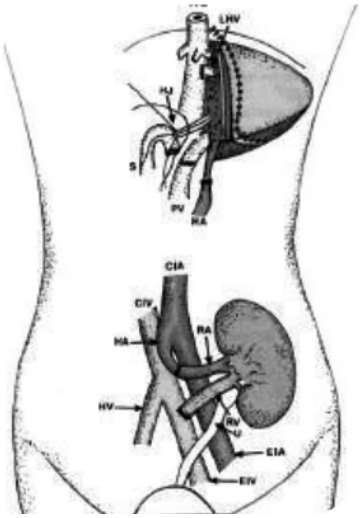
operation of its kind in the world and, with that operation, we proved that both kidney and liver could be used from the same donor using careful surgical technique [24].

The scarcity of deceased-donor organs and the problems with graft-body weight disparity for adult recipients in living donor liver transplantations led us to initiate the heterotopic auxiliary segmental liver transplantation program in 1998. The aim of this technique is to take advantage of the remaining function of the cirrhotic liver. Use of this technique has increased the living donor pool and has even allowed us to use one deceased donor to provide tissue for two liver transplant recipients [25—32] (Fig. 13).

## Where Are We Today?

In 1993, we consolidated the accumulated resources and established Baskent University as an umbrella organization to promote our medical and social education goals. At Baskent University, we continued to develop our pioneering research program and to improve on our successful transplantation record. Vigorous efforts made by our group have resulted in an increased number of transplantations and effective immunosuppressive protocols. These advancements have led to a dramatic improvement in allograft survival over the years. Notwithstanding considerable achievements, a significant shortage of deceased donors remains a problem, and key efforts

Nevin Teke (mother — donor) and Ayşenur Teke (daughter — recipient)




Surgical Technique

Figure 12. **The first combined liver-kidney transplantation in the World, Turkish Organ Transplantation and Burn Treatment Foundation Hospital**

Deceased-Donor Partial Liver Transplantations. 17 years old Nihal Güngör (1998) and 27 years old Sırma Erceyiş (2007). Still alive

Living-Related Liver Transplantation. 40 years old Çağın Sığın (1981). Transplantation from mother (1999). Deceased Donor Retransplantation due to rejection (2002). Still alive

Figure 13. **Heterotopic auxiliary segmental liver transplantations in Turkey, Baskent University Ankara Hospital**

continue to be made to address it by educating the Turkish public about organ transplantation and donation. We initiated the establishment of 14 hospitals/outpatient clinics, 24 hemodialysis centers, 3 peritoneal dialysis centers and 2 rehabilitation centers and allocated our own resources to this project.

As of October 2021, a total of 3,256 kidney transplantations were performed at our 4 centers. Of these, 2,536 (77.9%) involved living-related and 720 (22.1%) deceased donors. In addition, our team performed a total of 695 liver transplantations (483 (69.5%) living donor transplants and 212 (30.5%) deceased donor transplants), 142 heart transplantations, 2 heart valve transplantations, 2 pancreas transplantations, 369 cornea transplantations, and 1,204 bone marrow transplantations (Table 1).

Today, in Turkey, there are 948 specialized centers that focus on organ transplantation (Table 2). In addition, there are 886 hemodialysis centers and 133 peritoneal units throughout Turkey. The number of dialysis patients is 64,633 and the number of dialysis machines is 17,759.

Continuous accumulation of knowledge and experience, combined with high-technology equipment and a specialized team of physicians, allows providing the most advanced, research-supported and systematic treatment to patients in Turkey. In 2001, the Turkish Ministry of Health founded the National Coordination Center with the aim of consolidating all related resources under an umbrella organization. This center is responsible for the promotion of transplantation activities, especially for deceased-donor organ procurement. It is encouraging to see that, despite existing extreme deceased donor shortage, organ procurement has increased since the center was established.

Table 1. **Baskent University Team Transplantation Activities in Turkey from November, 1975 to October, 2021**

| Organ/tissue donor | Living donor | Deceased donor | Total |
|---|---|---|---|
| Kidney | 2,536 | 720 | 3,256 |
| Liver | 483 | 212 | 695 |
| Heart | 0 | 142 | 142 |
| Heart valve | 0 | 2 | 2 |
| Pancreas | 0 | 2 | 2 |
| Cornea | 0 | 369 | 369 |
| Bone marrow | 1,204 | 0 | 1,204 |

Table 2. **Transplantation Centers in Turkey**

| Transplant Type | Number of centers |
|---|---|
| Kidney | 79 |
| Liver | 47 |
| Heart | 15 |
| Lung | 3 |
| Pancreas | 8 |
| Bone Marrow | 138 |
| Cornea | 607 |

## Organizations and Societies

Organizations and societies are the major cornerstones for the development and advancement in the various facets of transplantation. Since 1975, throughout my scientific studies, I have founded various national and international societies with the aim of coordinating transplantation activities and setting up cooperation in this field.

In 1977, the Turkish Dialysis and Transplantation Society was established and the first meeting was held in Bursa on June 4–6, 1980 [4]. In 1980, the Turkish Organ Transplantation and Burn Treatment Foundation was founded with the aim of promoting organ donation, supporting patients with insufficient financial resources, creating a platform for international collaboration and cooperation as well as development of training programs and opening new dialysis and transplantation centers.

After attending the First International Middle East Symposium on Organ Transplantation organized by Prof. George Abouna in December 1982, I realized that there was no cooperation and coordination among the Middle Eastern countries. Therefore, I established the Middle East Dialysis and Organ Transplantation Foundation (MEDOTF) in 1984 for the purpose of facilitating organ sharing and procurement in the Middle East. The First Meeting of the Foundation was held in Istanbul on November 17–20, 1985.

After organizing The First Meeting of the Middle East Dialysis and Organ Transplantation Foundation (MEDOTF), I realized that there was a need for an international society in the region. The Middle East Society for Organ Transplantation (MESOT) was initially founded in Turkey in July 1987, and was subsequently incorporated and registered as a nonprofit international scientific society with Swiss Chamber of Commerce, Bern, in June 1988.

In 1990, the Turkish Transplantation Society (TOND) was established by our team. From its inception, its main goal is to tackle many of the problems that are being faced these days in the field of transplantation in Turkey and all over the world. Our efforts to promote and encourage research and education in the field of organ transplantation continue to this day and, with great commitment and enthusiasm from members and organizers alike, the Society has held 14 international scientific congresses both in Turkey and outside Turkey so far.

In 2014, The Turkic World Transplantation Society (TDTD) was established by our team. For the past 25 years, my team and I have been working with colleagues in the Mid Asia region to assist them in establishing successful treatments for end stage organ disease as well as education and training. TDTD aims to create an arena for communication and collaboration in the field of organ transplantation among the Turkic States of the World. There are currently more than 500 members from Azerbaijan, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan and Turkey [33]. Today, TDTD is actively encouraging centers in the region to start kidney and liver transplant programs to prevent patients seeking transplant services outside their country, which are often costly, with equal if not less favorable results, and can lead to cases of unethical transplant practice.

## Organ Trade and Transplant Tourism

Deceased-organ donation is the greatest challenge in the field of organ transplantation today. Millions of people die and are buried with healthy organs, which could save the lives of many patients who continue to wait on transplant lists. This is the responsibility of the international transplant community to ensure that the growing demand for organs is met within transparency, ethical and legal boundaries and to create a system of meeting the organ demand entirely with deceased organ donation. Some possible solutions to the obstacles that are faced with regard to organ donation and transplantation include:

- expansion of funding resources;
- establishment of the national organ procurement centers;
- encouragement of an organ sharing network and registry;
- addressing religious and social concerns;
- elimination of commercial transplantation and organ trafficking.

To sum up, success in setting up a transplantation system depends on legislation, coordination and education [34].

**Declaration of interests**

The authors have no conflicts of interest to declare.

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# Трансплантація в Туреччині та регіоні

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Узагальнено основні події історії трансплантації в Туреччині та регіоні.

У 1975 р. ми провели першу в Туреччині пересадку нирки за життєвими показаннями. У 1978 р. ми здійснили першу трансплантацію нирки від померлого донора, використовуючи орган, наданий Eurotransplant. У 1979 р. був прийнятий закон про підготовку, зберігання і трансплантацію органів та тканин. Перша в Турції трансплантація нирки від померлого донора була виконана нашою командою в 1979 р. У 1988 р. відбулася ще одна новаторська подія в Туреччині, на Близькому Сході та в Північній Африці: перша успішна трансплантація печінки від померлого донора, а в 1990 р. наша команда здійснила першу в Туреччині, регіоні та Європі педіатричну сегментарну трансплантацію печінки за життєвими показаннями. Через місяць була успішно проведена трансплантація печінки (лівої частки) від дорослого до дорослого. 16 травня 1992 р. ми провели першу комбіновану трансплантацію печінки та нирки від живого донора, що стала першою операцією такого роду у світі. У період з листопада 1975 р. до жовтня 2021 р. ми виконали трансплантацію 3256 нирок у лікарнях університету Хаджеттепе, а пізніше — в університеті Баскент і, починаючи з 1988 р., 695 трансплантацій печінки. За даними Міністерства охорони здоров'я, з 2002 р. до 20 жовтня 2021 р. у різних центрах Туреччини було проведено 46 115 трансплантацій нирки, 17 868 трансплантацій печінки, 1153 трансплантації серця ≥ 198 трансплантацій підшлункової залози. У 2001 р. Міністерство охорони здоров'я створило Національний координаційний центр як головну організацію для сприяння трансплантації, особливо для отримання органів від померлого донора. Кількість трансплантацій щоденно зростає по всій країні, але цей процес гальмує брак донорських органів.

**Ключові слова:** трансплантація органів, історія трансплантації, трансплантаційний туризм

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# Prospective analysis of surgical and functional outcomes after total proctocolectomy with ileal pouch-anal anastomosis in 86 patients with ulcerative colitis

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Proctocolectomy with an ileal pouch-anal anastomosis is currently considered the procedure of choice for the majority of patients with ulcerative colitis. Certain controversies about pouch design and pouch-anal anastomosis technique remain a matter of debate, and possible advantages of laparoscopic approach are still being discussed.

**Objective** — to investigate short-term and long-term outcomes of laparoscopic and open restorative proctocolectomy for UC in terms of postoperative morbidity and pouch function depending on the three types of construction of a neorectum described in our research.

**Materials and methods.** 86 patients with inflammatory bowel disease underwent one-stage or two-stage restorative proctocolectomy. The two ileal pouch configurations were used: S-pouch — in 16 patients and J-pouch — in 70 patients. Removal of the distal rectum and ileal pouch-anal anastomosis were performed using transanal distal rectum mucosectomy followed by a handsewn pouch-anal anastomosis (n=45) or a double-stapled technique (n=31). Laparoscopic approach was applied in 39 patients, and open surgery — in 47 patients. The short-term (30 days after surgery) and long-term surgical outcomes were prospectively studied. The analysis of functional outcomes was based on the number of bowel movements a day, episodes of fecal incontinence, seepage, and urgency. Instrumental investigation included measurement of the anal sphincter pressures and ileal pouch threshold volume as well as the study of its residual volume. Statistical analysis was performed using SPSS statistical software.

**Results.** There was no postoperative mortality. In the laparoscopic group, 4 (10.3%) patients had early postoperative complications compared with 13 (27.7%) patients in the open surgery group, but the difference was not statistically significant (Fisher exact test value is 0.0579 at $p<0.05$). Pouch failure occurred in 4 patients. The second-stage laparoscopic restorative procedure revealed the abdominal cavity almost free of adhesions in 19 (86.4%) patients after laparoscopic total colectomy. The total number of early and late mucosectomy complications was significantly higher, 12 (75.0%) vs. 10 (26.0%) ($p=0.0018$), in patients managed with a handsewn S pouch-anal anastomosis than in patients treated with a J-pouch-anal anastomosis. Good functional outcomes were observed in 44 (51.0%) patients. A strong negative correlation was found between the pouch threshold volume and the number of bowel movements per 24 hours ($r=-0.7347$, $p<0.0001$). The seepage episodes were detected in 30 (34.8%) patients. The resting anal sphincter pressure was the only measured parameter which correlated accurately with the number of day and night seepage episodes ($r=-074$, $p<0.0001$).

**Conclusions.** Good functional outcomes of construction of a neorectum were associated with the resting anal sphincter pressure (≥ 30 mm Hg) and ileal pouch threshold volume (150—250 ml).

The S-shaped and J-shaped pouches demonstrated the same functional outcomes and posed similar risks. The S-pouch was associated with a higher postoperative morbidity ($p=0.0018$). There was no significant difference between laparoscopic and open surgery groups in terms of morbidity rate and functional outcomes. However, it was much easier to perform the second-stage surgery after laparoscopy due to less adhesion formation.

**Keywords**
ulcerative colitis, laparoscopic restorative proctocolectomy, ileal pouch function.

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Ulcerative colitis (UC) is the most common inflammatory bowel disease (IBD). In the 21st century, it is diagnosed worldwide [25]. Although medical therapy has improved over the past decades, colectomy rates remain up to 15 % [29].

Proctocolectomy and reconstruction with an ileal pouch-anal anastomosis (IPAA) has been considered the procedure of choice for the majority of patients with ulcerative colitis since its first description in 1978 [28]. Over the time, the procedure has undergone some modifications due to the development of the anorectal mucosectomy approach as well as introduction of the pouch-anal anastomosis technique and pouch configuration. Transanal mucosectomy with a handsewn IPAA is still considered the most complete curative surgical procedure for UC, especially when the distal rectal mucosa becomes inflamed or dysplastic [16]. The modification, in which the ileal pouch is stapled to the anus 1,5—2 cm above the dentate line, suggested in 1986 [8, 14], greatly simplified its implementation. At the same time, this procedure provides preservation of the anal transition zone. Each technique has both advantages and disadvantages in terms of long-term functional outcomes, operative and postoperative complications, and the risk of neoplasia. Consequently, the proper indications for their application are still being specified [3, 16]. Pouch configuration with either three (S-shape) or two (J-shape) loops of the small bowel is still in use, however, J-pouch construction [36] has become the most commonly used technique as it is safe and practical [24].

Despite strong data supporting the feasibility, durability and the maintenance of long- term functional outcomes of the procedure, certain controversies about the method of construction of a neorectum remain a matter of debate.

Laparoscopic approach for total proctocolectomy was introduced in 1992 for the purpose of reducing the incidence of surgical trauma, thus ensuring fast recovery [30]. Over the past 30 years, laparoscopic-assisted proctocolectomy with IPAA has been gradually gaining acceptance among the surgeons, however, the benefits and proper indications for laparoscopic approach are still being discussed [17].

**Objective** — to investigate short-term and long-term outcomes of laparoscopic and open restorative proctocolectomy for UC in terms of postoperative morbidity and pouch function depending on the three types of construction of a neorectum described in our research.

## Materials and methods

This is a prospective single-center and a single-surgeon study. Between 1997 and 2020, 86 patients with inflammatory bowel disease (IBD) underwent a one- or two-stage procedure for restorative proctocolectomy that was performed by one surgeon. 73 patients with preoperative diagnosis of UC and 13 patients with indeterminate colitis (IC) were included in the study. Patients with a preoperatively confirmed diagnosis of Crohn's disease were excluded from this study. 35 patients with UC underwent primary restorative (one-stage) proctocolectomy in an elective surgery setting. These patients had satisfactory nutrition status and low comorbidity. In all but one case, a temporary diverting ileostomy was applied.

38 patients with severe ulcerative colitis and 13 patients with indeterminate colitis were treated with a two-stage surgery in an emergency setting.

39 patients were operated using a laparoscopic technique: 17 patients underwent a primary restorative ileal-pouch procedure and 22 patients underwent two-stage laparoscopic ileal-pouch construction and a pouch-anal anastomosis that followed laparoscopic total colectomy and an end ileostomy. The technical aspects of laparoscopic restorative proctocolectomy have been previously reported in our study [15].

47 patients were operated using an open surgery technique: 18 patients underwent primary restorative proctocolectomy with an ileal pouch-anal anastomosis and 29 patients underwent the two-stage procedure for construction of an ileal-pouch and a pouch-anal anastomosis. 23 of them were operated after the open first-stage colectomy, and 6 patients — after the laparoscopic first-stage colectomy. The reason to choose open surgery for the second-stage procedure for these 6 patients was the presence of abdominal complications after the first-stage laparoscopic colectomy.

The two ileal pouch configurations were used: the S-pouch — in 16 patients and the J-pouch — in 70 patients. The S-pouch was constructed using one-layer continuous suturing of three ileal loops. The length of the S-pouch was about 12 cm and its volume was 120—130 ml. The J-pouch was constructed of two intestinal loops, using two sequential fires of an 80 mm GIA linear stapler. The length of the J-pouch was about 15 cm and its volume was 110—120 ml. For all but one laparoscopically operated patient, construction of a pouch was carried out outside the abdomen (Fig. 1).

Removal of the distal rectum and ileal pouch-anal anastomosis were also performed using two techniques. The first technique included transanal approach for the distal rectum mucosectomy followed by the hand-sewn pouch-anal anastomosis at the site of the dentate line (45 patients). The

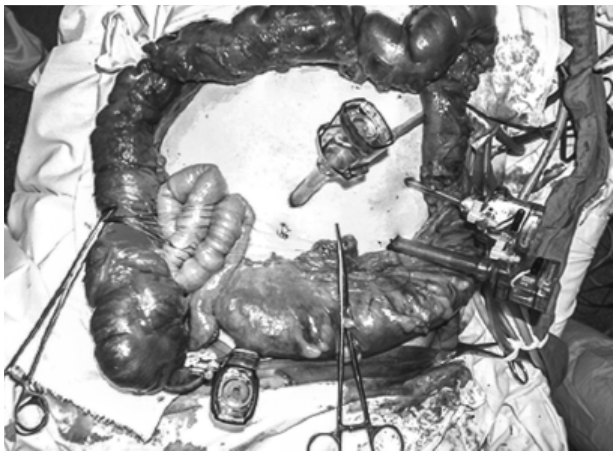

Figure 1. **Removed specimen after laparoscopic total colectomy, and extracorporeal performance of the ileal S-pouch**

second technique was administered as a procedure of double-stapling. The abdominal part of surgery involved a deep mesorectal dissection down to the levator ani muscles. Transection of the rectum was made using a linear endostapler 2—3 cm above the dentate line. The pouch-anal anastomosis was performed using a circular stapler 1.5—2.0 cm above the dentate line (31 patients). The first technique allows complete removal of the rectal mucosa. The second technique ensures the preservation of the anal transitional zone, however, leaving behind a cuff of inflamed distal rectum mucosa.

The combinations of pouch design and the pouch-anal anastomosis techniques used for both laparoscopic and open surgery are shown in Table 1.

Before diverting ileostomy closure, the pouch contrast media filling X-ray (pouchgram) was done, the anal sphincter resting pressures (RP), and the maximum squeeze anal sphincter pressure (SP) were measured. Follow-up was performed 6 months after surgery, one year after surgery, and annually thereafter.

The short-term (30 days after surgery) and long-term surgical outcomes were prospectively studied.

The analysis of functional outcomes was based on the number of bowel movements per 24 hours, episodes of fecal incontinence, seepage (during day and night), and urgency (inability to delay a bowel movement for more than 15 minutes). Physical examination was performed simultaneously with pouch endoscopy. In case of endoscopic signs of pouchitis, the pouch mucosa biopsy was performed. Instrumental investigation included measurement of anal sphincter pressures, ileal pouch threshold volume, as well as the study of ileal pouch emptying and its residual volume. The threshold volume was determined as the volume of the ileal pouch distension at the time of its filling until the intraluminal pressure reached 25 mm Hg. It was established experimentally that distention of the pouch up to the above-indicated pressure level evokes the urge to evacuate, coincident with the onset of high-pressure waves in the small bowel [34]. The residual pouch volume was calculated as a difference between threshold volume and single pouch evacuation volume.

Pouch failure was defined as the need for permanent fecal diversion with a proximal loop ileostomy with or without pouch excision.

Good functional outcomes were observed in patients with an adequate bowel function: the number of bowel movements was about 5—6 times per day and not more than 2 times at night with no or occasional urgency and good continence [35].

Table 1. **Operative details (a pouch design and anastomosis type) given by the surgical method (laparoscopy or open surgery) and by the stages of performance in 86 patients undergoing one-stage or two-stage restorative proctocolectomy**

| Method of surgery | ME+HS sIPAA | ME+HS jIPAA | DS jIPAA |
|---|---|---|---|
| Laparoscopic surgery | | | |
| Primary restorative (one-stage) procedure | 4 | 5 | 8 |
| 2nd stage procedure | 1 | 17 | 4 |
| Open Surgery | | | |
| Primary restorative (one-stage) procedure | 5 | 6 | 7 |
| 2nd stage procedure | 6 | 11 | 12 |
| Total | 16 | 39 | 31 |

Note. ME+HS sIPAA — mucosectomy with a handsewn S-ileal pouch-anal anastomosis; ME+HS jIPAA — mucosectomy with a handsewn J-ileal pouch-anal anastomosis; DS jIPAA — double-stapling J-ileal pouch-anal anastomosis.

**Statistical Analysis.** Categorical variables were compared using the $\chi^2$ or Fisher's exact test as appropriate. Continuous variables were compared using the T-test. Results with a p-value $< 0.05$ were considered statistically significant; all p-values were two tailed. Correlation of test results to functional outcomes was accomplished with the Pearson correlation coefficient. Statistical analysis was performed using SPSS statistical software.

## Results

86 consecutive patients underwent one- or two-stage colectomy, proctectomy, S- or J-pouch-anal anastomosis, and temporary diverting ileostomy closure. In the laparoscopic group, two (5.1 %) patients required conversion to open surgery due to bleeding in the pelvis. In both cases, the rectal stump dissection was complicated by pelvic fibrosis, which occurred after the formation of pelvic abscess resulting from the first-stage colectomy. Another major intraoperative complication observed in laparoscopic second-stage restorative surgery included damage to the posterior bladder wall caused by an attempt to dissect the rectal stump from the pelvic scar tissues. The complication was removed via laparoscopic sewing of the bladder wall.

In general, the second-stage laparoscopic restorative procedure revealed the abdominal cavity almost free of adhesions in 19 (86.4 %) of patients after laparoscopic total colectomy. The dense adhesions in the pelvis and complicated dissection of the rectal stump were noted in 3 patients due to pelvic abscess and presacral sinus formation after first-stage surgery (total colectomy). There were two cases of small bowel injury during the second-stage reconstructive surgery in the open surgery group. In all 86 cases the ileal pouch-anal anastomosis was completed successfully.

Bowel function was restored within 26 hours (in the range of 16 to 38 hours) after laparoscopic surgery, and within 38 hours (in the range of 24—60 hours) after open surgery. The difference in the time of bowel function restoration was statistically significant between the groups ($p = 0.004$).

There was no postoperative mortality. Early and late postoperative complications are given in Table 2.

In the laparoscopic group, 4 (10.3 %) patients developed early postoperative complications

Table 2. **Surgical morbidity in the laparoscopy and open surgery groups after restorative proctocolectomy (n = 86)**

| Index | ME+HS sIPAA | | | ME+HS jIPAA | | | DS jIPAA | | |
|---|---|---|---|---|---|---|---|---|---|
| | Lap. (n = 5) | Open (n = 11) | Total (n = 16) | Lap. (n = 22) | Open (n = 17) | Total (n = 39) | Lap. (n = 12) | Open (n = 19) | Total (n = 31) |
| Patients with early complications | 2 | 5 | 7 | 1 | 5 | 6 | 1 | 3 | 4 |
| Pouch-anastomotic leak | 1* | 1 | 2 | 1 | – | 1 | – | | |
| Incontinence | 1 | 1 | 2 | – | 1 | 1 | – | | |
| Pelvic abscess | – | 2 | 2 | – | 1 | 1 | 1 | 1 | 2 |
| Wound infection | – | 1 | 1 | – | 3 | 3 | – | 2 | 2 |
| Patients with late complications | 3# (60.0 %) | 9 (82.0 %) | 12 (75.0 %) | 2 (9.0 %) | 8 (47.0 %) | 10 (26.0 %) | 1 (8.0 %) | 8 (42.0 %) | 9 (29.0 %) |
| Parapouch presacral sinus | – | 1 | 1 | – | | – | | 1 | 1 |
| Distal pouch stricture | – | | – | 1 | 2 | 3 | – | 1 | 1 |
| Small-bowel obstruction | 1* | 1 | 2 | – | 1 | 1 | – | 2 | 2 |
| Pouch-vaginal fistula | – | 1 | 1 | – | | – | | 1 | 1 |
| Pouch-cutaneous fistula | 1 | 1 | 2 | – | | – | | – | |
| Pouchitis | 0 | 3 | 3 | 2 | 3 | 5 | 6 | 5 | 11 |
| Pouch failure | 1 | 1 | 2 | – | 1 | 1 | – | 1 | 1 |

Note. Lap. — laparoscopic.
* There was conversion to laparotomy in this case.
# Pouch-anastomosis leak and small bowel obstruction were observed in the same patient.

compared with 13 (27.7 %) patients in the open surgery group, however, the difference was not statistically significant (Fisher exact test value is 0.0579 at $p < 0.05$). In both groups, a pouch design did not cause any difference in the number of patients diagnosed with early complications.

Late postoperative complications occurred in 15 (17.4 %) patients, including 3 (7.7 %) patients in the laparoscopic group and 12 (25.5 %) patients in the open surgery group. All complications were surgically related. The difference in the number of patients with late complications was statistically significant between the groups ($p = 0.0444$).

The total number of early and late mucosectomy complications was significantly higher, 12 (75.0 %) vs. 10 (26.0 %) ($p = 0.0018$) vs. 9 (29.0 %) ($p = 0.0048$), in patients managed with a handsewn S pouch-anal anastomosis than in patients treated with a J-pouch-anal anastomosis or with a double-stapled J-ileal pouch-anal anastomosis.

Pouch failure occurred in 4 patients within a two-year follow-up: in 2 patients after mucosectomy followed by the S-ileal pouch-anal anastomosis, in 1 patient after the open J-pouch-anal anastomosis and in 1 patient after the double-stapled J-ileal pouch-anal anastomosis. In all 4 cases, there were noted some complications related to pouch surgery, including severe anal incontinence (2 patients), presacral sinus (1 patient), and pouch-cutaneous perineal fistula, combined with severe pouchitis (1 patient). There was no statistically significant difference between the groups in terms of a pouch design or anastomosis technique application. In one case, the pouch was removed and terminal ileostomy was done (the patient was suffering from anal incontinence and severe perineal skin irritation). In three cases, the diverting ileostomy was applied.

Pouchitis was seen in 19 (22.1 %) patients. No relationship between pouch design and pouchitis incidence was found. The main parameters of ileal pouch functioning are presented in Table 3.

Good functional outcomes were observed in 44 (51.0 %) patients. There was no statistically significant difference between laparoscopic (54.0 %) and open surgery (49.0 %) groups of patients ($p = 0.6611$). In terms of pouch-anal construction, there was no statistically significant difference in functional outcomes between the groups: good functional outcomes were seen in 7 (44.0 %) patients after mucosectomy with a handsewn S-ileal pouch-anal anastomosis, in 22 (56.0 %) patients after mucosectomy with a handsewn J-ileal pouch-anal anastomosis, and in 15 (48.0 %) patients after a double-stapled J-ileal pouch-anal anastomosis ($p = 0.6784$). However, a strong negative correlation was found between the ileal pouch threshold volume and the number of bowel movements per 24 hours (Fig. 2).

The threshold volume was increasing significantly during the first six months after ileostomy closure from $120 \pm 22$ to $235 \pm 26$ ml ($p < 0.01$) and then it did not change in a twelve-month period. The threshold volume remained almost the same in all groups of patients and did not depend on a pouch design and a method of anastomosis. In terms of a pouch design, the only statistically significant difference was found in the residual volume. It was significantly larger ($p = 0.0219$) in the S-pouch group of patients.

The seepage episodes were observed in 30 (34.8 %) patients. The resting anal sphincter pressure was the only measured parameter which

Table 3. **Functional outcomes of restorative proctocolectomy in 86 patients within 6 months after surgery**

| Index | ME+HS sIPAA (n = 16) | | ME+HS jIPAA (n = 39) | | DS jIPAA (n = 31) | |
|---|---|---|---|---|---|---|
| | Lap. (n = 5) | Open (n = 11) | Lap. (n = 22) | Open (n = 17) | Lap. (n = 12) | Open (n = 19) |
| BM per 24 hrs (median, range) | 8 (5—11) | 9 (5—12) | 6 (3—9) | 5 (4—11) | 6 (4—12) | 6 (4—13) |
| Urgency | 0 | 2 | 2 | 1 | 1 | 2 |
| Seepage | | | | | | |
| night | 2 | 1 | 3 | 5 | 2 | 4 |
| day and night | 1 | 2 | 3 | 2 | 2 | 3 |
| RP, mm Hg | 32 ± 8 | 36 ± 6 | 41 ± 8 | 40 ± 7 | 38 ± 5 | 43 ± 9 |
| SP, mm Hg | 120 ± 13 | 118 ± 15 | 128 ± 14 | 130 ± 16 | 135 ± 12 | 130 ± 12 |
| Threshold volume, ml | 165 ± 19 | 169 ± 17 | 179 ± 18 | 182 ± 17 | 187 ± 16 | 180 ± 18 |
| Residual volume, ml | 83 ± 12 | 78 ± 10 | 58 ± 9 | 60 ± 11 | 52 ± 9 | 55 ± 11 |

Note. Lap. — laparoscopic; BM — bowel movements; RP — resting anal sphincter pressure; SP — maximum squeeze anal sphincter pressure.

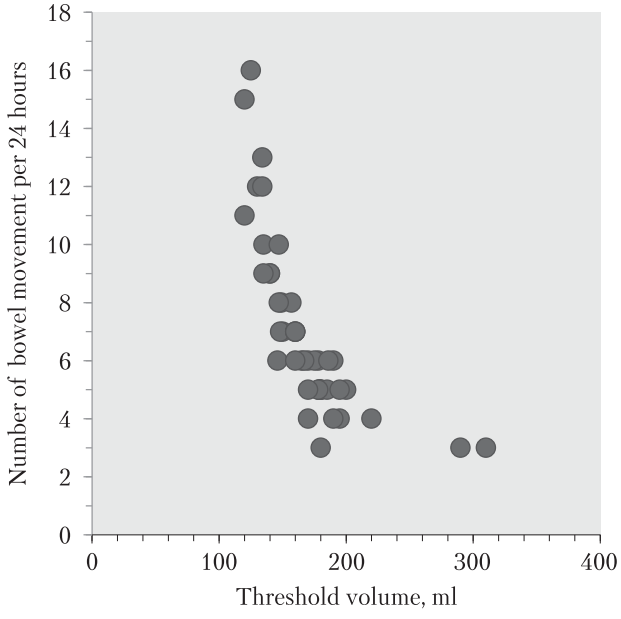


Figure 2. **The correlation between the ileal pouch threshold volume and the frequency of bowel movements** ($r = -0.7347$; $p < 0.0001$)

correlated with the number of day and night seepage episodes ($r = -074$; $p < 0.0001$).

In all patients with good functional outcomes, the resting anal pressure was ≥ 30 mm Hg.

The maximum squeeze anal pressure was increasing significantly within six (125 ± 13 mm Hg) and twelve (140 ± 18 mm Hg) months after ileostomy closure. There was no statistically significant difference between the groups. A weak negative correlation ($r = -0.034$; $p < 0.0001$) was found between squeeze anal pressure and the number of urgency episodes.

## Discussion

A well-known statement that a good pouch function depends mostly on the patient's sphincter function, pouch volume and compliance [2, 26] appears to be true. The current study proves that neorectal function must be assessed based on anal continence, the ability to control defecation and the number of bowel movements a day. Anal continence depends on the preservation of the anal sphincter function. The damage to the internal anal sphincter may be caused by the disease, age-related alterations, or by a surgeon during mucosectomy. Some authors assert that mucosectomy with a handsewn anastomosis results in poorer continence [4, 5, 10, 12, 13, 21]. Such a tendency was observed in the current study; however, the difference was not statistically significant.

The number of bowel movements depends on pouch capacity and pouch emptying ability [2]. The current study revealed that the pouch threshold volume is the most significant physiological parameter for the assessment of the pouch function. It has a strong negative correlation with the number of bowel movements. Another important stipulation is that the threshold volume was increasing during the first six months after pouch creation and then remained at the same level for years. In the published data, such terms as pouch capacity, pouch functional volume, and pouch distention ability have some differences in their interpretation. It might be explained by the difference in the values concerning a pouch threshold volume and a pouch functional volume described in several studies. Nonetheless, the importance of these parameters for functional results is highly supported [1, 19, 27, 35]. The surgical construction of an ileal pouch must be aimed at achieving an adequately large threshold volume and adequately small residual volume of the pouch at the same time. The S-pouch construction was suggested to be good enough for this task. But it appeared to be technically demanding [7]. And it was associated with a higher morbidity rate [23]. The study affirmed higher morbidity in the S-pouch group. Moreover, the increased residual volume was registered in the S-pouch group. Perhaps, the triplicated design of the S-pouch with a long efferent limb was a possible cause of reduced pouch emptying ability in comparison to the J-pouch. However, the motor characteristics of any pouch reproduce the motility pattern of the small bowel [19, 34]. So, further research should be designed to select patients for different types of neorectal construction based on their small bowel physiology, although pouch physiology remains, to some extent, unexplained [35].

Pouch failure ranges from 5 to 18 %, depending upon the length of follow-up [9, 22]. In the biggest data presented by the Fazio group eight years ago [6], pouch failure occurred in 197 (5.5 %) patients out of 3707 patients. In the current study, pouch failure was observed in 4 (4.7 %) cases and it was caused by surgery-related complications. In the most recent systematic review, which included 30 studies comprising 22,978 patients [9], the pouch failure rate was 7.8 % and 10.3 % after a median follow-up of ≥ 5 and ≥ 10 years following IPAA, respectively, which means that pouch failure and pouch-related complication rates did not exhibit an improvement over the results from previously published data. It was proved that pouch failure correlated with pelvic sepsis and pouch-related fistula but not with the leaks that completely healed. So, the authors suggest the treatment strategy to prevent acute leaks from becoming chronic leaks [24].

Pouchitis is the most common complication of IPAA but its pathogenesis is still being studied. Current hypotheses suggest that the development of pouchitis might be caused by recurrence of UC in the colon-like ileal reservoir, dysbiosis of ileal pouch microbiota, short chain fatty acid deprivation, mucosal ischemia, genetic susceptibility, and immune dysregulation [32]. Pouchitis can also be influenced by surgical factors, including handsewn anastomosis, anastomosis placement from pectinate line, S-pouch construction [20]. In the current study, pouchitis was seen in 22.1 % of patients. It was not associated with surgical factors or a pouch design. Recent systematic review and meta-analysis [33] support the conclusion that prevalence of pouchitis is much higher in patients with UC than in patients with familial adenomatous polyposis after the same surgical procedures. Does it mean that pouchitis is a disease-specific complication?

The laparoscopic technique for reconstructive proctocolectomy has been widely and extensively used in the last decade. A 90-day postoperative morbidity by decade was 38.3 % vs 50.0 % vs 48.0 % ($p < 0.0001$), but late morbidity decreased from 74.2 % through 67.1 % to 30.0 % ($p < 0.0001$) [31].

The comparison of the laparoscopic and open surgery groups demonstrated no statistically significant difference in terms of long-term and functional outcomes. Reasonable benefits of the laparoscopic approach are found in less surgical morbidity, quick bowel function recovery, and in more favorable conditions to provide second-stage restorative surgery (less adhesion formation in the abdominal cavity). The studies using diagnostic laparoscopy at the time of ileostomy closure [11] as well as the current study confirmed less adhesion formation with a minimally invasive approach. Further advantages of laparoscopic approach rely on robotic surgery, which greatly enhances surgical performance deep in the pelvis during proctectomy and construction of an anastomosis [18].

## Conclusions

An important indication for an ileal pouch-anal anastomosis is patient continence. The anal sphincter rest pressure should be ≥ 30 mm Hg.

The ileal pouch capacity may range between 150—250 ml within six months after surgery to obtain good pouch function.

Any pouch design (S or J) ensures the same functional outcomes and has the same risk of pouchitis. In the current study, postoperative surgical complications were more frequently associated with a S-shape construction. In terms of functional outcomes, there was no statistically significant difference between the groups after transanal mucosectomy followed by a handsewn pouch-anal anastomosis and a double-stapled pouch-anal anastomosis. Laparoscopy and open surgery result in the same morbidity rate and functional outcomes. However, the second-stage surgery was much easier to perform after the application of laparoscopic approach due to less adhesion formation.

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### Declaration of interests

The author declares no conflicts of interest.

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# Проспективний аналіз післяопераційних і функціональних результатів у 86 хворих на неспецифічний виразковий коліт, які перенесли тотальну проктоколетомію з тонкокишковим резервуарно-анальним анастомозом

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Тотальна проктоколектомія з формуванням резервуару з клубової кишки і резервуарно-анального анастомозу — є операцією вибору для переважної більшості хворих на неспецифічний виразковий коліт. Розбіжності в рекомендаціях існують, головним чином, у виборі дизайну резервуару і способу його анастомозування з анальним каналом. Продовжується дискусія і щодо переваг у використанні лапароскопічних технологій для таких втручань.

**Мета** — проаналізувати безпосередні, віддалені і функціональні результати тотальної проктоколектомії в залежності від способу формування неоректуму (три варіанти конструкції резервуару) і від методу оперування (лапароскопічний чи відкритий).

**Матеріали та методи.** Тотальна проктоколектомія зі створенням неоректуму у один або два етапи була виконана у 86 хворих на неспецифічний виразковий коліт. Використовувалися дві конфігурації тонкокишкових резервуарів: S-подібної форми (16 пацієнтів) і J-подібної форми (70 пацієнтів). Формування резервуарно-анального анастомозу відбувалося теж у два способи: ручним накладанням окремих вузлових швів трансанально на рівні зубчастої лінії після мукозектомії (45 пацієнтів) і бістеплерним механічним швом на 1,5 см вище рівня зубчастої лінії (31 пацієнт). Операції виконувалися лапароскопічним способом у 39 пацієнтів, відкритим — у 47. Аналізувалися безпосередні, віддалені, а також функціональні результати операції.

**Результати.** Післяопераційної летальності не було. Ранні післяопераційні ускладнення траплялися частіше у відкритій групі (27,7 %) аніж у лапароскопічній (10,3 %), проте різниця виявилася статистично не значущою (точний критерій Фішера — 0,0579; $p < 0,05$). Неспроможність резервуару мала місце у чотирьох випадках. Черевна порожнина була практично вільною від злук на момент виконання відновного етапу втручання після виконання тотальної колектомії лапароскопічним способом у 86,4 % хворих. Частота ранніх і віддалених післяопераційних ускладнень після формування S-подібних резервуарів була достовірно більшою, аніж після формування J-подібних резервуарів ($p = 0,0018$). Серед характеристик неоректуму виявлено чітку кореляцію з функціональними результатами для двох показників: порогового об'єму резервуара і числом випорожнень за добу ($r = -0,7347$; $p < 0,0001$), а також тонічного зусилля анального сфінктера і частотою епізодів нетримання вдень і вночі ($r = -0,74$; $p < 0.0001$). Епізоди нетримання мали місце у 30 (34,8 %) пацієнтів.

**Висновки.** Найважливішими чинниками вдалого функціонування неоректуму виявилися: тонічне зусилля анального сфінктера — не менше 30 мм рт. ст. і пороговий об'єм резервуара — у межах 150—250 мл. Резервуари J- чи S- подібної будови позначилися схожими функціональними результатами, проте післяопераційні ускладнення траплялися частіше серед пацієнтів з резервуарами S-подібної форми. Статистично достовірної різниці щодо післяопераційних ускладнень і функціональних результатів між групами хворих, оперованих лапароскопічно і відкритим способом, не виявлено, проте виконання наступного, відновного, етапу хірургічного лікування після лапароскопічної проктоколектомії було значно легшим, з огляду на мінімальний злуковий процес.

**Ключові слова:** неспецифічний виразковий коліт, лапароскопічна відновна проктоколектомія, тонкокишковий резервуар, функціональні результати.

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# A genomically stable molecular type of gastric cancer as a predictor of peritoneal relapse after radical surgical treatment

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Peritoneal metastases are commonly associated with gastric cancer (GC) recurrence after radical treatment. Thus, patients at a high risk of peritoneal relapse require adjuvant intraperitoneal chemotherapy during the initial treatment. Along with clinical and morphological predictors of peritoneal relapse, another approach in surgical oncology is proving to be promising today. It refers to the prediction of the risk of developing metachronous peritoneal metastases in various molecular types of GC.

**Objective** — to study the risk of peritoneal relapse in patients with the genomically stable type of GC in comparison to its other molecular types.

**Materials and methods.** 37 patients with GC were enrolled into the study and evaluated after the radical treatment. 19 (51.4%) patients formed a subgroup with peritoneal relapse and 18 patients (48.6%) were included into a subgroup without metachronous carcinomatosis in the long term. All patients underwent immunohistochemical study for the E-cadherin (CDH1 gene) expression in a gastric tumor. The genomically stable molecular type was identified on the basis of the aberrant E-cadherin (CDH1-mutated) tumor phenotype detection.

**Results.** There was a statistically significant difference ($p=0.022$, $\chi^2=5.22$) in the degree of aberrant E-cadherin expression in subgroups of patients with and without peritoneal relapse — 68.4 and 33.3%, respectively. Hence, it was noted that the genomically stable molecular type had a significant influence on the risk of peritoneal recurrence: the 2-year peritoneal relapse-free survival of GC patients with E-cadherin of aberrant type was 31.6%, and in GC patients with wild-type E-cadherin expression — 71.4% ($p=0.022$). The 2-year overall survival of GC patients with aberrant type E-cadherin expression was 36.8%, whereas in GC patients with E-cadherin of the wild type — 77.8% ($p=0.003$).

**Conclusions.** The study found that the genomically stable molecular type of GC may serve as a predictive factor associated with an increased probability of peritoneal relapse, as well as a prognostic factor due to its negative impact on patient prognosis. The genomically stable molecular type of GC may be used as a tool for forming a cohort of patients with indications for adjuvant intraperitoneal therapy.

**Keywords**
gastric cancer, peritoneal relapse, genomically stable molecular type, E-cadherin, peritoneal metastases, intraperitoneal chemotherapy.

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Currently, gastric cancer (GC) is the fifth most common cancer worldwide, with nearly one million new cases (5.6 % of all cancers) diagnosed in 2020 [12]. Peritoneal relapse is the most common pattern of GC recurrence [10, 15], which develops in 44.8 % of the 69.0 % of patients with serosal invasion after radical surgery [3, 10]. In order to reduce the risk of metachronous peritoneal carcinomatosis development, patients are advised to consider utilizing methods of adjuvant intraperitoneal chemotherapy at the initial stage of their treatment [6, 8, 11].

Thus, defining patients with a high risk of peritoneal recurrence and administering intraperitoneal chemotherapy to them still appears to be a challenge. Some pathological factors are associated with metachronous peritoneal metastasis: serosal invasion, diffuse infiltrative growth pattern, signet ring cell pathology, lymph node invasion, etc. [10]. Yet, in the age of precision medicine, patients get customized therapy designed based on molecular predictive factors [4]. The results of the next-generation sequencing available today enabled the creation of a molecular classification of GC. It distinguishes 4 molecular types of tumors: Epstein-Barr *virus* positive, microsatellite instability, genomically stable, and chromosomal instability [2].

The genomically stable type of GC is ultimately predetermined by the hereditary or somatic mutation of the CDH1 gene, coded by the cell-cell adhesion protein known as E-cadherin, and is characterized by the loss of E-cadherin expression on the cell membrane, which initiates the mobility of malignant cells. From the clinical perspective, the genomically stable type of GC is associated with the diffuse type of GC, according to the Lauren classification, and possesses a fairly strong affinity for peritoneal metastases [4].

Thus, the genomically stable type of GC, as a molecular predictor of peritoneal relapse, appears to be quite prospective. The identification of this molecular type may become an accurate tool in a complex personalized GC therapy. It may also allow us to identify patients who require adjuvant intraperitoneal therapy.

## Materials and methods

### Patients and specimens

The study is based on the analysis of the radical treatment effectiveness in 37 patients with localized and locally-advanced GC (pTis-4b, pN0-3b, M0) stages 0—IIIC. Of these patients, 19 (51.4 %) formed a subgroup with peritoneal relapse in the long term, and the remaining 18 (48.6 %) fell into a subgroup without metachronous carcinomatosis. These subgroups were selected as comparable pools of patients by qualitative composition regarding sex, age, the number of patients with the serous membrane invasion of the stomach, and the number of patients with the diffuse GC type (Table 1). The patients received treatment at the Department of Abdominal Surgery of the Lviv State Oncology Regional Treatment and Diagnostic Center in 2013—2018 (prospective clinical study). The ages of patients ranged from 42 to 76 years, and the average age was 60.23 ± 8.28 years. The diagnosis of GC in all patients was verified morphologically prior to the treatment onset. The GC study was conducted based on criteria from the TNM 7th edition classification (2009).

An immunohistochemical study of E-cadherin expression (CDH1 gene) was performed in 37 patients. The genomically stable molecular type was determined after the aberrant E-cadherin (CDH1-mutated) tumor phenotype had been confirmed.

### Immunohistochemistry assay

The tissue specimens were deparaffinized with xylene, rehydrated for antigen retrieval. Phosphate buffered saline was used to wash the slides, followed by treatment with 3 % hydrogen peroxide for 20 min to quench endogenous peroxidase activity. Then, the samples were preincubated with 10 % goat serum at room temperature for 30 min to prevent nonspecific staining. The sections were incubated with the following primary antibodies: Mouse anti-human Cadherin E Monoclonal Antibody (Clone HECD-1, MAD-000761Q — 1 : 50 dilution) 20 min in a humidified container, washed with phosphate buffered saline and the tissue slides were treated with a «UltraVision Quanto detection system HRP» by Thermo Scientific and stained with 3,3-diaminobenzidine tetrahydrochloride. Lastly, the sections were counterstained with Mayer's hematoxylin, dehydrated

Table 1. **Primary clinical and pathological characteristics of patients depending on the presense of relapse in the long term**

| Characteristics | With peritoneal relapse (n = 19) | Without peritoneal relapse (n = 18) |
|---|---|---|
| Men | 8 (42.1 %) | 8 (44.4 %) |
| Women | 11 (57.9 %) | 10 (55.5 %) |
| Age, years | 58.0 ± 6.18 | 61.0 ± 9.12 |
| Without serosal invasion | 2 (10.5 %) | 2 (11.1 %) |
| With serosal invasion | 17 (89.5 %) | 16 (88.9 %) |
| Diffuse type of GC | 16 (84.0 %) | 15 (83.0 %) |
| Intestinal type GC | 3 (16.0 %) | 3 (17.0 %) |

and mounted. We replaced the primary antibody with normal goat serum to obtain a negative control. The semi-quantitative immunohistochemistry results were evaluated by two independent pathologists who were blinded to the patients' clinical and biochemical information and the stained tissue sections were evaluated using a scale as follows: wild type — with preservation of membrane or cytoplasmic E-cadherin expression and aberrant type — with complete loss or expression < 10 % of cells.

### Follow-up

Patients were regularly followed-up after the operation. We performed ultrasonography every 3 months and chest radiography every 6 months during the first two postoperative years and every 6 months thereafter. Patients with inconclusive ultrasonography results underwent computerized tomography. Peritoneal relapse-free survival (PRFS) was measured from the date of surgery to the date of peritoneal recurrence or the final follow-up exam. Overall survival (OS) was measured from the date of surgery to the date of death or the last follow-up exam. The study was approved by the University Ethical Committee, which complied with the Declaration of Helsinki of 1975. Written informed consent was provided by all patients examined.

### Statistical analysis

Statistical analysis of the primary data was performed using SPSS 22 and Statistica 6 software. The censored Kaplan-Meier method was used to study the cumulative survival of patients, whereas the reliability of the survival difference in certain groups was determined using a log-rank coefficient. A multivariate analysis was performed using the $\chi^2$ index and the Cox model. To test statistical correlations, Pearson's linear correlation coefficient was used.

## Results and discussion

Wild (with preservation of membrane or cytoplasmic expression) and aberrant (with complete loss or expression < 10 % of cells) types of E-cadherin were observed in both diffuse (Fig. 1) and intestinal (Fig. 2) types of GC.

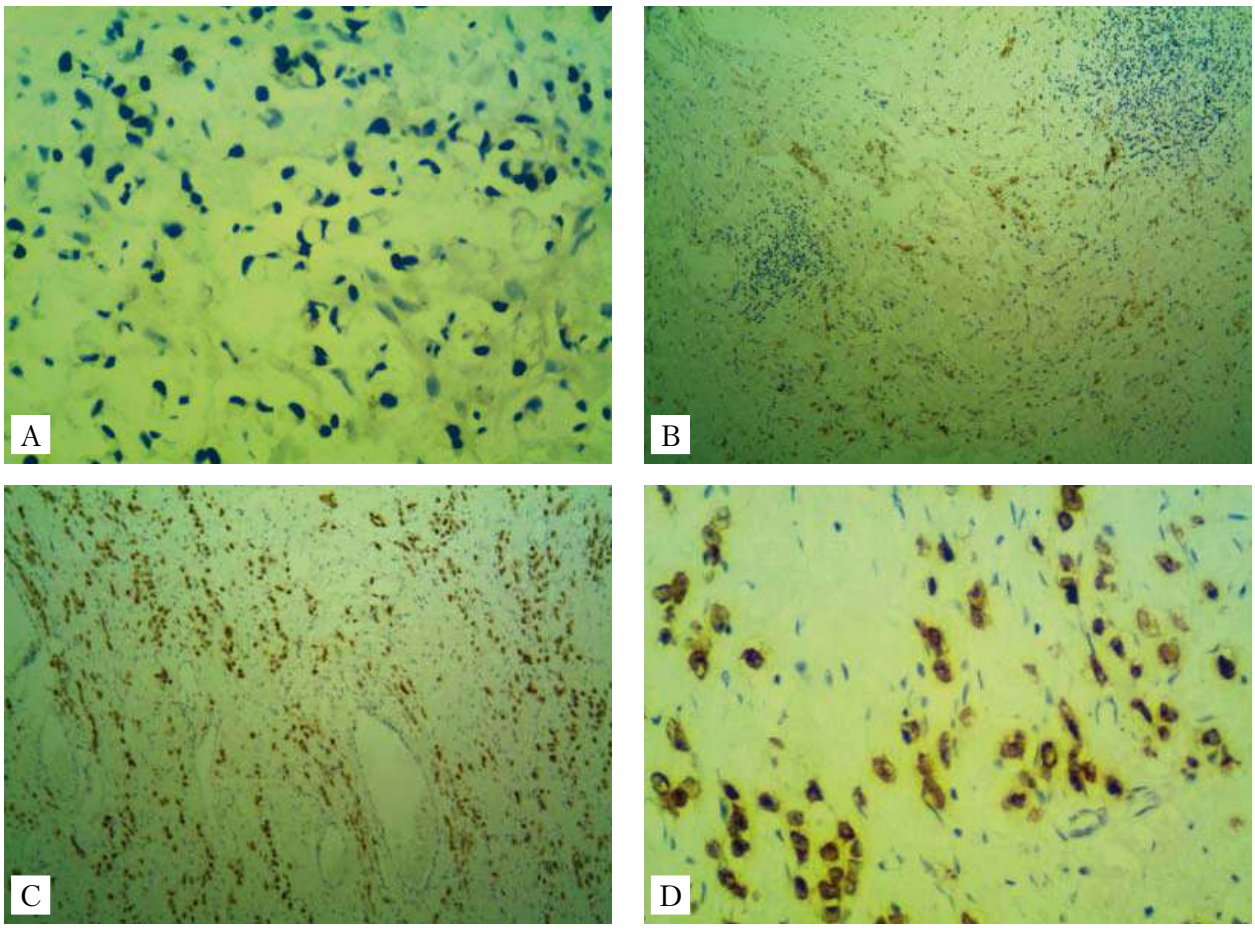


Figure 1. **Expression of E-cadherin in the histological specimen of diffuse gastric cancer: A — classic variant of the expression loss in signet-ring cell GC, aberrant type, × 400; B — preservation of membrane expression, wild type, × 100; C — preservation of membrane and cytoplasmic expression, wild type, × 100; D — preservation of membrane and cytoplasmic expression, wild type, × 200**

In subgroups of patients with and without intraperitoneal recurrence, there was a statistically significant difference ($p = 0,022$, $\chi^2 = 5,22$) in the presence of an aberrant type of E-cadherin expression (corresponding to the genomically stable molecular type of GC) — 68.4 % and 33.3 %, respectively.

In the diffuse GC type, the genomically stable type was found twice as often in patients with peritoneal relapse as in patients without peritoneal recurrence. All three cases of intestinal peritoneal recurrence of GC were characterized by loss of E-cadherin expression (Table 2).

Aberrant E-cadherin type statistically significantly worsened the relapse-free and overall survival of patients (Table 3, Fig. 3).

A statistically significant effect of aberrant E-cadherin in GC (genomically stable molecular type) on the risk of intraperitoneal recurrence was found due to the fact that the 2-year peritoneal relapse-free survival of patients with E-cadherin of the aberrant type in GC was 31.6 % against 71.4 % for patients with E-cadherin of the wild type in GC ($p = 0.022$) (Fig. 4).

Peritoneal relapse is the most common pattern of recurrence after the radical treatment of GC [15]. Peritoneal recurrence may relate to the intraoperative peritoneal dissemination that results from surgical manipulations [13]. However, the first and foremost reason for that is the presence of a microscopic pool of tumor cells in the peritoneum before the time of surgery, which derives from the biologic features of a tumor [4]. Previous research showed a strong affinity for metachronous peritoneal metastases in the diffuse type, undifferentiated and signet ring cell pathology [10, 15]. In order to reduce the level of peritoneal relapse in such patients, the whole range of adjuvant intraperitoneal chemotherapy methods is offered today, namely: hyperthermic intraperitoneal

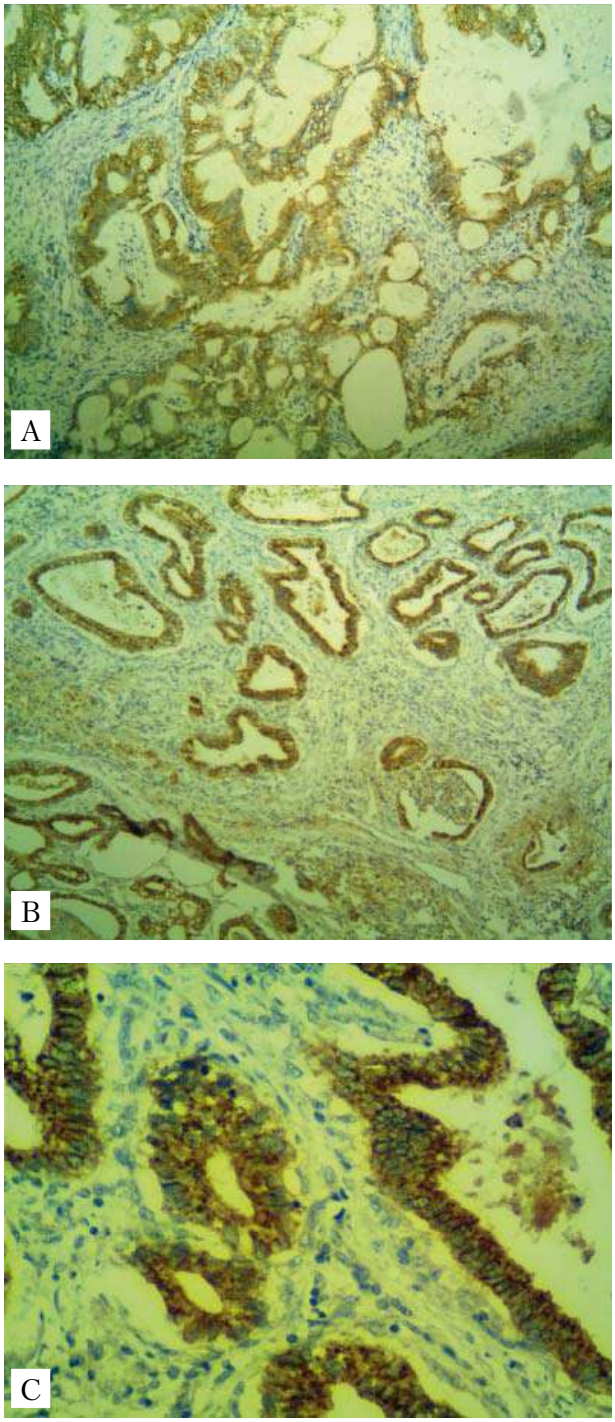


Figure 2. **Expression of E-cadherin in a histological specimen of an intestinal type of gastric cancer: A — classic variant of preservation of membrane expression, wild type, × 100; B — classical variant of preservation of membrane and cytoplasmic expression, wild type, × 100; C — classic variant of preservation of membrane and cytoplasmic expression, wild type, × 200; D — loss of expression, aberrant type, × 100**

Table 2. **The frequency of the genomically stable molecular type in GC patients based on the histological type by Lauren classification and peritoneal relapse**

| Characteristics | With peritoneal relapse in the long term (n = 19) | Without peritoneal relapse in the long term (n = 18) |
|---|---|---|
| Aberrant E-cadherin type | 13 (68.4 %) | 6 (33.3 %) |
| Wild E-cadherin type | 6 (31.6 %) | 12 (66.7 %) |
| Diffuse type of GC | | |
| Aberrant E-cadherin type | 10 (62.5 %) | 5 (33.3 %) |
| Wild E-cadherin type | 6 (37.5 %) | 10 (66.7 %) |
| Intestinal type of GC | | |
| Aberrant E-cadherin type | 3 (100.0 %) | 1 (33.3 %) |
| Wild E-cadherin type | 0 | 2 (66.7 %) |

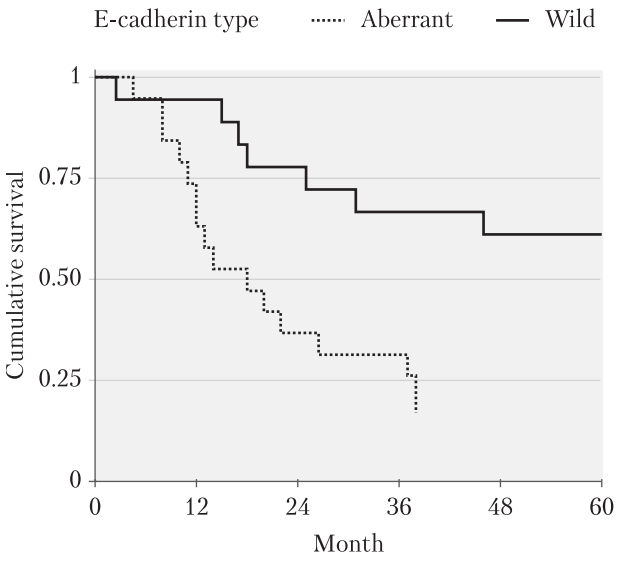


Figure 3. **Overall survival of patients with gastric cancer based on E-cadherin status**

Table 3. **The survival of GC patients based on E-cadherin status**

| Indicator | Aberrant type | Wild type | p |
|---|---|---|---|
| 2-year disease-free survival, % | 31.6 | 66.7 | 0.004 |
| Median disease-free survival, months | 13 | Not achieved | 0.005 |
| 2-year overall survival, % | 36.8 | 77.8 | 0.003 |
| Median overall survival, months | 18 | Not achieved | 0.004 |

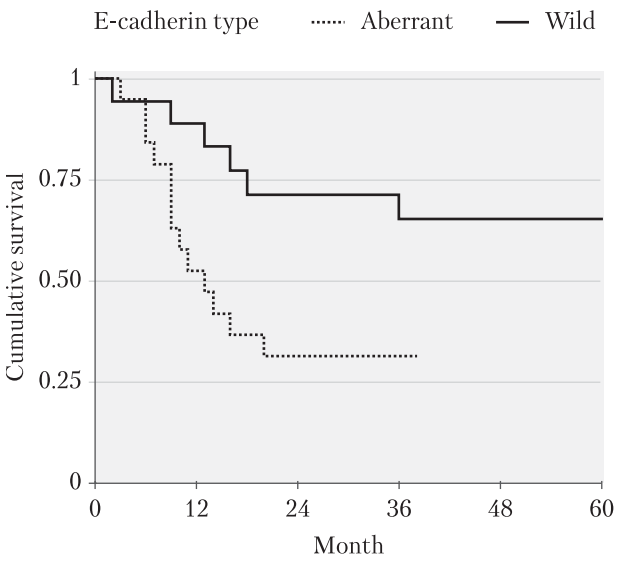


Figure 4. **Peritoneal relapse-free survival in gastric cancer patients based on E-cadherin status**

chemotherapy (HIPEC), early postoperative intraperitoneal chemotherapy (EPIC), extensive intraoperative peritoneal lavage (EIPL), etc. [6, 8, 9, 11]. Thus, in clinical practice, the study of prospective predictive factors for peritoneal relapse in GC cases, including molecular factors, may serve as a powerful tool for forming a cohort of patients with indications for adjuvant intraperitoneal therapy [14].

Germinogenic (hereditary) or somatic mutations in the gene CDH1, as well as its posttranslational disorders during carcinogenesis, cause the loss of E-cadherin expression on the surface of gastric carcinoma cells, resulting in their mobility and desquamation from the surface of the primary tumor on the serous membrane of the stomach. The presence of free malignant cells in the abdominal cavity, which have the potential for mesothelial adhesion or direct absorption into the sub-mesothelial layers through the lymphatic «hatches» of the peritoneum, is an integral part of the initiation of early stages of peritoneal metastasis of GC. The development of further stages of intraperitoneal carcinogenesis depends on the «favorable» factors for the tumor, which are regulated by autocrine and paracrine pathways [4].

In our research, the aberrant type of E-cadherin expression (that corresponds to the genomically stable molecular type of GC) was detected twice as often (68.4 %) in the subgroup of patients with peritoneal recurrence as in the subgroup without evidence of the latter (33.3 %, $p = 0.022$, $\chi^2 = 5.22$). Respectively, this molecular type of GC is

distinguished as a basic factor triggering the peritoneal dissemination processes of GC. For instance, in the diffuse GC type, two thirds of patients (62.5 %) with intraperitoneal recurrence were defined as aberrant E-cadherin type, while in the diffuse GC subgroup without intraperitoneal recurrence, the aberrant E-cadherin type was observed only in 33.3 % of patients. In addition, there were two cases of peritoneal relapse of the diffuse GC type without serous invasion, in which the loss of E-cadherin expression was determined — this confirms the aggressiveness and high potential for peritoneal metastasis of the genomically stable GC type. On the other hand, the intestinal type of GC is rarely accompanied by the development of metachronous peritoneal metastases [15]. Also, three cases of peritoneal relapse were observed in our study. They occurred along with the intestinal GC type; the loss of E-cadherin expression was detected in all these patients. These results prove the initiating and distinctive pathogenetic role of poor E-cadherin expression in the intraperitoneal recurrence processes for both (diffuse and intestinal) types of GC. Clinically, these results suggest that for the diagnosis of the genomically stable GC it is not sufficient to have histological evidence of diffuse type (which undoubtedly comprises the largest segment of the genomically stable type), whereas the evaluation of E-cadherin expression is necessary. The results of the monofactor analysis of our study have proved the statistically prospective influence of the aberrant type of E-cadherin expression on the risk of peritoneal recurrence, as well as the prospective deterioration of the recurrence-free and overall survival of patients. Other authors have also reported an increased risk of peritoneal relapse and a decreased prognosis in patients with aberrant E-cadherin [5, 7].

Thus, the loss of E-cadherin expression and the formation of the genome-stable molecular type GC phenotype is a key pathogenetic mechanism for triggering peritoneal GC metastasis, which is able to realize its potential even in intestinal GC or no serous gastric invasion. From a clinical standpoint, there is every reason to consider this molecular type as a predictive factor for the development of peritoneal relapse after radical surgical treatment of GC, as well as a prognostic factor due to its negative impact on patient prognosis.

## Conclusions

The study found that the genomically stable molecular type of GC may serve as a predictive factor associated with an increased probability of peritoneal relapse, as well as a prognostic factor due to its negative impact on patient prognosis. The genomically stable molecular type of GC may be used as a tool for forming a cohort of patients with indications for adjuvant intraperitoneal therapy.

### Declaration of interests

The authors declare that they have no conflicts of interest.

The authors declare no proprietary, financial, or other personal interests related to this article.

### Ethics approval and written informed consents statements

The study was approved by the University Ethical Committee, which complied with the Declaration of Helsinki of 1975. Patients gave written informed consent prior to study inclusion.

### Author contributions

Conception and design — R. Yarema, M. Ohorchak; acquisition of data — R. Yarema, M. Ohorchak, O. Petronchak, P. Hyrya, Y. Kovalchuk, V. Safiyan, O. Rilinh, M. Matusyak; analysis and interpretation of data — R. Yarema, M. Ohorchak, O. Petronchak, R. Huley, P. Hyrya, Y. Kovalchuk, V. Safiyan, O. Rilinh, M. Matusyak; drafting the article, critical revision of the article — R. Yarema.

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# Геномностабільний молекулярний тип раку шлунка як предиктор інтраперитонеального рецидиву після радикального хірургічного лікування

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Найчастішим шляхом рецидивування раку шлунка (РШ) після радикального хірургічного лікування є імплантаційні метастази. Такі хворі з високим ризиком інтраперитонеального рецидиву потребують ад'ювантної внутрішньочеревної терапії під час первинного лікування. Окрім клініко-морфологічних предикторів інтраперитонеального рецидиву, перспективним напрямом у хірургічній онкології є вивчення ризику метахронних перитонеальних метастазів при різних молекулярних типах РШ.

**Мета** — вивчити ризик інтраперитонеального рецидиву при геномностабільному типі РШ на тлі інших молекулярних типів.

**Матеріали та методи.** Проведено аналіз результатів радикального хірургічного лікування 37 хворих на РШ, із них 19 (51,4 %) з інтраперитонеальним рецидивом та 18 (48,6 %) без метахронного карциноматозу у віддалений період. У всіх хворих проведено імуногістохімічне дослідження експресії Е-кадгерину (ген CDH1) у пухлині шлунка. Геномностабільний молекулярний тип реєстрували у разі визначення Е-кадгерин аберантного (CDH1-мутованого) фенотипу пухлини.

**Результати.** Виявлено статистично значущу різницю ($p = 0,022$, $\chi^2 = 5,22$) за наявністю аберантного типу експресії Е-кадгерину між хворими з інтраперитонеальним рецидивом та без такого — 68,4 і 33,3 % відповідно. Установлено вірогідний вплив геномностабільного молекулярного типу на ризик метахронного карциноматозу: дворічна виживаність без інтраперитонеального рецидиву хворих на Е-кадгерин аберантний тип РШ становила 31,6 %, хворих на Е-кадгерин дикий тип РШ — 71,4 % ($p = 0,022$), дворічна загальна виживаність — відповідно 36,8 та 77,8 % ($p = 0,003$).

**Висновки.** Визначено вірогідну предиктивну щодо інтраперитонеального рецидиву та негативну прогностичну роль геномностабільного молекулярного типу РШ. Наявність останнього можна використовувати як інструмент для виділення групи хворих, яким необхідні ад'ювантні методи інтраперитонеального впливу.

**Ключові слова:** рак шлунка, інтраперитонеальний рецидив, геномно-стабільний молекулярний тип, Е-кадгерин, перитонеальні метастази, інтраперитонеальна хіміотерапія.

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# The impact of minimally invasive palliative decompression of bile ducts on quality of life in patients with distal malignant mechanical jaundice

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Palliative treatment for mechanical jaundice is aimed at improving patient quality of life (QoL) and prolonging life. The current QoL studies indicate that there is limited evidence on various techniques for decompression of bile ducts (BD) in terms of their impact on quality of life in patients with distal malignant mechanical jaundice, and their data are contradictory.

**The aim** of the study is to evaluate the effect of minimally invasive palliative techniques on QoL in patients with distal mechanical jaundice (MJ) after palliative decompression of bile ducts.

**Materials and methods.** From 2017 to 2021, 98 patients who underwent palliative decompression of bile ducts for distal MJ of malignant origin were examined. A validated MOS SF-36 questionnaire was used to assess patient QoL. The survey was conducted before the minimally invasive intervention and 2 months after it. Depending on the technique used for decompression of BD, patients were divided into the following groups: percutaneous transhepatic biliary drainage (PTBD) — 25, internal-external transpapillary biliary drainage (IETBD) — 19, internal-external biliary-jejunal drainage (IEBJD) — 29, and endoscopic retrograde biliary stenting (ERBS) — 25.

**Results.** Before treatment, a low level of patient QoL was detected in all groups on all scales of physical and psychological components of health (all $p > 0.05$). After 2 months, in the PTBD group, the indicator of the Mental Component Summary (MCS) decreased by an average of $6.9 \pm 1.2$ points (due to the deterioration of the indicator of social functioning scales by $12.5 \pm 5.0$ points and mental health by $11.1 \pm 1.8$ points), while the indicator of the Physical Component Summary (PCS) improved by $11.3 \pm 1.1$ points. In the IETBD and IEBJD groups, there was an improvement in MCS (by $11.7 \pm 1.3$ points and $13.0 \pm 1.1$ points, respectively) and PCS (by $5.2 \pm 1.2$ and $8.6 \pm 1.1$ points). With regard to MCS and PCS, slight improvement (by $4.7 \pm 2.2$ and $2.0 \pm 1.9$ points) was observed in the ERBS group.

**Conclusions.** The IEBJD technique provided important advantages in comparison with other minimally invasive palliative techniques for decompression of BD in terms of its impact on patient QoL. Patients in the IEBJD group had better PCS scores (on average, $47.3 \pm 1.3$ points) compared to the IETBD ($42.1 \pm 1.5$ points) and ERBS ($39.1 \pm 1.3$ points, $p < 0.05$) groups, and those in the PTBD group ($46.2 \pm 1.4$ points) had better scores than patients in the IETBD group ($p < 0.05$). In the IETBD and IEBJD groups, MCS scores were better $41.9 \pm 1.1$ and $40.3 \pm 1.1$ points, respectively) compared to the PTBD ($22.6 \pm 0.9$ points) and ERBS ($34.0 \pm 1.1$ points, $p < 0.05$) groups, and in the ERBS group, they were better than in the PTBD group.

**Keywords**
distal malignant jaundice, decompression of bile ducts, internal-external biliary-jejunal drainage, patient quality of life, MOS SF-36 questionnaire.

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Evaluation of the effect of any treatment on quality of life (QoL) has become a standard for assessing its effectiveness. The initial examination of patients with jaundice caused by malignant biliary obstruction (MBO) shows that 70—80 % of cases are subject only to palliative treatment, such as decompression of bile ducts (BD) [5]. Minimally invasive palliative techniques for decompression of BD in distal MBO are classified into two categories: antegrade (percutaneous transhepatic biliary drainage, PTBD, internal-external transpapillary biliary drainage, IETBD, internal-external biliary-jejunal drainage, IEBJD [18]) and retrograde (endoscopic retrograde biliary stenting, ERBS]. The choice of the BD decompression technique is a matter of debate [6]. One of the weighty arguments in favor of a particular technique may be better QoL after surgery. However, the effect of various BD decompression techniques on QoL in patients with distal MBO is understudied [11].

In 2002, N. S. Abraham et al. [1] defined the clinical characteristics of MBO that produced the greatest adverse effect on QoL in patients according to the MOS SF-36 questionnaire, and identified changes in QoL after retrograde BD decompression with a plastic stent. Weight loss and elevated bilirubin levels had the greatest impact on QoL baseline values in the multivariate analysis. A 33 % reduction in bilirubin levels was associated with significant improvements in social functioning and mental health. Baseline total bilirubin level exceeding 240 mmol/L was associated with no improvement in social functioning during one-month follow-up.

In 2008, Saluja S. S. et al. [16] assessed QoL in patients with stricture caused by gallbladder carcinoma who underwent the BD decompression using antegrade stenting with a plastic stent (27 patients) and retrograde stenting with a plastic stent (27 patients). Assessment of QoL was performed before the procedure and 1 and 3 months after it using QoL questionnaires of the European Organization for Research and Treatment of Cancer (EORTIC) and MOS SF-36 [2]. According to the MOS SF-36 questionnaire, the QoL values 1 and 3 months after the procedure were better in patients after antegrade stenting in terms of physical and mental health components, but not statistically significant. According to the EORTIC questionnaire, global health status was significantly better 3 months after antegrade stenting compared to the retrograde one (74 versus 30.5, respectively, $p = 0.02$). The authors attribute this to a lower percentage of early cholangitis after antegrade stenting (11 %) compared to the retrograde one (48 %), $p = 0.002$. (48 %, $p = 0.002$).

In 2010, there was a study on the association between pruritus and QoL before and 1, 4, 9, and 14 weeks after percutaneous biliary drainage/stenting in 102 patients with MBO [15], in which QoL was assessed using Functional Assessment of Cancer Therapy — Hepatobiliary instrument (FACT-HS) scale [8] and Visual Analog Scale for Pruritus (VASP) [23]. The authors noted a significant decrease in average values of QoL ($p < 0.01$) — from 101.3 before the procedure to 94.8 and 94.7 1 and 4 weeks after it, respectively. Improvements in QoL referred only to functional well-being and social/family well-being, while there were no changes in indicators of emotional and physical well-being.

Antegrade drainage/stenting has been shown to reduce pruritus and quite often hyperbilirubinemia to a level that is not contraindicated for chemotherapy but does not stop the relentless decline in the level of QoL, which is observed in patients whose average survival rate after treatment is less than 5 months.

The effect of endoscopic stenting with plastic stents on QoL in 164 patients with MBO was studied by Barkay O. et.al. in 2013 [3] using the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire before the procedure and 30 and 180 days after it. ERBS 30 and 180 days after the procedure resulted in statistically significant improvements in overall QoL scores and individual QoL scores (physical, emotional, and functional well-being) compared to pre-operative levels.

In 2016, Zhou Z. et al. [24] studied QoL and survival rate in 41 patients with MBO after using various endoscopic retrograde stenting/drainage methods in combination with radiation and chemotherapy. The study used the MOS SF-36 questionnaire and specific QLQ-C30 module, which also evaluates the symptoms typical for mechanical jaundice (jaundice, indigestion, pruritus, weight loss, and fever) [25]. The authors concluded that retrograde bile duct decompression methods combined with radiation and chemotherapy may be more effective in improving QoL and prolonging life.

Comparative assessment of the effect of plastic ($n = 73$) and metal stents (SEMS) (bare-metal ($n = 75$) and drug-eluting ($n = 71$)) on QoL in patients with distal MBO was conducted by D. Walter et al. [20]. Patients completed questionnaires before treatment, 14 days after treatment, and then monthly until 6 months or until death. According to the QLQ-C30 questionnaire, metal stents showed better results on two of the five functional scales (physical functioning ($p = 0.004$) and emotional functioning ($p = 0.01$)). In addition, patients with SEMS reported significantly less frequent symptoms of fatigue ($p = 0.01$), loss of appetite ($p = 0.02$), nausea, and vomiting (0.04) at the same time points after surgery.

In 2020, a group of authors [4] assessed the effect of access (right-sided or left-sided) in antegrade decompression of bile ducts on patient QoL. The researchers examined patients 7 days after the procedure using EORTC QLQ-BIL21 questionnaire [10]. In case of right-sided access, higher rates of intercostal pain, difficulty breathing, fatigue, anxiety, and drainage problems were recorded. Left-sided access provided better QLQ in patients.

The aim of the study is to evaluate the effect of minimally invasive palliative techniques on QoL in patients with distal mechanical jaundice (MJ) after palliative decompression of bile ducts.

## Materials and methods

The prospective study included 98 patients who underwent palliative BD decompression for distal MBO on the basis of the Department of Surgery with a course of Emergency and Vascular Surgery of O. O. Bogomolets National Medical University from 2017 to 2021.

A validated MOS SF-36 questionnaire was used to assess patient QoL [2]. The survey was conducted before mini-invasive intervention and 2 months after it.

The SF-36 Health Survey is a multi-item scale measuring 8 health domains: physical functioning (PF), role limitations because of physical health problems (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitations because of emotional problems (RE), and overall mental health (MH).

Such indicators as PF, RP, BP, and GH reflect the Physical Component Summary (PCS), whereas VT, SF, RE, and MH reflect the Mental Component Summary (MCS).

The inclusion criteria for the study were as follows: presence of mechanical jaundice, patient age over 18 years, any gender, and impossibility of performing radical surgery. The exclusion criteria were mechanical obstruction of bile drainage without jaundice syndrome, patient age under 18 years, high anesthetic risk (ASA 4), multiple metastatic liver damage, ascites, hemorrhagic diathesis, inflammatory diseases of the lungs and urinary tract, coagulopathy (international normalized ratio > 1.5), history of gastric resection for Billroth-II or Roux, refusal of the patient to do the questionnaire, as well as death of the patient during the study period.

In the presence of mechanical jaundice syndrome, confirmed clinically and in the laboratory, instrumental research methods were used to determine the cause of the disease and the level of the biliary block.

Ultrasound (General Electric Logiq P9 device) was used as a screening diagnostic method, as well as during minimally invasive procedures.

Among other radiation diagnostic tools, computed tomography (GE LightSpeed 64 multispiral computed tomography) was used to clarify the diagnosis. In case of insufficient information, magnetic resonance cholangiopancreatography was performed.

All patients also underwent duodenoscopy using various video endoscope models to assess the condition of Vater's papilla.

During surgical intervention, a General Electric ultrasound scanner and a Siemens Cios Alpha X-ray television unit with a C-arc were used.

According to the BD decompression techniques applied, the patients were divided into four groups (PTBD, IETBD, IEBJD, and ERBS).

The authors used their own BD drainage technique, IEBJD, which provided for the installation of special drainage to divert bile from BD to the initial loops of the small intestine due to the presence of two groups of lateral openings (proximal — located in BD and distal — located in the small intestine) at a distance from the distal border of the tumor to the initial loops of the small intestine [18]. This technique allows avoiding or significantly reducing reflux of intestinal contents into the bile ducts and, accordingly, the development of cholangitis [18].

Self-expanding metal stents (SEMS) were used to perform ERBS.

The intervention was considered technically successful if the drainage or stent was located in the planned area of the affected segment of the biliary tract and provided successful drainage of bile through drained or stented ducts.

The procedure was considered clinically successful if, during the first 10 days after the manipulation, the level of total serum bilirubin decreased by at least 50 % compared to the initial level [11].

The obtained data were analyzed using the IBM-SPPS Statistics 22 statistical package. Descriptive statistics was performed. The normality of the variable distribution was evaluated using the Shapiro-Wilk test. Quantitative comparative analysis of two independent groups was carried out using Student's t-test (in case of a normal distribution of variables; in case of its absence — Mann–Whitney U-test), and qualitative comparative analysis of groups was conducted using Pearson's chi-squared test. The null hypothesis of variable equality was rejected at $p < 0.05$.

## Results and discussion

From the medical history data, mechanical jaundice occurred in patients on average $15.2 \pm 0.2$ days

before the manipulation was performed (from 10 days to 22 days). According to the average duration of jaundice before surgery, patients in the study groups did not differ statistically significantly.

The average level of total serum bilirubin was 194.3 ± 0.7 mmol/L (from 67.2 to 389.6 mmol/L).

The study groups did not differ statistically significantly in the average content of total bilirubin before performing the surgical intervention.

Patients of the study groups as a whole did not differ statistically significantly in mean age, gender ratio, distribution by stage of the cancer process, TNM criteria (all $p > 0.05$), and etiological stricture factors (Table 1).

Baseline data showed a low level of QoL in all groups on all scales of physical and mental components of health (Table 2).

The technical and clinical success of minimally invasive procedures was achieved in all patients.

Two months after decompression of bile ducts in the PTBD group, there was a decrease in the mental component of health by an average of 6.9 ± 1.2 points due to deterioration in social functioning by 12.5 ± 5.0 points and mental health by 11.1 ± 1.8 points, resulting from the need for constant care about the bile receiver, as well as deterioration in food digestion (Fig. 1).

Two months after IETBD, there was an improvement in integrative indicators of physical (by an

Table 1. **Main characteristics of patient groups**

| Indicator | IEBJD (n = 29) | ERBS (n = 25) | IETBD (n = 19) | PTBD (n = 25) | Total (n = 98) |
|---|---|---|---|---|---|
| Age, years (M ± m) | 66.3 ± 2.1 | 62.6 ± 2.1 | 63.6 ± 3.0 | 65.5 ± 1.7 | 60.3 ± 1.7 |
| Male/female | 15/14 | 12/13 | 10/9 | 14/11 | 51/47 |
| Duration of jaundice, days (M ± m) | 14.1 ± 0.23 | 15.1 ± 0.21 | 16.3 ± 0.44 | 15.4 ± 0.45 | 15.1 ± 0.2 |
| Total serum bilirubin, μmol/L (M ± m) | 215.0 ± 14.8 | 208.9 ± 17.1 | 180.6 ± 20.9 | 183.2 ± 9.8 | 198.7 ± 8.9 |
| T (size or direct extent of the primary tumor) | | | | | |
| $T_2$ | 1 (3.4 %) | 3 (12.0 %) | 1 (5.3 %) | 1 (4.0 %) | 6 (6.1 %) |
| $T_3$ | 14 (48.3 %) | 12 (48.0 %) | 13 (68.4 %) | 12 (48.0 %) | 51 (52.1 %) |
| $T_4$ | 14 (48.3 %) | 10 (40.0 %) | 5 (26.3 %) | 12 (48.0 %) | 41 (41.8 %) |
| N (degree of spread to regional lymph nodes) | | | | | |
| $N_0$ | 3 (10.3 %) | 1 (4.0 %) | 1 (5.3 %) | 0 | 5 (5.1 %) |
| $N_1$ | 19 (65.5 %) | 21 (84.0 %) | 11 (57.9 %) | 19 (76.0 %) | 70 (71.5 %) |
| $N_2$ | 2 (6.9 %) | 1 (4.0 %) | 0 | 4 (48.0 %) | 7 (7.1 %) |
| $N_x$ | 5 (17.2 %) | 2 (8.0 %) | 7 (36.8 %) | 2 (8.0 %) | 16 (16.3 %) |
| M (presence of distant metastasis) | | | | | |
| $M_0$ | 12 (41.4 %) | 13 (52.0 %) | 11 (57.9 %) | 11 (44.0 %) | 47 (48.0 %) |
| $M_1$ | 13 (44.3 %) | 10 (40.0 %) | 6 (31.6 %) | 12 (48.0 %) | 41 (41.8 %) |
| $M_x$ | 4 (13.8 %) | 2 (8.0 %) | 2 (10.5 %) | 2 (8.0 %) | 10 (10.2 %) |
| Grade | | | | | |
| IIB | 1 (3.4 %) | 1 (4.0 %) | 1 (5.3 %) | 1 (4.0 %) | 4 (4.1 %) |
| III | 11 (37.9 %) | 8 (32.0 %) | 8 (42.1 %) | 9 (36.0 %) | 36 (36.7 %) |
| IV | 17 (58.6 %) | 16 (64.0 %) | 10 (52.6 %) | 15 (60.0 %) | 58 (59.2 %) |
| Tumor etiology | | | | | |
| Pancreatic cancer | 20 (69.0 %) | 17 (68.0 %) | 10 (52.6 %) | 18 (72.0 %) | 65 (66.3 %) |
| Cholangiocarcinoma | 5 (17.2 %) | 5 (20.0 %) | 6 (31.6 %) | 4 (16.0 %) | 20 (20.4 %) |
| Ampullary cancer | 2 (6.9 %) | 2 (8.0 %) | 3 (15.8 %) | 3 (12.0 %) | 10 (10.2 %) |
| Metastatic nodes | 2 (6.9 %) | 1 (4.0 %) | 0 | 0 | 3 (3.1 %) |

Table 2. **Patient quality of life associated with the disease before minimally invasive interventions**

| Indicator | IEBJD (n = 29) | ERBS (n = 25) | IETBD (n = 19) | PTBD (n = 25) |
|---|---|---|---|---|
| PF | 51.1 ± 5.1 (10.0—85.0) | 45.2 ± 3.7 (10.0—85.0) | 47.4 ± 3.1 (10.0—85.0) | 46.1 ± 3.4 (10.0—85.0) |
| RP | 37.1 ± 4.5 (0.0—75.0) | 33.3 ± 4.1 (0.0—75.0) | 38.8 ± 3.6 (0.0—75.0) | 36.1 ± 4.3 (0.0—75.0) |
| BP | 44.4 ± 5.1 (12.0—84.0) | 50.5 ± 2.9 (22.0—84.0) | 38.2 ± 4.1 (12.0—84.0) | 41.6 ± 4.7 (12.0—84.0) |
| GH | 32.9 ± 1.6 (15.0—45.0) | 33.5 ± 1.9 (15.0—55.0) | 31.8 ± 2.0 (15.0—55.0) | 30.8 ± 1.9 (15.0—55.0) |
| VT | 31.5 ± 2.5 (20.0—55.0) | 31.0 ± 1.7 (20.0—55.0) | 28.2 ± 1.6 (20.0—55.0) | 30.6 ± 1.9 (20.0—55.0) |
| SF | 41.4 ± 5.5 (12.5—75.0) | 32.5 ± 3.8 (12.0—75.0) | 31.4 ± 3.6 (12.5—75.0) | 32.6 ± 4.6 (12.0—75.0) |
| RE | 32.2 ± 3.4 (0.0—66.6) | 30.6 ± 3.5 (0.0—66.6) | 29.1 ± 3.4 (0.0—66.6) | 30.3 ± 3.5 (0.0—66.6) |
| MH | 40.5 ± 2.0 (24.0—56.0) | 35.3 ± 1.6 (16.0—56.0) | 35.3 ± 1.5 (24.0—56.0) | 35.8 ± 1.8 (16.0—56.0) |
| PCS | 38.7 ± 1.9 (25.7—51.0) | 37.1 ± 1.3 (25.7—51.0) | 36.9 ± 1.2 (25.7—51.0) | 36.7 ± 1.3 (25.7—51.0) |
| MCS | 28.9 ± 0.9 (27.0—37.0) | 29.3 ± 0.9 (20.6—37.0) | 28.6 ± 0.8 (22.3—37.0) | 29.5 ± 0.8 (20.6—37.0) |

Data are presented as Mean ± standard error of the mean (min — max).

average of 5.2 ± 1.2 points) and mental components of health (by 11.7 ± 1.3 points, all $p < 0.05$) (Fig. 2).

The improvement in the physical component of health is mainly associated with an increase in blood pressure (which corresponds to a decrease in pain) by an average of 22.3 ± 4.6 points, and the mental component of health — with an increase in social indicators (by 36.5 ± 4.7 points) and role functioning due to the emotional state (by 40.2 ± 4.4 points).

Slight changes in physical (on average by 2.0 ± 1.9 points) and mental components of health (on average by 4.7 ± 2.2 points) were observed in the ERBS group and could be explained by deterioration of the general health indicator and insignificant alterations in role-based physical and mental functioning (Fig. 3).

In the IEBJD group, two months after the procedure, there was an improvement in average values of all components of the SF-36 scale (Fig. 4).

It should be noted that the presence of external drainage did not negatively affect such indicators as vital activity, social functioning, role functioning, and mental health. On the contrary, the value of these indicators increased, that is, patients could perform a certain social role and did not avoid communication. At the same time, there was a decrease in pain syndrome and role functioning due to a physical condition, etc. Therefore, the IEBJD group showed an increase in the average values of integrative indicators — physical (by an average of 8.6 ± 1.1 points) and mental components of health (by an average of 13.0 ± 1.1 points).

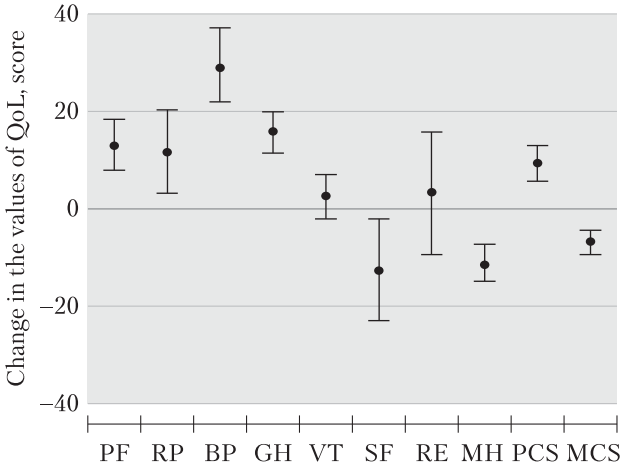


Figure 1. **Change in mean values (with 95 % CI) of QoL in the PTBD group two months after the BD decompression**

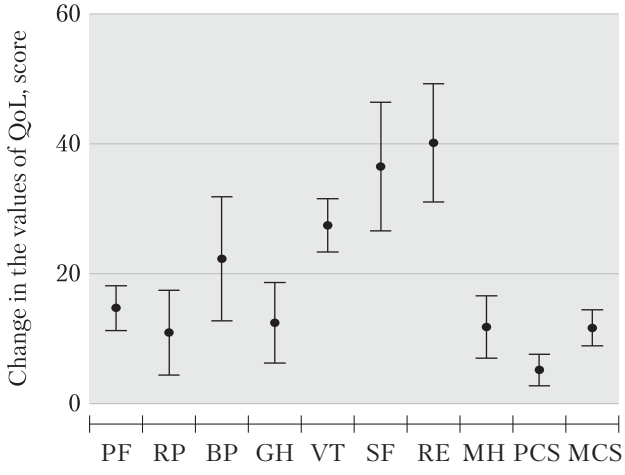


Figure 2. **Change in mean values (with 95 % CI) of QoL in the IETBD group two months after the BD decompression**

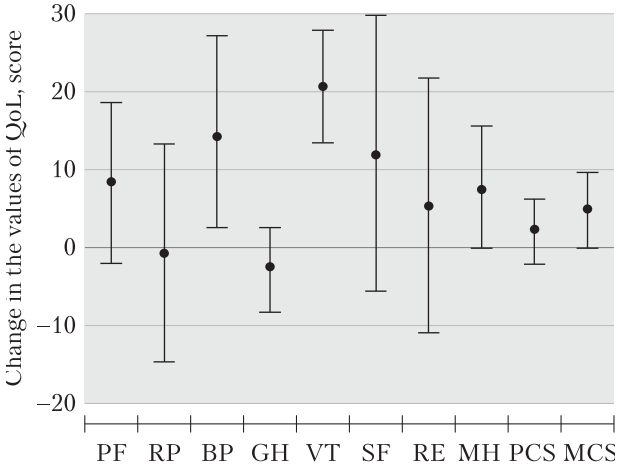


Figure 3. **Change in mean values (with 95 % CI) of patient QoL in the ERBS group two months after the BD decompression**

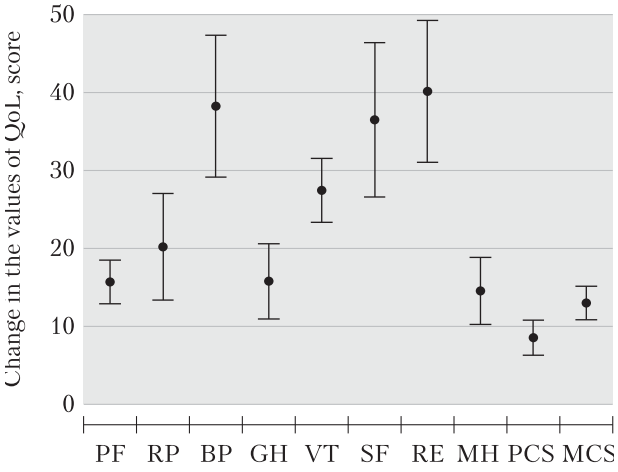


Figure 4. **Change in mean values (with 95 % CI) of patient QoL in the IEBJD group two months after the BD decompression**

Thus, two months after the BD decompression, the physical component of health was lower (39.1 ± 1.3 points) in the ERBS group compared to the PTBD group (46.2 ± 1.4 points) and the IEBJD group (47.3 ± 1.3 dietary supplements), and it was lower (42.1 ± 1.5 points, $p < 0.05$) in the IETBD group compared to the IEBJD group (Table 3). The average score of the mental component of health was the lowest in the PTBD group (22.6 ± 0.9 points) compared to other groups, and in the ERBS group (34.0 ± 1.1 points), it was statistically significantly less compared to the IETBD (40.3 ± 1.1 points) and IEBJD (41.9 ± 1.1 points) groups.

Therefore, 2 months after palliative treatment of distal malignant jaundice, the IEBJD technique provided important advantages in comparison with other techniques in terms of its impact on patient quality of life. Its benefits can be seen within the values of both integrative indicators (physical and mental components of health) and positive changes in individual MOS SF-36 scales.

The main goal of palliative care for patients with MBO is achieving improvement in their quality of life and prolonging life. Therefore, the QoL studies are necessary for choosing the best technique for decompression of bile ducts [16, 15]. However, there is limited evidence on various techniques for decompression of bile ducts (BD) in terms of their impact on quality of life in patients with distal malignant mechanical jaundice, and the existing studies explore different aspects of the problem and use different research tools (scales). A distinguishing characteristic of studying QoL in patients with MBO is a short duration of the study (from 30 to 180 days) due to low survival rates [23].

We carried out a comparative assessment of four techniques of BD decompression in patients with distal MBO in terms of changes in QoL indicators (for two months). These techniques differed by bile removal (external (PTBD), internal (ERBS), external-internal (IETBD and IEBJD)) and the absence (PTBD, IEBJD) or the presence (IETBD, ERBS) of direct connection of the duodenal lumen with the biliary tract.

Each of the methods of BD decompression has its disadvantages that can negatively affect patient QoL. So, for example, PTBD is associated with loss of a large amount of bile that needs to be consumed *per os*, and

Table 3. **Average scores of physical and mental health components 2 months after surgery**

| Indicator | | IEBJD (n = 29) | ERBS (n = 25) | IETBD (n = 19) | PTBD (n = 25) |
|---|---|---|---|---|---|
| PCS | Before surgery | 38.7 ± 1.9 | 37.1 ± 1.3 | 36.9 ± 1.2 | 36.7 ± 1.3 |
| | 2 months after | 47.3 ± 1.3 | 39.1 ± 1.3* | 42.1 ± 1.5* | 46.2 ± 1.4& |
| MCS | Before surgery | 28.9 ± 0.9 | 29.3 ± 0.9 | 28.6 ± 0.8 | 29.5 ± 0.8 |
| | 2 months after | 41.9 ± 1.1 | 34.0 ± 1.1* | 40.3 ± 1.1# | 22.6 ± 0.9*#& |

* The difference from the IEBJD group is statistically significant ($p < 0.05$).
# The difference from the ERBS group is statistically significant ($p < 0.05$).
& The difference from the IETBD group is statistically significant ($p < 0.05$).

the presence of a lifetime port on the skin [14]; ERBS is accompanied by damage to Vater's papilla and pancreas with the risk of bleeding and pancreatitis [9], and reflux of duodenal contents in the biliary tract in all patients [11], which leads to cholangitis and stent blockage [17]. IETBD, similar to ERBS, connects the duodenal lumen to the biliary tract and is associated with the risk of reflux-associated cholangitis [13, 12, 21, 22]. Patients after IEBJD and IETBD, as well as after PTBD, have a lifetime port on the skin, which causes some discomfort, but these techniques minimize the likelihood of bile loss outwards and duodenal-biliary reflux development [18].

According to our data, in the near future, minimally invasive BD decompression techniques will have different effects on certain aspects of patient QoL. The need for constant care about external drainage, as well as the need for constant use of bile, impairs the social functioning and mental health of patients, which is most evident after PTBD. Other techniques using percutaneous access (methods of external-internal drainage of BD) showed a statistically significant increase in the average values of scale indicators that form the mental component of health. Patients in the ERBS group showed a slight increase in these scales, statistically significant only for the VT indicator.

After ERBS, there were little ($p > 0.05$) changes in the physical health component (PCS) due to deterioration of the general health index (GH) and weak changes in the role-playing physical functioning index (RP). Instead, after using the techniques of external or external-internal drainage, an increase in the average values of PCS ($p > 0.05$) was noted. After two months, the mean PCS values were higher compared to the pre-operative level and the ERBS group ($p > 0.05$). Relatively worse PC scores after ERBS compared to retrograde techniques are probably associated with a higher incidence of early cholangitis [16, 18].

A comparative assessment of QoL in patients with distal mechanical jaundice after using various techniques of palliative antegrade and retrograde decompression of BD showed that after 2 months, the IEBJD and IETBD techniques, in contrast to the PTBD and ERBS, provided positive changes in the indicators of all scales of the MOS SF-36 questionnaire. The IEBED technique has advantages over IETBD in terms of PCS: $47.3 \pm 1.3$ points versus $42.1 \pm 1.5$ points, respectively ($p > 0.05$).

The current study has certain limitations: a relatively small number of patients in the comparison groups and the use of only one QoL questionnaire. In addition, the study did not include patients with total bilirubin values > 350 mmol/L and high anesthetic risk (ASA 4).

## Declaration of interests

The authors declare no conflicts of interest.

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## Ethics approval and written informed consents statements

All procedures performed in the study and involving human participants were carried out in accordance with the ethical standards of the institutional and/or national research committee, 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Written informed consent was obtained from all individual participants included in the study.

## Author contributions

Concept and design of the study: Y. M. Susak, L. Yu. Markulan, R. Y. Palytsya; literature review, discussion of the results: L. Yu. Markulan, R. Y. Palytsya; editing: Y. M. Susak, V. V. Teterina; materials and research methods, research results: R. Y. Palytsya.

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# Вплив малоінвазивної паліативної декомпресії жовчних проток при дистальній злоякісній механічній жовтяниці на якість життя хворих

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Основними завданнями паліативного лікування хворих із механічною жовтяницею є поліпшення якості життя (ЯЖ) і збільшення його тривалості. Досліджень ЯЖ хворих при використанні різних методик декомпресії жовчних проток (ЖП) проведено недостатньо, а їх дані суперечливі.

**Мета** — порівняти ЯЖ хворих з дистальною механічною жовтяницею (МЖ) після паліативної декомпресії ЖП з використанням малоінвазивних методик.

**Матеріали та методи.** У період з 2017 до 2021 р. обстежено 98 хворих, яким проведено паліативну декомпресію ЖП з приводу дистальної МЖ злоякісного генезу. Для оцінки ЯЖ застосовували валідизований опитувальник MOS SF-36. Опитування проводили до малоінвазивного втручання та через 2 міс після нього. Відповідно до методики декомпресії ЖП хворих розподілили на групи: черезшірна черезпечінкова холангіостомія (ЧЧХС) — 25, зовнішньо-внутрішня транспапілярна холангіостомія (ЗВТХС) — 19, зовнішньо-внутрішнє біліарно-еюнальне дренування (ЗВБЄД) — 29, ендоскопіне ретроградне біліарне стентування (ЕРБС) — 25.

**Результати.** До лікування виявлено низький рівень ЯЖ у всіх групах за всіма шкалами фізичного і психологічного компонентів здоров'я (всі $p > 0,05$). Через 2 міс у групі ЧЧХС показник психологічного компонента здоров'я (ПКЗ) знизився в середньому на (6,9 ± 1,2) бала (внаслідок погіршення показника шкал соціального функціонування на (12,5 ± 5,0) бала та психічного здоров'я на (11,1 ± 1,8) бала), тоді як показник фізичного компонента здоров'я (ФКЗ) поліпшився на (11,3 ± 1,1) бала. В групах ЗВТХС і ЗВБЄД відзначено поліпшення показників ПКЗ (відповідно на (11,7 ± 1,3) бала та (13,0 ± 1,1) бала) і ФКЗ (на (5,2 ± 1,2) та (8,6 ± 1,1) бала). В групі ЕРБС спостерігали мінімальну позитивну динаміку ПКЗ і ФКЗ (на (4,7 ± 2,2) та (2,0 ± 1,9) бала).

**Висновки.** Метод ЗВБЄД має переваги над іншими паліативними малоінвазивними методиками декомпресії ЖП щодо впливу на ЯЖ хворих. У хворих групи ЗВБЄД відзначено кращі показники ФКЗ (у середньому (47,3 ± 1,3) бала) порівняно із групою ЗВТХС ((42,1 ± 1,5) бала) та ЕРБС ((39,1 ± 1,3) бала, $p < 0,05$), у групі ЧЧХС ((46,2 ± 1,4) бала) — кращі, ніж у групі ЗВТХС ($p < 0,05$). У групах ЗВБЄД та ЗВТХС були кращі показники ПКЗ (відповідно (41,9 ± 1,1) і (40,3 ± 1,1) бала) порівняно із групою ЧЧХС ((22,6 ± 0,9) бала) та ЕРБС ((34,0 ± 1,1) бала, $p < 0,05$), а в групі ЕРБС — кращі, ніж у групі ЧЧХС.

**Ключові слова:** дистальна злоякісна жовтяниця, декомпресія жовчних проток, зовнішньо-внутрішнє біліарно-еюнальне дренування, якість життя хворих, опитувальник MOS SF-36.

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# Cervical mediastinoscopy in diagnosis and treatment of lung cancer

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Lung cancer remains the leading cause of cancer mortality. It ranks first in the incidence of cancer in the world. According to the European Association of Oncologists, the annual incidence of lung cancer is increasing with every passing year and amounts to about 1.8 million new cases worldwide. Men have a higher prevalence of lung cancer (33.8 per 100,000) than their female counterparts (13.5 per 100,000). In most cases, it is diagnosed at an advanced stage (III—IV), which is characterised by mediastinal lymphadenopathy. Early detection of lung cancer allows seeking early treatment. Lung cancer screening is used to find a tumour and/or lung cancer metastasis, determine its location and size as well as its morphological verification.

**Objective** — to define the most accurate invasive and non-invasive methods of verification and diagnosis of mediastinal lymphadenopathy and improve diagnosis and treatment of lung cancer through the extensive use of cervical mediastinoscopy and creation of an algorithm for its optimal use.

**Materials and methods.** The study included 146 patients. A wide range of clinical, laboratory, endoscopic (Endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA), Cervical Mediastinoscopy (CM)), radiographical (Computed tomography (CT), Positron emission tomography (PET)), morphological, immunohistochemical and statistical methods were used. Statistical analysis was performed using Statistics for Windows Version 10.0 (Stat Soft Inc., USA).

**Results.** The study involved 146 patients who underwent screening for mediastinal lymphadenopathy using mediastinoscopy. According to the laboratory findings, 98 patients had lung cancer. The rest of the cases were presented by other pathologies. Colorectal and stomach cancers were most commonly seen. In one case, the patient had a comorbidity, a combination of lung cancer and colorectal cancer.

**Conclusions.** Mediastinoscopy is the most effective diagnostic method for mediastinal lymphadenopathy, especially in lung cancer.

**Keywords**
mediastinoscopy, lung cancer, mediastinal lymphadenopathy.

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Cervical mediastinoscopy can be described as an invasive method that is used to examine the superior and middle mediastinum for staging of lung cancer and histological investigation of any mediastinal masses of unknown aetiology [2]. It was first described by Carlen in 1959 and is still used today to assess the size of mediastinal nodes observed on the CT-scan images and the stage of carcinoma [1, 7]. Cervical mediastinoscopy helped visualize subcarinal, upper and lower paratracheal lymph nodes. Three groups of lymph nodes were taken for biopsy [5]. The procedure has a low risk of significant complications, estimated at around 0.5% within the most effective series. The most common complication is an iatrogenic injury to the major vessels. Other reported complications include pneumothorax, left recurrent cartilaginous structure nerve paralysis, tracheal or esophageal rupture, wound infection and profuse haemorrhage. Thoracic CT-scan usually shows enlarged lymph nodes. It is primarily used for non-invasive N-staging. Imaging techniques, among them CT-scan, can't help define a type of tumour,

whether it is benign or malignant, as enlarged lymph nodes could additionally be inflammatory, whereas normal-sized lymph nodes might contain malignancy [4]. CT-scan alongside with mediastinoscopy (with biopsy) and endoscopic ultrasonography (EUS)-guided fine needle aspiration (FNA) biopsy, transbronchial needle aspiration (TBNA) diagnostic assay, and CT guided transthoracic FNA diagnostic assay are widely-used procedures for tissue confirmation, with variable yields and complications [13]. According to the data published by the European Association of Oncology, about 1.6 million new cases of lung cancer are diagnosed annually worldwide [10]. Men have a higher prevalence of lung cancer (33.8 per 100,000) than their female counterparts (13.5 per 100.000) [3]. Early diagnosis is essential for successful treatment of this pathology as it allows patients receive early and personalized treatment [8]. Cancer diagnosis includes investigation of the tumour, its location, size, spread, and morphological verification [14]. The most common non-invasive methods include laboratory examinations, chest radiography, magnetic resonance imaging (MRI), computerized tomography (CT), PET/CT, osteoscintigraphy, which may show the presence, development and localization of the oncological growth. These procedures are applied as a primary stage of diagnostic process and help choose an appropriate invasive technique for morphological verification [9, 11, 16]. Accurate diagnosis of lung cancer requires a range of invasive procedures such as transthoracic puncture biopsy, fibrobronchoscopy with biopsy, transbronchial biopsy (EBUS TBNA), transesophageal biopsy (EUS-FNA), video thoracoscopy with biopsy, cervical mediastinoscopy (CM), and open biopsy [12, 15].

**Objective** — to define the most accurate invasive and non-invasive methods of verification and diagnosis of mediastinal lymphadenopathy and improve diagnosis and treatment of lung cancer through the extensive use of cervical mediastinoscopy and creation of an algorithm for its optimal use.

## Materials and methods

The study was conducted at the Oncology clinic of the Department of Oncology of Bogomolets National Medical University (Kyiv, Ukraine) and at Kyiv Clinical Railway Transport Hospital No. 3 from 2016 to 2021. The study involved 146 patients who underwent screening for mediastinal lymphadenopathy using mediastinoscopy. A wide range of clinical, laboratory, endoscopic (Endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA), Cervical Mediastinoscopy (CM)), radiographical (Computed tomography (CT), Positron emission tomography (PET)), morphological, immunohistochemical and statistical methods were used. Enlarged mediastinal lymph nodes seen on the CT-scan image was an indication for mediastinoscopy. Mediastinoscopy was performed under general anaesthesia, with a patient lying on their back and a roller beneath their shoulders. The first anatomical landmark was a jugular notch, above which a skin incision was created within the lower third of the neck in the transversal direction. The second anatomical landmark was a trachea. After dissection of the pretracheal fascia, the trachea was exposed, and the forefinger was inserted into the wound canal, the paratracheal tissue was stratified, and a mediastinoscope was inserted. The third anatomical landmark is a tracheal bifurcation. Paratracheal areas, tracheal bifurcation, and the main bronchi were examined. Enlarged lymph nodes were taken for excision biopsy from different sites. Patients were discharged from the hospital on the day of surgery or the following day.

The study was conducted according to the provisions of the Helsinki Declaration of Human Rights, and every participant gave their written informed consent.

Statistical analysis was performed using Statistics for Windows Version 10.0 (Stat Soft INC., USA). Parameters are given within the form $M \pm m$, where M is an average value, m is the standard deviation. In the case of $p < 0.05$, variations were set as statistically significant.

## Results and discussion

The study involved 146 patients who underwent screening for mediastinal lymphadenopathy using mediastinoscopy. According to the laboratory findings, 98 patients had lung cancer. The rest of the cases were presented by other pathologies. Colorectal and stomach cancers were most commonly observed. In one case, the patient had a comorbidity, a combination of lung cancer and colorectal cancer.

The inspection of enlarged lymph nodes allowed discovering of their different combinations. In the majority of cases, the samples of three groups of lymph nodes were taken. (Table 1). Cervical mediastinoscopy was primarily used for N-staging in patients with carcinoma. The sensitivity of CT-scan was 97.6 % — (95 %CI [89.3—100.0). Additionally, a reliable specificity indicator was established at 46.5 (95 % CI [32.3—61.2]) and a low probability of false-negative rate — 0.05 (95 % CI [0.01—0.26]). (Table 2). To compare CT-scan with mediastinoscopy, lung resection with lymph node dissection

Table 1. **The ratio of different combinations in affected lymph nodes in patients with lung cancer**

| Parameter | Cases, % |
|---|---|
| 2R, 4R, 7 | 18,38 |
| 4R, 4L, 7 | 21,5 |
| 4L, 7 | 9,3 |
| 2R, 4R | 7,73 |
| 4R, 4L | 5,2 |
| 4R | 9,12 |
| 2R, 4R, 4L, 7 | 2,62 |
| 2R | 2,83 |
| 2R, 2L, 4R, 4L | 3,9 |
| 2L, 4L, 10L, 4R | 1,26 |
| 4R, 7 | 7,44 |
| 2R, 4R, 4L | 6,34 |
| 4R, 10R | 3,38 |

Table 2. **Parameters of diagnostic value of CT-scan compared to the results of histologic investigations in patients with lung cancer who underwent cervical mediastinoscopy**

| Parameter | Value (95 % CI) |
|---|---|
| Sensitivity | 97.6 (89.3—100.0) |
| Specificity | 46.5 (32.3—61.2) |
| Youden's index | 0.44 (0.31—0.57) |
| Area under ROC curve | 72.1 (65.6—78.6) |
| Diagnostic odds ratio | 36.5 (6.4—97.8) |

was performed in 12 cases in patients who underwent preoperative mediastinoscopy. The histological results were consistent in all cases. However, for the determination of sensitivity and specificity, the group is statistically insignificant. Further investigation of more patients is necessary and, therefore, is planned.

According to chest CT-scan, in patients with carcinoma, mediastinal lymph nodes from 10 to 14.9mm were discovered in 78 (54.76 %) patients and 15 mm in 68 (45.24 %) patients. Lung cancer metastases within the mediastinal lymph nodes were detected in 98 (67.12 %) patients. According to the CT-scan data, in 48 (32.87 %) patients, mediastinal pathology was not caused by lung cancer metastasis. The histologic distribution was as follows: squamous cell lung cancer — 23.8 % cases, adenocarcinoma — 57.1 %, small cell carcinoma — 19.04 %. Consistent with the classification, TNM — $T_4N_3M_0$ — 10, $T_4N_2M_0$ — 9, $T_4N_2M_1$ — 6, $T_3N_3M_1$ — 6, $T_3N_2M_0$ — 9, $T_3N_0M_0$ — 9, $T_2N_3M_1$ — 8, $T_2N_3M_0$ — 16, $T_2N_3M_1$ — 3, $T_2N_2M_1$ — 3, $T_2N_0M_0$ — 15, $T_1N_2M_0$ — 4. The results of the surgical histologic examination of mediastinal lymph nodes coincided with the histologic results of operative cervical mediastinoscopy in all cases (100.0 [97.1—100.0]). False negative rate zero.01 [0.25—2.89] was unreliable. Cervical mediastinoscopy influenced the selection of treatment techniques.

Cervical mediastinoscopy is a safe, accurate and cost-effective procedure that minimizes hospital stays and initiates adequate treatment immediately after receiving the results of histopathological examination. The main advantage of this technique is its high diagnostic value — sensitivity is about 81.8 %, and specificity — 100 %. This technique allows sampling of morphological material sufficient to perform a histologic, immunohistochemical and molecular investigation that makes it possible to diagnose a disease and prescribe treatment objectively. Histologic analysis of mediastinal lymph nodes is feasible after using invasive diagnostic strategies like VATS, EBUS-TBNA, and cervical mediastinoscopy. The disadvantages of VATS are often thought of as invasiveness of the technique, the ability to perform only unilateral diagnostic test of lymph nodes, and a long hospital stay. The disadvantages of EBUS-TBNA are expensive equipment and the ability to perform diagnostic tests of a limited quantity of the material. N-staging of carcinoma could be a significant indication for mediastinoscopy. The most significant advantage of mediastinoscopy over other procedures is that this technique provides morphological confirmation of the tumour spread. However, the study suggests that chest CT-scan cannot be used as a complete technique for carcinoma staging. The method detects mediastinal lymph nodes accurately only in 52—58 % of cases. A CT-scan shows any affected lymph nodes larger than 1 cm. However, the frequency of false positives is more or less half-hour. According to the results of modern studies, on average, the sensitivity and

specificity of chest CT of intrathoracic lymph nodes metastases of carcinoma is 56—63 % and 52.75 %, severally, whereas, with mediastinoscopy, these indicators reach 98—100 % and 95—97 %, severally. In terms of sensitivity and specificity (80 % and 96—98 %, respectively), positron emission imaging approaches mediastinoscopy. Mediastinoscopy remains the most effective diagnostic investigation of choice for mediastinal pathology, especially in lung cancer [18].

## Conclusions

Cervical mediastinoscopy in patients with primary lung cancer helps establish a reason for the enlargement of mediastinal lymph nodes and verify the frequency of various combinations in the study groups as well as verify diagnosis and N status in all cases.

The sensitivity of CT was 97.6 % — (95 %CI [89.3—100.0). The reliable specificity was 46.5 (95 % CI [32.3—61.2]) and probability of false-negative rate — 0.05 (95 % CI [0.01—0.26]).

The results of operative microscopic anatomy examination of the mediastinal lymph nodes coincided with the histologic results of surgical cervical mediastinoscopy in all cases (100.0 [97.0—100.0]). False-negative rate 0.01 [0.25—2.89] was unreliable.

Cervical mediastinoscopy makes it possible to get enough tissue samples for immunehistochemical study to establish accurate diagnosis and prescribe proper treatment for patients with primary lung cancer.

### Declaration of interests

The authors declare no conflicts of interest.

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### Author contributions

R. Vereshchako: a study concept and design, critical review, final approval of the article; O. Piskorskyi: data collection and analysis, statistical analysis, writing the article; I. Sukhin: data collection and analysis, critical review.

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# Роль шийної медіастиноскопії у діагностиці та лікуванні раку легень

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Рак легені залишається основною причиною смерті від раку. Він посідає перше місце за захворюваністю на рак у світі. За даними Європейської асоціації онкологів, захворюваність на рак легені зростає. Щороку у світі реєструють близько 1,8 млн нових випадків раку легені. Чоловіки хворіють частіше, ніж жінки (відповідно 33,8 і 13,5 випадку на 100 тис. населення). Більшість діагностованих випадків припадає на III—IV стадії, для яких характерна медіастинальна лімфаденопатія. Рання діагностика дає змогу розпочати своєчасне лікування. Основним завданням діагностики раку легені є визначення локалізації, розмірів, поширення та морфологічна верифікація пухлини.

**Мета** — визначити найточніші інвазивні та неінвазивні методи верифікації і діагностики медіастинальної лімфаденопатії та поліпшити результати діагностики і лікування раку легені шляхом широкого застосування шийної медіастиноскопії та створення алгоритму її оптимального використання.

**Матеріали та методи.** У дослідження було залучено 146 пацієнтів. Використано загальноклінічні, лабораторні, ендоскопічні (ендобронхіальна ультразвукова трансбронхіальна голчаста аспірація (EBUS-TBNA), шийна медіастиноскопія), рентгенографічні (комп'ютерна томографія, позитронно-емісійна томографія), морфологічні, імуногістохімічні та статистичні методи дослідження. Для аналізу статистичних даних застосовували програму Statistics for Windows Version 10.0 (Stat Soft Inc., США).

**Результати.** Усім хворим виконано медіастиноскопію. У 98 діагностовано рак легені. Решта випадків були представлені іншими патологіями. Найчастіше виявляли колоректальний рак і рак шлунка. В одному випадку у пацієнта була супутня хвороба, поєднання раку легені та колоректального раку.

**Висновки.** Медіастиноскопія є найефективнішим методом діагностики лімфаденопатії середостіння, особливо для хворих на рак легені.

**Ключові слова:** медіастиноскопія, рак легені, медіастинальна лімфаденопатія.

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# Nutritional support for patients in general surgery

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The modern stage of development of surgery, especially minimal invasive technologies, has significantly changed the surgeons' thoughts about the perioperative period. Until the end of the twentieth century, pre- and postoperative fasting was the most important requirement in planned surgery. It was believed that it could help to avoid complications both during surgery and in the early postoperative period. H. Kehlet in his fundamental work outlined the factors that allowed to accelerate the patient's recovery after surgery, namely: the absence of preoperative fasting.

**Objective** — to evaluate the effectiveness of nutritional support for surgical patients within ERAS (Enhanced Recovery After Surgery) and ESPEN (European Society for Clinical Nutrition and Metabolism) protocols.

**Materials and methods.** This research included both traditional laparoscopic cholecystectomy (177 cases) and single-port transumbilical cholecystectomy (8); among laparoscopic bariatric interventions, the major part was represented by classical Roux-Y gastric shunting (28), as well as sleeve gastrectomy (5) and mini-gastric shunting (4); among 123 different laparoscopic hernioplasties, in 64 cases transabdominal preperitoneal (TAPP) was performed for bubonocele, intraperitoneal onlay mesh (IPOM) for postoperative ventral and umbilical hernias (59), laparoscopic crurography and fundoplication with and without alloplasty (33). For each type of surgery two groups we identified: control and experimental. Both groups were followed by ERAS protocols in addition to nutritional support. With the prior consent of patients before surgery: the experimental group received full perioperative nutritional support according to our local protocols using protein-enriched sip feeding formula Nutridrink Protein, the control group followed the traditional scheme of fasting during 12 hours before surgery and received regular drinking water instead of protein mixtures at the first postoperative day.

**Results.** We found statistically significant difference between control and experimental groups in assessing of two important parameters as hunger and weakness. The hunger after laparoscopic cholecystectomy was 1.5 times ($p < 0.001$), after laparoscopic hernia repair — 1.7 times ($p < 0.001$), after laparoscopic crurography and fundoplication — 1.26 times ($p < 0.001$), after laparoscopic bariatric intervention — 1.43 times, and after laparoscopic colon intervention — 1.9 times lower in the experimental group. The weakness after laparoscopic cholecystectomy was 1.8 times ($p < 0.001$), after laparoscopic hernia repair — 1.31 times ($p < 0.001$), after laparoscopic crurography and fundoplication — 1.68 times ($p < 0.001$), after laparoscopic bariatric intervention — 1.67 times ($p < 0.001$), and after laparoscopic colon intervention — 1.38 times ($p = 0.006$) stronger in the control group.

**Conclusions.** Traditional long-term preoperative fasting is inappropriate. Combined with other ERAS postulates, perioperative nutritional support for surgical patients has a great chance of success. In our research, early restoration of oral nutrition significantly decreases hunger and general weakness in the early postoperative period, which allows the patient quickly return to full life.

**Keywords**
enhanced recovery after surgery, nutritional support.

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The modern stage of surgery development, especially minimal invasive technologies, has significantly changed the surgeons' thoughts about the perioperative period. Until the end of the twentieth century, pre- and postoperative fasting was the most important requirement in planned surgery. It was believed that fasting could help to avoid complications both during surgery and in the early postoperative period. Fasting before surgery was the main guarantee to prevent regurgitation of gastric contents to the respiratory tract [1]. Regarding complete fasting in the first days after surgery, there was a general opinion about the prevention of nausea and vomiting, decrease the load on the anastomoses' stitches of the gastrointestinal tract (GIT).

At the end of the twentieth century, research began to appear on the impact of surgical treatment on the postoperative period. H. Kehlet from Denmark is the first person who conducted a fundamental study of the effects of surgical stress on the body recovery and identified ways to significantly reduce the symptoms of surgical stress. In this fundamental work he outlined the following factors that enhanced the patient's recovery after surgery: no preoperative fasting, antibiotic prophylaxis with a daily dose up to 30 minutes before the surgery, use of regional anesthesia, minimal invasive surgery, local infiltration anesthesia before surgery, intraoperative normothermia, administration of glucocorticoids, minimal drainage use, urethral catheters and nasogastric tubes, early (first hours after surgery) postoperative activation of the patient, early oral nutrition, thromboprophylaxis, effective pain control, medical prevention of nausea/vomiting (using antiemetics), use of NSAIDs to reduce the symptoms of inflammatory reaction [2]. He defined these postulates as Fast track surgery [3]. Later, in 2001, the ERAS organization (Enhanced Recovery After Surgery) was founded according to postulates of H. Kehlet and nowadays it unites scientists and practitioners whose goal is to process the evidence bases and develop recommendations (protocols) based on them for implementation in surgical clinics [4].

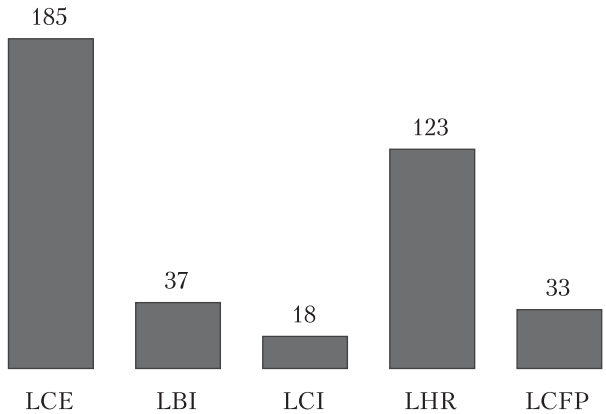
Why the perioperative nutritional support for surgical patients is so important component of ERAS? Surgery, as any intervention, causes SIRS (Systemic Inflammatory Response Syndrome), which accelerates the catabolism of glycogen, protein and fat. Free fatty acids and aminoacids enter the circulation to do protective and reparative functions instead of their main one — plastic (building) function [5]. The longer the catabolic phase lasts after surgery, the longer is the patient's recovery. Nutritional status is a risk factor for the development of postoperative complications. ESPEN (European Society for Clinical Nutrition and Metabolism) considers the main requirements of the perioperative period: integration of nutrition in the treatment of the patient at all stages; prevention of prolonged fasting state; continuation of oral nutrition as soon as possible after surgery; beginning of nutritional support before the onset of signs of nutritional deficiency; metabolic control (e.g. blood glucose control); reduction of factors that increase stress-related catabolism and reduce gastrointestinal function; minimization of time of action of paralytic medicines after artificial ventilation of lungs in the postoperative period; early mobilization to activate protein synthesis and restore muscle function [6].

**Objective** — to evaluate the effectiveness of nutritional support for surgical patients according to ERAS and ESPEN protocols

## Materials and methods

We have performed 363 surgery operations according to ERAS protocols (Fig. 1) during period from September 2019 to December 2021.

This research included both traditional laparoscopic cholecystectomy (LCE) (177 cases) and single-port transumbilical cholecystectomy (8); among laparoscopic bariatric interventions (LBI), the major part was represented by classical Roux-Y gastric shunting (28), as well as sleeve gastrectomy (5) and mini-gastric shunting (4); among 123 different laparoscopic hernioplasties, in 64 cases transabdominal preperitoneal (TAPP) was performed for bubonocele, intraperitoneal onlay mesh (IPOM) for postoperative ventral and umbilical hernias (59), laparoscopic crurography and fundoplication (LCFP) with and without alloplasty (33). For each




LCE — laparoscopic cholecystectomy; LBI — laparoscopic bariatric intervention; LCI — laparoscopic colon intervention; LHR — laparoscopic hernia repair; LCFP — laparoscopic crurography and fundoplication

Figure 1. **Differentiation of surgery interventions according to ERAS protocols**

type of surgery two groups we identified: control and experimental. Both groups were followed by ERAS protocols in addition to nutritional support. With the prior consent of patients before surgery: the experimental group received full perioperative nutritional support according to our local protocols, the control group followed the traditional scheme of fasting during 12 hours before surgery and received water instead of protein mixtures at the first postoperative day.

The experimental group of LCE consists of 101 patients: 88 women (87.13 %), 13 men (12.87 %), the control group consists of 84 patients: 73 women (86.9 %), 11 men (13.1 %). The average age in the experimental group was 48.6 ± 11.5 years; in the control group it was 47.6 ± 10.98 years. Group structure for LBI represented 18 patients for control group: 16 women (88.9 %), 2 men (11.1 %), average age was 43.2 ± 7.7 years; 19 patients for experimental group: 16 women (84.21 %), 3 men (15.8 %), average age was 41.3 ± 8.4 years. The control group for laparoscopic colon intervention (LCI) consists of 9 patients: 4 women (44.44 %), 5 men (55.56 %), the average age was 62.4 ± 8.9 years; the experimental group consists of 9 patients: 5 (55.56 %) women, 4 (44.44 %) men, the average age was 63.4 ± 8.5 years. Laparoscopic hernia repair (LHR) groups were formed by control group of 59 patients: 34 women (57.62 %), 25 men (42.38 %); average age was 44.1 ± 8.7 years; experimental group with 64 patients: 38 women (59.37 %), 26 men (40.63 %), the average age was 41.7 ± 8.3 years. After LCFP control group consisted of 16 patients: 9 women (56.25 %), 7 men (43.75 %), average age was 44.6 ± 7.8 years; experimental group consisted of 17 patients: 10 women (58.82 %), 7 men (41.18 %), average age was 45.6 ± 6.9 years.

According to our local protocols based on ERAS recommendations, the time of fasting is minimal. No later than 2 hours before surgery (general anesthesia) patients consumed 200 ml of warm boiled water with 5 g of glucose or sweet black tea of the same volume. In the absence of stomach pathology, there is no threat of regurgitation, because in 2 hours this fluid completely eliminates from the stomach. Carbohydrate intake increases the anabolic effect in the early postoperative period: decrease of postoperative nitrogen and protein loss, and maintenance of postoperative body weight and muscle function, decrease the risk of insulin resistance in the early postoperative period, which is actually a protective response to fasting. In addition, decrease of the thirst and hunger feelings reduces the feeling of surgery fear, which affects the strength of the body's stress response to intervention [7—10].

We have already had experience of using special adapted mixtures to restore early oral nutrition since 2011 [11]. We outlined the main requirements for postoperative nutrition as low dosage, adequate amounts of calories, easy using by patient, absorption in the proximal gastrointestinal tract, dietary fiber-free and glucose-free content. Nutridrink Protein special food product completely met these requirements on the Ukrainian market:

*Balanced composition:*

- High protein content in a low volume: 18 g per 125 ml.
- High energy content: 306 kcal per 125 ml.
- Contains vitamins and microelements (selenium, chrome etc.).
- Free of dietary fiber.
- Gluten-free product.

According to our local protocols, developed on the basis of ESPEN and ERAS recommendations, 2 hours before surgery all patients received 5 g of glucose dissolved with 200 ml of water. We adapted the diet for all patients undergone ERAS-compliant surgery according to the type of surgery. The preoperative and postoperative early nutrition regimen was provided as following: in 4 hours after extubating-administration 125 ml Nutridrink Protein (any chosen flavor) twice daily. Water consumption was limited according to patient's need. On the 2nd postoperative day, all patients received sip feeding nutrition according to the manufacturer's recommendations, 2—3 bottles per day.

The assessment was performed the day after surgery according to the criteria, that we have developed. There was ascertained the presence of nausea/vomiting, bloating, flatulence, defecation, and there was assessed the patients' feelings of hunger, thirst, general weakness, and depression on a scale from 1 to 10 (where 1 is the lowest intensity symptoms, 10 is the highest intensity).

## Results and discussion

We performed surveys on the first postoperative day. Results are represented in the Table.

Nausea/vomiting and bloating in all types of surgery did not correlate with the use of early postoperative nutrition in both groups and were statistically insignificant, but during hunger assessment we found statistically significant differences: the hunger after LCE was 1.5 times ($p < 0.001$), after LHR — 1.7 times ($p < 0.001$), after LCFP — 1.26 times ($p < 0.001$), after LBI—1.43 times, and after LCI — 1.9 times lower in the experimental group (Fig. 2).

During assessment of thirst only after bariatric interventions, we found a significant difference of 1.29

Table. **The questionnaire results of patients after various surgical interventions in the first postoperative day**

| Index | Group | LCE | LHR | LCFP | LBI | LCI |
|---|---|---|---|---|---|---|
| Number of patients | Control | 84 | 59 | 16 | 18 | 9 |
| | Experimental | 101 | 64 | 17 | 19 | ?? |
| Nausea/ vomiting | Control | 15 (17.86%) | 5 (8.47%) | 2 (12.5%) | 4 (22.22%) | 1 (9.0%) |
| | Experimental | 11 (10.9%) | 6 (9.37%) | 1 (5.88%) | 1 (5.26%) | 0 |
| | p | 0.256* | 0.889* | 0.953* | 0.305* | 1.000* |
| Bloating | Control | 11 (13.09%) | 12 (22.22%) | 1 (6.25%) | 3 (16.67%) | 1 (9.0%) |
| | Experimental | 8 (7.92%) | 8 (12.5%) | 0 | 1 (5.26%) | 0 |
| | p | 0.364* | 0.889* | 0.976* | 0.559* | 1.000* |
| Hunger | Control | 4.28 ± 0.90 | 4.75 ± 0.76 | 4.31 ± 1.25 | 3.94 ± 0.72 | 4.22 ± 1.39 |
| | Experimental | 2.84 ± 0.81 | 2.78 ± 0.63 | 3.41 ± 0.79 | 2.74 ± 0.99 | 2.22 ± 0.67 |
| | p | < 0.001** | < 0.001** | < 0.001** | < 0.001** | < 0.001** |
| Thirst | Control | 2.57 ± 0.65 | 2.32 ± 0.63 | 2.06 ± 0.57 | 2.72 ± 0.57 | 2.44 ± 0.53 |
| | Experimental | 2.4 ± 0.65 | 2.14 ± 0.56 | 1.82 ± 0.53 | 2.10 ± 0.57 | 2.00 ± 0.47 |
| | p | 0.069*** | 0.094*** | 0.221** | 0.003** | 0.156** |
| Flatulence | Control | 19 (22.61%) | 19 (32.2%) | 7 (43.75%) | 5 (27.78%) | 4 (44.44%) |
| | Experimental | 41 (40.59%) | 38 (59.37%) | 11 (64.71%) | 11 (57.89%) | 7 (77.77%) |
| | p | 0.014* | 0.005* | 0.396* | 0.135* | 0.342* |
| Defecation | Control | 12 (14.28%) | 6 (10.17%) | 6 (37.5%) | 2 (11.11%) | 2 (22.22%) |
| | Experimental | 26 (25.74%) | 18 (28.12%) | 9 (52.94%) | 8 (42.1%) | 6 (66.66%) |
| | p | 0.078* | 0.020* | 0.593* | 0.079* | 0.166* |
| General weakness | Control | 4.61 ± 0.71 | 3.36 ± 0.78 | 3.56 ± 0.73 | 4.22 ± 0.73 | 4.00 ± 0.67 |
| | Experimental | 2.56 ± 0.64 | 2.55 ± 0.71 | 2.12 ± 0.6 | 2.53 ± 0.61 | 2.89 ± 0.60 |
| | p | < 0.001** | < 0.001** | < 0.001** | < 0.001** | 0.006** |

Note. * Fisher z-transformation (according to Yates's correction).
** Wilcoxon Signed Rank Test.
*** Student's criteria.

times (p = 0.003) between the control and experimental groups. In the experimental group of patients, we observed a significant difference of 1.79 times (p = 0.014) and 1.84 times (p = 0.005) in flatulence (restoration of full intestinal motility) after LCE and LHR respectively. Defecation rate in the first postoperative day was statistically significant: in 2.76 times (p = 0.02) more often observed in patients after LHR.

After hunger assessment, where we received a statistically significant difference after all types of surgery, weakness was the next one. The weakness after LCE was 1.8 times (p < 0.001), after LHR — 1.31 times (p < 0.001), after LCFP — 1.68 times (p < 0.001), after LBI — 1.67 times (p < 0.001), and after LCI — 1.38 times (p = 0.006) stronger in the control group (Fig. 3).

Thus, we admit statistically significant difference between control and experimental groups in assessing of two important parameters: hunger and weakness. These two subjective parameters are included in the list of factors formulated by H. Kehlet [2], which do not allow fast recovery of patients' life quality after surgery and affect the prolongation of hospital stay. In the experimental groups after LCE and LHR, we associate fast recovery of intestinal motility with the absence of mechanical or saline bowel cleansing in patients in the preoperative period of these types of surgery, as it was after LBI and LCI. Although, we don't perform the bowel cleansing after LCFP. This may be due to the involvement of the esophagus and stomach during surgery, and to some extent provokes prolonged gastrointestinal paresis.

Guidelines ESPEN, based on an analysis of scientific research on perioperative nutrition of patients in general surgery and oncology, gives 27 recommendations, including preoperative use of liquid

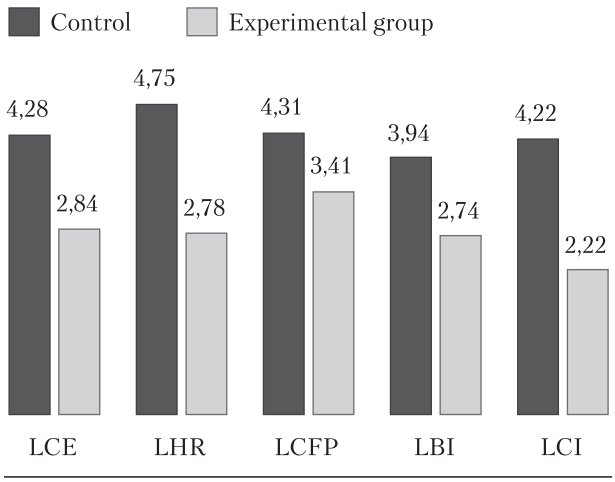



Figure 2. **Hunger in the first postoperative day**

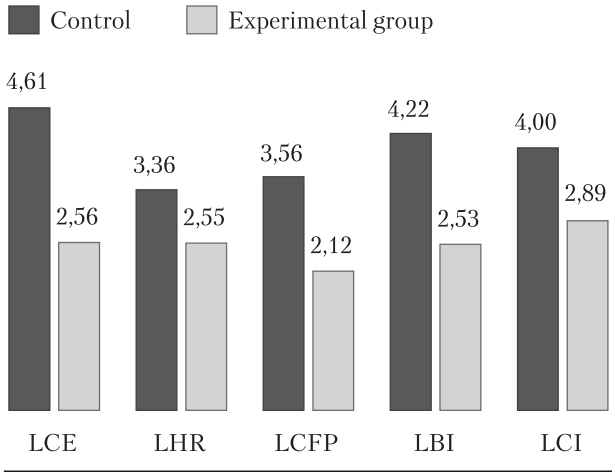



Figure 3. **Weakness in the first postoperative day**

carbohydrates, continuation of oral nutrition in the form of liquid mixtures in the first hours after surgery [6]. The daily requirement for energy is 25—30 kcal/kg, and for protein — 1.5 g/kg [12]. In our work, we follow all these recommendations for perioperative nutrition. Lobo et all. in 2009, based on MRI data of volunteers, proved that small amounts of liquid leave the healthy stomach in 60—90 minutes, so there is no need for long-term preoperative fasting [13]. Early continuation of oral nutrition is one of the main principles of ERAS and, in addition to decrease the level of postoperative complications, allows to speed up the recovery of patients and reduce the length of stay of patients in the hospital [14]. Early continuation of oral nutrition with special protein mixtures is also recommended after bariatric interventions. The level of protein requirement in obese patients in the postoperative period should be 60 g/day [6]. The only requirement for postoperative mixtures for bariatric patients is the absence of glucose as most of these patients have impaired glucose tolerance or type 2 diabetes. Therefore, we chose adapted glucose-free Nutridrink Protein (Nutricia) for the mentioned population of patients.

## Conclusions

There is no need in traditional durable preoperative fasting. Since the implementation of carbohydrate preoperative load into ERAS protocols there were no cases of regurgitation and asphyxia during tracheal intubation [6].

Early continuation (first hours after extubating) of oral nutrition does not affect the rate of digestive anastomoses complications [15, 16], does not cause discomfort to the patient, and decreases the risk of postoperative wound infection, decrease recovery time and therefore allows decrease the number of patients in the hospital.

In our research, early continuation of oral nutrition with protein-enriched sip feeding formula Nutridrink Protein significantly decreases hunger and general weakness in the early postoperative period, which allows quickly recovering patient to full life.

All above mentioned measures reduce the hospital system burden and saves money of health care facilities. It should be noted that only in combination with other postulates of the ERAS program perioperative nutritional support of surgical patients has a great chance of success.

### Declaration of interests

This work was supported by *Nutricia*.

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### Author contributions

Work concept and design, final approval of the article: O. Y. Ioffe; data collection and analysis: O. P. Stetsenko, M. S. Kryvopustov, T. V. Tarasiuk; responsibility for statistical analysis: M. S. Kryvopustov; writing the article: O. P. Stetsenko; critical review: Y. P. Tsiura, T. V. Tarasiuk

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# Нутритивна підтримка пацієнтів у загальній хірургії

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Сучасний етап розвитку хірургії, а саме малоінвазивних технологій, суттєво змінив уявлення хірургів про періопераційний період. До кінця XX ст. доопераційне та післяопераційне голодування було чи не найголовнішою умовою в плановій хірургії. Вважалося, що це дає змогу уникнути ускладнень як під час операції, так і в ранній післяопераційний період. H. Kehlet у своїй фундаментальній праці визначив чинник, що дає змогу пришвидшити відновлення пацієнта після хірургічної операції — відсутність доопераційного голодування.

**Мета** — оцінити ефективність нутритивної підтримки хірургічних пацієнтів у межах протоколів ERAS (Enhanced Recovery After Surgery) та ESPEN (European Society for Clinical Nutrition and Metabolism).

**Матеріали та методи.** Проаналізовано дані пацієнтів як після традиційної лапароскопічної холецистектомії (177 випадків), так і після однопортової трансумбілікальної холецистектомії (8). Серед лапароскопічних баріатричних втручань переважало класичне Roux-Y-шлункове шунтування (28). У 5 випадках проведено слів-резекцію шлунка, у 4 — міні-шлункове шунтування. Із 123 пацієнтів виконано лапароскопічні герніопластики: у 64 — TAPP при пахових грижах, у 59 — IPOM при післяопераційних вентральних та пупкових грижах, у 33 — лапароскопічна крурорафія та фундоплікація як з алопластикою, так і без неї. Для кожного виду оперативних втручань виділено дві групи — контрольну та дослідну. Обидві групи вели за протоколами ERAS, окрім нутритивної підтримки. За згодою пацієнтів до операції дослідна група отримувала повну періопераційну нутритивну підтримку згідно з локальними протоколами, контрольну групу вели за традиційною схемою — голодування 12 г до операції, замість протеїнових сумішей — питна столова вода в першу післяопераційну добу.

**Результати.** Виявлено статистично значущу різницю між контрольними та дослідними групами при оцінці двох важливих параметрів — відчуття голоду і відчуття слабкості. Після лапароскопічної холецистектомії відчуття голоду було в 1,5 разу нижче у дослідній групі ($p < 0,001$), після лапароскопічної герніопластики — у 1,7 разу ($p < 0,001$), після лапароскопічної крурорафії та фундоплікації — в 1,26 разу ($p < 0,001$), після лапароскопічного баріатричного втручання — в 1,43 разу, після лапароскопічних втручань на товстій кишці — в 1,9 разів. Після лапароскопічної холецистектомії сильнішим у 1,8 разу ($p < 0,001$) відчуття слабкості було у контрольній групі, після ЛГП — у 1,31 разу ($p < 0,001$), після лапароскопічної крурорафії та фундоплікації — в 1,68 разу ($p < 0,001$), після лапароскопічного баріатричного втручання — у 1,67 разу ($p < 0,001$), після ЛВТК — у 1,38 разу ($p = 0,006$).

**Висновки.** Традиційне тривале доопераційне голодування є недоцільним. У комплексі з іншими постулатами програми ERAS періопераційна нутритивна підтримка хірургічних пацієнтів має великий шанс на успіх. У нашій роботі раннє відновлення орального харчування значно зменшувало відчуття голоду та відчуття загальної слабкості в ранній післяопераційний період, що давало змогу швидше повернути пацієнта до повноцінного життя.

**Ключові слова:** прискорене відновлення після операції, періопераційний догляд нутритивна підтримка.

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# Effectiveness of the Erbisol® class in complex treatment of patients with liver cirrhosis

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Liver cirrhosis (LC) frequently results in severe complications, high mortality rate and disability in patients suffering from this disease, thus necessitating the study of its course, diagnosis and management. The principle of gradual elimination of pathological syndromes is fundamental in the treatment of LC. Complex therapy requires the use of medicines that act on the general links of pathogenesis. As LC causes damage to the cellular structure of the liver as well as interferes with the normal functioning of other organs and systems, it requires the prescription of medicines with metabolic and immunomodulatory properties. Experimental and clinical results of trials of *Erbisol* injections necessitated the study of their therapeutic properties in patients with LC. Immunomodulation, hepatoprotection and hepatoreparation play a crucial role in the management of LC.

**Objective** — to investigate the effectiveness of the *Erbisol*® class medications in complex treatment of patients with liver cirrhosis.

**Materials and methods.** The analysis of treatment outcomes in 57 patients with LC was carried out and is presented in this study. Patients were divided into two groups with 28 patients (15 males and 13 females) in the main group and 29 patients (18 males and 11 females) in the control group. All patients received a comprehensive basic therapy for the management of LC. The main group was also prescribed intramuscular injections of the *Erbisol*® class medicines (*Erbisol*® *Extra*, *Erbisol*® *Ultrapharm*) that were administered according to the manufacturer's instructions (Erbis Ukraine, https//erbisol.com.ua). Specific guidelines were followed during the examination of the patients. In both groups, patients with compensated LC had their liver function assessed according to the Child-Pugh scoring system. Their point scores were added and classified as class B: 8—9 points. All patients were distributed according to gender, age, duration of the disease and severity of the main syndromes. The effectiveness of treatment was evaluated based on clinical symptoms, severity, blood tests, elastography ultrasound and Doppler ultrasonography.

**Results.** The use of *Erbisol*® medicines significantly improved the dynamics of the clinical course of cirrhosis, relieved astheno-vegetative disorders, had a pronounced immunocorrective effect that was evidenced by changes in the ratio of serum protein fractions. In the main group, treatment outcomes were characterized by moderate regeneration of the liver parenchyma. It was confirmed by hemodynamic parameters and elastography data. The complex use of *Erbisol*® drugs helps to slow down and regress fibrosis, contributing to the favorable course of the disease.

**Conclusions.** Complex treatment with the *Erbisol*® class medications had a positive action on clinical and blood biochemical parameters and ensured a membrane-protective effect, regression of fibrosis, and improved hepatic blood flow.

**Keywords**
liver cirrhosis, management, hepatocytes, *Erbisol*® class medication, elastography.

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Liver cirrhosis (LC) is a life-threatening global health problem that is characterized by the formation of regenerative nodules due to different liver diseases [4, 7]. Many patients can progress to upper gastrointestinal bleeding (UGIB), hepatic encephalopathy (HE), hepato-renal syndrome and hepatocellular carcinoma (HCC) in the decompensated stage. Hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, and alcohol consumption are considered to be the major etiological factors of LC [1, 11, 14].

Liver cirrhosis (LC) frequently results in severe complications, high mortality rate and disability in patients suffering from this disease, thus necessitating the study of its course, diagnosis and management [2, 3, 10]. Liver cirrhosis is a serious, relatively prevalent, cause of global morbidity and mortality; recent estimates demonstrated that liver cirrhosis accounted for nearly 2.5 % of the total global deaths in 2017 — around 1.3 million deaths, ranking it as the 11th leading contributor to global mortality [6, 9, 12]. The distribution of liver cirrhosis shows notable ethnic and socioeconomic variations.

LC should be considered as a severe, progressive disease with systemic manifestations [7].

Until recently, liver cirrhosis was considered an irreversible process, which is manifested by «degradation» of the liver parenchyma and its replacement by collagen-rich tissues. Nowadays, most scientists consider fibrosis as a result of repeated damage and restoration of hepatocytes, and replacement by connective tissue — as a reparative process in response to chronic inflammation [4, 8, 17].

About 80.0 % of all diagnosed LC cases had an active course, and more than half of them were complicated with ascites. From 23.0 % to 43.0 % of patients passed away about one year after the onset of ascites. Early recognition and monitoring of liver cirrhosis are the cornerstones of optimal treatment outcomes and risk reduction in terms of complications observed in cirrhotic patients [6, 10]. The problem of surgical treatment and conservative therapy for LC has been comprehensively covered in the studies of many authors, however, surgical interventions are not effective enough, often entailing severe consequences [16]. Liver transplantation in LC effectively prevents the development of complications and, since 1980, has been excluded from the category of experimental operations. Nevertheless, Ukraine is experiencing certain difficulties in making this operation common in the treatment of patients with LC due to its high cost and the problems connected with organ donation [12, 15]. Implementation of the efferent methods allows producing syndromic effects on various pathogenetic factors that determine the activity of the pathological process [6, 13, 14].

Thereby, many issues, regarding the treatment tactics of LC, remain unresolved. The principle of gradual elimination of pathological syndromes becomes the main vector in the treatment of LC. Complex therapy in management of patients with LC requires drugs that act on the general links of pathogenesis. As LC causes damage to the cellular structure of the liver as well as interferes with the normal functioning of other organs and systems, it requires the prescription of medicines with metabolic and immunomodulatory properties [3, 8].

Experimental and clinical results of trials of *Erbisol* injections necessitated the study of their therapeutic properties in patients with LC. Immunomodulation, hepatoprotection and hepatoreparation play a crucial role in the management of LC.

In the pharmacological market of Ukraine there are original drugs of the *Erbisol*® class (*Erbisol*® *Extra*, *Erbisol*® *Ultrapharm*, *Erbisol*®) manufactured by Erbis Ukraine LLC (erbisol.com.ua). The drugs are composed of a complex of natural non-hormonal organic compounds, isolated from animal embryonic tissue, which contains glycopeptides, peptides, nucleotides, and amino acids. The immunomodulatory effect of these drugs is characterized by activation of macrophages of NK cells (CD3-/CD16/CD56$^+$) and T-killers (CD3$^+$/CD16$^+$/CD56$^+$), which have a high potential and destroy abnormal cells, thereby providing antifibrotic protection of the body [5].

Additionally, in patients with immunosuppression of T-cell immunity, the *Erbisol*® class normalizes the number of T-lymphocytes (CD3$^+$), T-helpers (CD4$^+$), cytotoxic T-lymphocytes (CD8$^+$), reducing the number and activation of B-lymphocytes. These drugs restore the balance of Th1 and Th2 cytokines by enhancing the production of interleukins (IL)-1, IL-2, IL-12, tumor necrosis factor α (TNF-α), and interferons (α, γ, β), which generally activate cellular immunity and suppress the production of IL-4 and IL-10. *Erbisol*® drugs activate hepatocyte repair processes, thus promoting liver regeneration, which is important in improving the course of the disease [5].

**Objective** — to investigate the effectiveness of the *Erbisol*® class medications in complex treatment of patients with liver cirrhosis.

## Materials and methods

The investigation is based on the analysis of treatment outcomes in 57 patients with liver cirrhosis, who were treated at the Kyiv Emergency Hospital from 2019 to 2021. Patients were randomly divided into two groups (the main group and the control group). The main group included 28 patients (15 males and 13

females). The control group consisted of 29 patients (18 males and 11 females). The age of patients ranged from 38 to 65 years (mean age 53.2 ± 1.2 years), mean disease duration — 5.6 ± 0.6 years.

The degree of liver failure was determined according to the scoring system suggested by C. Child, J. Turcotte (1964) and modified by R. Pugh et al. (1973). In the main and control groups, patients with compensated LC had their liver function assessed according to the Child-Pugh scoring system. Their point scores were added and classified as class B: 8—9 points respectively. Patients were distributed according to gender, age, duration of the disease, and severity of the main syndromes.

Chronic alcoholism accounts for 65 % of LC cases, being the most common cause of LC, viral hepatitis — 13 %, contact with pesticides — 14 %, cryptogenic cirrhosis — 8 %.

All patients (main and control groups) received a comprehensive basic therapy for the treatment of LC, which included infusions, aminoacids, saluretics, hepatoprotectors, glucose, vitamins, antioxidants, etc. For the treatment of ascites syndrome, the efferent methods were used and included staged treatment: laparocentesis, ascitoexfusion, ascitosorption-filtration, reascitoinfusion [2, 4]. The efferent treatments are performed at the department of extracorporeal detoxification.

During laparocentesis, withdrawal of ascitic fluid was performed into sterile containers. In order to achieve a higher concentration of ascitic fluid, it was necessary to remove residual water, electrolytes and low molecular weight compounds by using ultrafiltration with a multiFiltrate system. Immediately after ultrafiltration, the concentrate was sorbed on a hemosorbent for detoxification. *Extra*corporeally concentrated ascitic fluid was reinfused intravenously over one to three sessions. 1.0—1.5 L of concentrated ascitic fluid was injected in one session. The rate of reinfusion was 3—5 ml/min.

Plasmophoresis was performed on domestic blood fractions. Plasma exfusion was up to 1.0 to 1.4 L (average 1.2 ± 0.1 L) per operation. Replacement of plasma of concentrated ascitic fluid was performed at a rate of 1 : 1 or 1.0 : 1.5 in relation to the volume of exfused plasma, depending on the protein content in ascitic fluid concentrate [16].

The main group was also prescribed intramuscular injections of the *Erbisol*® class medicines (*Erbisol*® *Extra*, *Erbisol*® *Ultrapharm*) that were administered according to the manufacturer's instructions (*Erbis Ukraine*, https://erbisol.com.ua) (Table 1).

One treatment course lasts 22 days: 20 ampoules of *Erbisol*® *Ultrapharm* (U) + 40 ampoules of *Erbisol*® *Extra* (+).

All patients, who were admitted to the clinic, were examined according to a special algorithm, which included the study of complaints, medical history, objective examination data, and the results of laboratory, instrumental, radiological and ultrasonographic examination.

Elastography was performed on a Radmir Ultima scanner in the area of the right intercostal spaces using transabdominal convex (5 mHz) and linear (10 MHz) sensors for surface structures (3.5 MHz) sensor. The median value of these measurements characterized the liver parenchyma stiffness, and the result was expressed in kilopascals (kPa).

For interpretation of the results and staging of fibrosis, we referred to the study by L. Castera et al., according to which the level of fibrosis F0 corresponded to the value of elastography 5.8 kPa ≤ F1 ≤ 7.2 kPa (minimal changes), 7.2 ≤ F2 ≤ 9.5 kPa (moderate), 9.5 ≤ F3 < 12.5 kPa (significant), F4 ≥ 12.5 kPa (liver cirrhosis) [9]. In addition to general clinical blood tests and coagulogram, laboratory parameters of the functional state of the liver were studied. The immune status was also assessed at various stages of treatment, which included determination of plasma protein composition and immunoglobulins. Ultrasound Doppler flowmetry was used. The following parameters of hepatic blood flow were determined: artery diameter, blood flow velocity, portal vein was visualized so that the angle between the vessels and the sensor was less than 60°. The velocity of blood circulation in the portal vein and its diameter were measured during exhalation for 2—3 s [4].

This study evaluated the effectiveness of the *Erbisol*® class medicines in the treatment of patients with LC based on clinical symptoms, biochemical

Table 1. **Recommended regimen of drugs administration of Erbisol® Extra and Erbisol® Ultrapharm**

| Hours | Day | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 |
| 6:00—9:00 | | | | 2E | 2E | 2E | 2E | 2E | 2E | 2E | 2E | 2E | 2E | 2E | 2E | 2E | 2E | 2E | 2E | 2E | 2E | 2E |
| 21:00—24:00 | U | U | U | U | U | U | U | U | U | U | U | U | U | U | U | U | U | U | U | U | E | E |

Note. E — Erbisol® Extra (1 ampoule = 2 ml), 2E — 2 ampoules of Erbisol® Extra (4 ml); U — Erbisol® Ultrapharm (1 ampoule = 2 ml).

parameters, and the findings of shear wave elastometry and doppler flowmetry.

Informed consent was given by patients and the study was conducted in compliance with the Helsinki Declaration of 1975 and its revision in 1983.

Statistical processing was performed by using a licensed computer application program *Statistica (Statgraf* and *StatSoft)*. The data was entered and verified using *Microsoft Excel*. The quantitative data were expressed as mean and standard error of the mean. Student's t-test and Mann–Whitney U-test were used to analyze quantitative data. Normality of the data was assessed using Shapiro–Wilk test. A two-tailed $p \leq 0.05$ was considered statistically significant.

## Results

The findings of the study demonstrated that, in the main group, the *Erbisol*® class medicines significantly improved the dynamics of the clinical course of LC (Table 2), which was evidenced by reduced symptoms of astheno-vegetative disorders (weakness, fatigue and inhibition) and dyspepsia (flatulence, heaviness and pain in the right hypochondrium). In almost all patients, icteric skin and sclera were successfully treated. In contrast to the main group, after treatment, patients in the control group were still complaining of nausea, pain in the epigastric region and in the right hypochondrium ($p < 0.05$). In the control group, patients had yellowing of the skin and sclera ($p < 0.05$). Both subjective and objective signs of the disease after treatment indicate poorer treatment outcomes in the control group.

In patients, who received complex treatment with the *Erbisol*® class medication, the duration of dyspeptic and astheno-neurotic syndromes was significantly reduced. The duration of hyperenzymemia was decreased by 4 days and hyperbilirubinemia — by 3 days. Complex therapy helped reduce the average number of hospital bed days by 6.5 days.

These data demonstrate a positive effect of the *Erbisol*® class medications on the duration of clinical symptoms. The dynamics of the laboratory data shows that, in the main group, the liver synthesis and detoxification function started improving within the 1st week of treatment, while, in the control group, in most cases, these indicators did not improve by the end of treatment (Table 3).

Table 2. **Clinical and laboratory characteristics of the effectiveness of comprehensive treatment of patients with LC**

| Syndrome | Duration, days | |
|---|---|---|
| | Main group | Control group |
| Dyspeptic syndrome | 8.6 ± 0.6 | 10.8 ± 0.8* |
| Astheno-vegetative syndrome | 13.8 ± 1.2 | 17.6 ± 1.2* |
| Jaundice syndrome | 16.2 ± 1.8 | 19.2 ± 1.0 |
| Hyperenzymemia — ALT | 10.1 ± 1.3 | 13.5 ± 1.2* |
| Ascitic syndrome | 10.9 ± 1.1 | 19.2 ± 2.1** |
| Average bedday | 11.3 ± 1.6 | 17.8 ± 0.9* |

Note. Statistically significant difference: * $p < 0.05$; ** $p < 0.01$.

Table 3. **The main biochemical indicators of the functional state of the liver before and after treatment**

| Indicator | Norm | Main group | | Control group | |
|---|---|---|---|---|---|
| | | Before | After | Before | After |
| Total protein, g/L | 65—85 | 56.20 ± 0.85 | 63.40 ± 0.81 | 56.10 ± 0.72 | 57.6 ± 0.6* |
| Albumins, g/L | 35—50 | 22.50 ± 0.15 | 28.6 ± 0.2 | 22.6 ± 0.2 | 23.6 ± 0.2 |
| Total bilirubin, μmol/L | 8.5—20.5 | 57.22 ± 0.24 | 34.22 ± 0.24 | 57.12 ± 0.24 | 52.22 ± 0.24 |
| ALT, U/L | 4—40 | 89.2 ± 2.2 | 51.4 ± 2.4 | 90.4 ± 2.8 | 76.3 ± 2.6* |
| AST, U/L | 5—34 | 76.4 ± 1.8 | 41.2 ± 1.6 | 75.5 ± 1.6 | 48.3 ± 1.3 |
| GGTP, U/L | 8—54 | 83.4 ± 2.2 | 56.3 ± 2.1 | 82.4 ± 2.2 | 60.2 ± 2.1 |
| Thymol test, units | 0—4 | 4.9 ± 0.2 | 3.2 ± 0.3 | 4.9 ± 0.3 | 3.8 ± 0.2 |
| Alkaline phosphatase, U/L | 35—123 | 150.2 ± 4.6 | 128.6 ± 3.8 | 149.8 ± 4.4 | 130.6 ± 3.6 |
| Urea, mmol/L | 2.5—8.2 | 9.8 ± 0.2 | 7.8 ± 0.5 | 9.9 ± 0.4 | 8.4 ± 0.6 |
| PTI, % | 90—100 | 68.8 ± 1.2 | 88.7 ± 0.14 | 68.4 ± 1.3 | 69.1 ± 0.2 |

Note. * Statistically significant difference ($p < 0.05$) comparing with the main group after medical treatment.

Table 4. **Dynamics of elasticity index in patients with LC, kPa**

| Term | Main group | Control group |
|---|---|---|
| 1st day | 21.5 ± 1.6 | 23.4 ± 1.3 |
| 30th day | 20.7 ± 1.5 | 23.1 ± 1.2 |
| 3 month | 19.3 ± 1.3 | 22.9 ± 1.2 |
| 6 month | 16.6 ± 1.7 | 22.6 ± 1.2 |
| 12 month | 14.2 ± 1.1 | 21.2 ± 1.2 |

It should be noted that, in the main group, complex use of medications of the *Erbisol*® class allowed to achieve a pronounced immunocorrective effect, which was manifested by significant changes in the percentage of serum protein fractions. The percentage of albumin increased from 37.3 % ± 5.1 % to 51.3 ± 6.3 % ($p < 0.01$).The level of γ-globulins decreased from 37.5 % ± 8.3 to 22.6 ± 5.3 % ($p < 0.01$), and the albumin-globulin ratio (A/G) decreased accordingly, exceeding one. As shown by our study, in the main group, after treatment, patients with LC had a moderate regeneration of the liver parenchyma, which was confirmed by hemodynamic parameters and elastography. Immediate and long-term treatment outcomes were analyzed using the average elasticity index (Young's index) according to shear wave elastography (Table 4). The elasticity index (Young's index) was 21.5 ± 1.6 kPa in the main group, 23.2 ± 1.3 kPa in the control group, which corresponds to the fibrosis index (F4).

Analysis of fibrosis (Young's index) stiffness showed that patients, who received the *Erbisol*® class medicines, had moderate reduction in fibrosis for 12 months, and the study reached the F4-F3 limit.

Analysis of hemodynamic parameters of hepatic blood flow showed a relative improvement in the main group (Table 5).

There was a moderate decrease in the diameter of the portal vein by 2.0 ± 0.6 mm in 11 patients of the main group and by 1.1 ± 0.1 mm in 9 patients of the control group; improvement of the portal blood flow was observed in the main group. During the period of conservative treatment, a decrease in the amount of ascitic fluid was observed in 7 patients of the main group (in two patients, decompensated ascites became compensated) and in 2 patients of the control group. Surgical and efferent staged methods (laparocentesis, ascitoexfusion, ascitofiltration-sorption, reascitoinfusion) were used in 15 patients with refractory ascites (7 — in the main group and 8 — in the control group). In the main group, recurrence of refractory ascites occurred in 1 patient and in the control group — in 4 patients.

In the main group, 3 patients died: 2 patients had bleeding from varicose veins of the esophagus and 1 patient had progressive hepatic decompensation. In the control group, 4 patients died: 2 patients had bleeding from varicose veins of the esophagus, 1 — hepato-renal decompensation, and 2 — infectious complications.

It should be noted that, in the main group, the patients, who underwent several courses of *Erbisol*® drugs, had reduced symptoms of edema-ascitical and dyspeptic syndromes, which resulted in improving the quality of life of patients with LC. It indicates a pronounced membrane-protective effect of the complex use of drugs of the *Erbisol*® class, which helps to slow down and regress fibrosis, reduce the production of collagen in the liver, thus contributing to a favorable course of the disease.

## Discussion

Over the past 10 years, the prevalence of chronic hepatitis and LC has increased by 2.5 times in Ukraine. It should be noted that the main cause of death in patients with LC is liver failure and coma. That is why in decompensated patients with cerebral palsy (Child-Pugh class B, C), surgical treatment is risky. A comprehensive treatment aimed at improving liver function and reducing fibrotization by various methods can be the only effective option. Patients with LC need medications that have an

Table 5. **Parameters of hepatic blood flow before and after treatment**

| Indicator | Main group | | Control group | |
|---|---|---|---|---|
| | Before | After | Before | After |
| Blood flow velocity in the portal vein, cm/s | 21.3 ± 1.6 | 26.6 ± 1.2 | 22.3 ± 1.1 | 23.2 ± 1.5* |
| The diameter of the portal vein, sm | 1.44 ± 0.09 | 1.26 ± 0.07 | 1.43 ± 0.05 | 1.42 ± 0.07* |
| Volumetric blood flow velocity in the hepatic artery, mL/min | 135.3 ± 14.1 | 148.5 ± 13.9 | 135.7 ± 1.6 | 137.1 ± 11.2* |

Note. * Statistically significant difference ($p < 0.05$) comparing with the main group after medical treatment.

effect on the general links of pathogenesis. Various disorders causing damage to the liver cells as well as affecting other organs and systems in LC prompted the authors to use drugs with metabolic and immunomodulatory effects. Many approaches to treating LC have been proposed over the last decade, but none have shown a clear positive effect [2, 4, 16].

The results of this study indicate that drugs, domestically manufactured and known as the *Erbisol*® class, are promising for the treatment of LC, especially in patients with LC class A, B by Child-Pugh. However, these findings should be confirmed by larger clinical trials with a more homogeneous sample of patients. More studies on the effectiveness of the *Erbisol* class medications in the treatment of patients with cyrotic liver damage are required to determine its role in the management of various degrees of liver cirrhosis. Apparently, insufficient information on the effectiveness of the *Erbisol* class medications is largely due to the significant heterogeneity of the clinical variants of LC as well as lack of generally accepted recommendations on the dosage of the drug and the duration of the therapeutic course for this pathology. Nevertheless, the variety of biochemical and immunological effects determines the possibility of its prescription for almost any clinical form of liver cirrhosis. However, the effect on the histological characteristics of LC requires further study. Thus, by reducing liver damage, medications of the *Erbisol* class can prevent the development of liver failure. This explains their greater efficiency in compensated and subcompensated stages of LC, in which liver function is relatively preserved. The obtained results indicate that prolonged use (for 2 years) of the *Erbisol* class medications does not trigger any serious adverse reactions as they are well tolerated and safe.

## Conclusions

Complex treatment with the *Erbisol*® class medications has a positive effect on clinical and biochemical parameters, induces a membrane-protective effect, and improves hepatic blood flow, which results in a favorable course of the disease.

The study found that, within 6 and 12 months, the *Erbisol*® class medications used in the treatment of patients with LC significantly reduced ($p < 0.05$) the density of the liver parenchyma according to shear wave elastography, indicating a slowdown and regression of fibrosis.

No side effects were observed during the treatment with the *Erbisol*® class medications. The results of our research allow us to recommend the *Erbisol*® class medications for the treatment of patients with LC.

### Declaration of interests

The authors, who participated in this study, stated that they had no conflicts of interest regarding this manuscript.

### Author contributions

The contribution of all authors to this work is the same.

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# Ефективність застосування препаратів класу «Ербісол®» у комплексному лікуванні хворих на цироз печінки

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Необхідність вивчення особливостей перебігу, діагностики та лікування хворих на цироз печінки (ЦП) зумовлена розвитком тяжких ускладнень, високою летальністю і частою інвалідизацією хворих. Принцип поетапного усунення патологічних синдромів є основним у лікуванні ЦП. Комплексна терапія хворих на ЦП потребує застосування лікарських препаратів, які діють на загальні ланки патогенезу. Порушення клітинної структури печінки та інших органів і систем при ЦП є підставою для використання препаратів метаболічної та імуномодулювальної дії. Експерементальні та клінічні результати випробовувань препаратів класу «Ербісол®» зумовили необхідність вивчення їх лікувальних властивостей у хворих на ЦП, в яких імуномодуляція, гепатопротекція і гепаторепарація відіграють важливу роль.

**Мета** — дослідити ефективність використання препаратів класу «Ербісол®» у комплексному лікуванні хворих на ЦП.

**Матеріали та методи.** Проаналізовано результати лікування 57 хворих на ЦП. Пацієнтів розподілили на дві групи: основну — 28 пацієнтів (15 чоловіків та 13 жінок) і контрольну — 29 пацієнтів (18 чоловіків та 11 жінок). Усі пацієнти отримували комплексну базисну терапію ЦП. Основна група додатково отримувала внутрішньом'язові ін'єкції препаратів класу «Ербісол®» («Ербісол® Екстра», «Ербісол® Ультрафарм») за схемою, рекомендованою виробником («Ербіс Україна», erbisol.com.ua). Стадія компенсації хворих на ЦП за системою Чайлда-Пью становила 9—11 балів (клас В), відповідно у хворих основної та контрольної груп. Пацієнти в групах були співставними за розподілом статей, віком, тривалістю захворювання, ступенем вираженості основних синдромів.

Оцінювали ефективність лікування хворих на ЦП за клінічною симптоматикою, біохімічними показниками, результатами зсувнохвильової еластометрії та допплерофлуометрії.

**Результати.** Використання препаратів класу «Ербісол®» сприяло значному поліпшенню динаміки клінічного перебігу захворювання та зменшенню астено-вегетативних порушень, дало змогу досягти виразного імунокоригувального ефекту, про що свідчила зміна співвідношення білкових фракцій сироватки крові. В динаміці лікування хворих основної групи спостерігали помірну регенерацію паренхіми печінки, що підтверджено гемодинамічними показниками та даними еластографії. Комплексне застосування препаратів класу «Ербісол®» сприяє уповільненню та регресу фіброзу, що зумовлює сприятливий перебіг захворювання.

**Висновки.** Комплексне лікування хворих на цироз печінки, з використанням препаратів класу «Ербісол®», має позитивний ефект на клінічні та біохімічні показники, мембранопротекторну дію, сприяє регресу фіброзу, поліпшує печінковий кровоплин.

**Ключові слова:** цироз печінки, гепатоцити, «Ербісол®», еластографія.

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# Primary pancreatic lymphoma: a rare tumour that mimics pancreatic carcinoma. Clinical case

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Primary pancreatic lymphomas are extremely rare. Clinically, primary pancreatic lymphomas usually present with symptoms of pancreatic carcinoma. A localized and well-circumscribed tumour that replaces most of the pancreatic gland and compression of the blood vessels are radiological features of lymphoma, which are similar to pancreatic adenocarcinoma. Many patients are diagnosed with lymphoma after radical resection. It's a challenging clinical task for physicians, radiologists, and pathologists.

We report a case of primary pancreatic lymphoma that was confirmed by surgical resection. A 60-year-old woman came to the clinic with non-specific upper abdominal pain that lasted 8 weeks. Computed tomography (CT) scan showed a mass in the body of the pancreas, involving the superior mesenteric artery and the celiac trunk, and regional lymphadenopathy. Endoscopic ultrasound-guided fine needle aspiration of the pancreatic mass was performed. A morphological pattern indicated ductal carcinoma. The tumour board determined the treatment plan (chemotherapy) for the patient. The patient underwent 3 courses of GEMCAP chemotherapy in our hospital. A follow-up radiological exam showed no improvement. The chemotherapy regimen was changed to FOLFIRINOX. The patient underwent 6 courses of the FOLFIRINOX regimen.

A follow-up magnetic resonance imaging of the pancreas showed tumour regression by more than 90 % in comparison with the previous study. The patient underwent distal pancreatosplenectomy with standard lymph node dissection. Postoperative period was uncomplicated. These pathological results confirm the diagnosis of diffuse B-cell lymphoma.

**Conclusions.** This case shows that lack of tissue can make histological examination of FNA specimens challenging and mistakes can happen due to rare occurrence of primary pancreatic lymphomas.

**Keywords**
pancreatic lymphoma, pancreas, non-Hodgkin lymphoma.

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Primary pancreatic lymphoma is a rare tumour that accounts for less than 0.5 % of pancreatic tumours [1], and is frequently clinically misdiagnosed as pancreatic cancer. Overwhelming majority of patients are diagnosed with lymphoma only after invasive radical resection.

Out of the two main types of lymphoma (Hodgkin's and non-Hodgkin's lymphomas), non-Hodgkin's lymphomas more often invade extra lymphatic organs. Therefore, the most common histological type of pancreatic lymphoma is non-Hodgkin's lymphoma [7].

A localized and well-circumscribed tumour that replaces most of the pancreatic gland and compression of the blood vessels are radiological features of lymphoma, which are similar to pancreatic adenocarcinoma [3].

The prognosis of lymphoma is more favourable compared to adenocarcinoma (median overall survival: 53 months compared with less than 18 months) [2, 5].

EUS-FNA (Endoscopic Ultrasound-Guided Fine-Needle Aspiration) of the pancreatic lesion accompanied with advanced immunohistochemistry

are always perfect diagnostic tools that allow making a final diagnosis and avoiding unnecessary surgical intervention in the treatment of extranodal lymphomas. But in some cases, histological examination can be quite challenging [4, 6].

## Case Presentation

A 60-year-old woman without any significant medical history presented with non-specific upper abdominal pain that lasted 8 weeks. She was examined in the local clinic and underwent abdominal computed tomography (CT). A mass in the body of the pancreas, 45 mm in a greater dimension, completely involving SMA (the superior mesenteric artery) and the celiac trunk, regional lymphadenopathy and small liver cysts were found on contrast-enhanced abdominal CT. No signs of dilation of the pancreatic duct were found (Fig.1). Endoscopic ultrasound-guided fine needle aspiration of the pancreatic mass was performed. Cytological report showed signs of connective tissue with the presence of several epithelioid cells with signs of cytologicalatypia. Immunohistochemical report showed negative reaction for total cytokeratin, positive reaction for IMP3, and negative reaction for CD56. A morphological pattern and the results of immunohistochemistry indicated ductal carcinoma (Fig.2).

There were no pathological findings on EGDS (esophagogastroduodenoscopy). The patient was referred to our hospital with the diagnosis of pancreatic adenocarcinoma $cT_4N_0M_0$. The carbohydrate antigen 19—9 and CEA levels were not elevated. Magnetic resonance imaging (MRI) confirmed non-metastatic origin of liver lesions and the presence of the mass in the body of the pancreas (Fig. 3).

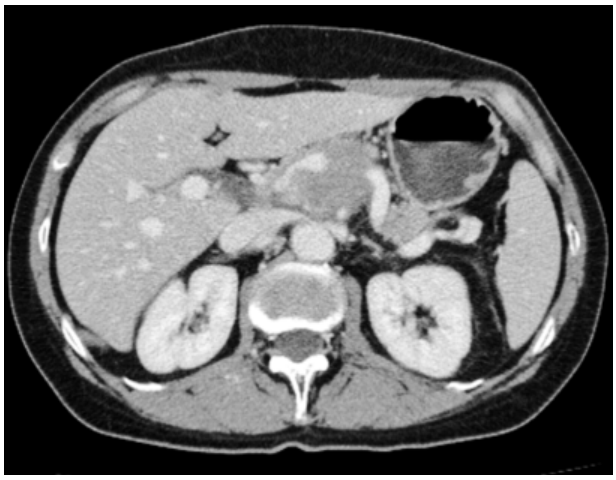

Figure 1. **CT (26/12/17). Abdominal CT findings: a 4.5-cm hypervascular mass with a rough border can be observed in the body of the pancreas. The mass semicirculary covers the celiac trunk, the superior mesenteric artery, common hepatic artery**

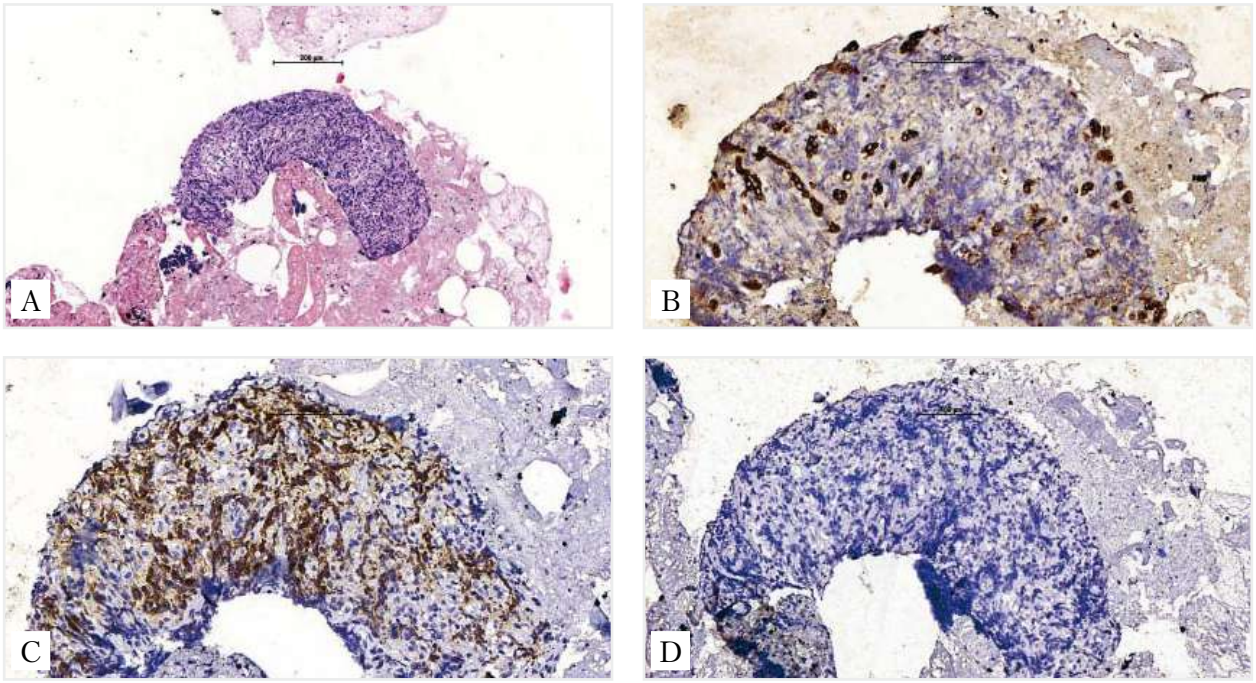


Figure 2. **Preoperative histology and immunohistochemistry:** A — FNA biopsy specimen. Some cells show a variable degree of cytological atypia. H&E (original magnification, × 70); B — pankeratin (clone CKAE1-AE3) highlights epithelial cells typical for ductal carcinoma. Differential with chronic pancreatitis is necessary (original magnification, × 150); C — IMP3 (which is positive in many malignancies) is positive in cells surrounding epithelial cells (original magnification, × 175); D — loss of expression of the CD56 which is normally positive in non-neoplastic ductal epithelium (original magnification, × 135)

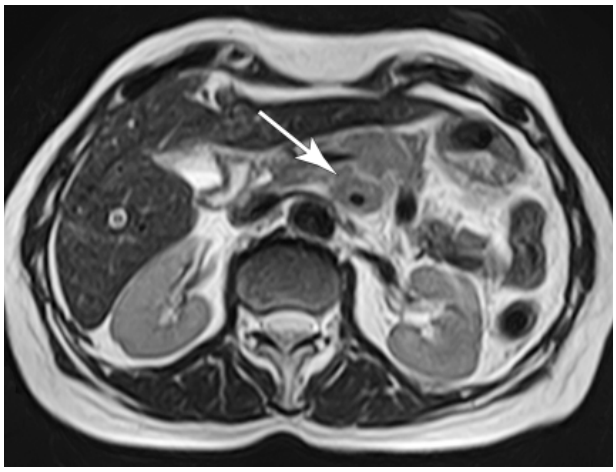

Figure 3. **MRI (20/01/18). MRI findings: The mass in the body of the pancreas that covers the celiac trunk and the common hepatic artery, liver cysts. After administration of a contrast, an increase of the MR signal in the arterial, portal, and venous phases was not visualized**

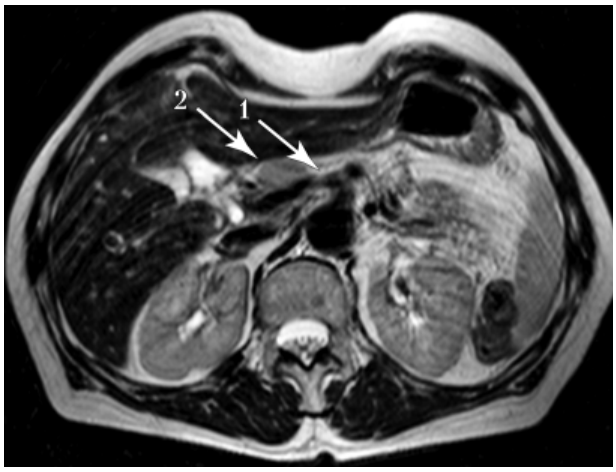


Figure 4. **MRI (31/08/18). MRI findings: In the isthmus of the pancreas, an area up to 2 mm enveloping the superior mesenteric artery (1) with a single lymph node of 12 groups (2) was determined**

The patient underwent 3 courses of GEMCAP chemotherapy in our hospital. A follow-up radiological exam showed no improvement. The chemotherapy regimen was changed to FOLFIRINOX. The patient underwent 6 courses of the FOLFIRINOX regimen.

## Control

Magnetic resonance imaging of the pancreas determined tumour regression by more than 90 % in comparison with the previous study with a single lymph node of 12 groups (Fig. 4). The MRI diagnosis was adenocarcinoma of the pancreatic body $cT_1N_1M_0$.

According to the decision of the tumour board, the patient was offered an operative treatment.

Physical examination revealed good nutritional status (BMI (Body mass index) — 22.67 kg/m$^2$). Laboratory tests at admission demonstrated normal serum amylase 38 U/L, bilirubin 0.1471mg/dL, albumin 38 g/L. The carbohydrate antigen 19—9 level was 9.41U/mL, CEA levelwas 5.71 ng/mL.

The patient underwent distal pancreatosplenectomy with standard lymph node dissection. Postoperative period was uncomplicated. The patient was discharged home on the 9th postoperative day.

Pathological findings: a tumour tissue consists of solid layers of atypical lymphoid cells with a moderate amount of eosinophilic cytoplasm and atypical nuclei containing granular chromatin. There is a large number of tumour cells mitosis figures. Such tumour structure most closely corresponds to a large cell lymphoma (Fig. 5). Tumour cells are positive for CD20 and bcl-2, negative for CD3, CD5, SOX-11, tdt, CD30, c-myc. Approximately 80 % of tumour cells were positive for the Ki-67 proliferation marker. These results confirm the diagnosis of diffuse B-cell lymphoma. Moreover, tumour cells were positive for FoxP1 and bcl-6, and negative for CD10. According to the Visco-Young algorithm, this phenotype is common for a lymphoma originating from activated lymphocytes (ABC subtype) (Fig. 6). The diagnosis of diffuse large B-cell non-Hodgkin's lymphoma (ABC subtype), stage IIEA, was made.

Multidisciplinary tumour board recommended a dynamic observation.

4 months after the operation, the patient underwent PET-CT (22/01/2019). There were no signs of disease recurrence.

Primary pancreatic lymphoma is quite challenging for diagnostics. There are no specific clinical features of primary pancreatic lymphoma. They are similar to those that appear in pancreatic carcinoma.

Similar radiological findings do not facilitate the diagnostic process. In this clinical case, there was more radiological data for pancreatic carcinoma such as invasive growth of the tumour, involving surrounding blood vessels.

Ca19—9 is the most useful tumour marker in pancreatic carcinoma [8], but can be misleading as it may also be elevated in other malignancies, particularly of the upper gastrointestinal tract, including primary pancreatic lymphomas, especially when biliary obstruction is present [4], and decreased in pancreatic adenocarcinoma. Without definitive pathology diagnosis, potentially curable conditions such as primary pancreatic lymphoma as well as

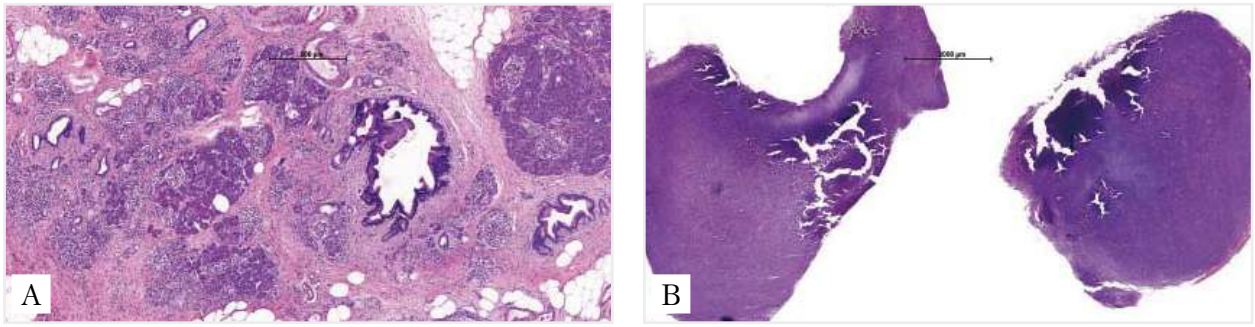


Figure 5. **Postoperative histology:** A — postoperative specimen shows no ductal adenocarcinoma H&E (original magnification, × 30); B — regional lymph nodes with lymphoma features H&E (original magnification, × 10)

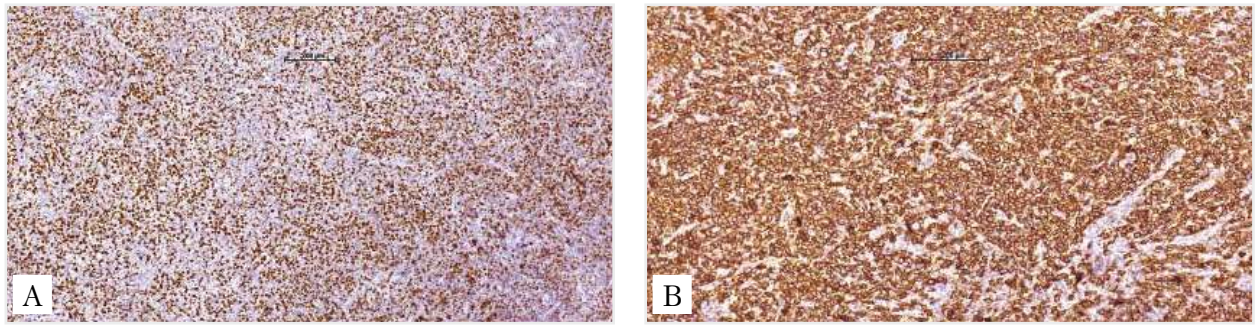


Figure 6. **Postoperative immunohistochemistry:** A — Ki-67 in lymphoma (original magnification, × 55); B — CD20 immunostain highlights B-cell lymphoma (original magnification, × 80)

other malignancies with more favourable prognosis may be misdiagnosed.

EUS-FNA of the pancreatic lesion with immunohistochemistry are great diagnostic tools when there is enough material for an advanced immunohistochemical panel [9]. This case shows that lack of tissue can lead to misinterpretation of the results as all necessary investigations can't be performed. The combination of factors — loss of expression of CD56 and strong expression of IPM3 — manifested ductal adenocarcinoma. Re-examination of the preoperative material after receiving the postoperative pathological report made it possible to suspect the presence of signs of lymphoma.

This case shows that histological examination of FNA specimens is challenging in case of lack of tissue and mistakes can happen.

## Declaration of interests

The authors of this case report declare that they have no competing interests. The authors declare that they have no affiliations with or involvement in any organization or entity with any financial interest or nonfinancial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter discussed in the manuscript. The authors of this case report declare that no financial support nor grant support has been received for the preparation of the manuscript.

## Ethics approval

The authors have no ethical conflicts to disclose.

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# Первинна лімфома підшлункової залози: рідкісна пухлина, яка імітує карциному підшлункової залози. Клінічний випадок

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Первинні лімфоми підшлункової залози зустрічаються вкрай рідко. Клінічно первинні лімфоми підшлункової залози зазвичай репрезентуються симптомами раку підшлункової залози. Рентгенологічні ознаки лімфоми, такі як локалізована, з чіткими краями пухлина, яка заміщує більшу частину підшлункової залози, компресія судин, подібні до аденокарциноми підшлункової залози. У багатьох пацієнтів з первинними панкреатичними лімфомами встановлюють діагноз після радикальної резекції. Це складне клінічне завдання як для лікарів і рентгенологів, так і для патогістологів.

Ми презентуємо випадок первинної лімфоми підшлункової залози, що виникла в тілі підшлункової залози, що було підтверджено після хірургічної резекції. Жінка 60 років звернулася в клініку з 8-тижневим неспецифічним болем у верхній частині живота. Комп'ютерна томографія підтвердила наявність утворення в тілі підшлункової залози, що залучає верхню брижову артерію та черевний стовбур з регіонарною лімфаденопатією. Виконано ендоскопічну аспіраційну біопсію пухлини тіла підшлункової залози під ультразвуковим контролем. Морфологічна картина була на користь протокової карциноми. Мультидисциплінарна комісія рекомендувала хворій пройти хіміотерапію. У нашій лікарні пацієнтці було проведено 3 курси хіміотерапії GEMCAP з негативною рентгенологічною динамікою. Схема хіміотерапії була змінена на FOLFIRINOX. Пацієнтка пройшла 6 курсів хіміотерапії за схемою FOLFIRINOX.

Контрольна магнітно-резонансна томографія підшлункової залози показала регрес пухлини більш ніж на 90 % порівняно з попереднім дослідженням. Пацієнтці було виконано дистальну панкреатоспленектомію зі стандартною лімфодисекцією. Післяопераційний період протікав неускладнено. Післяопераційні патогістологічні результати підтвердили діагноз дифузної В-клітинної лімфоми.

**Висновки.** Цей випадок показує, що гістологічне дослідження зразка, одержаного за допомогою тонкогольної аспіраційної біопсії, є складним у разі нестачі матеріалу і можуть статися помилки у діагностиці та лікуванні через рідкість первинних лімфом підшлункової залози.

**Ключові слова:** лімфома підшлункової залози, підшлункова залоза, неходжкінська лімфома.

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# Surgical management of a dog bite in a patient with comorbidities. Case study

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Millions of people worldwide require urgent medical care annually due to bites and injuries inflicted by wild or domestic animals. Injured patients most frequently suffer from extensive and deep wounds resulting in traumatic shock of different degrees. The extensive wounds are characterized by severe damage to fascial muscles, tendons, bones, major vessels and nerve trunks. Therefore, the management of patients attacked by wild or domestic animals includes the elimination of life-threatening conditions and the application of various techniques and methods of reconstructive plastic surgery and their combinations to preserve the injured areas of the body (most commonly limbs). In each particular case, the prognosis and the choice of the most effective reconstructive surgery technique for the treatment of a wound defect depend on the state of the deep structures of the injured limb. The «reconstructive ladder principle» ensures the selection of the most appropriate treatment strategy, as it focuses on the nature of the injury and the patient's overall health status, thus providing an adequate assessment of all possible surgical risks, general postoperative complications and challenges in wound healing. This algorithm allows prioritizing the most beneficial techniques from simple to difficult, as well as considering the «second line» methods. The «second line» methods are defined as simpler techniques that may be applied in case of some complications occurring after the administration of the primary method. Some additional difficulties may be experienced throughout the period of wound management in children and the elderly, in patients with complicated comorbidities and exacerbation of chronic diseases.

This article presents a case study of a patient undergoing the treatment for an extensive and deep bite wound that is complicated by acute coronary syndrome and severe cardiogenic shock in the early postoperative period.

**Keywords**
dog bite, a wound, microsurgical reconstruction, free flap, heart attack.

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Millions of people worldwide require urgent medical care annually due to bites and injuries inflicted by wild or domestic animals [2]. Injured patients most frequently suffer from extensive and deep wounds resulting in traumatic shock [5].

The treatment of extensive tissue loss remains a major surgical challenge, as it cannot be closed primarily.

The «reconstructive ladder principle» ensures the selection of the most appropriate treatment strategy [1, 8].

Some additional difficulties may be experienced throughout the period of wound management in the elderly with complicated comorbidities or acute exacerbation of chronic diseases [3].

This article presents a case study of a patient undergoing the treatment for extensive and deep bite wound that is complicated by acute coronary syndrome and severe cardiogenic shock in the early postoperative period.

## Case presentation

A 60-year-old male was admitted for a dog bite injury. He presented with extensive wounds on the 3/4 of the lower leg, massive blood loss and

third-degree traumatic shock. No signs of extensive damage to the muscles and tendons were observed. A portion of the tibia was exposed and the defect was 4 cm in length (Fig. 1). The patient's medical history revealed two heart attacks, severe atherosclerosis, and unstable angina pectoris. Clinically, the foot remained viable.

The surgical reconstruction using local skin flaps was proposed after the evaluation of the lower leg tissue condition that revealed a significant edema, an extensive wound, and multiple vascular traumas. Conservative treatment with negative pressure wound therapy (NPWT) was chosen for the lateral surface of the lower leg with the following skin grafting. Free anterolateral thigh (ALT) perforator flap was used for the wound coverage on the medial surface of the lower leg. After a washout procedure and debridement of the wound and two days of NPWT, the patient underwent the surgical reconstruction. The skin flap was anastomosed to the posterior tibial artery (the end-to-side technique) and the vein (the end-to-end technique). During the procedure, severe atherosclerosis was noted in the recipient's artery walls, as well as in the walls of the arteries on which the flap was formed. Before the skin flap coverage, the open tibia area was fenestrated (Fig. 2, 3).

Despite pathological blood vessel changes, a clinical observation showed adequate blood flow in the skin flap (Fig. 4).

Postoperative period was generally uneventful. The skin flap was viable. On the second post-operative day, the minor venous congestion was observed but it was not progressing (Fig. 5). The anastomosis functioning was confirmed via Doppler control.

On postoperative day 7, the patient complained of sharp deterioration of his health condition, persistent and intense chest pain. Acute coronary syndrome and severe cardiogenic shock were diagnosed. The patient was transferred to the specialized department of the other hospital for the management of the life-threatening conditions. Unfortunately, severe circulatory failure led to the skin flap necrosis. On day 7, on repeated admission to the Burn and Plastic Surgery Center the skin flap necrosis was reported (Fig. 6).

After the removal of the necrotic skin flap, the granulation tissue growth out of the fenestrated tibia holes was noted (Fig. 7).

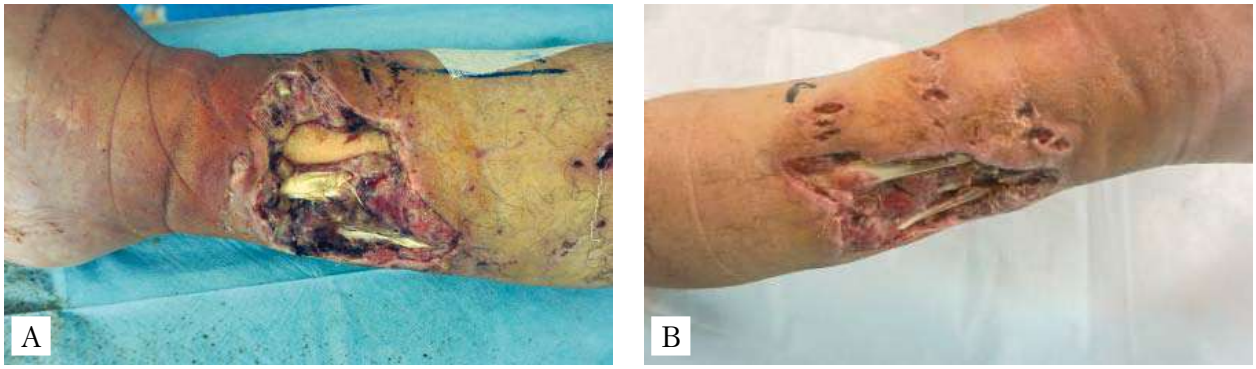


Figure 1. **Bite wound, day 5 after injury: medial (A) and lateral (B) lower leg surface**

Figure 2. **Anterolateral (ALT) flap harvesting**

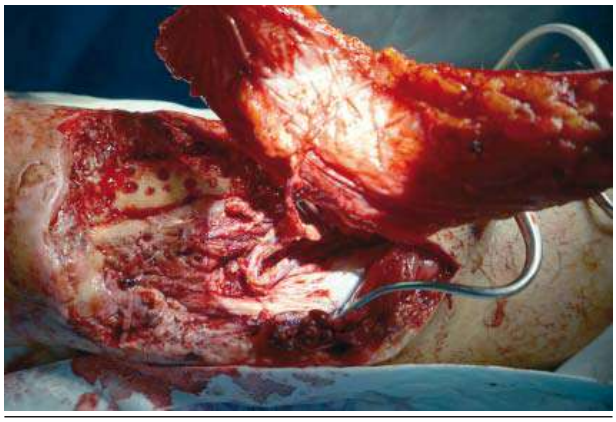

Figure 3. **ALT flap transferred to the wound area and connected to the blood flow. The open tibia area was fenestrated**

Figure 4. **Transferred ALT flap with adequate blood circulation at the end of the surgery**

Figure 5. **Postoperative day 3. The skin flap with venous congestion**

Figure 6. **Skin flap necrosis after cardiogenic shock**

Figure 7. **Medial lower leg wound after necrotic skin flap removal**


Figure 8. **NPWT of two lower leg wounds**

Taking into account the patient's overall condition and severe atherosclerosis of the blood vessels in the lower leg that had been diagnosed during a microsurgical operation phase, any variant of the skin flap reconstruction was excluded.

It was decided to choose the simplest but appropriate strategy of wound management — conservative treatment with NPWT (Fig. 8).

After 3 weeks of NPWT, the wounds were filled with granulated tissue indicating satisfactory conditions for skin grafting (Fig. 9).

Both wounds were covered with the skin grafts under local anesthesia. The lower extremity is fully functional. Walking ability is preserved (Fig. 10).

The treatment of extensive wounds, involving the extremities, is quite often significantly complicated by chronic diseases of the patients. In the elderly, comorbidities and severe traumas almost always mutually complicate each other, thus increasing the risk of severe postoperative and even life-threatening complications during any phase of the treatment.

Therefore, the most effective surgical treatment requires a lot of flexibility from a surgeon when it comes to choosing a suitable therapy, as well as considering the plan B measures. When patients have several wounds, it is acceptable to use several methods simultaneously. For the wounds with exposed bones, it is appropriate to use the skin flaps with their own blood supply, whereas for the partial thickness wounds without exposed bones, it may be sufficient to perform wound debridement and intensive NPWT with skin graft transplantation. For the coverage of exposed bones, it is recommended to consider the methods by their complexity, from the simplest to the most complex. However, when the application of the local

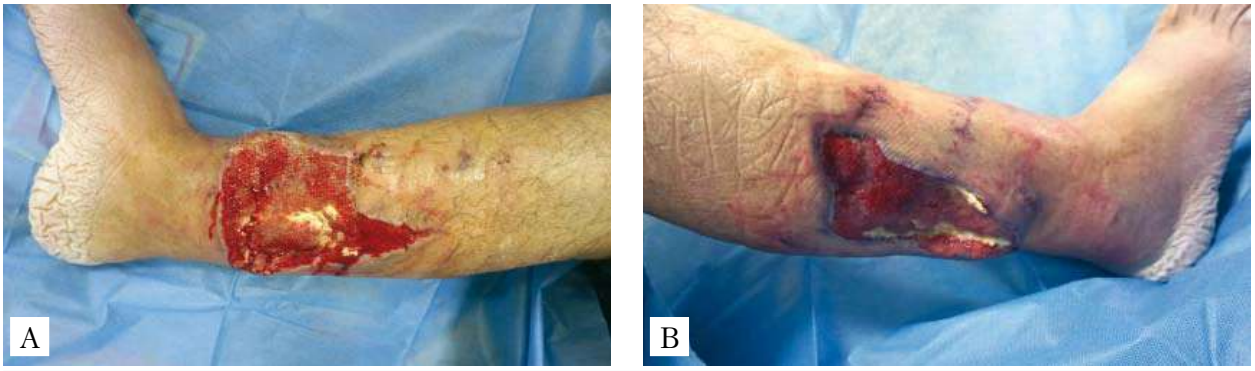


Figure 9. **Wounds after NPWT therapy filled with granulated tissue: medial (A) and lateral (B) surface**

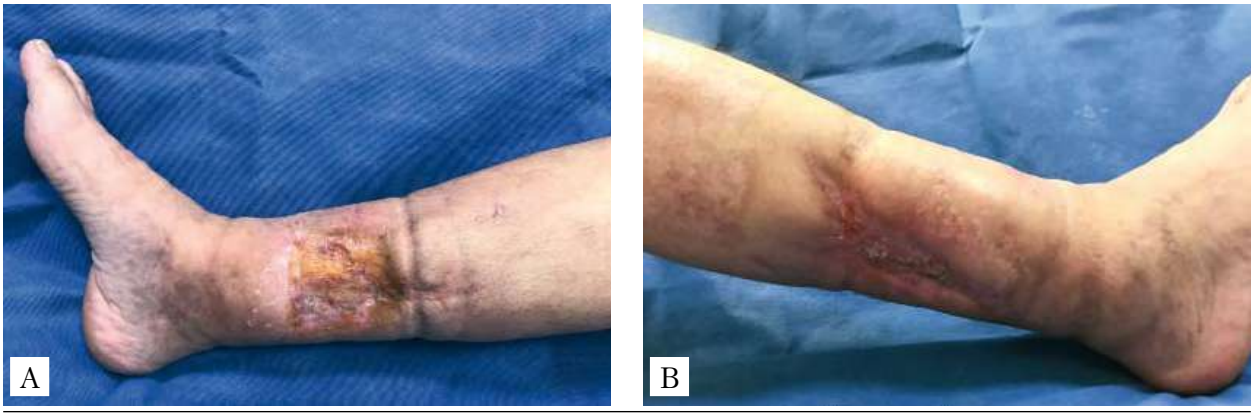


Figure 10. **Result of the wound treatment and skin grafting 1 month after operation: medial (A) and lateral (B) surface**

skin flaps is impossible, the skin flaps with microvascular anastomosis should be used. Even though this complex surgical technique poses the greatest surgical risks, it still remains more beneficial than a technically simpler cross-leg flap operation, since, in the elderly, the long-term maintenance of a lying position may trigger the exacerbation of heart problems, lung diseases or orthopedic conditions, thus significantly complicating proper medical care in the postoperative period. Nevertheless, the cross-leg flap operation using the contralateral leg as a recipient still remains the ultimate plan B even at highly advanced clinics [4, 7]. Prediction of possible complications and plan B should be an integral part of any microsurgery. For example, it is recommended to perform cortical bone fenestration for granulated tissue growth stimulation. It should be noted that the presence of chronic diseases (especially of the circulatory system) poses high surgical risks, leads to acute deteriorations, critical ischemic complications. Thus, the surgeons should not underestimate the potential of simpler methods for the treatment of extensive wounds. However, they should be ready to administer long-term wound treatment, which may produce less aesthetic result but will definitely preserve an extremity and its function [6].

## Conclusions

Even the clinics applying high tech microsurgical reconstructive methods cannot guarantee the intended result of the treatment due to the adverse effects exerted by local and general factors on wound healing. The specialists should be ready to apply plan B, which is a suitable surgical technique for each particular case.

### Declaration of interests

The authors declare that they have no conflicts of interest.

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None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this manuscript.

### Ethics approval and written informed consents statements

Treatment of the patient was conducted fully in accordance with the Helsinki Declaration.

Informed consent was obtained from all individual participants included in the study.

Treatment of the patient was not related to any of the clinical trials.

**Author contributions**

P. O. Badiul: the idea of the publication, surgery, writing the manuscript, photo documentation, review of the scientific literature; S. V. Sliesarenko: the idea of the publication, surgery, patient care, administrative and material support; O. V. Nosulko: surgery, patient care; O. I. Rudenko: surgery, patient care, writing the manuscript.

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# Хірургічне лікування укусу собаки у пацієнта із супутніми захворюваннями. Клінічний випадок

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Щорічно в світі до клінік невідкладної медицини звертаються десятки тисяч постраждалих з приводу укусів як домашніх, так і диких тварин. Дуже часто травмовані пацієнти мають значні за площею та глибиною рани та різний за ступенем тяжкості травматичний шок. Для великих укушених ран часто характерні тяжкі ураження фасцій, м'язів, сухожилок, кісток, магістральних судин і нервових стовбурів. Як наслідок, під час лікування постраждалих від нападу тварин нерідко доводиться усувати небезпечні для життя стани для збереження травмованих ділянок тіла (найчастіше — кінцівок), застосовувати різні техніки і методики реконструктивної пластичної хірургії та їх комбінації. Саме статус глибоких структур ураженої кінцівки найчастіше визначає прогноз у конкретному випадку та найперспективніший спосіб реконструктивного лікування ранового дефекту. Для вибору оптимальної тактики ведення укушених ран доцільно застосовувати «алгоритм реконструктивних сходинок». Його концепція враховує найімовірніші ризики під час оперативних втручань та післяопераційних ускладнень як з боку рани, так і щодо загального стану пацієнта, зумовлені характером ушкодження і актуальним статусом хворого. Зазначений алгоритм дає змогу обрати кращий із методів, розглядаючи їх за пріоритетом (від простішого до складнішого) та з урахуванням «резервних» методів. До останніх відносять простіші способи, які застосовують у разі появи ускладнень при використанні первинно обраного. Часто менеджмент пацієнта ускладнює дитячий або похилий вік, наявність складної супутньої патології, загострення хронічних захворювань під час лікування ран. Наведено випадок лікування великих глибоких укушених ран у пацієнта з виразною супутньою патологією.

**Ключові слова:** укус собаки, рана, мікрохірургічна реконструкція, вільний клапоть, інфаркт.

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# The effects of bariatric surgery procedures on the gut microbiota, features of genetically mediated predisposition to obesity, forecasting algorithms for surgical treatment outcomes. Literature review

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Obesity is one of the major challenges facing modern medicine in the 21st century. Medically complicated obesity cases lead to a significant deterioration in quality of life and are associated with excess morbidity and increased mortality. According to the WHO, more than 24 % of the world's population over 18 years of age is overweight. About 3.9 million people of working age died in 2018 due to obesity and its complications. Today, bariatric surgery is the most effective in treating obesity, as it allows achieving optimal metabolic outcomes. After bariatric surgery, the desired effect can be produced by the response of the intestinal microbiome to postoperative anatomical and physiological changes in the gastrointestinal tract.

**The aim** of this study was to conduct a comprehensive literature review and evaluate the effects of bariatric surgery on the human intestinal microbiome.

The literature review revealed a stable correlation between quantitative and qualitative characteristics of the intestinal microbiota and bariatric surgery, regardless of the type of a bariatric surgical operation. Roux-en-Y Gastric Bypass, Mini-Gastric Bypass and Sleeve Gastrectomy are the most commonly used bariatric operations in the world. The outcomes of these procedures show a sharp change in the proportion of different microbial phyla, including *Firmicutes*, *Bacterioides* and *Escherichia*, as well as changes in the gene expression parameters of these groups at different time periods after surgery.

An increasing number of the reported bariatric interventions worldwide necessitates the study of pathophysiological mechanisms of intermicrobial relationships, which can contribute to better outcomes of surgical treatment of obesity and the development of algorithms for predicting them.

**Keywords**
obesity, obese patients, Roux-en-Y gastric bypass, research, body mass index, gut microbiome, weight loss.

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In the 21st century, the global spread of obesity became pandemic. Obesity takes one of the highest positions in the rankings of causes of death from complications and factors associated with deterioration in the quality of life. It is one of the most challenging and urgent issues in world medicine.

According to the World Health Organization (WHO), obesity is defined as the excessive accumulation of adipose tissue in the human body, which results in weight gain and the development of chronic diseases that significantly impair quality of life. Obesity is recognized as a risk factor in the development of diseases such as hypertension, atherosclerosis, type 2 diabetes, non-alcoholic liver disease, colorectal cancer, hypercoagulation [56].

Obesity is one of the most challenging public health issues in Ukraine. According to the research conducted in 2012, 53 % of Ukrainians were overweight, out of which about 20 % were diagnosed with obesity, and their number is constantly increasing. According to the data presented by the WHO in 2016, 58.4 % of people over 18 years

were overweight and 25 % of adults were obese. In Ukraine, 48.9 % of the adult population were overweight in 1990 [56].

The continuously increasing number of obese people worldwide is strong evidence of its global spread which is associated with malnutrition and hypodynamics, constant psychological stress, neurological and endocrine disorders. In the highly developed industrial countries, including the United States, the United Kingdom, European countries, China, etc., there has been reported an increase in the prevalence of obesity both among adults and among children [39].

Obesity is an extremely mild disease to diagnose and one of the most difficult to treat. The condition is most commonly managed by diet therapy, lifestyle modifications, drug therapy and bariatric surgery, which is a leader among the methods of radical treatment of obesity.

Bariatric surgery is recognized by the world medical community as the most effective in treating obesity due to its low comorbidity rates and an ability to improve the quality of life. The effects of bariatric surgery on weight loss and comorbidity rates depend, among other factors, greatly on the intestinal microbiome, which is an important system, even an organ that plays a leading role in the regulation of lipid and glucose metabolism [13].

Nowadays, the most frequently performed surgical interventions in the world are Roux-en-Y Gastric Bypass, and Sleeve Gastrectomy. RYGB combines two powerful mechanisms of weight loss that are defined as restrictive and malabsorptive. The procedure includes the creation of a small (30—50 ml) gastric «pouch», which ensures the exclusion of the larger part of the stomach from the digestive process, and the formation of the Roux-en-Y anastomosis, which makes it impossible to pass food through the distal stomach, duodenum and proximal jejunum, and at the same time, doesn't block the entry of bile and pancreatic juices into the intestinal tract distal to an entero-entero anastomosis, thus ensuring a full digestive process. Sleeve Gastrectomy is an example of an isolated restrictive effect [4, 11]. A powerful metabolic effect is achieved due to the resection of the stomach along with the compulsory removal of its fundus and the formation of «sleeves» with a volume of 100—150 ml. The surgery reduces the amount of food stored and digested in the stomach by dozens of times as well as decreases the «satiety threshold» afferent impulses in response to stomach fullness. After surgery, weight loss is also achieved due to the total reduction in the synthesis of ghrelin, a hormone that induces hunger, resulting from the removal of the gastric fundus, which is the main location of APUD-system cells that synthesize this hormone [9].

There are 3 types of surgical treatment for obesity. The restrictive surgical procedures include Laparoscopic Gastric Banding and Sleeve Gastrectomy. The malabsorptive surgical procedures are known as biliopancreatic diversion and jejunoileal bypass, but they are not used today in view of their low efficacy and severe complications. The combined type of surgical treatment, which is most often used due to its potent metabolic effect, comprises Roux-en-Y Gastric Bypass and biliopancreatic bypass [47].

Due to postoperative anatomical changes and some surgical peculiarities of the operated areas, there are numerous functional changes within the gastrointestinal tract: a hypertrophy of the villi of the small intestinal mucosa in response to malabsorption; nodular lymphoid hyperplasia of the small intestine in response to low amounts of chyme and hydrochloric acid and an increase in the amount of infectious agents in the intestinal lumen; an increased reactivity of APUD-system due to lack of mechanostimulation and chemostimulation in the gastrointestinal tract; a hypertrophy of muscle fibers in the intestinal wall, as a reaction to insufficient mechanical processing of chyme in the stomach and changes in the intestinal microbiota, which is one of the least studied issues [12].

A microbiota is a «community» of microorganisms that live, reproduce, and function in a particular environment. Among the whole set of microbes that function in the human body, it is common to distinguish commensals, symbiotes and pathogens. Another concept related to the classification of microorganisms that colonize the human body is the microbiome. A microbiome is a pool of genetic material of microorganisms that live in a specific environment and function in conjunction with the biological, physical and chemical laws of this «area» [15].

It is known that the human body is colonized by about 1.4 billion microbial organisms, of which about 90 % colonize the gastrointestinal tract. More than 35,000 bacterial families are classified in the colon, among which the most common are *Firmicutes* (including gram-positive species *Clostridium*, *Eubacterium*, *Ruminococcus*, *Butyrivibrio*, *Anaerostipes*, *Roseburia*, *Faecalibacterium*, etc.), *Bacteroides* (including gram-negative species *Bacteroides*, Porphyromonas, *Prevotella*, etc.), *Proteobacteria* (including gram-negative *Enterobacteriaceae*), *Actinobacteria* (with gram-positive *Bifidobacterium*), *Fusobacteria*, and *Verrucomicrobia* (including *Akkermansia*, etc.). These families, groups and species represent more than 90 % of the total colon microbiome. The most important, in terms of the proper functioning of the

colon, microorganisms are obligate anaerobes from the *Bacteroides*, *Eubacterium*, *Clostridium*, *Ruminococcus*, *Peptococcus*, *Peptostreptococc*us, *Bifidobacterium* species, and *Fusobacterium*, and facultative anaerobes such as *Escherichia*, *Enterobacter*, *Enterococcus*, *Klebsiella*, *Lactobacillus* and *Proteus* [1, 18].

Presently, some fundamental theses on the functioning of the intestinal microbiome are known. One of the most important discoveries in this field of science is the so-called microbial genome (MG), which, similarly to DNA molecules in the nuclei of human cells and fingerprints, is unique to each person [31]. The microbial genome is the totality of all genetic material synthesized in the nuclei of all microbial cells present in the human gastrointestinal tract. It is able to affect the synthesis of enzymes and proteins that are directly and indirectly involved in the metabolism of trace elements, nutrients and their derivatives that are absorbed or partially metabolized in the intestinal lumen. According to «Iuliu Hatieganu» University of Medicine and Pharmacy, Cluj-Napoca, Romania, the number of substances encoded by genes of microbial origin, which regulate (directly or indirectly) the process of intra-intestinal metabolism in the human body, is 6—9 % of the total number [37].

Adults have the intestinal microbiome as one of the most variable organs of the human body, so it shows a very high rate of changes in microbial homeostasis and intercolonial relationships in response to changes in external or internal state of the «host organism». One of the most powerful triggers for such changes is a change in a diet. Changes in the microbiome occur 4 days after the start of the diet, regardless of its aim — a decrease or increase in body weight [11].

Some genetic and environmental factors may alter the etiopathogenesis of obesity. The scientists have also concluded that the intestinal microbiome has a significant effect on energy metabolism, fat and carbohydrate metabolism, which affects the processes leading to obesity and its consequences. The researchers report that obese people have less variability in intestinal microorganisms than patients with normal body mass index (BMI), as well as the inability of microorganisms that colonize the large intestine to produce enzymes that metabolize fats and fatty acids [32].

In any environment, there are some differences in body weight among individuals. These variations are partly the result of genetic factors. The idea that obesity may have a genetic component is not new, given that it has long been known that obesity is often a familial pathology [12, 19]. In fact, some studies have shown that children's BMI strongly correlates with parental obesity. The children whose both parents are obese have a higher risk of the development of obesity compared to the children with parents who do not suffer from this pathology. However, it is difficult to distinguish in family studies whether this correlation is the result of genetic predisposition or environmental factors. In part, this issue could be addressed by studying twin or foster children by providing evidence of genetic influence on BMI. A meta-analysis of 31 twin studies showed that for adults, the variation in BMI due to genetic differences ranges from 47 % to 80 % [44]. More recent study by Silventoinen et al. [30] presented analysis of 87,782 pairs of twins and their parents and concluded that genetic factors play an important role in increasing BMI. According to these data, studies of adopted children have shown no reliable link between their body weight and obesity of their parents. These studies have shown that the BMI of adopted children is strongly correlated with biological parents, and less with foster parents [20].

It is known that genes contribute to differences in body weight within a single population. Interestingly, some genes identified as causing obesity in rodent models [2] have also been determined as contributing to severe obesity in humans. Nonsyndromic monogenic forms of obesity are the result of mutations in one gene and affect ~5 % of the population. These mutations in loss of function are rare and usually cause differences in eating behavior and parameters of energy homeostasis. The major parts of these mutations have been identified in the genes LEP (leptin synthesis), leptin receptor (LEPR), melanocortin-4 receptor (MC4R) and pro-opiomelanocortin (POMC). And a recent study has discovered a deletion of the POMC gene with a 12 % allele frequency in Labrador Retrievers, which affects their body weight and food behavior, showing the importance of genetically mediated changes in leptin/melanocortin parameters for the obesity phenotype [16].

In turn, polygenic obesity is the most common form of obesity in modern society, where the environment contributes to weight gain due to the availability of large amounts of food and lack of physical activity. With the development of technology and the completion of the Human Genome Project, our knowledge of the genetic basis of obesity has increased significantly in recent years. Several studies have identified more than 100 loci in the human genome associated with BMI when comparing groups of people with normal weight and obesity. The first locus that is undoubtedly associated with obesity by approach of the World Gene Association (GWA), was a gene associated with mass and obesity (FTO).

Subsequent GWA studies and meta-analyzes have identified a number of options associated with widespread obesity. The latest GWAS meta-analysis have identified 97 BMI-associated loci (56 of which were new) in a study of 339,224 European adults, representing 2.7 % of BMI variation [19].

It is known that obese patients have quantitative changes in the families of colon microbes, namely, a decrease in the number of *Bacteroides* and an increase in members of the *Firmicutes* family. The scientists have noted that a diet rich in fatty acids leads to the development of fatty liver disease, visceral obesity, and an increase in the number of *Bacteroides* against the background of declining *Firmicutes* population among intestinal microbiomes. Some studies, refuting all previous claims, show that there is no relationship between weight gain and the volume of *Bacteroides* and *Firmicutes* [8].

Some investigations suggest that the microbiota, as a large organ and a huge cluster of genetic material, plays a significant role in the development of metabolic syndrome and obesity. However, there is limited evidence of the behavior of the intestinal microbiome in the case of BMI ≥ 30, as the vast majority of microbiome studies have been performed with people who have a BMI ≤ 30 [26].

A study conducted by a team of scientists, including endocrinologists, nutritionists, gastroenterologists at the University of Malaga, Spain [44] examined fecal samples from 28 obese patients who underwent surgery using RYGB and SGE techniques. Patients received only surgical treatment using these techniques, and therefore they were divided into two groups: 1a — patients after RYGB; 2a -patients after SGE. All patients were examined 3 weeks before surgery and 3 months after surgery. The results were contradictory. There was a significant difference in the characteristics of bacterial colonies of the intestine after the use of two different methods of surgical treatment of obesity. The researchers concluded that despite the extremely short postoperative period, the intestinal microbiome changed significantly in both groups of patients, so the adaptive capacity of the intestinal flora was extremely high, and that was caused not by weight loss but by dynamic replacement of some clusters of microbes by others. Changes in intraintestinal pH in response to surgery indicate the likely impact of surgical treatment of obesity on the microbiome [10, 41].

In 2018, J. Aron-Wisnievski et al. from the Institute of Microbiology and Nutrition filled some gaps in the knowledge of the intestinal microbiome. In the course of their research, they found that different behaviour patterns of intestinal microorganisms, namely gene expression of proteins involved in lipid metabolism, principles of colony formation, growth rate and death of opportunistic pathogens and «beneficial» flora, are dependent on the «microbial gene richness» (MGR). This gene significantly correlates with the incidence of cardiovascular and metabolic diseases in obese patients [3].

The study, based at the Pitié-Salpêtrière Hospital Obesity Unit in Paris, involved 61 women with a BMI ≥ 35 kg/m$^2$ who were offered bariatric intervention, namely RYGB. On dividing into two cohorts, including women with and without MGR, and in the absence of episodes of antibiotics within 3 months before the study, and anamnestic data on acute gastrointestinal diseases, patients were examined for many parameters, namely: anthropometric data, clinical and biochemical blood profiles, a lipid profile, a glucose tolerance test, as well as DNA sequencing of fecal samples for the formation of quantitative indicators of microbial colonization of the intestine, and determination of serum MGR. These indicators were studied during several visits: one week before RYGB, 1, 3 and 12 months after the intervention. The results showed that 75 % of observed and operated women with BMI BMI ≥ 35 kg/m$^2$ had a high level of MGR in serum one week before RYGB. One year after bariatric obesity correction, MGR levels decreased in most patients, and lipid and glucose profiles showed significant improvement, pointing at a direct effect of bariatric surgery on the evolution of intestinal microflora in response to malabsorption [23].

A series of studies of the intestinal microbiome of laboratory mice were conducted at Iuliu Hatieganu, University of Medicine and Pharmacy, Cluj-Napoca, Romania. The researchers formed two cohorts: mice, which from birth to the time of the study had no external effects on their own microbiome, and were raised in conditions as close as possible to natural. And the 2nd group of mice, grown in the most comfortable conditions for weight gain, but a week before the experiments they were transplanted feces from mice of the first group. As a result, it was found that mice from the 1st cohort showed an increase in body weight by 42 %, despite the lack of food, and mice in cohort N 2 gained about 60 % of the initial weight. Analyzing these data, we can assume that in cases of adaptation to stressful conditions, the intestinal microbiome influences body weight more than a diet itself [58].

In the course of this study, it was found that in sterile raised mice, a deficiency of 4 nutrients, namely vitamin A, iron, folic acid and zinc, provokes the breakdown of groups of microorganisms characteristic of humans. For example, a lack of vitamin A in

the diet leads to the growth of colonies of *Bacteroides vulgatus*, a deficiency of vitamin $B_{12}$ encourages the growth of *Faecalibacterium prausnitzii* and *Roseburia*, resulting in a decrease in the number of *Escherichia* coli. There has also been a reduction in the colonies of *Firmicutes* and *Bacteroidetes* in response to reduced production of antioxidant nutrients (vitamins C and E), and at the same time the formed «gap» in the microbial ecosystem has been filled with *Shigella*e and *Salmonella*e microbes [54]. This study was confirmed by E. O. Verger and J. Aron-Wisnewsky, who analyzed the results of micronutrient deficiency in patients 1 year after RYGB [11, 54], and by D. Ciobârcă et al., who also analyzed changes in the intestinal microbiome in terms of deficiency of micronutrients during the postoperative period after bariatric surgery [13].

The simultaneous study conducted at Iuliu Hatieganu, University of Medicine and Pharmacy, Cluj-Napoca, Romania evaluated the effects of bariatric surgery on the intestinal microbiosystem. Analysis of the long-term effects of RYGB and gastric resection on the microbiota consisted of fecal mass transplantation both from operated human patients 9 years after surgery and from obese people to non-obese laboratory mice. Two weeks after transplantation, laboratory mice-recipients of feces of operated patients gained $46 \pm 7.3$ % less weight than mice-recipients of feces from obese people, under exactly the same living conditions and diets [20].

M. Osto et al. at the University of Veterinary Physiology in Zurich studied the effects of bariatric treatments for obesity, namely RYGB, on the intestinal microbiome of rats. The RYGB method was chosen because of its effectiveness in weight loss, reduction of hyperglycemia, and changes in postprandial hormonal reactions [40, 57].

Analysis of the intestinal microbiota from fecal samples taken from rats and humans after RYGB shows a decrease in colonies of microorganisms from the groups *Firmicutes* and *Bacteroidetes*, which, according to the scientists from the Institute of Veterinary Physiology, plays a significant role in postoperative weight loss and changes in metaprandial and postprandial fats [7].

For the study, there were selected 16 male rats, acclimatized in the conditions of individual living at a temperature of $21 \pm 2$ °C, with an unlimited amount of food and water during a week. Out of 16 individuals, two groups were randomly selected. The first group underwent RYGB surgery and the second group underwent laparotomy with gastrostomy and gastrojejunostomy (control group). A group of 8 rats underwent a classic RYGB with the formation of biliopancreatic and alimentary loops and a common canal about 25—32 cm long. A similar approach was applied in the control group, which had gastrostomy and gastrojejunostomy performed. In both groups, the survival rate after surgery was 93.7 % (15 out of 16 patients underwent surgery) [7, 9].

The operations resulted in a significant weight reduction in the rats, which underwent RYGB, compared with the control group. The study demonstrated that the volume of bacterial colonies in the alimentary and biopancreatic loops in RYGB-transferred rats was significantly higher than the volume of bacteria in the small intestine of control rats. For groups of microbial organisms, there was an increase in the *Bifidobacterium* and Lacto*bacterium* groups, and a decrease in the *Firmicutes* and *Bacteroidetes* groups. The scientists believe that the exclusion of the proximal segment of the small intestine from the digestive process has a major impact on the microbiocenot, which is most likely a decisive factor causing changes in the intestinal microbial system as humoral agents are produced in the proximal small intestine. Additionally, these changes are independent of changes in body weight. The experiments did not reveal a plausible relationship between quantitative or qualitative changes in the microbiota and changes in body weight. Therefore, the conclusion is obvious — changes in the intestinal microbiome do not seem to occur due to weight change, but due to cessation or change in the regulation of postprandial humoral agents [49]. A similar study was conducted by Y. Shao et al., who proved identical changes in the microbiome in response to changes in the anatomy of the gastrointestinal tract of rats [22].

An experiment involving laboratory rats was performed at the Department of Medical Microbiology, Utrecht University Medical Center, Utrecht University, and Surgery Department, Catharina Hospital Eindhoven. Fourteen rats that had previously been kept on a specific diet to provoke morbid obesity (an increase in body weight by an average of $44.4 \pm 6.2$ %) were involved and examined to determine the microbiological patterns of colonization of their colon. From the 14 rats, 9 were selected, which were operated by RYGB and Sleeve Gastrectomy (6 and 3, respectively), the others represented the control group. Out of 9 operated rats, 3 died from postoperative complications, and six others showed a steady decrease in body weight by an average of $36.0 \pm 2.7$ %, without correlation with surgery type. Five unoperated rats included in the control group underwent fecal microbiota transplantation, which resulted in an average weight loss of $25.7 \pm 2.3$ %. To sum it up, the effectiveness of surgical treatment of

morbid obesity significantly depends on the microbiological component [48]. The analogical experiment conducted by Y. Kang et al. showed similar results [29].

In 2018, at the Department of Public Health, the University of Auckland in New Zealand, there was found a close correlation between changes in the gut microbiome after RYGB and SG and type II diabetes regression, which was confirmed in the R. Murphy et al. study [17]. The method of research was DNA typing of fragments of the microbial genome obtained from fecal samples. The study involved 14 patients of different sex and age suffering from morbid obesity and type II diabetes. Patients were randomly divided into two groups of 7 patients in each. 1 year after surgery, 100 % regression of hyperglycemia was achieved (HbA1c within 4.8 ± 1.1 %) without drug compensation in both groups [32]. The DNA study of microbial genome fragments in fecal samples resulted in a sharp increase in *Firmicutes* and *Actinobacteria* genetic material and a decrease in *Bacteroidetes* from RYGB patients, and a decrease in *Bacteroidetes*-specific genetic fragments of patients after gastric tube resection. Patients in both groups (namely 12 out of 14) showed an increase in the presence of *Roseburia* genome in the fecal samples. Conclusion: patients who underwent RYGB showed more significant functional and quantitative changes in the intestinal microbiome than patients after sleeve gastrectomy [49].

A study at the Hvidovre Clinic in Denmark highlights the metabolic effects of surgery and their impact on the microbiome of patients who participated in the experiment. The study included 13 people (5 men and 8 women), who were selected according to the following criteria: age over 20 years; BMI ≥ 40 kg/m$^2$, or BMI ≥ 35 kg/m$^2$ and comorbid conditions in the preoperative period, such as type II diabetes mellitus and/or hypertension; method of surgical treatment — RYGB. Patients were examined in two directions — metabolic parameters, studied by pre- and postoperative blood serum, and fecal microbiome, namely its quantitative and qualitative changes, and all patients followed a specially designed, individual diet during 3 months, which provoked weight loss by an average of 8 %. Thus, from the 13 patients in the experiment, seven had type 2 diabetes mellitus, one had impaired glucose tolerance, and five had normal pre- and postprandial serum glucose levels, respectively. Biomaterial collection for fecal microbiome was performed three times — 3 months before surgery, the day before surgery and one year after surgery [21].

Microbial DNA was extracted from 200 mg of each portion of frozen faeces using the Illumina HiSeq 2000 apparatus. On average, 77 % of the genetic material was organized into the genetic catalog of each patient with subsequent interpretation and grouping according to the Kyoto Encyclopedia of Genes and Genome. It allowed grouping the genetic patterns of microbial families of fecal microbiocenosis quantitatively and qualitatively and determining the biological reality of the experiment [19].

As a result, there was a 100 % change in the qualitative and quantitative pattern of the microbiome. 10 patients did not have statistically significant changes in the microbiome after a course of diet therapy, and three patients had an increase in *Lactobacilli*, Actynomyces and *Escherichia coli*, respectively. In contrast, in all samples taken 1 year after surgical treatment of obesity, there were statistically significant ($p \geq 0.05$) changes in the microbiome, most noticeable in the Actynomyces, *Proteobacteria*, *Klebsiella pneumoniae*, and *Enterococcus faecalis* groups. Considering the outcomes of surgical treatment in terms of changes in metabolic parameters, 5 patients had a positive effect in the form of a decrease in plasma glucose by an average of 1.4 ± 0.4 mmol/L and 8 patients had no significant metabolic effect after surgery. Summing up the results of the described experiment, it can be concluded that obese patients (BMI ≥ 40 kg/m$^2$) with comorbid conditions had quantitative and qualitative changes in the intestinal microbiome during the postoperative period after RYGB, and statistically significantly ($p \geq 0.05$) improved tolerance to glucose during postoperative period [3, 51].

Various authors describe changes in the intestinal microbiome, especially after restrictive bariatric surgery. The study, which involved 110 operated patients who underwent gastric sleeve resection, showed a significant increase in total microbial quantity and genetic representation of the microbial flora of the colon within 3 months after SG, which lasted from 1 to 2 years. In contrast, R. Murphy et al. [16] did not find any significant changes in the intestinal microbiota of 13 patients within 3 months after SG, but observed an increase in the number of colonies of *Roseburia intestinalis* associated with glycemic reduction for all 13 patients [17].

The scientists at the Department of Medical Microbiology, Utrecht University Medical Center, Utrecht University, and I. Ulker and H. Yildiran, Faculty of Food Hygiene, Ankara, Turkey, studied the change in microbiome of patients after surgical treatment of obesity. In the postoperative period, 2 major factors influencing the variability of intestinal microbiome patterns were identified: changes in food behavior and malabsorption. The researchers also identified several microbiological

patterns, so-called enterotypes, that can be observed depending on the diet followed by patients after bariatric surgery. For example, an enterotype with a prevalence in the microbial population of the *Prevotella* family is formed when a person follows a diet rich in carbohydrates. The enterotype, where Bacterioides predominate, is more usual for the so-called Western diet, which is rich in animal proteins and fats [53].

The Department of Upper GI Surgery, Beaumont Hospital, Ireland was the first to create a model that allows, by selecting several criteria, determining the optimal method of surgical treatment of obesity. In other words, the decision-making model is a mathematical, programmable process aimed at choosing the most effective, in terms of metabolic effect, as well as the most beneficial treatment strategy [34].

Researchers Y.- C. Lee and W. L.Wu searched for a decision-making model for bariatric treatment of obesity. They analyzed the outcomes of 3 types of surgery, including RYGB, SG (sleeve gastrectomy) and OAGB (one-anastomosis gastric bypass/mini-gastric bypass), in terms of the number and severity of complications, objective clinical and metabolic improvements and a change in the patient's quality of life [57].

The simulated analysis of the decisions made was carried out after the creation of special software TreeAge Pro Software 2019, which reproduced a virtual «reference patient», based on a five-year analysis of 9757 operated patients. The reference patient is a mathematically calculated virtual human model, objective and clinical data of which is a statistical sample of all analyzed patients, and this patient was a woman with a BMI—40.1 kg/m$^2$, aged 40 years, with concomitant type 2 diabetes. The international scale QALY (quality adjusted life years) was also developed, which is based on 2 main criteria — the lifespan and the quality of life. One point on the QALY scale is one year of an ideal life.

The findings showed that RYGB received an average of 3.47 points on the QALY scale, OAGB — 3.65 points and SG — 3.80 points over a 5-year period. In terms of metabolic effect and the number and severity of complications, the leader among all interventions was RYGB, after which the metabolic and clinical effect was 86 % (22.0—88.5 %), OAGB — 71.8 % (60.0—95.7 %) and SG with a result of 75.3 % (52.0—86.4 %).

Based on the statistical calculations of the analyzed parameters, the researchers found that the highest efficiency in terms of the probability of achieving metabolic effect and quality of life in the postoperative period was RYGB (probability — 80.0 % (69.0—89.9 %)), which was slightly inferior to OAGB (probability — 75.9 % (69.0—93.0 %)) and SG (probability — 72.2 % (55.0—95.5 %)). However, the decision-making strategy modeled on the TreeAge Pro Software 2019 platform showed that OAGB, which was statistically significantly different from RYGB, should be the method of choice in the treatment of a «reference» patient [6].

## Conclusions

Obesity, as a global pandemic, requires both a comprehensive approach to treatment and modern solutions. Bariatric surgery plays a crucial role in the treatment of obesity and the elimination of its comorbidities. This review of the literature shows that bariatric surgery and the elimination of metabolic disorders are closely related to changes in the intestinal microbiome. However, it is not clear yet whether these changes in the intestinal microbiome lead to an improvement in the patient's metabolic status, and whether the microbiome in the postoperative period corresponds to the average concept of «healthy microbiome». Discovering the exact correlations between changes in the microbiome after bariatric surgery is a complex and long-term process and opens new strategic directions for the treatment of obesity and its associated conditions, as well as predicts the effectiveness of the chosen surgical treatment.

### Declaration of interests

The author declares no conflicts of interest.

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# Вплив баріатричних методик лікування ожиріння та його коморбідних процесів на стан кишкової мікробіоти, особливості генетично-опосередкованої схильності до ожиріння, прогнозування результатів хірургічного лікування. Огляд літератури

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У XXI ст. ожиріння є однією з найбільших проблем сучасної медицини, оскільки це захворювання і його ускладнення призводять до значного погіршення якості життя людини та є чинником ризику розвитку багатьох патологічних процесів і смерті. За даними ВООЗ, понад 24 % населення світу віком понад 18 років мають надлишкову масу тіла. Близько 3,9 млн осіб працездатного віку померли в 2018 р. унаслідок ожиріння та його ускладнень. Нині золотим стандартом лікування хворих на ожиріння є баріатрична хірургія, яка має доведену ефективність (оптимальний метаболічний ефект). Один із механізмів, що дають змогу досягти бажаної мети після баріатричних операцій, — реакція кишкового мікробіому на зміну анатомії та багатьох фізіологічних процесів шлунково-кишкового тракту.

Проведено аналіз світових літературних джерел для визначення зв'язку між баріатричною хірургією та змінами в кишковому мікробіомі людини. Виявлено стійкий зв'язок з кількісними та якісними характеристиками кишкової мікробіоти незалежно від різновиду баріатричної операції. Результати операцій, які найчастіше виконують у світі (Roux-en-Y Gastric bypass, mini-gastric bypass, рукавна резекція шлунка), демонструють різку зміну співвідношення мікробних кластерів, переважно *Firmicutes*, Bacterioides та *Escherichia*, а також параметрів експресії генів зазначених груп мікроорганізмів у різні періоди після операції.

З огляду на збільшення кількості баріатричних втручань у світі актуальним є вивчення патофізіологічних механізмів взаємозв'язків між мікроорганізмами для поліпшення результатів хірургічного лікування ожиріння та розробки методики їх прогнозування.

**Ключові слова:** ожиріння, пацієнти з ожирінням, шлункове шунтування по методиці Roux-en-Y, дослідження, індекс маси тіла, кишковий мікробіом, зниження ваги.

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