ISSN 2786-5584 PRINT
ISSN 2786-5592 ONLINE

Ukrainian
Peer-Reviewed Scientific
and Practical Medical Journal

GENERAL SURGERY

1 (4) | 2023

ЗАГАЛЬНА ХІРУРГІЯ

Cryo-assisted resection of primary breast cancer en bloc

Multimodal approach to pain management in thoracic surgery

Keystone flaps in reconstruction of defects resulting from shrapnel and mine-explosive injuries

Ukraine NOW ua

WWW.GENERALSURGERY.COM.UA

VIT-A-POL PUBLISHING COMPANY

ISSN 2786-5584 PRINT
ISSN 2786-5592 ONLINE
DOI 10.30978/GS

Bogomolets National Medical University
Національний медичний університет імені О. О. Богомольця

Ukrainian
Peer-Reviewed Scientific and Practical Medical Journal

1 (4) | 2023

GENERAL SURGERY

ЗАГАЛЬНА ХІРУРГІЯ

Український рецензований науковий спеціалізований медичний журнал

Founded in May 2021
Qpuarterly journal

Заснований у травні 2021 року
Виходить 4 рази на рік

The journal is registered as a professional edition of scientific research in the field of medicine and approved as a «B» list journal by the Ministry of Education and Science of Ukraine
Order of the Ministry of Education and Science of Ukraine No 1166 as of December 23, 2022, Appendix 3

Журнал включено до Переліку наукових фахових видань України з медичних наук. Категорія «Б»
Наказ МОН України № 1166 від 23.12.2022 р., Додаток 3

Indexed in | Журнал індексується в міжнародних наукометричних базах та каталогах
Index Copernicus, CrossRef, Vernadsky National Library of Ukraine, Google Scholar, OUCI, Scilit, WorldCat

Kyiv | VIT-A-POL LLC | 2023

Editor-in-Chief
Susak Y. M. (Ukraine)

Deputy Editor-in-Chief
Ioffe O. Y. (Ukraine)

Editorial Board
Badyul P. O. (Ukraine), Dihtyar V. A. (Ukraine), Dronov O. I. (Ukraine), Druzhyna O. M. (Ukraine), Dubrov S. O. (Ukraine), Haberal M. (Turkey), Havrylyuk A. M. (Ukraine), Horbatyuk O. M. (Ukraine), Ioffe O. Y. (Ukraine), Keck T. (Germany), Khomenko I. P. (Ukraine), Khomiak I. V. (Ukraine), Khranovska N. M. (Ukraine), Kolosovych I. V. (Ukraine), Kopchak K. V. (Ukraine), Korpan N. (Austria), Lapshyn H. (Germany), Levytskyi A. F. (Ukraine), Liubich L. D. (Ukraine), Oliynyk O. V. (Ukraine), Plaudis H. (Latvia), Rybalchenko V. F. (Ukraine), Skivka L. M. (Ukraine), Sliesarenko S. V. (Ukraine), Strik M. (Germany), Tsema I. V. (Ukraine), Unukovych D. (Sweden), Yarema R. R. (Ukraine)

Executive Secretaries
Markulan L. Y. (markulan@ukr.net)
Teterina V. V. (vikateterina@ukr.net)

Головний редактор
Сусак Я. М. (Київ)

Заступники головного редактора
Іоффе О. Ю. (Київ)

Редакційна колегія
Бадюл П. О. (Дніпро), Дігтяр В. А. (Дніпро), Дронов О. І. (Київ), Дружина О. М. (Київ), Дубров С. О. (Київ), Haberal M. (Туреччина), Гаврилюк А. М. (Львів), Горбатюк О. М. (Київ), Іоффе О. Ю. (Київ), Keck T. (Німеччина), Хоменко І. П. (Київ), Хомяк І. В. (Київ), Храновська Н. М. (Київ), Колосович І. В. (Київ), Копчак К. В. (Київ), Корпан М. М. (Австрія), Лапшин Г. В. (Німеччина), Левицький А. Ф. (Київ), Любич Л. Д. (Київ), Олійник О. В. (Київ), Plaudis H. (Латвія), Рибальченко В. Ф. (Київ), Сківка Л. М. (Київ), Слєсаренко С. В. (Дніпро), Strik M. (Німеччина), Цема Є. В. (Київ), Unukovych D. (Швеція), Ярема Р. Р. (Львів)

Відповідальні секретарі
Маркулан Л. Ю. (markulan@ukr.net)
Тетеріна В. В. (vikateterina@ukr.net)

Founders
Bogomolets National Medical University
VIT-A-POL limited liability company

Certificate of state registration
KB No 24849-14789P granted May 7, 2021

Approved for printing by the Academic Council of Bogomolets National Medical University
Protocol No 8 signed March 30, 2023

Засновники
Національний медичний університет імені О. О. Богомольця
Товариство з обмеженою відповідальністю «ВІТ-А-ПОЛ»

Свідоцтво про державну реєстрацію
КВ № 24849-14789Р від 07.05.2021 р.

Рекомендовано Вченою радою Національного медичного університету імені О. О. Богомольця
Протокол № 8 від 30.03.2023 р.

Publishing
VIT-A-POL limited liability company
Office 3, 19a Academician St. Yefremov, Kyiv, 03179
Tel. +38044 298-00-60. E-mail: vitapol3@gmail.com
Certificate of publishing business entity
DK No 4757 granted August 05, 2014

Project manager Bernyk O. M.
Translation and editing Holik O. V.
Design Mamchych V. S.

Signed for printing March 31, 2023
Circulation 500 copies
Printed by FOP Hordukova I. E.
20, Pryvokzalna street, Kamyanets-Podilskyi
(USREOU code 2228230489)

Printed on acid-free paper

Видавець
Товариство з обмеженою відповідальністю «ВІТ-А-ПОЛ»
03179, м. Київ, вул. Академіка Єфремова, 19а, оф. 3
Тел. (44) 298-00-60. E-mail: vitapol3@gmail.com
Свідоцтво суб'єкта видавничої справи
ДК № 4757 від 05.08.2014 р.

Менеджер проєкту Берник О. М.
Переклад та редагування тексту Голік О. В.
Комп'ютерна верстка Мамчич В. С.

Підписано до друку 31.03.2023 р.
Наклад 500 прим. Ум. др. арк. 7,67
Друк ФОП Гордукова І. Є.
м. Кам'янець-Подільський, вул. Привокзальна, 20
(Код ЄДРПОУ 2228230489)

Надруковано на безкислотному папері

Advertisers are responsible for the content of their advertising materials.

Articles are published under a Creative Commons Attribution-NoDerivatives 4.0 International License (CC BY-ND 4.0)

Відповідальність за зміст рекламних матеріалів несе рекламодавець.

Статті у журналі публікуються на умовах ліцензії CC BY-ND 4.0

© *2023* Bogomolets National Medical University
© *2023* VIT-A-POL limited liability company

© *2023* Національний медичний університет імені О. О. Богомольця
© *2023* Товариство з обмеженою відповідальністю «ВІТ-А-ПОЛ»

BIOGRAPHIES

БІОГРАФІЇ

ORIGINAL RESEARCH

ОРИГІНАЛЬНІ ДОСЛІДЖЕННЯ

CASE SERIES

СЕРІЯ ВИПАДКІВ З ПРАКТИКИ

REVIEWS

ОГЛЯДИ

UDC 929 Ishchenko:616-051](477)
DOI http://doi.org/10.30978/GS-2023-1-4

ISSN 2786-5584 PRINT
ISSN 2786-5592 ONLINE

Professor Ivan Mykolayovych Ishchenko — Heracles of Ukrainian medicine

The article focuses on the professional and scientific path of Professor Ivan Mykolayovych Ishchenko. He was a leading Ukrainian surgeon, a renowned scientist, an accomplished teacher, and a great humanist who formed the ideology of surgical science. Professor Ishchenko defined and developed promising directions for scientific research in the fields of military field surgery, urology, traumatology, neuro- and thoracic surgery, and tissue transplantation. His scientific interests included the surgical treatment of diseases of the biliary tract, liver, and stomach as well as theoretical and practical issues of anesthesia administration.

Happiness self finds the way to strong spirit!
Indian proverb

Ivan Mykolayovych Ishchenko was a leading Ukrainian surgeon, a renowned scientist, an accomplished teacher, and a great humanist who «breathed» medicine and inspired others with his hard work and commitment. For him, work was a mental and vital necessity and the only conceivable form of existence. His professional and moral development took place mainly under the influence of the scientific schools of such outstanding surgeons as M. M. Volkovich, E. H. Chernyakhivskyi, and O. P. Krymov. This created favourable conditions for determining the scientific and physiological direction of his research. Professor Ishchenko was one of the leaders in clinical surgery and helped form its ideology. He defined and developed promising directions for progressive scientific research in the fields of military field surgery, urology, traumatology, neuro- and thoracic surgery, and tissue transplantation. His scientific interests included the surgical treatment of diseases of the biliary tract, liver, and stomach, as well as theoretical and practical issues of anesthesia administration. Professor Ishchenko wrote more than 100 scientific works, including 3 monographs and 2 textbooks. All of his scientific works stand out for their comprehensiveness and academicism.

The professional path of Professor Ishchenko was not only difficult because of his intensive work but also distressing due to the period of general repression. It should be noted that the scientist witnessed the key historical events of the 20th century, including revolutions, wars, and regime changes, which could not but influence his outlook.

Ivan Mykolayovych Ishchenko was born on June 22, 1891 in the village of Pustovarivka, Skvyr district, Kyiv region.

After he finished his training at the Kyiv medical school, Professor Ishchenko entered the medical faculty of St. Volodymyr University and graduated in 1917. Due to his remarkable academic achievements, he received a recommendation from the Academic Council of the university regarding his participation in scientific research. However, Professor Ishchenko began his medical career as a surgeon and a military doctor. He made his way from a junior resident, head of the surgical and urological department, consultant surgeon, and chief surgeon of the Kyiv Military Clinical Hospital, where he worked until 1953, to the chief surgeon of the Kyiv Military District. Ivan Mykolayovych Ishchenko devoted almost 40 years of his professional activity to the military medical service.

During the Second World War, Professor Ishchenko was the chief surgeon of the South-Western Front and managed the surgical service of the fronts in the South-Western direction. With the

introduction of military ranks for doctors, he was awarded the military rank of major general of the medical service in 1943.

Ivan Mykolayovych Ishchenko spent a lot of time in the combat zones at the front. He also visited battalion and regimental medical centres, medical stations, and field mobile hospitals to check on the work of surgeons, give them instructions, and teach them the techniques of surgical operations. In the most difficult and complicated cases, he operated on patients. During the war, Professor Ishchenko performed more than three thousand operations, including 500 on the head and 200 on the spinal cord, blood vessels, and peripheral nerves. He dealt with issues related to military field surgery, including gunshot wounds to the brain and peripheral nerve fibers. Professor Ishchenko investigated the impact of cerebral pressure in head injuries on vital bodily functions. The beginning of this scientific research was his dissertation for the degree of Doctor of Medical Sciences «Materials for the Pathogenesis and Treatment of Acute Cerebral Pressure Syndromes of Traumatic Origin», which was brilliantly defended by him in 1941. Professor Ishchenko studied the pathogenesis of sympathetic reflex dystrophies and proved the effectiveness of novocaine blockade of the sinoarotid zone in a number of diseases and in brain damage syndrome. He confirmed the need for early surgical interventions for gunshot injuries to peripheral nerves. In the treatment of causalgia syndrome with damage to the nerves of the upper limbs, he suggested extirpation of the second thoracic sympathetic node, and in the case of damage to the nerves of the lower limb, the second lumbar node. In his scientific works, he described the technique for performing gangliotomy, rhizotomy, and periarterial sympathectomy.

Professor Ishchenko clarified the segmental sensitive innervation of abdominal organs in studies on the use of a paravertebral novocaine block.

In his work «Neurological Basis in Surgical Diagnosis of Diseases of Abdominal Organs» (1928), Ivan Mykolayovych Ishchenko described in detail the significance of the Zakharyin-Ged zones for diagnosing acute diseases of the abdominal organs.

Professor Ishchenko combined military service with the work of a teacher and a scientist, joining teaching activities at the Kyiv Medical Institute in 1920 and the faculty surgical clinic in 1927. In 1934, for his significant achievements in practical medicine, science, and education, he was awarded the academic title of professor without the defence of a doctoral thesis.

In 1937, Ivan Mykolayovych Ishchenko was appointed to the post of deputy director of the Kyiv Institute of Emergency Surgery and Blood Transfusion and also served as its scientific director. Theoretical and practical issues of hemotransfusion in shock and acute blood loss, craniocerebral trauma, burns, blood transfusion in surgical infection, blood transfusion from a universal donor, preservation of blood, and use of blood in malignant neoplasms were successfully developed on the basis of the institute. The section on blood transfusion was included in the course of propaedeutic surgery.

In 1944, Professor Ishchenko headed the department of general surgery of the Kyiv Medical Institute, and after the death of O. P. Krymov, he was transferred to the Department of Faculty Surgery, which he ran from 1956 to 1968. In this way, the tradition of selecting the most accomplished surgeon-scientist was preserved in order to strengthen and further develop the scientific, pedagogical, and clinical activities of the Department of Faculty Surgery.

Many years of cooperation with O. O. Bogomolets became the reason for the scientist's constant interest in elucidating the pathophysiological changes in the patient's body during a wide variety of surgical diseases. He researched the pathogenesis and treatment of wound sepsis, the problem of allergy in surgical pathology, and new types of anesthesia (endotracheal anesthesia, muscle relaxation).

Professor Ishchenko conducted a series of successful experimental studies on tissue transplantation to investigate the interaction between the transplant and the patient's body. In his work, «The Phenomenon of Immunity in Homotransplantation of Tissues and Organs» (1935), he confirmed that after organ and tissue transplantation, the recipient's body produces antibodies that bind complement in the Bordet-Jangu reaction. He was the first to pay attention to the peculiarities of engraftment of retransplanted tissues and discover the dependence of the transplant on the physiological activity of the recipient's connective tissue.

In the conditions of the experiment and then in the clinic, Ivan Mykolayovych Ishchenko demonstrated the high efficiency of the use of antireticular cytotoxic serum (ACS). Later, he investigated the positive effect of ACS on the regeneration of bone fractures under experimental conditions.

In the post-war years, the subject of I. M. Ishchenko's scientific research was related to such problems as peptic ulcer disease of the stomach and duodenum, surgical diseases of the liver and biliary tract, blood transfusion, acute blood loss, nephrectomy, treatment of thermal burns, and complex treatment of stomach and mammary gland cancer. He was among the first in Ukraine to use hypothermia, ganglioblockers, and neuroleptics to improve narcosis. As

a result, the scientist published a scientific work on «Morphological Changes of Internal Organs and the Nervous System under the Influence of Hypothermia and Ganglio-Blocking Substances» (1958). His monographs «Operations on the Biliary Tract» and «Operations on the Biliary Tract and Liver» (1960) became the desk books of every surgeon. A separate place in his scientific activity belonged to research on the problem of geriatric surgery. The surgeon determined the indications for surgery very carefully and reasonably, taking into account the patient's age and general condition.

Professor Ishchenko was convinced that a surgeon should constantly and persistently work on improving surgical techniques and remember that anatomical science would always be a solid foundation for active surgery.

I. M. Ishchenko's lectures were distinguished by the depth of problem analysis, the novelty, and the clarity of their ideas. They were carefully prepared, as demonstrative as possible, and understandable for students. Professor Ishchenko was against the unnecessary use of foreign words in surgery. He used them only in cases of absolute necessity, although he knew five European languages. His lectures were attended not only by students but also by doctors and military surgeons because they contained the most recent information in the field of surgery. In his lectures, there were lessons on caring, humanity, deontology, and commitment.

Ivan Mykolayovych Ishchenko was a «teacher of everything in the world», who taught not by morals but by the example of his own behaviour and actions. He paid great attention not only to the development of surgical and pedagogical skills in his students but also to their general level of culture. He taught to love not only one's profession but also one's native land, its culture, and its writers and artists.

The Academy of Sciences of Ukraine elected Professor Ishchenko as a corresponding member in 1945, which distinguished him as a scientist. The time of his presidency is still considered the Golden Age of the Kyiv Scientific Society of Surgeons. He retired in 1968.

Ivan Mykolayovych died in 1975 after a long and serious illness.

Professor Ishchenko is the Heracles of Ukrainian medicine, personifying enormous strength, indomitability, hard work, and perseverance. His surgical, scientific, and pedagogical achievements find their application in various fields of medicine and in medical education, and his high human qualities, life wisdom, and great nobility continue to inspire new generations of surgeons and scientists.

References

1. Національний медичний університет імені О. О. Богомольця. Кафедра хірургії № 1. Історія кафедри. https://web.archive.org/web/20080914204146/http://www.nmu.edu.ua/kaf19-1.php.
2. Бойчак МП. Історія Київського військового госпіталю. Київський госпіталь — навчальна та наукова база медичного факультету університету Св. Володимира і Київського медичного інституту. Преса України. Київ, 2005 — С. 509.
3. Братусь ВД, Фомін ПД. Сторінки виникнення й розвитку хірургії в Україні. Хірургічні школи. Кафедри хірургії. Тернопіль: ТДМУ, 2005:248.

N. P. Lytvynenko, O. V. Holik, L. G. Zavernyi, M. S. Kryvopustov, Y. P. Tsiura, T. V. Tarasiuk

Bogomolets National Medical University, Kyiv

Професор Іван Миколайович Іщенко — Геракл української медицини

Н. П. Литвиненко, О. В. Голік, Л. Г. Заверний, М. С. Кривопустов, Ю. П. Цюра, Т. В. Тарасюк

Національний медичний університет імені О. О. Богомольця, Київ

Висвітлено професійний та науковий шлях професора Івана Миколайовича Іщенка — провідного українського хірурга, високоавторитетного вченого, майстерного викладача і великого гуманіста, який формував ідеологію хірургічної науки, визначав та розвивав перспективні напрямки наукових досліджень у сфері військово-польової хірургії, урології, травматології, нейрон- та торакальної хірургії, трансплантації тканин, хірургічного лікування захворювань жовчних шляхів, печінки та шлунка, теорії та практики наркозу.

UDC 618.19-006.6-089.87:615.832.9
DOI http://doi.org/10.30978/GS-2023-1-7

ISSN 2786-5584 print
ISSN 2786-5592 online

Cryo-assisted resection of primary breast cancer en bloc and tumor cryoablation connected with local drug delivery and targeting of tumor fluids. Experimental and clinical studies

M. M. Korpan[1, 2], Yueyong Xiao[3], Xiaofeng He[3], O. I. Dronov[2]

[1] International Institute of Cryosurgery, Rudolfinerhaus Hospital, Vienna, Austria
[2] Bogomolets National Medical University, Kyiv
[3] Chinese PLA General Hospital, Beijing, China

✉ Mykola Korpan: institut@cryosurgery.at; kafedra1nmu@gmail.com

N. N. Korpan, https://orcid.org/0000-0003-0497-8420
Yueyong Xiao, https://orcid.org/0000-0003-4718-2836
O. I. Dronov, MD, https://orcid.org/0000-0001-9639-6721

Objective — to use cryosurgery in combination with simultaneous peritumoral and intratumoral tracer injections of blue dye for further lymphatic mapping in the treatment of primary breast tumors. The effectiveness of intraoperative cryoprobe-assisted injection of blue dye and cytotoxic-tracer mixture for locoregional drug targeting in the VX2 tumor model as well as its translational significance for cryo-assisted breast tumor surgery with blue dye alone were evaluated. Sentinel lymph node mapping, pathological determination of the tumor, and resection margins were achievable.

Materials and methods. Thirty-nine patients with primary breast cancer in stages I to IV, aged 52,4 (±19) years (mean, standard deviation (SD) years), were randomly selected, treated at the Rudolfinerhaus Private Clinic in Vienna, Austria, and included in this preliminary clinical study. Under computed tomography guidance, we injected 2 ml of cytotoxic-tracer mixture in five aliquots into the margins of 16 frozen or normothermic VX2 tumors. We evaluated the intraoperative and post-operative drug targeting and therapeutic efficacy at the tumor-host interface by means of computer tomography, gross examination, and histopathology. In thirty-four T1 to T4 primary breast cancers, we performed an ultrasound-guided cryoprobe-assisted tumor freezing-thawing cycle, blue dye-guided lymphatic mapping, and surgery. We examined an intraoperative and freshly resected specimen and the blue dye distribution pattern in the tumor-host interface, lymph node(s), breast parenchyma, and resection cavity.

Results. 29 of the 38 patients had localized primary breast cancer, which was estimated to be resectable without neoadjuvant chemotherapy. 87 % of patients had one to twelve stained axillary lymph nodes, while 72 % of patients had another quadrant and resection cavity stained. Fluid-impervious frozen VX2 or breast tumors transported drug(s) in an arc-like pattern at the tumor-host interface regardless of freeze dose, number of freeze-thaw cycles, drug dose fractionation, tumor characteristics, or tumor dimensions. During melting, the cytotoxic-tracer mixture spread within 50 % of the VX2 tumor and mirrored that of the tumor-host interface; it was massive in normothermia. In VX2, the CT gap corresponded to 20 % of the focal margin necrosis in pathology. In both studies, blue dye dose-staining spread linearly in the tumor-host interface and tumor.

Conclusions. The study paves the way for intraoperative cryo-assisted cure options for primary breast cancer. We have shown that our cryosurgical technique of repeatedly freezing deep tumors for en bloc resection or for *in situ* ablation of primary breast cancer, facilitated by IOUS monitoring, can be coupled with the simultaneous injection of dye tracers during conventional surgery, which then allows for lymphatic mapping. Intraoperative freezing-assisted drug delivery and targeting techniques during cryoablation of the VX2 tumor translate successfully to locoregional blue dye targeting and lymphatic mapping during cryo-assisted surgery of breast cancer. We explored the ability of our strategy to prevent tumor cell migration, but not that of injected tracers, to the lymphovascular drainage during conventional resection of frozen breast malignancies.

Keywords
Experiment, VX2 tumor, clinical study, primary breast cancer, cryo-assisted tumor resection, cryoablation, intratumoral tracer injection, lymphatic mapping.

ARTICLE • Received 2022-09-15 • Received in revised form 2022-11-02
© 2023 Authors. Published under the CC BY-ND 4.0 license

Cryoablation for primary and secondary breast cancer is a well-known procedure [1, 2]. Surgical resection of a frozen tumor has also been previously proposed for primary and secondary breast cancer [3, 4].

Local control of disease and breast cancer–specific survival rates are related; strategies that reduce the rates of local recurrence at 5 and 10 years translate into an improved breast cancer– specific survival rate at 15 years [5].

Various intraoperative (IO) techniques aim at detecting and eliminating residual disease or cell shedding during breast surgery. Margin assessment, sentinel lymph node mapping and biopsy, resection cavity shaving (RCS), partial breast irradiation (PBI), or photodynamic therapy (PDT) are common procedures [4, 5]. During breast conserving surgery, most local recurrences in the conserved breast appear close to the tumorectomy cavity [6—8]; pathologic studies of mastectomy specimens have shown that tumor cells rarely extend 4 cm beyond the index lesion [8]. These clinicopathological facts have spurred the development of techniques that target the tumor bed [9], such as routine circumferential cavity shaving [5] or PBI. The latter aim at decreasing the reoperation rates, the side effects of whole breast irradiation (WBI), the treatment duration — accelerated PBI (APBI) — and associated costs. Encouraging results are now available for a selected series of early breast cancer patients. However, PBI and APBI are still controversial in the medical community [9] and are not wildly available in most health-care settings. Regarding RCS, most surgeons opt for selective rather than circumferential cavity shaving. Additionally, the determination of an optimal clear margin for invasive cancer is still a challenge, given that even a negative margin does not indicate the absence of residual disease in the breast. Surgery can lead to increased dissemination of epithelial cells [10, 11] and the local secretion of growth factors [12] that may stimulate tumor cell proliferation or metastasis formation. Perioperative chemotherapy (CTx) [13, 14] or neoadjuvant local intra- or peritumoral chemotherapy (NLCTx) [15] has been used to prevent surgery-induced dissemination or tumor growth. Local washing and multiple CTx platinum agent injections in the resection cavity, breast and axillary region during modified radical mastectomy were shown to be safe and effective at decreasing exfoliated tumor cells and potentially improving the 3-year disease-free survival rate [16].

There is room for intraoperative loco-regional adjuvant therapies during breast conserving surgery for the prevention of tumor cell shedding and the extension of tumor-free margins without resecting additional tissue or doing PBI. The goal is to reduce the 20 % to 40 % positive margin and reoperation rates after partial mastectomy [17], while still allowing conventional adjuvant RT, CTx, endocrine therapy, or targeted therapy. Such a strategy is based on the cryothermal handling and containment of the target tumor [18, 19] and the simultaneous local injection of cytotoxic drugs targeting tumor margin fluidic pathways. The rationale for this combined technical approach stems from the freezing-mediated tumor cell-fluid entrapment, the dosing advantages of local chemotherapy [15] and its combination with cryosurgery or systemic chemotherapy (CTx). Tumor freezing prevents cells from seeding into circulation [20] or shedding during tumor manipulation and resection [21]. The extrusion and transport of interstitial fluids at the frozen-unfrozen interface [22—26] (F-UI) during the tissue freeze-thaw process have considerable potential for the transport of drugs. Indeed, the freezing-extruded tumor fluids contain concentrated tumor metabolic byproducts and debris [24—25]; a «soup» that transiently settles and accumulates in the unfrozen hypothermal region surrounding the frozen mass during a cryosurgical freeze-thaw cycle. Some soup molecules, such as albumin, are natural carriers for drugs [27], including patent blue V (PBV). Thus, we used the unfrozen hypothermal region transport potential for a drug locally deposited at the F-UI. We have explored the spatio-temporal aspect of this drug transport at the ice and tumor margin in various *in vitro*, *ex vivo*, and *in vivo* experimental tumor model [28, 30] with free drug and/or drug-carrying device systems. In two recent human studies, [30, 31] we have also evaluated the freezing-induced transport and distribution of blue dye tracers, methylene blue or PBV, which are known for their ability to map the breast lymphatic drainage or bind to albumin [33, 34].

In this work, we evaluated the translational value of a cryoprobe-assisted drug delivery technique targeting the tumor margin, first in a VX2 tumor model [30], and then in human breast tumor [32]. We described the distribution and tumor-kill pattern of a tracer-and-therapeutic mixture (TTM) deposited under CECT imaging at the frozen edge of a tumor during cryoablation. The procedure simulated the clinical presentation and combined ablation and drug therapy of peritumoral residual disease. We tested the clinical translatability of the VX2 procedure on twenty-six T1-T4 resectable primary breast tumors with special attention to applicability, safety, and efficacy. We injected the blue dye alone under ultrasound (US) guidance at the edge of the frozen breast tumor before surgical resection. Our

first goal was to map the lymphatics and assess the intraoperative pattern and distribution of the dye before and after surgical resection. Our secondary endpoint was the postoperative evaluation of the resected specimen to assess the circumferential distribution of the dye at the tumor-host interface.

Finally, we compared the experimental and clinical data and discussed the implications for developing intraoperative fluid-mediated locoregional containment therapies during breast conserving surgery.

Materials and methods

Overall study design

The first step sought to evaluate the intraoperative (IO) flow and distribution of a tracer therapeutic mixture (TTM) injected locally in a single site of VX2 tumor margin, in a normothermic or cryoablated tumor (CA). The conservative cryothermal dosing consisted in maintaining the frozen-unfrozen interface (F-UI) on tumor gross margin during five repeat freeze-TTM injection-and-thaw cycles (FIT). Each FIT cycle was repeated every three to five minutes. The TTM dose was half the mean tumor volume.

The second step sought to replicate the VX2 drug delivery technique in breast cancer patients while adjusting the technical parameters to two IO clinical requirements: map the lymphatics and achieve a conventional resection of a frozen tumor, i.e., cryo-assisted (CR) breast conserving surgery or radical mastectomy, without undue prolongation of general anesthesia. We injected in the F-UI the same blue dye (BD) dose as in the VX2 study, regardless of the tumor volume. The F-UI had to overlap the tumor margin and about 10 mm of normal tissue before injection. The injection needle was always inserted into the tumor margin, facing the axilla. We investigated whether and how much tumor volume, and thus frozen zone perimeter, would affect BD uptake and its spatio-temporal distribution, compared to VX2.

The third step compared the distribution, spread, and pattern of the BD tracer in the excised specimen, host tissue, and breast lymphatics at gross examination. The image-guided combinatorial local treatment of a peripheral macroscopic residual tumor burden was modelled as part of the VX2 study.

The breast cancer (BRCA) study involved the BD tracer as a surrogate for a small cytotoxic molecule; it assessed intraoperatively (IO) its marginal circumferential and radial spread and pattern as related to the injected dose or cryothermal dose. The VX2 TTM tested the possible therapeutic effect of low-dose epirubicin [29] aliquots in combination with repeat freeze-thaw cycles (CACH) compared to a normothermic tumor (ITCH).

Experimental Study: VX2

The current study, which was previously published in part, [30] can be summarized (Table 1) as follows: bilaterally implanted VX2 tumors develop into 4 milliliter (mL) masses in the paravertebral muscle. Our goal was to assess the safety and kill effect of tumor-conservative cryoablation and simultaneous local injection of tracer therapeutic mixture (TTM), the CACH procedure (n = 28), on the interstitial distribution and marginal targeting of the TTM. Observation data were compared to the injection-alone procedure ITCH (n = 11) in a normothermic tumor. The

Table 1. **Technical and imaging parameters (adapted in part from ref. 32)**

Study	Approach technique	Tumor volume, mm^3	Number of FT cycles	Injection type, volume, BD (dose)	Tumor F dose	Injection timing, frequency	Tracer D imaging
VX2	PC (n = 0) CACH (n = 28) ITCH (n = 11)	4 ± 0.5 (3.6—4.5)	5	TTM, 2 ± 0.2 mL (1.5 mg/mL)	Up to Tm 0 mm	End F, one per FT cycle	IO-CT CECT
BRCA	Open CR (n = 39)	33.5 cm (0.8—158)*	2	BD 2 (10 mg/mL)	Tm positive 0—10 mm	End F, 1st F	IO-US visualization

CACH, cryoablation + local chemotherapy (epirubicin); ITCH, intratumor chemotherapy; CR, cryoresection; FT, freeze-thaw; Tm, tumor margin; TTM, tracer and therapeutic mixture; BD (V/V), blue dye dilution. IO-CT/IO-US, intraoperative computed tomography/ultrasonography; CECT, contrast enhanced CT; D, distribution; Vis, visualization

VX2: Five TTM aliquots were injected at a slow flow rate (ca 0.9 mL/min) up to a 2 mL total dose. Each injection (ITCH) or freeze-injection (CACH) sequence was repeated every 3 to 5 minutes. The percutaneous (PC) FT, CT, and CECT-guided procedures contain the frozen margin at tumor margin level. At each time point, two animals were euthanized for tumor specimen gross examination and histopathology.

BRCA: A bolus of 2 mL of the BD dose was injected in one minute in the deep aspect of the frozen tumor margin-breast interface (figure 2) under US guidance. The frozen margin expands about 10 mm in normal breast tissue; such a positive freeze margin is more harmful to peripheral tumor cells than the VX2 neutral freeze dose. This cryo-assisted resection (CR) of the melting breast mass precedes the axillary exploration. * We assumed a spherical shape for BRCA tumors. The average maximal diameter of a freshly resected and bisected tumor was 4 cm.

Table 2. **Patient clinicopathological characteristics (UICC TNM Classification, 8th ed., 2016) (n = 39)**

Characteristic	Number of patience
Stage	
I	8
T_1	8
N_0/N_1	7/1
M_0	8
II	17
T_2	17
$N_0/N_1/N_2$	14/2/1
M_0	17
III	8
T_3	8
$N_2/N_4/N_6$	5/2/1
M_0/M_1	5/3
IV	6
T_4	6
N_{12}/N_{14}	5/1
M_1	6
Pathology	
Invasive ductal carcinoma of no special type	29
Invasive lobular carcinoma	8
Mixed	2
Unifocal	28
Multifocal	7
ulMulticentric	4
Grade	
G1	0
G2	12
G3	27
Mammary location	
Right	28
Left	11
Upper outer quadrant	17
Lower outer quadrant	9
Upper inner quadrant	6
Lower inner quadrant	2
Nipple area	5

methylene blue concentration in the TTM volume was 1.5mg/mL. The treatment was percutaneous (PC), under computed tomography (CT) guidance to evaluate the intraoperative TTM flow pattern. Contrast-enhanced CT (CECT) and pathological examination of resected tumors at days 3, 7, and 10 evaluated and compared the contrast agent localization, the dye spatial localization, and the marginal kill. Epirubicin (Epi) dissolved in absolute ethanol is the therapeutic component of the TTM, which also includes methylene blue and ioversol.

Clinical Study: Primary breast cancer

The acute study, which was previously published in part [32], was conducted in a single center, The Rudolfinerhaus Private Clinic, in Vienna, Austria. Thirty-nine patients, aged from 21 to 74 years (mean — 52.4, SD — 19), presenting with primary breast tumors, stages I to III, or *de novo* stage IV, were randomLy selected and treated (Table 2). Tumor size: mean — 4 × 2.7 cm, SD — 3.1 × 2.1 cm. All patients gave oral or written informed consent. All but two patients received chemotherapy before surgery.

Following intraoperative tumor freezing with ultrasound-guided marginal injection of 2 mL of BD, conventional resection of the frozen mass and breast tissue, dubbed cryo-assisted resection en bloc (CR), was conducted [32]. The tumor margin of the resected specimen was marked with sutures for spatial orientation. The frozen tumor samples were subjected to tumor characterization and margin evaluation. Thirty-two patients were operated on with curative intent, including radical mastectomy in seven cases. In seven patients, palliative cryoablation was carried out. The staining pattern and distribution in the resected specimen, the breast parenchyma, and the resection cavity were measured and photographed. 28 patients had sentinel lymph node biopsy, and 11 patients underwent axillary lymph node dissection for lymph node staging, axillary exploration and lymph node clearance. In 4 patients, axillary lymph node dissection was followed by the examination of frozen sections (see Table 2).

Methodological convergences and divergences

The authors had no connection during the course of the research. The VX2 was a 10-day acute study whose results were completely available prior to developing the clinical protocol. We tailored the drug delivery technique to the clinical requirements and the preferences of the breast tumor surgeon, Dr. Mykola M. Korpan (see Table 1). Although the growth and invasion patterns of VX2 tumors [35] differ from those of breast tumors [36], the model was considered relevant for translation to human

breast tumors. The rationale was that the cooling-injection timing neutralizes the potential influence of tumor vascularization, capillary lymphatics, and tumor fluids, thus allowing comparative evaluation of the drug's interstitial flow and transport in unfrozen peritumoral tissue.

Study converging parameters were the drug injection intervening during the end of freezing (see Table 1), and needle positioning in the tumor margin. We used a single liquid nitrogen- powered probe, a single injection needle, tumor side, and a similar 2 mL injection volume. The latter matched known values for lymphatic mapping [37] in breast cancer, and the injection side was oriented toward the axillary region to facilitate BD migration in this direction.

Study diverging parameters were the approach, the number of FT cycles, and the fractionation of the injected dose; the blue dye concentration; the tumor size (see Table 1); and the location of the frozen margin relative to the tumor edge. The 17G (1.47mm) penetrating cryoprobe developed a symmetrical ice ball growth into the VX2 tumor; for the BRCA study, a flat cylindrical cryoprobe — 20mm to 50 mm in diameter- contacted the surgically exposed tumor surface, which resulted in an ellipsoidal, asymmetric ice ball growing faster on the surface than in the depth. Finally, the five repeat FITs including partial thaw sequences (FIT), simulated a «waving» of the TTM dose at the frozen-unfrozen (F-UI) margin interface of the VX2 tumor. Given the unchanged tracer distribution pattern from the first to the fifth cycle, only two FT cycles were used for the clinical study, a widely recognized clinical technique [38]. The full-dose injection of breast tumor took place before completion of the first freeze sequence, when the F-UI reached needle [32]. During the VX2 percutaneous or BRCA surgical approach, we made every effort to minimize the risk of unwanted reflux or drug loss through paths of least resistance, such as the probe, the needle tract, or the surgical wound. We injected the deep aspect of the frozen or normothermic lesion margin under CT (VX2) or US guidance for BRCA. For the latter, we undercut only the superficial aspect of the tumor, where we positioned the contacting probe. The VX2 TTM tested a possible therapeutic effect of low-dose epirubicin [30] in combination with freeze-thaw (CACH) compared to a normothermic tumor (ITCH). For BRCA, we used blue dye (BD) tracers as surrogates for small cytotoxic drugs. We injected patent blue 2.5 % (PBV) in 31 patients and methylene blue 1 % aqueous solution in 8 patients. All BRCA tumors received a single, similar dose on one tumor side to evaluate the influence of tumor volume on tracer distribution and migration.

Results

The ice zone margin has a directional and patterning effect on the flow and initial distribution of the injectate dosing.

Table 3, Fig. 1, 2 show that the injectate, irrespective of its composition, spreads along the frozen tumor mass in an arc-like pattern. The injectate accumulates at the outer edge of the frozen mass, i.e., the frozen tumor-unfrozen tissue interface. During the freezing process, the core of the frozen zone is impervious, and the frozen margin acts as a channel to fluid transport. Indeed, the intraoperative spread of the injectate is remarkably similar in both studies. Upon resection and bisection of a fresh sample, the tumor margin stains blue over an average of 35 % to 50 % of the perimeter. In order to compare this spread, we have averaged the volume of BRCA tumors (see Table 1) and found that tumor staining is a linear function of the BD dose.

The first freezing was sufficient to pattern the concomitant injectate flow, which spread along the tumor margin regardless of the conservative (VX2) or curative (BRCA) freezing procedure.

From the first to the fifth freezing sequence, the concurrent repeated injection of aliquots of contrast agent and BD tracer resulted in the same arc-like

Table 3. **Injectate dosing and distribution in tumor (adapted in part from ref. 32)**

Study	Vi/Vt	MB conc., mg/mL	Vd	Tm, %	Tc, %	Vd/Vi	V_{MB}/Vt, mg/mL	Tm Kill
Vx2 No F (n =18)	0.5	1.5	NA	10	80	0.9	0.8	None
Vx2 F (n =21)	0.5	1.5	Arc-like	50	8. 80	0.8	0.8	20 %
BRCA F (n =39)	0.06	10	Arc-like	35	3. 30	5.5	0.7	NA

Tracer distribution, Vd, is described in freshly resected, bisected sample by pattern, and spread in % of target area, on Day 0; n is the number of tumors. Calculation is modelling tumor as a spheroid. F, freeze; Vi/Vt, injectate to tumor volume ratio; Vd/Vi, tracer distribution in tumor; Tm, tumor margin; Tc, tumor core; mb, methylene blue; VMB/Vt, estimate of tracer accumulation in tumor margin and core; Kill, marginal necrosis.

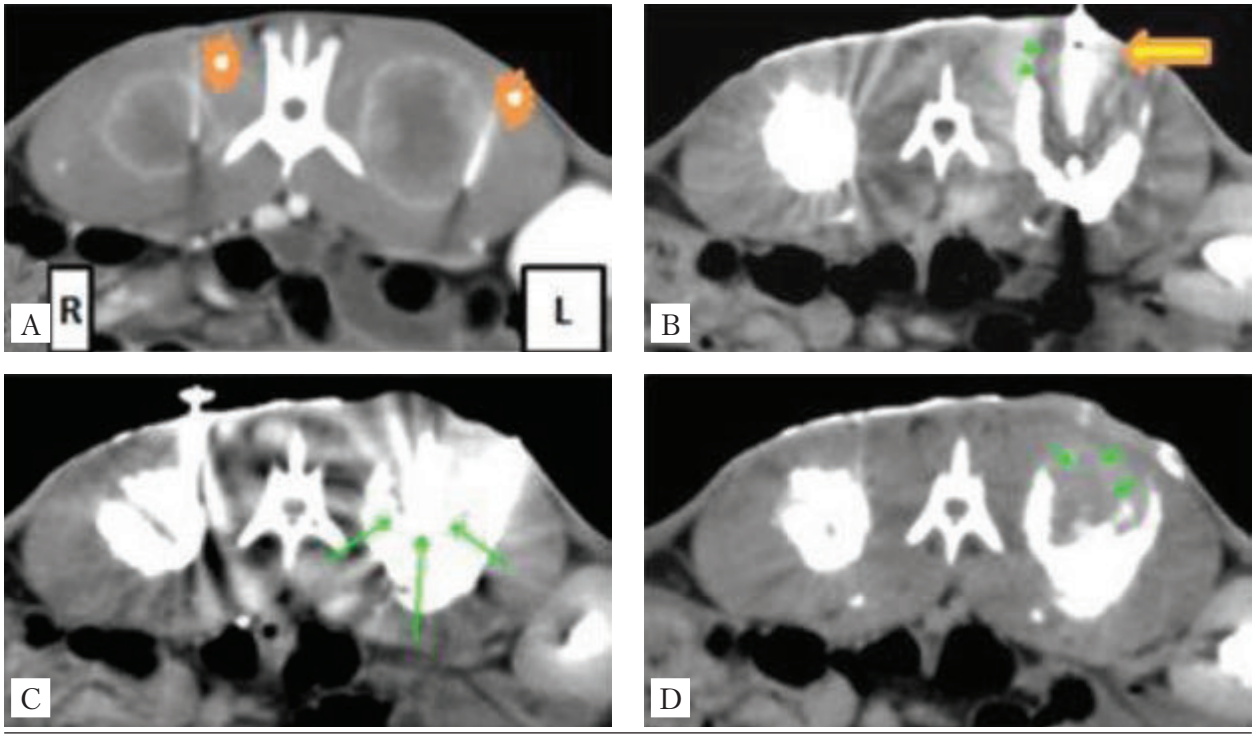

Figure 1. **CT-guided percutaneous injection, ITCH, (R) or cryoprobe-assisted injection, CACH, (L) of therapeutic mixture in the VX2 tumor margin (adapted from ref. 30). A. CECT guided needle (asterisk) positioning along enhancing tumor rim (white arrows); B. at end of first 0.4 mL injection sequence, the TTM contrast agent tracer (ioversol) does not permeate the frozen core of the left side tumor, penetrated with cryoprobe (yellow arrow), but permeate the unfrozen tumor of right side; tracer flows along the L ice margin with an arc-like pattern. Reflux through the needle tract is minimal; C. during the thaw period following each injection, the marginal tracer penetrates the melting ice towards tumor core (green arrows); D. 20 minutes after the procedure, a larger amount of fluid and tracer, 50 % of the injectate, leaks out of the left side tumor core (short green arrows) during probe and needle removal compared to the right side**

distribution pattern at the frozen-unfrozen interface of the VX2 tumor margin (see Fig. 1*B*). During the first freezing, the conservative cryoablative procedure propagated the frozen margin at VX2 tumor margin level, and the following freeze cycles were adjusted in cooling intensity and duration to keep the ice margin steady. Thus, the tumor margin was sequentially freezing and melting, which resulted in the transient co-accumulation of tumor extruded fluids and tracers during the repeat intensity-modulated freeze-thaw cycles. This was observed during the first freeze of a BRCA tumor, whose frozen margin was impervious to the BD but could engulf the tracer during its planned progression in normal breast tissue resulting in an arc-like marginal staining pattern that did not change during the re-freeze sequence (see Fig. 2*B*, 2*C*).

The tumor margin and tumor host interface permeation to TTM or BD were both affected by the freeze-thaw cycle.

Whether steady (VX2) or advancing (BRCA), the frozen rim kept the co-injected drug tracers from permeating the frozen tumor mass. This effect was constant and independent of the frozen rim dimension and tumor characteristics. Remarkably, the arc-like pattern of the drug tracers mirrored the shape of the frozen rim, an effect that lasted throughout the freezing period if the injection needle tip was in the unfrozen region and before the ice margin. During tumor freezing, co-injected PBV or methylene blue tracers did not permeate the frozen core, regardless of their concentration. However, BD deposited before the advancing ice margin, as exemplified for BRCA, accumulated in the wider positive ice margin, a slushy mixture of fluids and ice crystals. The blue staining of the unfrozen rabbit muscle facing the steady ice margin of Fig. 3*A* is narrow in comparison with the large coloration of breast parenchyma surrounding the tumor (see Fig. 2*C*). During the thaw period, regardless of its duration or that of the preceding freezing time, 20 minutes for VX2 or seven minutes for BRCA, melting tumor margins became permeable to dye penetration towards the tumor core. Comparing the injection of a frozen and an unfrozen VX2 tumor, the injectate's penetration into the tumor was immediate in the latter

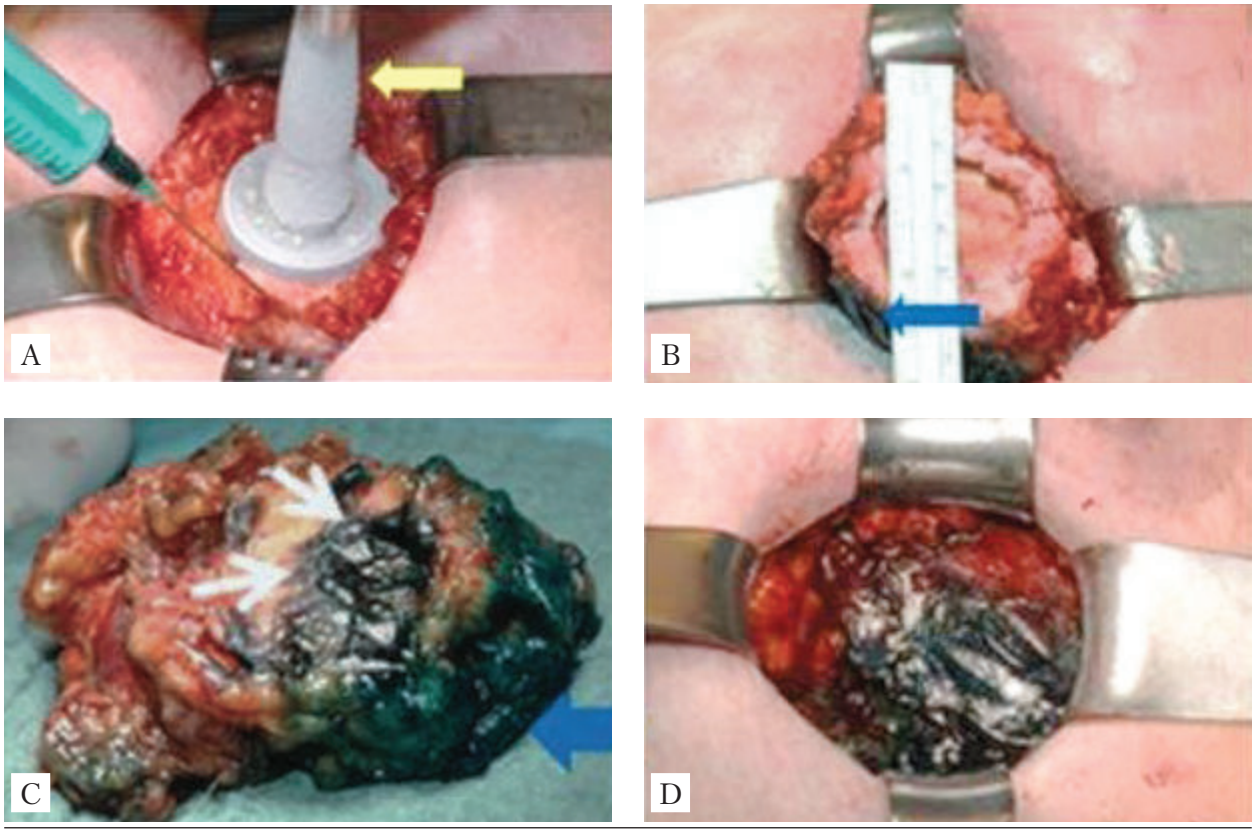

Figure 2. **Intraoperative ultrasound-guided cryo-assisted blue dye (BD) injection and en bloc resection of breast tumor $T_2N_0M_0$ (adapted from ref. 32). Patient D. J.; A. aspect of surgical wound following methylene blue injection in frozen tumor margin, during pull out of needle. The US transducer has been removed. The cylindrical liquid nitrogen cryoprobe (yellow arrow), 50mm diameter, makes a 89 cm^3 ellipsoidal ice zone in three minutes that engulfs the 5.45 cm^3 tumor located in the upper outer quadrant; B. following an 8 minutes thaw and a second freeze, margin of melting tumor evidences BD distribution in an arc-like pattern (blue arrow); C. the freshly excised bi-sectioned sample, a 71 cm^3 mass, exhibits similar BD intratumor permeation pattern (white arrows), and its diffusion in nearby breast fatty and fibro-glandular tissue (large blue arrow); D. blue staining of resection cavity is obvious. Two sentinel lymph nodes were removed, non-metastatic at pathology. BD reflux in surgical wounds and in the needle track is minimal during freezing; we estimated that about 50 % of BD migrated to the contiguous breast**

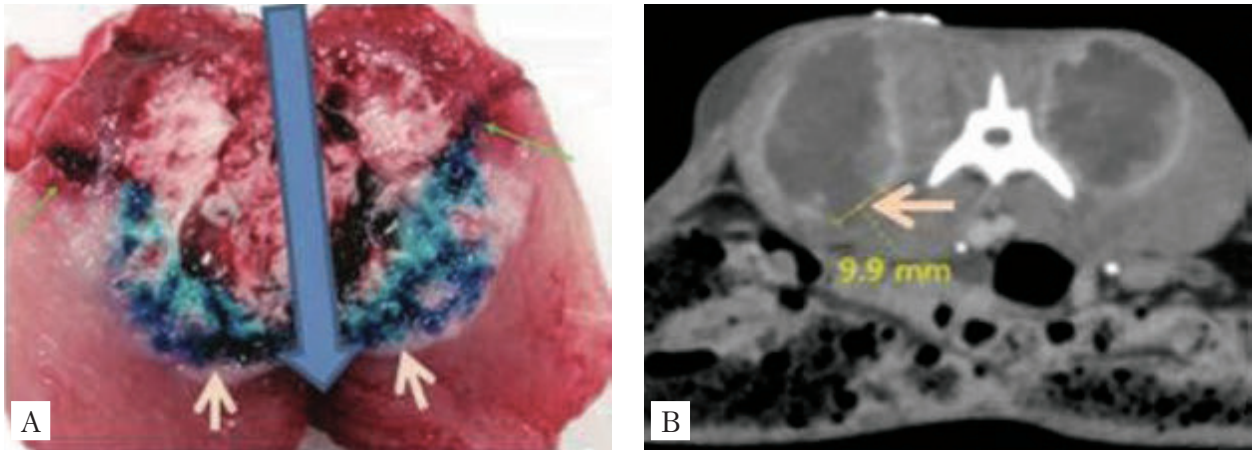

Figure 3. **VX2 tumor margin drug targeting and focal killing (adapted from ref. 32) A. One hour post CACH procedure, transected right side tumor along probe tract (blue arrow) evidences predominant BD staining of tumor margin-muscle interface (orange arrows). The injection needle track (green arrows) stains blue from BD reflux during injection. Right: CECT imaging on day 10 shows a gap of contrast agent (orange arrow) in the enhanced marginal rim, compared to an integral rim in the injection only on the left side. Histopathological focal margin necrosis coincides with the gap**

and delayed in the former. Although qualitative, the tracer uptake evaluation within the tumor looked similar for both groups when the melting process was complete. This observation holds true for frozen BRCA tumors; although blue dye was injected before the end of the freezing process, it penetrated the tumor core during the thawing sequence.

Tracer migrated in host tissue and breast lymphatic vessels

In both studies, we observed a rapid migration of the tracer, either the contrast agent and/or blue dye, in the normal tissue surrounding the tumor. From the frozen margin of the breast tumor, about 50 % of the BD dose was transported to the contiguous breast parenchyma and drained into the lymphatics. A little amount tended to reflux along the needle tract and superficial wound. The injectate reflux ratio along the needle track in the VX2 study ranged from 6 % to 17 %, with a frequency of 13 % to 50 % for the CACH vs. ITCH group. Following probe pullout, nearly 50 % of the injectate was lost through the probe track, along with tumor necrotic debris and fluids (see Fig. 1*D*). We did not compensate for this intraoperative reflux in either study. For 69 % of BRCA patients, BD injectate was transported to a single contiguous quadrant in 18 out of 26 patients and stained the resection cavity in all cases. Twenty-two patients (84.6 %) had 1 to 12 stained axillary lymph nodes, as seen in Table 4. The time lost during the freeze-thaw injection protocol averaged 20 minutes for BRCA, which did not prolong the anesthesia much and had no consequence on the patient's recovery or wound healing. As expected, starting during the intervention, the patient's urine stained blue. No allergies or durable skin staining were noted. Surgery was uneventful as determined by the preoperative plan, intraoperative lymphatic mapping, SLN, and tumor margin evaluation.

Drug dose distribution and effect

Tracer distribution volume was evaluated on a freshly resected tumor based on localization and percentage coverage of the target area. We assumed spheroid tumor geometry. In Table 3, we show that the injectate to tumor volume ratio (Vi/Vt) is one order of magnitude lower in BRCA (mean volume) compared to the VX2 tumor. After deduction of the estimated dose lost ~50 % (Vd/(Vi-50 %)) to migration in the breast or through the probe tract of the VX2 target, a quantifiable and quite similar estimate of tracer accumulation (Vmb/Vt) in the tumor margin (Tm) and tumor core (Tc) ranges respectively from 0.7 mg/mL to 0.8 mg/mL. The tracer spread pattern is also similar in Tm and Tc.

Cryothermal dose affected cryoablation and cryoresection

The BRCA cryo-assisted resection case of Fig. 2 illustrates the large frozen mass, or freeze dose, that engulfs the tumor and normal breast tissue. The latter is 15 times greater than tumor volume. It is a positive freeze margin, whose contours cover tumor margins along with normal tissue. The tumor freeze dose, estimated in percentages of frozen tumor and host tissue in Table 2, is 100 % for VX2 and > 100 % for BRCA. Assuming an ellipsoidal geometry for the frozen tissue, we have calculated a freeze dose of median 43.6 mL and range 24—177 mL, which means that all targeted BRCA tumors were properly frozen. The resection line is located in normal breast parenchyma, 3cm to 4cm off the palpable and visible frozen contours. The intraoperative selective re-resection rate (Table 4) for close, < 2 mm, or positive margin is 15 %. As expected, freshly excised VX2 tumors after conservative cryoablation exhibited viable tumor clusters in pathological samples of frozen margin [29].

Discussion

The lack of an effective, translatable strategy for the local delivery of cytotoxic drugs to breast tumors during surgery, has limited the clinical potential of intraoperative local chemo-immunotherapies [15, 39—41].

The goal is to improve local control of disease without the side effects of resection cavity shaving

Table 4. **Blue dye migration and surgical option in breast cancer patients (n = 39)**

Characteristic	Number of patience
Number of BD breast quadrants	
One	12 (69 %)
Two	12 (12 %)
Three	15 (19 %)
SLN identification rate	32 (84.6 %)
LN mts	9
Selective RCS	14 (15 %)
BCS	31
RM	15
Sentinel lymph node biopsy	39
Aaxillary lymph node dissection	18

BD migrated to one or two contiguous quadrants in 81 %, and in SLN in 84.6 %. The intraoperative selective RCS ratio for positive or close margin (< 2 mm) was 15 %.
SLN, sentinel node; RCS, resection cavity shaving.

or APBI. Strategies that reduce the rates of local recurrence at 5 and 10 years translate into an improved breast cancer–specific survival rate at 15 years [5]. Even a modest 10 % reduction in the reexcision rate would prevent reoperation in 10,000 to 20,000 of the 180,000 American women who undergo lumpectomy annually in the United States [42]. We propose a cryoprobe-assisted local drug injection and resection strategy of solid tumors to minimize tumor fluid leakage and maximize drug targeting of the tumor-host margin interface during breast conserving surgery.

We have previously demonstrated that a solution of a small molecular tracer, alone or co-formulated with a cytotoxic drug, migrates in tumor fluid dissemination pathways after being injected in the tumor margin. We have shown that concurrent tumor freezing modulates the direction and spread of this migration [30, 32]. However, there is a lack of demonstration that the VX2 cryoablation tumor model is translatable to cryoprobe-assisted surgery, i.e., cryoresection of a human breast tumor. There is no known study linking cryosurgical ablation and cryosurgical resection combined with local adjuvant therapy. In the present study, we extend our previous findings that freeze-thaw assisted local injection of active drug and ablation procedure of VX2 animal tumor are applicable to freeze-thaw assisted local tracer injection and breast conserving surgery in human patients.

The rationale for the translatability of this intraoperative cryothermal and drug-mediated therapy adjuvant to two seemingly opposite local curative procedures, i.e., ablation versus resection, stems from the initiating common event: subzero cooling of living tissues immobilizes all fluids and fluid communication pathways within frozen mass. There is an interruption of blood, lymphatic, and interstitial fluid flow in and out of the tumor [38].

We hypothesized that, during freezing, the local transport of a co-injected drug along the frozen mass would be similar for a higshly vascularized, aggressive tumor like VX2 or for a breast tumor, regardless of their pathological characteristics. A potential advantage of this combinatorial approach is the tumor cell-fluid entrapment, and the lower dosing of local chemotherapy [15] that can be associated with systemic chemotherapy (CTx). Tumor freezing would prevent cells from seeding into circulation [21] or shedding during tumor manipulation and resection [21]. The extrusion and transport of tumor interstitial fluids at the frozen-unfrozen interface [22—25] during the freeze-thaw process have considerable potential for the transport of drugs. Indeed, the freezing-extruded tumor fluids contain tumor metabolic by-products and debris [25, 26], i.e., a «soup» that transiently settle and accumulate in the frozen-unfrozen interface region (F-UI) surrounding the frozen mass during a freeze-thaw cycle.

Some soup molecules, such as albumin, are natural carriers for drugs [27], including patent blue (PBV). Thus, the F-UI [22] region has considerable potential for the transport of a locally deposited drug.

The value of this targeted cryothermal-mediated drug delivery technique is its translatability from the VX2 model to breast cancer. With regard to the spatio-temporal drug transport in the F-UI, the imageable or visible tracer(s) distribute at the frozen outer rim with a similar arc-like pattern (Fig. 1*B*, 2*B*, 3*A*) in both studies. Although the freezing-assisted injection duration is eight times longer and the average frozen mass is much smaller in VX2 compared to BRCA, the frozen margin, regardless of its size, is the drug driver; drug transport within unfrozen interstitial fluid pathways follows the pressure gradient created between the needle tip and peritumoral environment. Remarkably, the tracer distribution pattern along the VX2 tumor did not change from the first to the fifth injection. We inferred that the first freeze dose, which was similar in both studies, draws the directional transport of the tracer that will remain unchanged with an additional dose of either. Additionally, this pattern was predictable from *in vitro*, *ex vivo*, and experimental observations of free drugs and/or drug-carrying devices injected and transported along frozen tumor margins [28, 29]. We discovered that injecting the F-UI over the tumor margin level for the VX2 tumor or progressing towards normal breast parenchyma for the BRCA tumor resulted in the drug permeating more widely at the latter tumor margin than at the former tumor margin. The extent of tracer radial spread could be attributable to the crystallization of the drug aqueous solution caught in the ice-water phase (slushy ice) at the advancing ice rim location [28]. The injection pressure gradient, a function of the injection rate and tissue compliance, along with the frozen rim, likely contributed to bulk flow in the tumor margin and environment.

As a result, tracer was transported outwardly during freezing in both studies, as shown in Fig. 1*B* and 2B. Although the no-freeze injection, ITCH series, in the VX2 margin demonstrated an initial tracer distribution pattern resembling the freeze-assisted pattern, the ensuing flow was toward the tumor core without accumulation in the margin. This finding suggests that the density of interstitial fluid paths of least resistance is higher towards the

tumor necrotic core than at the tumor-muscular interface, thus facilitating the inward direction of the convective flow.

Table 3 shows that tumor staining correlates with blue dye dose, not injectate volume; for similar injection rate and injected fluid volume, an equal stained/unstained ratio was observed on freshly resected samples of VX2 and BRCA tumors, although the averaged BRCA volume (33.5 cm^3) was eight times larger than that of the VX2 tumor (see Table 1). Such a result was predictable. Indeed, blue dye-guided localization of nonpalpable breast tumor shows a direct relation between dose and stained tissue [43]. To evaluate the BD dose distributed in the tumor target, we assumed that a part migrated in the tumor and margin, and the rest migrated in the breast parenchyma, lymphatics, tumor-host interface, and blood vessels; an additional amount was lost to reflux through the surgical wound, the injection needle track, or the probe track.

Based on the tumor-stained volume, we assumed that 60 % to 70 % of the TTM or BD dose was transported along and away from the outer rim of the frozen VX2 or BRCA tumor, within open interstitial fluid channels [36] with a flow velocity and intensity related to the injection pressure gradient, tumor-to-host interface compliance, and hydraulic conductivity. The injection results in a high-velocity bulk flow. Such pressure gradient disperses the injected solution in fluid paths and spaces of lower resistance, i.e., tumor margin, tumor necrotic spaces, the tumor-host interface, and further away in the host organ. Tumor-draining blood and lymphatic vessels wash out the injectate, which may also reflux through the needle track.

The drug dose and freeze-mediated injection technique proved efficient at mapping lymphatic drainage in BRCA patients. Indeed, one to twelve nodes of the axillary region stained blue (see Table 4) in 22 of 39 cases (84.6 %), a detection rate that is comparable to conventional BD-guided lymphatic mapping [37]. Although the VX2 study did not investigate the tracer's transport to lymphatic drainage, its dispersion along the frozen margin and tumor- muscular interface resulted in its interstitial drainage. Mapping BRCA lymphatic drainage by injecting a bolus dose of BD tracer into a single deep side of frozen tumor margin raises some questions: was the injection side chosen to face the axilla optimal for transporting tracer preferentially towards the axilla? Was the pressure-mediated bulk flow away from the frozen tumor margin the preeminent factor in the permeation of the lymphatics leading to axilla? The fact that the tracer (see Table 4) migrated from the deep aspect of the tumor margin to a single contiguous quadrant in 69 % of cases before reaching the axilla suggests that lymphatic drainage is directed towards the axilla rather than the internal mammary region [45]. Indeed, 25/39 patients had tumors located outside the upper outer quadrant (see Table 1), in which we did not evidence any internal mammary lymphatic drainage.

Local drug delivery strategies have been investigated [46] for nearly five decades as a means to achieve high concentrations of chemotherapeutics (CTx), augment drug targeting of specific tumor structure, and reduce the side effects of systemic chemotherapy. Local delivery of CTx could sterilize resection margins, and possibly the tumor lymphatic drainage as well [40, 41]. Cryoablation has been combined with systemic or local adjuvant CTx to induce cryothermal lethal damages closer to the frozen margin [47], allowing for better control and prediction of the ablative effect. Physicians have designed and optimized cryo-assisted localization (CAL) and cryoablation (CA) to provide better margin clearance and cosmetic results compared to lumpectomy in small unifocal breast tumors [48].

Our VX2 preclinical study investigated the feasibility and efficacy of intraoperative freeze-thaw assisted drug delivery and tumor margin targeting, which differed from previously published combined adjuvant cryoablation-chemotherapy strategies [47]. Our drug delivery strategy consists in using both the tumor margin and the ice rim as tunable gel-solid interfaces for accessing and controlling drug distribution over targeted tissue. The working hypothesis, based on previous *in vitro* and pre-clinical studies, is that transient drug entrapment occurs at higher concentrations in the peripheral region of the frozen tissue. Frozen VX2 tumors exhibit a solid impervious core and low compliant margin, are made of a slushy ice-water mixture, are partially permeable to the injectate that gets distributed along the solid tumor mass and in the contiguous muscular tissue of Figure 3. The marginal drug targeting that lasts a few hours translates into moderate tissue kill; necrosis is about 20 % of the stained margin on histological samples, and matches with a gap in the tumor rim of post-operative CECT imaging (Figure 3). Whether this focal necrosis was the result of an additive or synergistic freeze-thaw and drug effect remains an open question. Our previous studies [29] suggest an additive effect; they demonstrated that the slow release of low-dose cytotoxic from microcapsules deposited in the frozen margin of the prostate tumor resulted in focal killing subsequent to the combined cytotoxic effects of sublethal slush ice and drug injury. Our BRCA study replicated the VX2 protocol with a BD tracer

only to investigate its spread along the frozen tumor margin. Remarkably, the peripheral spread was quite similar in both studies, i.e., ranging from 35 % to 50 % (see Table 3). We infer that the nanosized tracers and drugs (< 10 micrometers) were trapped and released from the frozen-thawed tissues over successive periods of time corresponding to the initial peripheral freezing-and-bulk flow sequence and the delayed more central tissue thaw and drug trapping sequence. Due to their small size, the molecules migrate quickly from the point of delivery, which explains the fast rate of staining (< 10 minutes) observed in the draining lymphatics during the operation. Given that about two thirds of the dose is lost to drainage, reflux, or dilution in the wound or probe track without affecting the peripheral spread, we think that drug targeting of the entire tumor periphery would be achieved with 0.1 to 0.3mL of a 1 % solution of methylene blue injected in the deep aspect of three tumor sides, a dosage published by Tang et Al [43] for BD-guided cryolocalization of non-palpable breast tumors.

Another implication of this study is the implementation of local targeted chemotherapy for solid tumors by delivering the drug(s) to the tumor margin. The finding that the injected solution rapidly permeated the tumor core from its marginal location, either in the no-freeze ITCH group of VX2 study or in both studies during the thaw period, suggests the presence of fluid channels bridging the inner tumor and exterior tumor environment during tumor growth [36]. Thus, the tumor margin seems an optimal region for direct delivery of diagnostic or therapeutic molecules. The transient obstruction of margin fluid channels during freezing and their re-opening during melting make the freeze-thaw process an on-off switch for tumor-host fluid communication pathways, the interstitial fluid channels. In short, the freeze-thaw process aids tumor margin permeation to small molecules in a tunable directional manner [31]. The entrapment of a tracer within the tumor core during and after thawing, as observed in the VX2 study, suggests the use of freeze-thaw assisted injection of an active drug not only during resection but also in the resection cavity margins. Local cytotoxic injections would aid in priming residual tumor cells for adjuvant systemic therapies [49, 50], and/or radiotherapy [6].

The clinical validation of our tumor fluid management protocol during breast conservation surgery will require additional steps. Although we could not demonstrate whether and to what extent frozen breast tumor resection reduces or prevents cell shedding from tumor manipulation, our cryosurgical technique was designed to kill as many cells as possible [51—54]. Given that the freeze-thaw process that occurs during cryoablation or cryoresection induces tumor necrosis and apoptosis, both of which may modulate antitumor immunity, our protocol could supplement the latter with local cytotoxic and/or immuno-modulator agents [54—57]. Our next research step will investigate the biological and cellular composition of wound fluids, and seek to optimize the cryothermal energy dosing and blue dye delivery to target the whole tumor periphery.

We are aware of some of the study's limitations. The short VX2 and BRCA series forbade any quantitative data evaluation. Another limitation may involve different biomechanical characteristics of the tissue hosting the tumor: the back muscle for VX2 and the breast fibro-glandular and fatty tissue for BRCA. The fluid drainage through the interstitium may differ for both tissues, particularly during TTM bulk flow in the VX2 tumor margin in contact with stiff muscular tissue. We could have implanted the VX2 tumor in the breast and examined the peritumoral lymphatic capillaries [59]. We believed that our protocol would be easier to implement in order to demonstrate the feasibility of marginal targeting and its translatability to BRC.

Conclusions

This study confirms that intraoperative blue dye-guided lymphatic mapping with a single deep tracer injection in the margin of a frozen breast tumor is feasible. The frozen-thawed tumor-host interface region behaves as an impervious and trapping zone for small molecules. The targeted cryothermal mediated drug delivery developed during VX2 tumor implant ablation translates into successful margin and lymphatic targeting during cryo-assisted resection of breast tumor. The widespread technique of blue dye-guided lymphatic mapping during breast cancer surgery could benefit from simultaneous tumor margin freezing and serve as a platform for designing a new locoregional breast tumor-containment therapy strategy.

In memoriam

Dr. Sajio Sumida, Tokyo, Japan, his scientific work greatly contributed to modern clinical applications of cryomedicine and cryosurgery.

Acknowledgements

The authors would like to thank all colleagues at the International Institute of Cryosurgery and the medical staff of the Rudolfinerhaus Hospital operating theatre, Vienna, Austria, for their support and participation in the study. The

authors would like to acknowledge Patrick Le Pivert, MD, PhD, Interventional Drug Delivery Systems and Strategies, Jacksonville, USA, for his expert opinion and comment.

Declaration of interests

All authors declare absence of conflict of interest with respect to the research, authorship, and/or publication of this article.

Funding. This manuscript did not receive specific funding. The VX2 study work was largely supported by the Animal Experimental Centre of the Chinese PLA General Hospital, Beijing, China.

Published research connected to the study

This study uses some raw data from two papers originally published in TCRT, http://doi.org/10.1177/1533034615593855, and http://doi.org/10.1177/1533034617746294.

Authors contributions

M. M. Korpan, Yueyong Xiao, Xiaofeng He, O. I. Dronov created the study protocol; compiled and analyzed all data, wrote and critically revised the manuscript. M. M. Korpan, O. I. Dronov developed the protocol application to the breast cancer study; conducted the surgery and collected breast cancer data. Yueyong Xiao, Xiaofeng He designed the protocol application to the VX2 study. Xiaofeng He carried out the VX2 experiments, collected and analyzed data.

All authors the manuscript and gave consent for publication.

References

1. Korpan NN. Hepatic cryosurgery for liver metastases. Long-term follow-up. Ann Surg. 1997; 225(2):193-201. doi: 10.1097/00000658-199702000-00007.
2. Niu L, Zhou L, Korpan NN, Wu B, Tang J, Mu F, et al. Experimental study on pulmonary cryoablation in a porcine model of normal lungs. Technol Cancer Res Treat. 2012; 11(4):389-94. doi: 10.7785/tcrt.2012.500286.
3. Korpan NN. Cryosurgery: early ultrastructural changes in liver tissue in vivo. J Surg Res. 2009; 153(1):54-65. doi: 10.1016/j.jss.2008.02.063.
4. Nomori H, Yamazaki I, Kondo T, Kanno M. The cryoablation of lung tissue using liquid nitrogen in gel and in the ex vivo pig lung. Surg Today. [Journal Article; Research Support; PubMed]. 2017; 47(2):259-64. doi: 10.1007/s00595-016-1363-z.
5. Chagpar AB, Killelea BK, Tsangaris TN, et al. A Randomized, Controlled Trial of Cavity Shave Margins in Breast Cancer. N Engl J Med. 2015;373(6):503-10. doi:10.1056/NEJMoa1504473.
6. Sabel MS. Locoregional therapy of breast cancer: maximizing control, minimizing morbidity. Expert Rev Anticancer Ther. 2006;6(9):1281-99. doi:10.1586/14737140.6.9.1281.
7. Offersen B V., Overgaard M, Kroman N, Overgaard J. Accelerated partial breast irradiation as part of breast conserving therapy of early breast carcinoma: A systematic review. Radiother Oncol. 2009;90(1):1-13. doi:10.1016/j.radonc.2008.08.005.
8. Holland R, Veling SH, Mravunac M, Hendriks JH. Histologic multifocality of Tis, T1-2 breast carcinomas. Implications for clinical trials of breast-conserving surgery. Cancer. 1985;56(5):979990. http://www.ncbi.nlm.nih.gov/pubmed/2990668.
9. Hickey BE, Lehman M, Francis DP. Partial breast irradiation for early breast cancer (Review) Summary of Findings for the Main Comparison. 2016;(7). doi:10.1002/14651858.CD007077.pub3. www.cochranelibrary.com.
10. Pachmann K. Tumor Cell Seeding During Surgery—Possible Contribution to Metastasis Formations. Cancers (Basel). 2011;3(4):2540-53. doi:10.3390/cancers3022540.
11. Choy A, McCulloch P. Induction of tumour cell shedding into effluent venous blood breast cancer surgery. Br J Cancer. 1996;73(1):79-82. http://www.ncbi.nlm.nih.gov/pubmed/8554988.
12. Ramolu L, Christ D, Abecassis J, Rodier JF. Stimulation of breast cancer cell lines by post-surgical drainage fluids. Anticancer Res. 2014;34(7):3489-92.
13. Harless WW. Revisiting perioperative chemotherapy: the critical importance of targeting residual cancer prior to wound healing. BMC Cancer. 2009;9:118. doi:10.1186/1471-2407-9-118.
14. van der Hage JA, van de Velde CJ, Julien JP, et al. Improved survival after one course of perioperative chemotherapy in early breast cancer patients. long-term results from the European Organization for Research and Treatment of Cancer (EORTC) Trial 10854. Eur J Cancer. 2001;37(17):2184-93. http://www.ncbi.nlm.nih.gov/pubmed/11677105.
15. Goldberg EP, Hadba AR, Almond B, Marotta JS. Intratumoral cancer chemotherapy and immunotherapy: opportunities for nonsystemic preoperative drug delivery. J Pharm Pharmacol. 2002;54(2):159-80. doi:10.1211/0022357021778268.
16. Chen, JX. Pan, M. Li J. Clinical observation of intraoperative local chemotherapy with lobaplatin in breast cancer modified radical mastectomy. Int J Clin Med. 2017;10(7):10834-9.
17. McCahill LE, Single RM, Aiello Bowles EJ, et al. Variability in reexcision following breast conservation surgery. JAMA J Am Med Assoc. 2012;307(5):467-75. doi:10.1001/jama.2012.43.
18. Le Pivert PJ, Le Petit JC, Fraisse J, Cuiilleret J, Brizard CP. Controlled cryotumorectomy of breast cancers. Technical and theoretical aspects. Les colloques de l'INSERM, Cryoimmunologie/Cryoimmunology. 1976;62:267-78.
19. Le Pivert P. Basic considerations of the cryolesion In: Ablin RJ, ed. Handbook of cryosurgery. New York, NY: Marcel Dekker; 1980. P. 15-68.
20. Camara O, Kavallaris A, Nöschel H, Rengsberger M, Jörke C, Pachmann K. Seeding of epithelial cells into circulation during surgery for breast cancer: the fate of malignant and benign mobilized cells. World J Surg Oncol. 2006;4(1):67. doi:10.1186/1477-7819-4-67.
21. Tarkowski R, Rzaca M. Cryosurgery in the treatment of women with breast cancer-a review. Gland Surg. 2014;3(2):88-93. doi:10.3978/j.issn.2227-684X.2014.03.04.
22. Teo KY, Dutton JC, Han B. Spatiotemporal Measurement of Freezing-Induced Deformation of Engineered Tissues. J Biomech Eng. 2010;132(3):031003. doi:10.1115/1.4000875.
23. Han B, Miller JD, Jung JK. Freezing-induced fluid-matrix interaction in poroelastic material. J Biomech Eng. 2009;131(2):021002. doi:10.1115/1.3005170.
24. Bumsoo Han, Ka Yaw Teo. Effects of freezing on intratumoral drug transport. In: 2009 Annual International Conference of the IEEE Engineering in Medicine and Biology Society. 2009. IEEE; 2009:246-9. doi:10.1109/IEMBS.2009.5333804.
25. Wright J, Han B, Chuong C-J. Biphasic Investigation of Tissue Mechanical Response During Freezing Front Propagation. J Biomech Eng. 2012;134(6):061005. doi:10.1115/1.4006682.
26. Wiig H, Tenstad O, Iversen PO, Kalluri R, Bjerkvig R. Interstitial fluid: the overlooked component of the tumor microenvironment? Fibrogenesis Tissue Repair. 2010;3(1):12. doi:10.1186/1755-15363-12.
27. Hoogenboezem EN, Duvall CL. Harnessing albumin as a carrier for cancer therapies. Adv Drug Deliv Rev. 2018;130:73-89. doi:10.1016/j.addr.2018.07.011.
28. Le Pivert, PJ. Translational cryosurgery in lung tumor therapy, cryoimmunotherapy, cryochemotherapy, nanocryosurgery : basics and applications. In: Cryosurgery for lung cancer. Hongwu Wang, Kecheng Xu, Peter Littrup (Eds). New York: Springer Wien; 2012. Chapter 1.6. P. 1-38. http://doi.org/10.13140/RG.2.1.5114.2644.
29. Le Pivert PJ, Morrison DR, Haddad RS, et al. Percutaneous tumor ablation: microencapsulated echo-guided interstitial chemotherapy combined with cryosurgery increases necrosis in prostate cancer. Technol Cancer Res Treat. 2009;8(3):207-16. doi:10.1177/153303460900800305.
30. He X, Xiao Y, Zhang X, et al. Percutaneous tumor ablation: cryoablation facilitates targeting of free epirubicin-ethanol-ioversol solution interstitially coinjected in a rabbit VX2 tumor model. Technol Cancer Res Treat. 2016;15(4):597-608. doi:10.1177/1533034615593855.
31. Rzechonek A, Blasiak P, et al. The Bi-directional migration of a dye tracer injected at the edge of primary or secondary lung tumors during surgery. Initial study on 33 patients and clinical implications. Inter Collegas. 2017;4(3):106-19. https://inter.knmu.edu.ua/?journal=pub&page=article&op=viewFile&path%5B%5D=177&path%5B%5D=179.

32. Korpan NN, Xu K, Schwarzinger P, Watanabe M, Breitenecker G, Le Pivert P. Cryo-assisted resection en bloc, and cryoablation in situ, of primary breast cancer coupled with intraoperative ultrasound-guided tracer injection: a preliminary clinical study. Technol Cancer Res Treat. 2018;17:1533034617746294. doi:10.1177/1533034617746294.
33. Tsopelas C, Sutton R, Bs M. Why certain dyes are useful for localizing the sentinel lymph node. J Nucl Med. 2002;43:1377-82. http://jnm.snmjournals.org/content/43/10/1377.
34. Alarcon E, Edwards AM, Aspee A, et al. Photophysics and photochemistry of dyes bound to human serum albumin are determined by the dyelocalization. Photochem Photobiol Sci. 2010;9(1):93-102. doi:10.1039/B9PP00091G.
35. Liu Y, Ren W, Liu C, et al. Contrast-enhanced ultrasonography of the rabbit VX2 tumor model: Analysis of vascular pathology. Oncology Letters. 2012;4:685-90. https://doi.org/10.3892/ol.2012.819.
36. Gritsenko PG, Ilina O, Friedl P. Interstitial guidance of cancer invasion. Journal of Pathology. 2012;226(2):185-99. http://doi.org/10.1002/path.3031.
37. Li J, Chen X, Qi M, Li Y. Sentinel lymph node biopsy mapped with methylene blue dye alone in patients with breast cancer: A systematic review and meta-analysis. PLoS One. 2018;13(9):e0204364. doi:10.1371/journal.pone.0204364.
38. Baust JG, Gage AA, Bjerklund Johansen TE, Baust JM. Mechanisms of cryoablation: clinical consequences on malignant tumors. Cryobiology. 2014;68(1):1-11. doi:10.1016/j.cryobiol.2013.11.001.
39. Ehrhart N, Dernell WS, Ehrhart EJ, et al. Effects of a controlled-release cisplatin delivery system used after resection of mammary carcinoma in mice. Am J Vet Res. 1999;60(11):1347-51.
40. Chen WX, Pan M, Li J, Zhao JH, Zhou JW, Tang JH. Clinical observation of intraoperative local chemotherapy with lobaplatin in breast cancer modified radical mastectomy. Int J Clin Exp Med. 2017;10(7):10834-9.
41. Baitchev G, Gorchev G, Deliisky T, Popovska S, Raitcheva TZ. Perioperative locoregional application of mitoxantrone in patients with early breast carcinoma. J Chemother. 2001;13(4):440-3. doi:10.1179/joc.2001.13.4.440.
42. Cody HS 3rd, Van Zee KJ. Reexcision — The Other Breast Cancer Epidemic. N Engl J Med. 2015;373:568-9. PMID:26244311.
43. Tang J, Wang X, Wu YP, et al. Significance of methylene blue dye for localization biopsy of nonpalpable breast lesions. Chin J Cancer. 2009;28(1):79-81. http://www.cjcsysu.cn/cn/article.asp?id=14395.
44. Less JR, Posner MC, Boucher Y, Borochovitz D, Wolmark N, Jain RK. Interstitial hypertension in human breast and colorectal tumors. Cancer Res. 1992;52(22):6371-4. http://www.ncbi.nlm.nih.gov/pubmed/1423283.
45. Kong AL, Tereffe W, Hunt KK, et al. Impact of internal mammary lymph node drainage identified by preoperative lymphoscintigraphy on outcomes in patients with stage I to III breast cancer. Cancer. 2012;118(24):6287-96. doi:10.1002/cncr.27564.
46. Wolinsky JB, Colson YL, Grinstaff MW. Local drug delivery strategies for cancer treatment: gels, nanoparticles, polymeric films, rods, and wafers. J Control Release. 2012;159(1):14-26. doi:10.1016/j.jconrel.2011.11.031.
47. Goel R, Anderson K, Slaton J, et al. Adjuvant approaches to enhance cryosurgery. J Biomech Eng. 2009;131(7):074003. doi:10.1115/1.3156804.
48. Ananthakrishnan P, Balci FL, Crowe JP. Optimizing surgical margins in breast conservation. Int J Surg Oncol. 2012;2012:585670. doi:10.1155/2012/585670.
49. Wang J, Lu Z, Gao Y, Wientjes MG, Au JL. Improving delivery and efficacy of nanomedicines in solid tumors: role of tumor priming. Nanomedicine (Lond). 2011;6(9):1605-20. doi:10.2217/nnm.11.141).
50. Hohenforst-Schmidt W, Zarogoulidis P, Darwiche K, et al. Intratumoral chemotherapy for lung cancer: re-challenge current targeted therapies. Drug Des Devel Ther. 2013;7:571-83. doi:10.2147/DDDT.S46393.
51. Korpan NN (ed.). Atlas of Cryosurgery. New York: Springer Publisher; 2001. 524 p.
52. Korpan NN. Cryosurgery: ultrastructural changes in pancreas tissue after low temperature exposure. Technol Cancer Res Treat. 2007;6:59-67.
53. Korpan NN. Cryoscience and cryomedicine: deciphering of the effect of deep low temperatures on living matter. Low Temp Med. 2010;36(3):76-83.
54. Korpan NN (ed.). Basics of Cryosurgery. Vienna: Springer Publisher; 2001. 325 p.
55. Haen SP, Pereira PL, Salih HR, Rammensee HG, Gouttefangeas C. More than just tumor destruction: Immunomodulation by thermal ablation of cancer. Clin Dev Immunol. 2011;2011. doi:10.1155/2011/160250 1.
56. Slovak R, Ludwig JM, Gettinger SN, Herbst RS, Kim HS. Immunothermal ablations — boosting the anticancer immune response. 2017:1-15. doi:10.1186/s40425-017-0284-8.
57. Apetoh L, Ladoire S, Coukos G, Ghiringhelli F. Combining immunotherapy and anticancer agents: The right path to achieve cancer cure? Ann Oncol. 2015;26(9):1813-23. doi:10.1093/annonc/mdv209.
58. Nelson D, Fisher S, Robinson B. The «Trojan Horse» approach to tumor immunotherapy: targeting the tumor microenvironment. J Immunol Res. 2014;2014:1-14. doi:10.1155/2014/789069.
59. Li J, Yang X-J, Hu L-N, Sun C-X, Yao C-G. Impacts of steep pulsed electric fields on lymphatic capillaries in VX2 implanted breast cancer in rabbits. Ai Zheng Chinese J Cancer. 2006;25(2):159162. http://www.ncbi.nlm.nih.gov/pubmed/16480578.

Кріо-асистована резекція первинного раку молочної залози в один блок та кріоабляція пухлини в супроводі з місцевою доставкою ліків із прицілом на рідинний стан пухлини. Експериментально-клінічні дослідження

М. М. Корпан [1, 2], Юєйонг Ксяо [3], Ксяофенг Ге [3], О. І. Дронов [2]

[1] Міжнародний інститут кріохірургії, Рудольфінергаус клініка, Відень, Австрія

[2] Національний медичний університет імені О. О. Богомольця, Київ

[3] Китайський народний військовий загальний госпіталь, Пекін

Мета — лікування первинної пухлини молочної залози із застосуванням кріо в поєднанні з одночасним навколо- та внутрішньопухлинним введенням синього барвника для оцінки лімфатичного картування. Було визначено локальну регіонарну ефективність інтраопераційної ін'єкції синього барвника та суміші цитотоксичних індикаторів із застосуванням кріозонду в моделі пухлини VX2, а також її трансляційну цінність у кріохірургії пухлини молочної залози лише з використанням синього барвника. Картування сторожових лімфатичних вузлів, патологічне визначення пухлини та межі резекції були досяжними.

Матеріали та методи. Тридцять дев'ять пацієнтів віком (52,4 ± 19,0) року (середнє значення, стандартне відхилення) з первинним раком молочної залози I—IV стадій були рандомізовано відібрані та проліковані у приватній клініці Rudolfinerhaus у Відні, Австрія. Під контролем комп'ютерної томографії було введено 2 мл суміші цитотоксичних індикаторів у п'яти аліквотах на краю 16 заморожених або нормотермічних пухлин VX2. Було оцінено інтраопераційну та післяопераційну ефективність доставки препарату та його терапевтичну ефективність у первинній пухлині за допомогою комп'ютерної томографії, загального обстеження та патоморфологічного дослідження. Тридцяти чотирьом пацієнтам з первинними формами раку молочної залози від T1 до T4 було виконано цикл заморожування-розморожування пухлини за допомогою кріозонду під контролем ультразвуку, картування лімфи із застосуванням синього барвника та оперативне втручання. Досліджували резектований зразок, поширення синього барвника по поверхні первинної пухлини, лімфатичний(і) вузол(и), паренхіму молочної залози та порожнину резекції.

Результати. Двадцять дев'ять із 38 пацієнтів мали локалізований первинний рак молочної залози, який, за оцінками, був операбельним без необхідності застосування неоад'ювантної хіміотерапії. 87 % мали від одного до дванадцяти забарвлених пахвових лімфатичних вузлів; у 72 % було виявлено поширення барвника на інший квадрант і резекційну порожнину. Непроникні для рідини заморожені VX2 або пухлини молочної залози транспортували препарат(и) за дугоподібною схемою на межі «пухлина-хазяїн» незалежно від дози заморожування, кількості циклів заморожування-розморожування, фракціонування дози препарату, характеристик пухлини або розмірів пухлини. Під час плавлення суміш цитотоксичних індикаторів поширювалася в межах 50 % пухлини VX2 і відображала межу «пухлина — хазяїн»; цей процес був масштабним при нормотермії. Пробіл на знімку КТ відповідав 20 % некрозу фокального краю при патології (VX2). В обох дослідженнях дозове фарбування синім барвником відбувалося лінійно на поверхні межі «пухлина-хазяїн» і в пухлині.

Висновки. Дослідження прокладає шлях для варіантів інтраопераційного кріолікування первинного раку молочної залози. Ми показали, що нашу кріохірургічну техніку багаторазового заморожування глибоких пухлин для резекції en bloc або для абляції первинного раку молочної залози in situ, сприяючи моніторингу IOUS, можна поєднати з одночасним введенням індикаторних барвників під час традиційної хірургії, що потім дозволяє проводити лімфатичне картування. Інтраопераційні методи введення препаратів за допомогою заморожування та таргетування під час кріоабляції пухлини VX2 успішно перетворюються на локорегіональне таргетування синім барвником і лімфатичне картування під час кріоасистентної хірургії раку молочної залози. Ми дослідили здатність нашої стратегії запобігати міграції пухлинних клітин, але не введених індикаторів, до лімфатичного дренажу при стандартній резекції заморожених злоякісних пухлин молочної залози.

Ключові слова: експеримент, пухлина VX2, клінічне дослідження, первинний рак молочної залози, резекція пухлини із застосуванням кріо, кріоабляція, внутрішньопухлинна ін'єкція індикатора, лімфатичне картування.

FOR CITATION

Korpan NN, Yueyong Xiao 3, Xiaofeng He 3, Dronov OI. Cryo-assisted resection of primary breast cancer en bloc and tumor cryoablation connected with local drug delivery and targeting of tumor fluids. Experimental and clinical studies. General Surgery (Ukraine). 2023;1;7-20. http://doi.org/10.30978/GS-2023-1-7.

UDC 617.541-089.5-009.7:616-089.168
DOI http://doi.org/10.30978/GS-2023-1-21

ISSN 2786-5584 print
ISSN 2786-5592 online

Multimodal approach to pain management in thoracic surgery

H. Poniatovska [1, 2], S. Dubrov [1, 2]

[1] Bogomolets National Medical University, Kyiv
[2] Communal non-profit enterprise «Kyiv City Clinical Hospital No 17»

✉ Halyna Poniatovska: slavuta.halyna@gmail.com

H. Poniatovska, http://orcid.org/0000-0001-7224-4213
S. Dubrov, http://orcid.org/0000-0002-2471-3377

The American Cancer Society estimated that 68,820,000 men and 61,360,000 women in the United States of America would die from lung and bronchial cancer in 2022, which is equal to 21 % of all cancer deaths. Patients who undergo thoracotomy have a higher risk of postoperative complications due to the severe pain syndrome that typically develops after surgery. Even though there has been extensive research on the advantages and disadvantages of various perioperative analgesia techniques, the search for the best and safest still continues.

Objective — to improve the results of perioperative anesthesia in patients undergoing thoracotomy by choosing the optimal method of analgesia.

Materials and methods. A total of 59 patients with lung cancer who underwent thoracotomy at the communal non-profit enterprise «Kyiv City Clinical Hospital No 17» from 2018 to 2020 were included in an open-label noncommercial randomized controlled clinical trial. Patients were divided into 2 groups: the multimodal analgesia (MA) group (32 patients) and the epidural analgesia (EA) group (27 patients). According to the concept of preemptive analgesia, patients in the MA group received 1000 mg of paracetamol and 50 mg of dexketoprofen intravenously 1 hour before surgery. In the postoperative period, dexketoprofen and paracetamol were administered every 8 hours in combination with epidural analgesia. During postoperative epidural analgesia, patients received 40 mg of a 2 % lidocaine solution through a catheter inserted into the epidural space (Th5—Th6) and a ropivacaine 2 mg/mL (3—14 mL/h) infusion. Patients in the EA group received only epidural analgesia in the postoperative period. After placement of an epidural catheter in the epidural space (Th5—Th6), they had an injection of 40 mg of a 2 % lidocaine solution and an epidural infusion of ropivacaine 2 mg/ml (3—14 mL/h).

Results. The study groups did not demonstrate a statistically significant difference in terms of age, hight, weight, a grade of anesthesiological risk (ASA), blood loss, surgery duration, and surgical volume ($p > 0,05$). The level of analgesia was assessed using the numerological rating scale (NRS) after 3, 6, 24, and 32 hours after surgery. Every research stage revealed a significant difference in the level of pain syndrome between the study groups ($p < 0.05$). Patients in the EA group experienced more severe pain syndrome than those in the MA group. Consequently, 7 patients (26 %) in the EA group were anesthetized with morphine 10 mg intramuscularly compared to 3 patients (9 %) in the MA group.

Conclusions. In patients undergoing thoracic surgery, a multimodal analgesic approach, which includes the use of COX-2 and COX-3 inhibitors in combination with epidural analgesia, has been shown to produce better analgesia compared to epidural anesthesia alone. The beneficial effect of multimodal analgesia was seen in a significant difference ($p < 0.05$) in the intensity of pain syndrome between the study groups in the early postoperative period after thoracotomy.

Keywords
NSAIDs, enhanced recovery after surgery, multimodal analgesia, postoperative pain.

ARTICLE • Received 2023-02-01 • Received in revised form 2023-02-27
© 2023 Authors. Published under the CC BY-ND 4.0 license

19.3 million new cases of cancer were registered in 2020. Lung cancer is the second most common cancer worldwide. It is the most common cancer in men and the second most common cancer in women. In 2020, there were 2,206,771 new cases of lung cancer diagnosed in both genders and at all ages worldwide. It is 11.4 % of the total 19,292,789 new cases of cancer globally.

According to the data provided by the American Cancer Society, lung cancer is by far the leading

cause of cancer death, making up 1,796,144 cases per year, or 18 % of all cancer deaths [29]. The American Cancer Society estimated that 68,820,000 men and 61,360,000 women in the United States of America would die from lung and bronchial cancer in 2022, which is equal to 21 % of all cancer deaths [4].

Oncological diseases of the upper and lower respiratory tract are the most common causes of morbidity and mortality in the structure of malignant neoplasms in Ukrainian men aged from 30 to 74 years. According to the data provided by the National Cancer Registry (bulletin No 22) for 2020, the incidence rate of malignant neoplasms of the trachea, bronchi, and lungs was 15.2 % and the mortality rate was 16.5 % [1]. The total number of registered patients with oncological diseases of the trachea, bronchi, and lungs was 32,701 per 100,000 population (23,539 per 100,000 population in men and 9,162 per 100,000 population in women) [2].

43.3 % of patients with the 4th stage of malignant neoplasms of the trachea, bronchi, and lungs were identified for the first time in Ukraine in 2021. For other stages, this indicator was as follows: 7.9 % with the 1st stage, 7.8 % with the 2nd stage, and 30 % with the 3rd stage [2].

Cigarette smoking is the number one risk factor for lung cancer. The CDC reports that people who smoke cigarettes are 15 to 30 times more likely to develop lung cancer or die from lung cancer than people who do not smoke. Even smoking a few cigarettes a day or smoking occasionally increases the risk of lung cancer [8]. The tobacco epidemic is one of the greatest public health threats that the world has ever faced. Tobacco kills more than 8 million people each year worldwide. More than 7 million of those deaths are the result of direct tobacco use, while around 1.2 million are the result of nonsmokers being exposed to second-hand smoke [14]. Mostly, lung cancer requires complex treatment, which includes surgery (atypical resection, lobectomy, or pneumonectomy). The extent of surgical intervention depends on the stage, morphological characteristics, and localization of the tumor. A thoracotomy is a surgical procedure in which an incision is made between the ribs for the purpose of inserting a retractor for further visualization and removal of the tumor. Operative interventions on the lungs, such as a thoracotomy, which is one of the most painful procedures, are accompanied by severe pain syndrome in the postoperative period and can lead to an increased number of cases of chronic pain syndrome after hospital discharge [13, 16, 24].

Among the factors that may be linked to postoperative pain are intraoperative damage to the ribs caused by the insertion of a retractor, damage to the intercostal nerves, the use of drains, rib raising, suturing technique, etc.

Due to the severe pain syndrome in the postoperative period, patients who undergo thoracotomy have an increased risk of developing postoperative complications, with pneumonia and atelectasis prevailing [7]. In most cases, these complications result from impaired sputum evacuation due to the patient's inability to adequately cough up sputum and a significant decrease in breathing volume [7, 11, 13, 17].

Complications increase the patient's recovery time and the length of hospital stay, which leads to rising costs of medical treatment and a longer period of temporary disability. Since pain is a subjective sign, doctors often underestimate its intensity for a particular patient. As a result, the chance of developing complications in the postoperative period increases. According to the US Institute of Medicine, from 30 % to 75 % of patients report severe pain despite anesthesia [9].

Modern perioperative analgesia includes multimodal analgesia, which combines the administration of two or more analgesic drugs that act on the transduction, transmission, modulation, and perception of pain impulses.

An Enhanced Recovery After Surgery (ERAS) program, or «fast-track surgery», was pioneered by H. Kehlet, a Danish colorectal surgeon, in the 1990s. It is an evidence-based multimodal approach that has been shown to limit surgical trauma burden, relieve pain, and ensure early and uneventful postoperative recovery. The ERAS program addresses perioperative care concerns, aspects of the surgical technique, and the postoperative period in patients who undergo surgical treatment [19, 31]. ERAS is based on pathophysiological principles that allow for reduced postoperative stress, pain relief, early mobilization, and the commencement of early oral nutrition [20].

There are many methods of perioperative analgesia for patients undergoing thoracic surgery, but the search for the best method of analgesia is still ongoing. The gold standard of this procedure is the placement of an epidural catheter at the level of Th5–Th6 in the epidural space with the aim of further administration of anesthetics for analgesia at the appropriate level. Analgesia is achieved by blocking the transmission of impulses along the nerve endings of the spinal cord. Nevertheless, not all studies have shown the advantage of epidural analgesia over alternative types of regional anesthesia [27].

Epidural analgesia (EA) is most often used in thoracic surgery. However, since oncological diseases of the trachea, bronchi, and lungs are among the 5 most common nosological forms of malignant

neoplasms that affect men aged 30 to 74 years in Ukraine, it is necessary to take into account possible complications that may arise during or after placing an epidural catheter [2]. The most frequent side effects of epidural analgesia are hypotension in the intraoperative and postoperative periods, dizziness, itching at the puncture site, and uneven or unilateral analgesia due to improper positioning of the epidural catheter [15].

In 1983, C. J. Woolf first proposed the concept of preemptive analgesia. In his study, he provided evidence of central sensitization, which he described as the formation of complex pain syndrome after irritation. Preemptive analgesia involves the administration of analgesic drugs before surgery in order to prevent postoperative pain [21]. In 2002, H. Kehlet and I. Dahl observed no benefit from the preoperative administration of nonsteroidal anti-inflammatory drugs compared to the postoperative one, evaluating the level of postoperative analgesia and the development of chronic pain syndrome [23].

Nonsteroidal anti-inflammatory drugs (NSAIDs), which are part of multimodal anesthesia, suppress the body's inflammatory response to a stimulus, such as surgery, by inhibiting cyclooxygenase (COX) [32]. Since the stress response to surgery may increase the risk of exacerbation of a gastric ulcer, NSAIDs should be cautiously prescribed to prevent bleeding from the gastrointestinal tract [28].

A study that involved 250 randomized patients who had recently undergone surgery showed that 80 % of patients experienced acute pain after surgery, and almost 25 % of patients experienced side effects after taking pain medication [5].

Even though there has been extensive research on the advantages and disadvantages of various perioperative analgesia techniques, the search for the best and safest still continues.

Objective — to improve the results of perioperative anesthesia in patients undergoing thoracotomy by choosing the optimal method of analgesia.

Materials and methods

The study was conducted according to the ethics principles of the Helsinki Declaration, GCP (Good Clinical Practice), and the Law of Ukraine «On Medications» and was approved by the Ethics Commission of Bogomolets National Medical University. After being informed about the research, all patients signed a research participant agreement.

The scientific research work «Optimization of Perioperative Management of Patients in Cardiothoracic Surgery» served as the foundation for this study. A total of 59 patients with lung cancer who underwent thoracotomy at the communal non-profit enterprise «Kyiv City Clinical Hospital No 17», Department of Anesthesiology and Intensive Therapy of Bogomolets National Medical University, from 2018 to 2020 were included in an open-label noncommercial randomized controlled clinical trial. Randomization was performed using an unequal randomization method. Patients were divided into 2 groups: the multimodal analgesia (MA) group and the epidural analgesia (EA) group. There were 32 patients in the MA group and 27 patients in the EA group.

According to the concept of preemptive analgesia, patients in the MA group received 1000 mg of paracetamol and 50 mg of dexketoprofen intravenously 1 hour before surgery. In the postoperative period, dexketoprofen and paracetamol were administered every 8 hours in combination with epidural analgesia. During postoperative epidural analgesia, patients received 40 mg of a 2 % lidocaine solution through a catheter inserted into the epidural space (Th5—Th6) and a ropivacaine 2 mg/mL (3—14 mL/h) infusion.

Patients in the EA group received only epidural analgesia in the postoperative period. After placement of an epidural catheter in the epidural space (Th5–Th6), they had an injection of 40 mg of a 2 % lidocaine solution and an epidural infusion of ropivacaine 2 mg/mL (3—14 mL/h).

The inclusion criteria were: (1) men and women 30 to 80 years old; (2) lung cancer requiring surgery; (3) a PS of 0 to 1 on the ECOG scale; (4) a signed research participant agreement; (5) absence of concomitant pathology or concomitant pathology in stable remission (ASA classes II—III); (6) a negative pregnancy test and the use of effective contraceptives during the entire study and 3 weeks after it; or inability to have children (hysterectomy or tubal ligation, a clinical diagnosis of infertility); or menopause for more than 1 year (absence of menstruation for at least 12 months). Adequate methods of contraception include surgical sterilization, the double-barrier method of contraception, local contraception, and the ability to follow all the statements of the agreement.

The exclusion criteria were: (1) refusal to participate in the research; (2) age under 30 or over 80; (3) hypersensitivity to dexketoprofen, paracetamol, ropivacaine, or lidocaine; (4) malignant neoplasms of the heart, pericardium and/or large vessels; (5) hemoglobin level < 90 g/L at the time of surgery; (6) participation in any other clinical trial; (7) gastric or duodenal ulcer with a risk of bleeding in the anamnesis; (8) kidney failure or liver failure; (9) pregnancy or lactation; (10) massive

intraoperative blood loss requiring transfusion of formed blood elements; (11) diabetes mellitus (type 1 and type 2); (12) any other subcompensated or decompensated somatic diseases, or those assessed as severe or moderate (ASA class IV).

The standard and analytical data models were created in Excel and in Statistica 10, respectively. All calculations and graphs were made in the Statistica 10 application.

Results and discussion

Since the principal goal of preemptive analgesia is rapid recovery, it is important to provide adequate pain relief and early mobilization of patients in the early postoperative period, which can be achieved through a multimodal approach [20]. The presence of side effects and complications related to the placement of an epidural catheter explains the search for alternative pain relief techniques. It is recommended to insert an epidural catheter into the thoracic spine at the level of the 5th—6th vertebra during thoracotomy. It is assumed that manipulation at a higher level increases the risk of neurological damage to the spinal cord. As an alternative to catheterization of the epidural space, the effectiveness of intravenous administration of non-steroidal anti-inflammatory drugs (NSAIDs), such as tramadol and lornoxicam, has been reported in patients after thoracotomy. The authors noted a reduction in side effects and pulmonary complications in patients who received NSAIDs intravenously [18].

Maintaining proper breathing in patients who have had respiratory surgery is crucial for ensuring adequate ventilation. Respiratory complications in the early postoperative period may be associated with depression of the respiratory center due to the action on the mureceptors of the respiratory center, increased muscle tone, decreased respiratory volume, and increased hypercapnia [3, 22, 25].

Our study shows a reduction in the need for opioid prescriptions since a decrease in blood pressure in patients after the administration of opioids is highly undesirable and pulmonary surgery requires a restrictive approach to infusion therapy [6].

A total of 59 patients participated in the study. The study groups did not demonstrate a statistically significant difference in terms of age, hight, weight, a grade of anesthesiological risk (ASA), blood loss, surgery duration, and surgical volume ($p > 0,05$). Table 1 presents demographic data of the groups.

18 lobectomies, 8 pneumonectomies, 4 atypical lung resections, and 2 bilobectomies were performed in the MA group, compared to 17 lobectomies, 6 pneumonectomies, 3 atypical lung resections, and 1 bilobectomy in the EA group. Figure presents surgical volume for each group.

Table 1. **Characteristics of patients by age, gender, height, weight, a grade of anesthesiological risk (ASA), blood loss, surgery duration and surgical volume**

Index	MA group (n = 32)	EA group (n = 27)
Age, years	57.4 ± 11.2	57.02 ± 10.3
Male/female	26/13	28/9
Weight,kg	75.5 ± 13.4	76.7 ± 16.7
Height, cm	170.9 ± 6.7	169.4 ± 7.5
ASA: II/III	27/5	23/4
Blood loss, mL	369.0 ± 69.3	358.0 ± 76.3
Duration of surgery, min	137.5 ± 91.8	164.0 ± 61.06

All $p > 0.05$.

Blood pressure, heart rate, respiration rate, and SpO_2 were evaluated during the patients' stay in the ICU. Additionally, all patients in both groups were administered nasal or mask oxygen with a flow of 3—4 L/min for the first 12—24 hours after surgery.

The level of analgesia was assessed using the numerological rating scale (NRS), where 0 mm is the absence of pain and 100 mm is unbearable pain. Pain control assessment times were 3, 6, 24, and 32 hours after surgery.

Analgesia was considered effective if the pain level was up to 50 mm according to the NRS scale and there was no need for additional morphine analgesia. Table 2 present comparison of NRS valuesin particular groups after surgery.

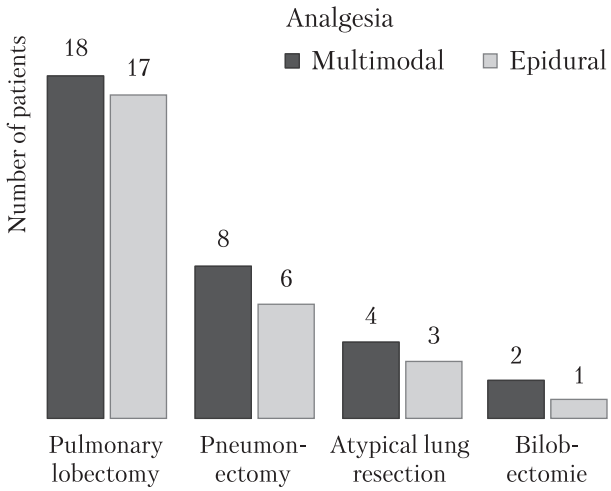

Figure. **Differentiation of operations for each group**

Table 2. **Comparison of NRS values in the study groups 3, 6, 24, and 32 hours after surgery**

Index	MA group	EA group
3 hours after surgery	21.4 ± 1.3	31.2 ± 2.1*
6 hours after surgery	25.3 ± 1.7	37.4 ± 1.8*
24 hours after surgery	28.1 ± 1.5	34.6 ± 2.3***
32 hours after surgery (during coughing)	31.7 ± 2.1	41.2 ± 2.7**
Requirement for additional analgesia with morphine	3 (9 %)	7 (26 %)

* $p < 0.001$; ** $p < 0.01$; *** $p < 0.05$.

The assessment of pain syndrome 3 hours after surgery showed that patients in the EA group experienced more intensive pain syndrome than patients in the MA group, although the indicator corresponded to mild or moderate pain. 6 hours after surgery, 4 patients (14 %) in the EA group reported severe pain that was not reduced by an increased bolus injection volume of ropivacaine into the epidural catheter. These patients were anesthetized with 1 mL of 1 % morphine intramuscularly. Only 2 patients (6 %) in the MA group reported severe pain and were also anesthetized with 1 mL of 1 % morphine intramuscularly. A day after surgery, early mobilization was used in both groups, which included sitting on the bed. Another 3 patients (11 %) from the EA group reported pronounced pain along with irritating effect of mobilization and cough. They were anesthetized with an additional dose of morphine. In the MA group, only 1 patient (3 %) reported pronounced pain. 32 hours after surgery, patients in both groups were subjectively satisfied with the level of analgesia, which was estimated to be less than 40 mm on the NRS scale during rest. Therefore, the level of analgesia was assessed during coughing. Although all patients in both groups did not report pain before being asked to cough up sputum, patients in the EA group reliably reported more severe pain during coughing.

More than one analgesic modality is used to achieve effective pain control after surgery. Systemic administration of two or more drugs that are strategically combined to block pain perception at various locations in the peripheral and central nervous systems while providing analgesia may improve pain relief and reduce opioid consumption [12].

In many other studies, multimodal analgesia provided better analgesia with more rapid postoperative recovery and a lower number of side effects. It most likely has a positive impact on further outcomes [10, 30]. ERAS protocols, minimally invasive surgery, and intraoperative anesthetic management improve the prognosis and safety of thoracic surgery.

Admission to the ICU is especially recommended for patients with comorbidities, a reduced cardiopulmonary reserve, extensive lung resections, or those requiring support due to life-threatening organ failure. Intensive cardiorespiratory monitoring, proper management of thoracic drainage, aggressive pain control (multimodal analgesia and regional anesthesia), nausea, and multimodal rehabilitation are key elements for avoiding adverse effects during the postoperative period [26].

Conclusions

The increasing incidence of lung cancer worldwide contributes to the growing necessity of surgical treatment. After thoracotomy, patients require the safest and most effective method of analgesia. In patients undergoing thoracic surgery, a multimodal analgesic approach, which includes the use of COX-2 and COX-3 inhibitors in combination with epidural analgesia, has been shown to produce better analgesia compared to epidural anesthesia alone. The beneficial effect of multimodal analgesia was seen in a significant difference ($p < 0.05$) in the intensity of pain syndrome between the study groups in the early postoperative period after thoracotomy.

Preemptive analgesia in combination with epidural analgesia produces a satisfactory level of analgesia and allows for reduced use of opioids in the early postoperative period.

Declaration of interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors contributions

H. Poniatovska: idea, design, materials and methods, formalization, statistics; S. Dubrov: materials and methods, design, data processing, conclusions.

References

1. Федоренко ЗП, Гулак ЛО, Михайлович ЮЙ та ін. Рак в Україні, 2020-2021. Захворюваність, смертність, показники діяльності онкологічної служби [Електронний ресурс]. Бюлетень Національного канцер-реєстру України 2021;22. http://www.ncru.inf.ua/publications/BULL_22/index.htm
2. Федоренко ЗП, Сумкіна ОВ, Гулак ЛО, Горох ЄЛ та ін. Рак в Україні, 2020-2021. Захворюваність, смертність, показники діяльності онкологічної служби [Електронний ресурс]. Бюлетень Національного канцер-реєстру України 2022;23. http://www.ncru.inf.ua/publications/BULL_23/index.htm

3. Algera MH, Olofsen E, Moss L, et al. Tolerance to opioid-induced respiratory depression in chronic high-dose opioid users: a model-based comparison with opioid-naïve individuals. Clin Pharmacol Ther. 2021 Mar;109(3):637-45. doi: 10.1002/cpt.2027. Epub 2020 Oct 5.
4. American Cancer Society. Cancer Facts & Figures 2022. Information and Resources about for Cancer: Breast, Colon, Lung, Prostate, Skin. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2022.html
5. Apfelbaum J, Chen C, et al. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. Anesth Analg 2003 Aug;97(2):534-40. doi: 10.1213/01.ANE.0000068822.10113.9E
6. Baldo BA. Toxicities of opioid analgesics: respiratory depression, histamine release, hemodynamic changes, hypersensitivity, serotonin toxicity. Arch Toxicol. 2021 Aug;95(8):2627-42. doi: 10.1007/s00204-021-03068-2. Epub 2021 May 11.
7. Carr DB, Goudas LC. Acute pain. Lancet. 1999 Jun;353(9169):2051-8. doi: 10.1016/S0140-6736(99)03313-9.
8. CDC. Centers for Disease Control and Prevention. What are the risk factors for lung cancer? https://www.cdc.gov/cancer/lung/basic_info/risk_factors.htm
9. Chauvin M. Prise en charge post-opératoire. La douleur après l'intervention chirurgicale [Postoperative patient management. Pain after surgical intervention]. Presse Med. 1999 Jan 30;28(4):203-11. (In French)
10. Dunn LK, Durieux ME, Nemergut EC. Non-opioid analgesics: Novel approaches to perioperative analgesia for major spine surgery. Best Pract Res Clin Anaesthesiol. 2016;30:79-89.
11. Fiorelli A, Morgillo F, Milione R, et al. Control of post-thoracotomy pain by transcutaneous electrical nerve stimulation: effect on serum cytokine levels, visual analogue scale, pulmonary function and medication. Eur J Cardiothorac Surg. 2012 Apr;41(4):861-8; discussion 868. doi: 10.1093/ejcts/ezr108.
12. Gelman D, Gelmanas A, Urbanaitė D, Tamošiūnas R, Sadauskas S. Role of multimodal analgesia in the evolving enhanced recovery after surgery pathways. Medicina (Kaunas). 2018 Apr 23;54(2):20. doi: 10.3390/medicina54020020.
13. Gerner P. Postthoracotomy pain management problems. Anesthesiol Clin. 2008 Jun;26(2):355-67. doi: 10.1016/j.anclin.2008.01.007
14. Global Burden of Disease [database].Washington, DC: Institute of Health Metrics; 2019. IHME, accessed 17 July 2021.
15. Horlocker TT, Vandermeuelen E, Kopp SL, et al. Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Fourth Edition). Reg Anesth Pain Med. 2018 Apr;43(3):263-309. doi: 10.1097/AAP.0000000000000763.
16. Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. National Academies Press; 2011. 382 p.
17. Iyer A, Yadav S. Postoperative care and complications after thoracic surgery. in principles and practice of cardiothoracic surgery. Intech Open; 2013. https://doi.org/10.5772/55351
18. Jin J, Min S, Chen Q, Zhang D. Patient-controlled intravenous analgesia with tramadol and lornoxicam after thoracotomy: A comparison with patient-controlled epidural analgesia. Medicine (Baltimore). 2019 Feb;98(7):e14538. doi: 10.1097/MD.0000000000014538. PMID: 30762794; PMCID: PMC6408084.
19. Kehlet H, Dahl JB. The value of «multimodal» or «balanced analgesia» in postoperative pain treatment. Anesthesia & Analgesia. 1993 Nov;77(5):1048-56.
20. Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. Ann Surg. 2008 Aug;248(2):189-98. doi: 10.1097/SLA.0b013e31817f2c1a. PMID: 18650627.
21. Kissin I. Preemptive analgesia. Anesthesiology Anesthesiology. 2000 Oct;93(4):1138-43. doi: 10.1097/00000542-200010000-00040.
22. Mercadante S. Opioid analgesics adverse effects: the other side of the coin. Curr Pharm Des. 2019;25(30):3197-202. doi: 10.2174/1381612825666190717152226.
23. Møiniche S, Kehlet H, Dahl JB. A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief: the role of timing of analgesia. Anesthesiology. 2002 Mar;96(3):725-41. doi: 10.1097/00000542-200203000-00032
24. Montes A, Roca G, Sabate S, Lao JI, Navarro A, et al; GENDOLCAT Study Group. Genetic and Clinical Factors Associated with Chronic Postsurgical Pain after Hernia Repair, Hysterectomy, and Thoracotomy: A Two-year Multicenter Cohort Study. Anesthesiology. 2015 May;122(5):1123-41. doi: 10.1097/ALN.0000000000000611
25. Moran BL, Myburgh JA, Scott DA. The complications of opioid use during and post-intensive care admission: A narrative review. Anaesth Intensive Care. 2022 Mar;50(1-2):108-26. doi: 10.1177/0310057X211070008. Epub 2022 Feb 16.
26. Muñoz de Cabo C, Hermoso Alarza F, Cossio Rodriguez AM, Martín Delgado MC. Perioperative management in thoracic surgery. Med Intensiva (Engl Ed). 2020 Apr;44(3):185-191. English, Spanish. doi: 10.1016/j.medin.2019.10.012. Epub 2019 Dec 20. PMID: 31870510.
27. Rawal N. Epidural technique for postoperative pain: gold standard no more? Reg Anesth Pain Med. 2012;37(3):310-7. doi: 10.1097/AAP.0b013e31825735c6.
28. Sostres C, Gargallo CJ, Arroyo MT, Lanas A. Adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs, aspirin and coxibs) on upper gastrointestinal tract. Best Pract Res Clin Gastroenterol. 2010 Apr;24(2):121-32.
29. Sung, H, Ferlay, J, Siegel, RL, Laversanne, M, Soerjomataram, I, Jemal, A, Bray, F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021:71:209-249. https://doi.org/10.3322/caac.21660
30. Tan M, Law LS, Gan TJ. Optimizing pain management to facilitate Enhanced Recovery after Surgery pathways. Can J Anesth. 2015;62:203-18. [CrossRef] [PubMed]
31. Upp J, Kent M, Tighe PJ. The evolution and practice of acute pain medicine. Pain Med. 2013 Jan;14(1):124-44. doi: 10.1111/pme.12015.
32. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nat New Biol. 1971 Jun 23;231(25):232-5.

Мультимодальний підхід до знеболювання в торакальній хірургії

Г. Б. Понятовська [1, 2], С. О. Дубров [1, 2]

[1] Національний медичний університет імені О. О. Богомольця, Київ

[2] КНП «Київська міська клінічна лікарня № 17»

За прогнозом Американського онкологічного товариства, у 2022 р. 68 820 000 чоловіків і 61 360 000 жінок у США мали померти від раку легенів і бронхів, що становить 21 % від усіх смертей від раку. У зв'язку з виразним больовим синдромом у післяопераційний період у хворих, які перенесли операцію торакотомії, підвищується ймовірність розвитку післяопераційних ускладнень. Попри наявність великої кількості публікацій у медичних ресурсах про переваги та недоліки того чи того методу періопераційного знеболювання, триває пошук найкращого та найбезпечнішого методу.

Мета — поліпшити результати періопераційного знеболювання пацієнтів при торакотомії шляхом вибору оптимального методу.

Матеріали та методи. У відкрите некомерційне рандомізоване контрольоване клінічне дослідження було залучено 59 хворих на рак легені, які перенесли торакотомію в Київській міській клінічній лікарні № 17 у період з 2018 до 2020 р. Пацієнтів розподілили на дві групи: групу мультимодальної аналгезії (МА) — 32 пацієнти та групу епідуральної аналгезії (ЕА) — 27 пацієнтів. Відповідно до концепції превентивної аналгезії пацієнти групи МА отримували 1000 мг парацетамолу та 50 мг декскетопрофену внутрішньовенно за 1 год до розрізу. У післяопераційний період декскетопрофен та парацетамол вводили кожні 8 год у поєднанні з епідуральною аналгезією (40 мг 2 % розчину лідокаїну при встановленні катетера в епідуральний простір (Th5–Th6) та ропівакаїн у дозі 2 мг/мл (3—14 мл/год) у післяопераційний період). Пацієнти у групі ЕА отримували лише епідуральну аналгезію (після встановлення епідурального катетера в епідуральний простір (Th5–Th6) вводили 40 мг 2 % розчину лідокаїну, у післяопераційний період — епідурально ропивакаїн у дозі 2 мг/мл (3—14 мл/год)).

Результати. У досліджуваних групах не виявлено статистично значущої різниці ($p > 0,05$) за віком, зростом, масою тіла, ступенем анестезіологічного ризику (ASA), об'ємом крововтрати, тривалістю та обсягом оперативного втручання. Рівень аналгезії оцінювали за нумерологічною шкалою (NRS) через 3, 6, 24 і 32 год після операції. У групі ЕА виявлено статистично значущо більшу різницю за рівнем больового синдрому на кожному етапі дослідження ($p < 0,05$). Сім (26 %) пацієнтів цієї групи отримали додаткове знеболювання морфіном у дозі 10 мг внутрішньом'язово, у групі МА — 3 (9 %).

Висновки. Мультимодальний підхід до знеболювання хворих, які перенесли торакальні операції, який передбачає використання препаратів циклооксигенази-2 і циклооксигенази-3 та епідуральної аналгезії, продемонстрував кращий рівень аналгезії порівняно з епідуральною аналгезією. Про це свідчила статистично значуща ($p < 0,05$) різниця при оцінці виразності больового синдрому в ранній період після торакотомії.

Ключові слова: НПЗП, прискорене відновлення після операції, мультимодальна аналгезія, післяопераційний біль.

FOR CITATION

Poniatovska H, Dubrov S. Multimodal approach to pain management in thoracic surgery. General Surgery (Ukraine). 2023;1;21-27. http://doi.org/10.30978/GS-2023-1-21.

UDC 616.367-003.7-089.832-036.8
DOI http://doi.org/10.30978/GS-2023-1-28

ISSN 2786-5584 print
ISSN 2786-5592 online

Results of laparoscopic choledocholithoextraction and choledochoscopy for difficult choledocholithiasis: a single centre experience

Y. M. Susak, M. M. Maksimenko, L. Y. Markulan, R. V. Honza, I. I. Tiuliukin, V. V. Volkovetskii

Bogomolets National Medical University, Kyiv

✉ Vitalii Volkovetskii: vitalikvolkovetsky@gmail.com

Y. M. Susak, http://orcid.org/0000-0002-5102-485X
M. M. Maksimenko, http://orcid.org/0000-0003-2507-1238
L. Y. Markulan, http://orcid.org/0000-0003-2879-5012
R. V. Honza, http://orcid.org/0009-0007-9357-3260
I. I. Tiuliukin, http://orcid.org/0000-0001-7965-2922
V. V. Volkovetskii, http://orcid.org/0000-0003-3843-9783

The management of difficult choledocholithiasis, which accounts for 10—15 % of all cases of bile duct stones, has not yet been definitively defined. One of the treatment options for difficult choledocholithiasis is laparoscopic choledocholithoextraction combined with choledochoscopy.

Objective — to evaluate the experience of a single centre in the treatment of difficult choledocholithiasis using laparoscopic choledocholithoextraction and choledochoscopy.

Materials and methods. A total of 47 patients, including 16 (34 %) men and 31 (66 %) women with difficult choledocholithiasis, were enrolled in the study and received treatment at our centre. All patients were operated on using laparoscopic choledocholithoextraction combined with choledochoscopy. Thereafter, the results of treatment were analysed for the cohort of patients. In the study, we identified the causes of difficult choledocholithiasis and evaluated the achievement of complete bile duct clearance, the surgery duration, total and postoperative bed days, complications, and mortality.

Results. All patients underwent laparoscopic choledocholithoextraction combined with choledochoscopy. The causes of difficult choledocholithiasis were as follows: characteristics of bile duct stones — 27 (57.4 %), altered anatomy of the organs of the hepatopancreatobiliary zone — 11 (23.6 %), specific location of bile duct stones — 9 (19.1 %). After laparoscopic choledocholitoextraction combined with choledochoscopy, complete bile duct clearance was achieved in 95.7 % of cases. The average duration of the operation was 130.0 ± 14.7 min. The length of hospital stay after surgery was, on average, 14.3 ± 1.7 days. 4 (8.5 %) patients had complications corresponding to classes II (2 (4.2 %)) and III (2 (4.2 %)) according to the standardized Clavien-Dindo classification (2009).

Conclusions. Laparoscopic choledocholithoextraction combined with choledochoscopy can be used as one of the technologies for the treatment of difficult choledocholithiasis.

Keywords
difficult choledocholithiasis, laparoscopic choledocholithoextraction, laparoscopic choledochoscopy.

ARTICLE • Received 2023-02-12 • Received in revised form 2023-03-02
© 2023 Authors. Published under the CC BY-ND 4.0 license

The frequency of bile duct stones in patients with symptomatic gallstone disease varies widely and reaches 5—33 %, according to age [13, 26, 33]. In 85—90 % of cases, choledocholithiasis is successfully treated with endoscopic papillosphincterotomy (EPST) and lithoextraction, which are currently the standard treatment for this pathology [12, 26, 32—34]. However, in 10—15 % of cases, choledocholithiasis is considered endoscopically difficult, and other technologies and equipment are needed to solve this problem [12, 14, 32—34]. Laparoscopic choledocholithoextraction combined with choledochoscopy is a promising direction for the treatment of difficult choledocholithiasis [2, 4, 18, 23, 33].

Table 1. **Criteria for difficult choledocholithiasis [26]**

Category	Condition	Basis
Characteristics of bile duct stones	Large stone (> 15 mm) Multiple choledocholithiasis (> 3 stones, size > 10 mm) Atypical form of bile duct stones (barrel-shaped)	Indication for lithotripsy Impossibility of stone extraction with the Dormia basket
Location of bile duct stones	Intrahepatic ducts Bile duct stones above the stricture of the duct Mirizzi syndrome	Difficulty in reaching bile duct stones
Altered anatomy	Stenosis of the esophagus, stomach, or duodenum Condition after gastrectomy and Billroth II gastric resection Parapapillary diverticulum Vitreous edema of the duodenum	Difficulty in reaching the major duodenal papilla
Patient condition	Various terminal states Significant coagulation disorders	High risk of fatal complications

To date, there is no single consensus on the definition of difficult choledocholithiasis, and there are no standards for the treatment of this pathology [2, 7, 13, 26].

Objective — to evaluate the experience of a single centre in the treatment of difficult choledocholithiasis using laparoscopic choledocholithoextraction and choledochoscopy.

Materials and methods

The study was performed at the Department of Surgery No 2 of the Communal non-profit enterprise «Kyiv City Clinical Hospital of Emergency Medical Care», specializing in the treatment of diseases of the hepatopancreatobiliary zone, which is the clinical base of the Department of Surgery with a Course in Emergency and Vascular Surgery at O.O. Bogomolets National Medical University. A total of 47 patients, including 16 (34 %) men and 31 (66 %) women with difficult choledocholithiasis, were enrolled in the study and received treatment at our centre. Thereafter, the results of treatment were analysed for the cohort of patients. The average age of patients was 60.3 ± 1.9 years (men — 57.8 ± 1.9 years; women — 62.2 ± 1.9 years). The study participants fell between the ages of 32 and 82. All patients underwent laparoscopic choledocholithoextraction combined with choledochoscopy.

Difficult choledocholithiasis was assigned based on the presence of severity factors complicating endoscopic retrieval of common bile duct stones (Table 1).

The diagnosis of difficult choledocholithiasis was established using ultrasound of the abdominal cavity, duodenoscopy, and endoscopic retrograde cholangiopancreatography. Computerized tomography with contrast and magnetic resonance cholangiopancreatography were additionally used in 2 (4.3 %) and 1 (2.1 %) patients, respectively, because ultrasound sometimes failed to provide adequate visualization of the common bile duct and biliary tree. The risks of choledocholithiasis were determined according to the criteria of the American Society of Gastrointestinal Endoscopy (Table 2) [20].

We collected and analysed the following data: demographic indicators, the achievement of complete bile duct clearance, recurrent choledocholithiasis within a year, the presence and severity of cholangitis according to the severity grading of cholangitis (Tokyo Guidelines 2013) (Table 3, 4), jaundice (serum bilirubin rises to 2 to 2.5 mg/dL) [14], the diameter of the common bile duct, number of bed days before and after surgery, and total bed days, the patients' physical status according to the ASA classification, and previous surgical interventions. Postoperative complications were

Table 2. **Predictors of choledocholithiasis [20]**

Predictors	Description
Very strong	Common bile duct stone on ultrasound Clinical manifestations of cholangitis Elevated total bilirubin level > 4 mg/dL
Strong	Dilated common bile duct on ultrasound (> 6 mm) Elevated total bilirubin level (1.8—4.0 mg/dL)
Moderate	Elevated LFTs (ALT, AST) Age > 55 years Clinical manifestations of biliary pancreatitis

Table 3. **Severity grading of cholangitis [4]**

Grading of acute cholangitis	Description
Grade I (mild)	Grade I cholangitis does not meet the criteria of grade III or grade II acute cholangitis at initial diagnosis
Grade II (moderate)	Abnormal white blood cells count (≥ 12,000 mm^3, ≤ 4,000 mm^3) High fever (≥ 39 °C) Age (≥ 75 years old) Hyperbilirubinemia (total bilirubin ≥ 5 mg/dL) Hypoalbuminemia (standard deviation 0.7)
Grade III (severe)	Grade III (severe) acute cholangitis is defined as acute cholangitis that is associated with the onset of dysfunction in at least one of any of the organs/systems from Table 4

Table 4. **Dysfunction of organs/systems associated with grade III acute cholangitis**

Disfunctions	Parameters
Cardiovascular	Hypotension required dopamine ≥ 5 μg/kg per min or any dose of epinephrine
Neurological	Disturbance of consciousness
Respiratory	$PaO_2/FiO_2 \leq 300$
Renal	Oliguria, serum creatinine ≥ 2,0 mg/dL
Hepatic	International normalized ratio ≥ 1,5
Hematological	Platelet count ≤ 100,000 mm^3

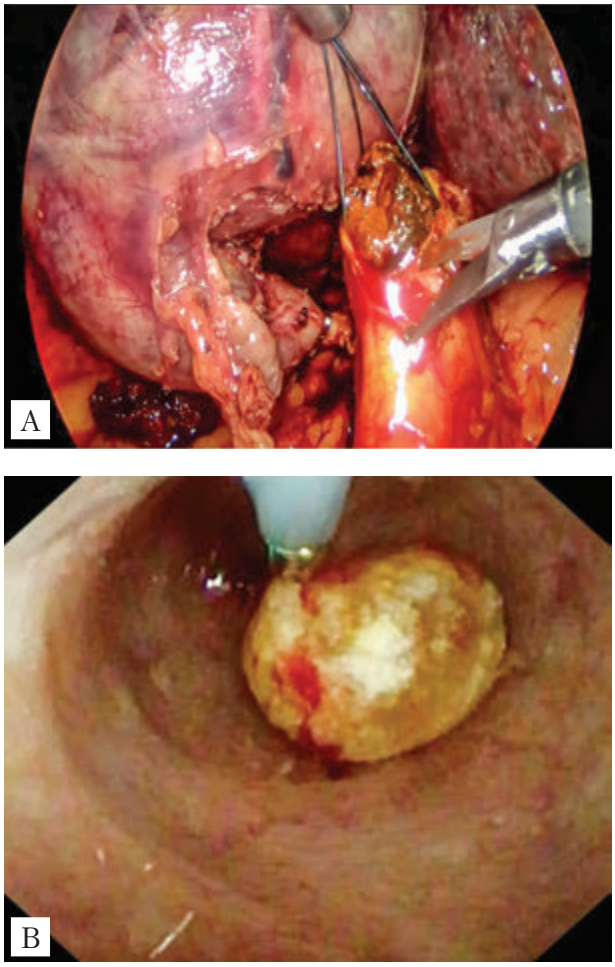

Figure 1. **Choledocholitotomy combined with choledocholithoextraction (A) and choledochoscopy guided choledocholithoextraction (B)**

determined according to the standardized Clavien-Dindo classification (2009) [9].

Patients underwent laboratory tests (complete blood count, blood biochemistry, urinalysis, analysis of arterial blood gases and electrolytes) and instrumental tests (ECG, X-ray of the chest and abdominal cavity, ultrasound examination of the abdominal cavity and retroperitoneum, EFGDS).

Methodology of laparoscopic choledocholithoextraction and choledochoscopy

Laparoscopic choledochoscopy was performed using Olympus CHF-V choledochofibroscopes (Japan) with a diameter of 5 mm.

The surgical procedure was conducted under general anesthesia. A standard 4-port technique used for laparoscopic cholecystectomy was administered, and a separate port was placed in the projection of the common bile duct for subsequent choledochoscopy. The central part of the common bile duct was isolated, and the cystic artery was ligated. A clip was applied to the proximal part of d. cysticus. The gallbladder was left and used for traction during manipulations on the common bile duct. An incision of 15 to 40 mm was made in the central part of the common bile duct, depending on the situation, after which choledocholithoextraction was performed using the Dormia basket (Fig. 1A).

The bile ducts were washed with a 0.9 % sodium chloride solution heated to 37 °C, which helped wash out small stones from the common bile duct. With the help of choledochoscopy, all reachable segments of the bile ducts were visualized, including the ampulla of Vater (the major duodenal papilla). When calculi were detected, choledocholithoextraction was performed using the Dormia

baskets through the working channel of the choledochofibroscope (Fig. 1B).

After choledocholitoextraction, choledochoscopy was performed for direct visualization of the biliary tract through an incision (Fig. 2). Thereafter, the incision into the bile duct was closed with knotted sutures (absorbable monofilament 4/0). Drainage of the bile ducts was required in cases of incomplete removal of bile duct stones or purulent cholangitis. In the presence of a gallbladder, a cholecystectomy was carried out.

Descriptive statistics are used in the research. The data are presented as the arithmetic mean ± standard error of the arithmetic mean (M ± m). A comparison of the mean values of two variables was performed using the Mann-Whitney U-test. Calculations were performed using the IBM SPSS Statistics 22.0 program.

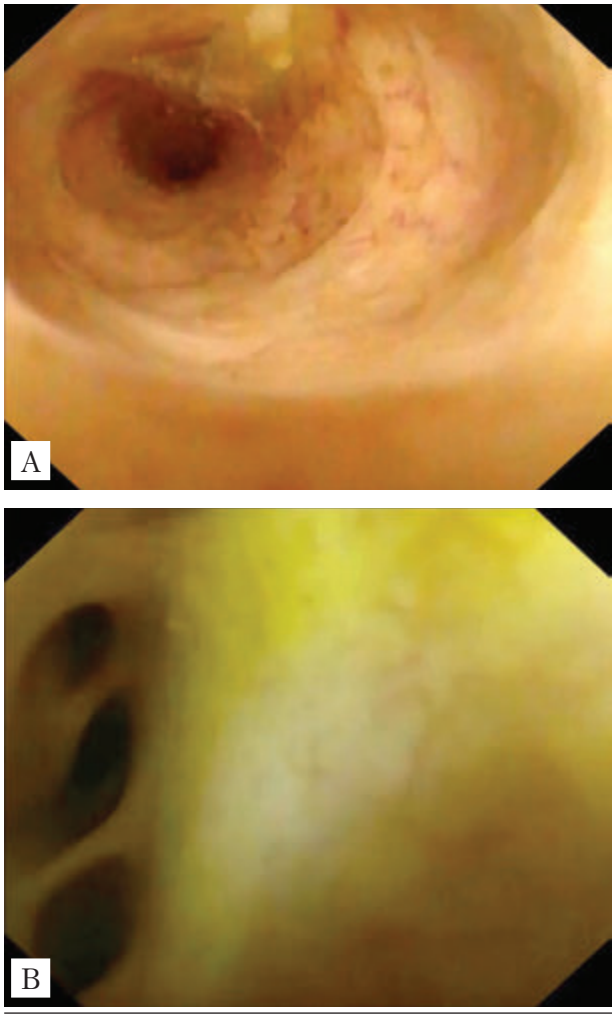

Figure 2. **Choledochoscopy: A — distal part of the bile duct after choledocholithoextraction; B — intrahepatic bile ducts after choledocholithoextraction**

Results and discussion

6 (12.8 %) patients were hospitalized within the first 24 hours, whereas 41 (87.2 %) patients were admitted after 24 hours from the time of pain onset.

The main indicators allowing classify choledocholithiasis as complex were as follows: characteristics of bile stones — 27 (57.4 %); altered anatomy of the organs of the hepatopancreatobiliary zone — 11 (23.6 %); location of the stones in the bile ducts — 9 (19.1 %) (Table 5).

In 14 (29.8 %) patients, concomitant pathology of the stomach and duodenum was detected, in particular, parapapillary diverticulum — in 8 (17 %), gastric ulcer — in 2 (4.3 %), duodenal ulcer — in 1 (2.1 %), and papillitis — in 3 (6.4 %). 14 (29.8 %) patients had acute pancreatitis of various degrees of severity, and 35 (63.8 %) had cholangitis.

A total of 6 (12.8 %) patients underwent operations on the organs of the upper abdominal cavity in the past. The preoperative physical status of patients was assessed according to the ASA PS classification (the American Society of Anesthesiologists Physical Status Classification System) and graded as ASA I in 6 (12.6 %), ASA II in 27 (57.4 %), and ASA III in 14 (30.0 %).

In 40 (85.1 %) patients with jaundice, the level of total bilirubin ranged from 32.3 to 253.4 μmol/L (from 1.9 to 14.8 mg/dL), with an average of 89.6 ± 9.2 μmol/L (5.2 ± 0.54 mg/dL).

The bile duct stones were found in the terminal part of the bile ducts in 23 (48.9 %) cases and in the distal part in 14 (29.8 %) cases (Table 6).

Table 5. **Cases of complex choledocholithiasis (n = 47)**

Indicator of complex choledocholithiasis	Number of cases
Characteristic of bile stones	27 (57.4 %)
Large stone (> 15 mm)	10 (21.2 %)
Multiple choledocholithiasis (> 3 stones, size > 10 mm)	16 (34.0 %)
Atypical form of bile duct stones (barrel-shaped)	1 (2.1 %)
Altered anatomy of the organs of the hepatopancreatobiliary zone	11 (23.6 %)
Condition after Billroth II gastric resection	4 (8.5 %)
Parapapillary diverticulum	7 (14.8 %)
Location of the stones	9 (19.1 %)
Intrahepatic ducts	5 (10.6 %)
Mirizzi syndrome	4 (8.5 %)

Table 6. **Location of bile duct stones in the bile duct (n=47)**

Location (a segment of the bile duct)	Number of cases
Terminal	23 (48.9%)
Distal	14 (29.8%)
Central	4 (8.5%)
Proximal	4 (8.5%)
Intrahepatic	2 (4.2%)

Table 7. **Results of laparoscopic choledocholithoextraction and choledochoscopy for difficult choledocholithiasis**

Parameter	Value
Surgery duration, min	130.0 ± 14.7 (85—180)
Diameter of the common bile duct, mm	12.4 ± 0.7 (7—24)
Size of extracted bile duct stones, mm	6.7 ± 0.5 (3—25)
Number of extracted bile duct stones	4.4 ± 0.5 (1—24)
External drainage of the common bile duct	5 (10.6%)
Grade II complications*	2 (4.2%)
Grade III complications*	2 (4.2%)
Conversions	1 (2.1%)
Number of bed-days before surgery	7.2 ± 2.8 (1—35)
Number of bed-days after surgery	14.3 ± 1.7 (7—22)
Total number of bed-days	21.0 ± 1.9 (7—62)

Note. Quantitative data are presented as mean and average deviation and range (M ± m (min—max)), categorial data are presented as a number of cases and percentage.
* Complications according to the standardized Clavien-Dindo classification [9].

On average, during laparoscopic choledocholithoextraction combined with choledochoscopy, 4.4 ± 0.5 bile duct stones (from 1 to 24) were removed, while according to ultrasound, the average number of stones was 1.7 ± 0.2 (from 1 to 4). Additionally, the diameter of the common bile duct (intraoperatively) ranged from 7 to 24 mm, with an average of 12.4 ± 0.7 mm, which corresponded to ultrasound data in 86% of cases.

The average values of the maximum size of bile duct stones according to ultrasound data were smaller than the actual values: 6.7 ± 0.5 mm (3—25 mm) versus 8.9 ± 0.7 mm (4—25 mm), ($p < 0.05$).

External drainage of the common bile duct was performed in 5 (10.6%) patients due to incomplete removal of bile duct stones in 2 (4.3%) and the presence of purulent cholangitis and biliary microcholedocholithiasis in 3 (6.2%).

The operative intervention lasted an average of 130.0 ± 14.7 min (85—180 min).

Complete bile duct clearance was achieved in 95.7% of cases.

A total of 4 (8.5%) patients had grade II (2 (4.2%)) and III (2 (4.2%)) complications according to the standardized Clavien-Dindo classification (2009) and leakage of bile through the wound drainage collector (2 (4.2%)).

After laparoscopic cholelithoextraction combined with choledochoscopy, 2 (4.3%) patients needed endoscopic papillosphincterotomy (EPST), lithoextraction, and endobiliary stenting due to unsuccessful retrieval of difficult bile duct stones.

Conversion was performed in 1 (2.1%) case due to suspicion of neoplasia of the common bile duct.

The average bed-day before surgery was 7.2 ± 2.8 days (from 1 day to 35 days), the postoperative bed-day was 14.3 ± 1.7 days, and the total bed-day was 21 ± 1.9 days. Summarized data on treatment results are given in Table 7.

Discussion

Endoscopic and laparoscopic methods are used in the treatment of patients with difficult choledocholithiasis [1, 12, 21, 23, 26, 33, 34].

Both methods, including one-stage laparoscopic choledocholithoextraction combined with choledochoscopy and two-stage EPST with lithoextraction and prelaparoscopic or postlaparoscopic cholecystectomy, are effective in the treatment of difficult choledocholithiasis [12, 23, 26, 33, 34]. In modern hepatobiliary surgery, preference is given to two-stage treatment of patients (endoscopic papillosphincterotomy combined with lithoextraction) [12, 26, 32]. This is probably due to the almost 50-year experience of the use of EPST and lithoextraction. In 1974, K. Kawai et al. [18] and M. Classen et al. [8] first implemented and described this technique.

In the case of transpapillary interventions, failures and complications are possible, the frequency of which increases in the case of complex choledocholithiasis [3, 32]. There is also a growing need to use additional methods of endoscopic lithoextraction, which increases the duration and cost of the operation and, depending on the chosen lithoextraction method, is accompanied by certain complications in 3.6—9.0% of cases [3, 32]. Failures in

endoscopic lithoextraction can occur during choledochal cannulation (parapapillary diverticulum, internal papillary diverticulum, inability to differentiate the major duodenal papilla) [3, 32] or lithoextraction [6, 34], mainly in the case of difficult choledocholithiasis.

According to the literature, the frequency of complications arising from transpapillary interventions is 5—18 %. Among them, the most common are acute pancreatitis, perforation of the duodenum, bleeding, and cholangitis [4, 14]. After EPST, complications were recorded in 9.4—11.1 % of cases [13, 20, 29].

If endoscopic lithoextraction methods are ineffective, laparoscopic or open choledocholithoextraction combined with choledochoscopy can be the method of choice [4, 13, 28]. This technique has been used since the mid-1990s, initially for diagnostic purposes and later to extract bile duct stones [19].

With the development of laparoscopic surgery and instrumentation, laparoscopic choledocholithoextraction combined with choledochoscopy is becoming a safer and more effective method in the treatment of choledocholithiasis and can be used primarily in cases of difficult choledocholithiasis as well as when transpapillary interventions are ineffective for certain reasons [2, 15, 25]. Laparoscopic choledocholithoextraction combined with choledochoscopy as a one-stage procedure does not require a delayed cholecystectomy. In combination, they reduce the need for repeated transpapillary interventions, provide direct visualization of the biliary system, and preserve the function of the ampulla of Vater, which prevents the occurrence of duodenobiliary reflux and reflux cholangitis and maintains the autonomy of the hepatopancreatobiliary zone. In some studies, the frequency of complications ranges from 7 % to 12.5 % [15, 17, 20, 28] which is consistent with our data.

In our study, bile leakage from the common bile duct sutures was the main complication. It was reported in 4.2 % of cases. This indicator was lower than those described by other authors (9.5 % [17], 4.35 % [15], and 7.2 % [28]).

After choledocholithoextraction combined with choledochoscopy, complete bile duct stone clearance was observed in 95.7 % of cases, compared to 82—100 % in other studies [11, 18, 34].

According to our data, there were no recurrences of choledocholithiasis after laparoscopic choledocholithoextraction combined with choledochoscopy during 1 year of observation, while according to other authors, they were recorded in 1.3—4.3 % of cases [7, 15, 20, 28].

In our study, no choledochal strictures or fatal consequences were reported after a year of observation. This is consistent with the data of other authors [11, 14, 34].

The average postoperative bed-day in our study was slightly longer 14.3 ± 1.7 days than reported by other authors (9.2 ± 2.5 days [15], 9.0 ± 3.6 [29], and 12.7 ± 1.8 [21]), which can be explained by different criteria for discharge of patients from the hospital.

The duration of surgical intervention as reported in the literature varies significantly: 133.2 min [15], 231.4 min [13], and 120 min [29]. These differences can be attributed to the variety of causes and severity of difficult choledocholithiasis in individual samples. In our study, the average duration of the operation was 130 ± 14.7 min (depending on the pathological changes caused by the disease, from 85 to 180 min).

The findings of our study show that the technique of laparoscopic choledocholithoextraction combined with choledochoscopy in cases of difficult choledocholithiasis is effective and safe. It allows for visualization of the extrahepatic bile ducts and controlled retrieval of all stones and is a one-stage surgical treatment that ensures the integrity of the ampulla of Vater and the absence of postoperative complications typical of transpapillary interventions. The benefits of this technique attest to the expediency of its use.

Conclusions

Laparoscopic choledocholithoextraction combined with choledochoscopy can be used as one of the technologies for the treatment of difficult choledocholithiasis. It is a one-stage surgical procedure that ensures the absence of complications typical of transpapillary interventions.

The unicentricity of our study is its limitation.

Declaration of interests

The authors declare that they have no conflicts of interest.

Authors contributions

Conception and design: Y. M. Susak, M. V. Maksimenko; acquisition of data: L. Y. Markulan, V. V. Volkovetskii; drafting the article Y. M. Susak; critical revision of the article: R. V. Honza, I. I. Tiuliukin.

References

1. Настащенко І.Л. Транспапілярні втручання з приводу гострого панкреатиту. Клінічна хірургія. 2015;(8):32-4. http://nbuv.gov.ua/UJRN/KlKh_2015_8_10.
2. Alexakis N, Connor S. Meta-analysis of one- vs. two-stage laparoscopic/endoscopic management of common bile duct stones. HPB (Oxford). 2012 Apr;14(4):254-9. doi: 10.1111/j.1477-2574.2012.00439.x. Epub 2012 Feb 3. PMID: 22404264; PMCID: PMC3371212.
3. Angsuwatcharakon P, Rerknimitr R. Cracking Difficult Biliary Stones. Clin Endosc. 2021 Sep;54(5):660-668. doi: 10.5946/ce.2020.256-IDEN. Epub 2021 Mar 16. PMID: 33721976; PMCID: PMC8505192.

4. Atstupens K, Plaudis H, Saukane H, Rudzats A. The role of choledochoscopy in transductal laparoscopic common bile duct exploration. General Surgery. 2021;1:10-7. https://doi.org/10.30978/GS-2021-1-10.
5. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, Tsiotos GG, Vege SS; Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis-2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013 Jan;62(1):102-11. doi: 10.1136/gutjnl-2012-302779. Epub 2012 Oct 25. PMID: 23100216.
6. Brewer Gutierrez OI, Bekkali NL. H., Raijman I, Sturgess R, Sejpal DV, Aridi HD, Sherman S, Shah RJ, Kwon RS, Buxbaum JL, Zulli C, Wassef W, AdLer DG, Kushnir V, Wang AY, Krishnan K, Kaul V, Tzimas D, DiMaio CJ, Ho S, Petersen B, Moon JH, Elmunzer BJ, Webster GJ. M., Chen YI, Dwyer LK, Inamdar S, Patrick VB, Attwell A, Hosmer A, Ko C, Maurano A, Sarkar A, Taylor LJ, Gregory MH, Strand DS, Raza A, Kothari S, Harris JP, Kumta NA, Manvar A, Topazian MD, Lee YN, Spiceland CM, Trindade AJ, Bukhari MA, Sanaei O, Ngamruengphong S, Khashab MA. Efficacy and Safety of Digital Single-Operator Cholangioscopy for Difficult Biliary Stones. Clin Gastroenterol Hepatol. 2018 Jun;16(6):918-926.e1. doi: 10.1016/j.cgh.2017.10.017. Epub 2017 Oct 24. PMID: 29074446.
7. Cai H, Sun D, Sun Y, Bai J, Zhao H, Miao Y. Primary closure following laparoscopic common bile duct exploration combined with intraoperative cholangiography and choledochoscopy. World J Surg. 2012 Jan;36(1):164-70. doi: 10.1007/s00268-011-1346-6. PMID: 22086256.
8. Classen M, Demling L. Endoskopische Sphinkterotomie der Papilla Vateri und Steinextraktion aus dem Ductus choledochus [Endoscopic sphincterotomy of the papilla of vater and extraction of stones from the choledochal duct (author's transl)]. Dtsch Med Wochenschr. 1974 Mar 15;99 (11):496-7. German. doi: 10.1055/s-0028-1107790. PMID: 4835515.
9. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, de Santibañes E, Pekolj J, Slankamenac K, Bassi C, Graf R, Vonlanthen R, Padbury R, Cameron JL, Makuuchi M. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009 Aug;250(2):187-96. doi: 10.1097/SLA.0b013e3181b13ca2. PMID: 19638912.
10. Costi R, Gnocchi A, Di Mario F, Sarli L. Diagnosis and management of choledocholithiasis in the golden age of imaging, endoscopy and laparoscopy. World J Gastroenterol. 2014 Oct 7;20 (37):13382-401. doi: 10.3748/wjg.v20.i37.13382. PMID: 25309071; PMCID: PMC4188892.
11. Dehesa A, Muñoz P, Morant P, Accuracy of New 2019 ASGE Criteria for the Prediction of Choledocholithiasis. Validation Study on Patients with Symptomatic Cholelithiasis. 2021 Published by Elsevier Inc.
12. Doshi B, Yasuda I, Ryozawa S, Lee GH. Current endoscopic strategies for managing large bile duct stones. Dig Endosc. 2018 Apr;30 Suppl 1:59-66. doi: 10.1111/den.13019. PMID: 29658655.
13. Gad EH, Zakaria H, Kamel Y, Alsebaey A, Zakareya T, Abbasy M, Mohamed A, Nada A, Abdelsamee MA, Housseni M. Surgical (Open and laparoscopic) management of large difficult CBD stones after different sessions of endoscopic failure: A retrospective cohort study. Ann Med Surg (Lond). 2019 May 31;43:52-63. doi: 10.1016/j.amsu.2019.05.007. PMID: 31198552; PMCID: PMC6556483.
14. Hungness ES, Soper NJ. Management of common bile duct stones. J Gastrointest Surg. 2006 Apr;10(4):612-9. doi: 10.1016/j.gassur.2005.08.015. PMID: 16627230.
15. Jinfeng Z, Yin Y, Chi Z, Junye G. Laparoscopic management after failed endoscopic stone removal in nondilated common bile duct. Int J Surg. 2016 May;29:49-52. doi: 10.1016/j.ijsu.2016.03.037. Epub 2016 Mar 19. PMID: 27000719.
16. Joseph A, Samant H. Jaundice. StatPearls Publishing;2022. PMID: 31334972.
17. Karaliotas C, Sgourakis G, Lanitis S, Kouloura S, Karkoulias K. Laparoscopic transcystic or transcholedochal choledochoscopy during common bile duct exploration for stones? Differences and similarities. Hellenic Journal of Surgery. 2015;87:394-406. https://doi.org/10.1007/s13126-015-0246-x.
18. Kawai K, Akasaka Y, Murakami K, Tada M, Koli Y. Endoscopic sphincterotomy of the ampulla of Vater. Gastrointest Endosc. 1974 May;20(4):148-51. doi: 10.1016/s0016-5107 (74)73914-1. PMID: 4825160.
19. Kelley WE Jr, Sheridan VC. Laparoscopic choledochoscopy with a small-caliber endoscope. A safe and effective technique for laparoscopic common bile duct exploration. Surg Endosc. 1995 Mar;9(3):293-6. doi: 10.1007/BF00187771. PMID: 7597601.
20. Koc B, Karahan S, Adas G, Tutal F, Guven H, Ozsoy A. Comparison of laparoscopic common bile duct exploration and endoscopic retrograde cholangiopancreatography plus laparoscopic cholecystectomy for choledocholithiasis: a prospective randomized study. Am J Surg. 2013 Oct;206(4):457-63. doi: 10.1016/j.amjsurg.2013.02.004. Epub 2013 Jul 17. PMID: 23871320.
21. Lee SJ, Choi IS, Moon JI, Choi YW, Ryu KH. Comparison of one-stage laparoscopic common bile duct exploration plus cholecystectomy and two-stage endoscopic sphincterotomy plus laparoscopic cholecystectomy for concomitant gallbladder and common bile duct stones in patients over 80 years old. J Minim Invasive Surg. 2022 Mar 15;25(1):11-17. doi: 10.7602/jmis.2022.25.1.11. PMID: 35603338; PMCID: PMC8977497.
22. Lyu Y, Cheng Y, Li T, Cheng B, Jin X. Laparoscopic common bile duct exploration plus cholecystectomy versus endoscopic retrograde cholangiopancreatography plus laparoscopic cholecystectomy for cholecystocholedocholithiasis: a meta-analysis. Surg Endosc. 2019 Oct;33 (10):3275-3286. doi: 10.1007/s00464-018-06613-w. Epub 2018 Dec 3. PMID: 30511313.
23. Manes G, Paspatis G, Aabakken L, Anderloni A, Arvanitakis M, Ah-Soune P, Barthet M, Domagk D, Dumonceau JM, Gigot JF, Hritz I, Karamanolis G, Laghi A, Mariani A, Paraskeva K, Pohl J, Ponchon T, Swahn F, Ter Steege RW. F., Tringali A, Vezakis A, Williams EJ, van Hooft JE. Endoscopic management of common bile duct stones: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy. 2019 May;51(5):472-491. doi: 10.1055/a-0862-0346. Epub 2019 Apr 3. PMID: 30943551.
24. Mattila A, Mrena A, Kellokumpu I. Cost-analysis and effectiveness of one-stage laparoscopic versus two-stage endolaparoscopic management of cholecystocholedocholithiasis: a retrospective cohort study. BMC Surgery. 2017;17:79. https://doi.org/10.1186/s12893-017-0274-2.
25. Nastashenko IL. Analysis of causes of unsatisfactory results of endoscopic transpapillary interventions. Surgery. Eastern Europe. 2018;7(2):260-4.
26. Oh CH, Dong SH. Recent advances in the management of difficult bile-duct stones: a focus on single-operator cholangioscopy-guided lithotripsy. Korean J Intern Med. 2021 Mar;36(2):235-246. doi: 10.3904/kjim.2020.425. Epub 2020 Dec 1. PMID: 32972127; PMCID: PMC7969058.
27. Qadri S, Khan M, Khan M. Use of pneumatic lithotripsy for managing difficult CBD calculi. Int J Surg. 2011;9(1):59-62. https://doi.org/10.1016/j.ijsu.2010.08.009.
28. Quaresima S, Balla A, Guerrieri M, Campagnacci R, Lezoche E, Paganini AM. A 23 year experience with laparoscopic common bile duct exploration. HPB (Oxford). 2017 Jan;19(1):29-35. doi: 10.1016/j.hpb.2016.10.011. Epub 2016 Nov 24. PMID: 27890483.
29. Tai CK, Tang CN, Ha JP, Chau CH, Siu WT, Li MK. Laparoscopic exploration of common bile duct in difficult choledocholithiasis. Surg Endosc. 2004 Jun;18(6):910-4. doi: 10.1007/s00464-003-8216-8. Epub 2004 Apr 21. PMID: 15095079.
30. Takada T, Strasberg SM, Solomkin JS, Pitt HA, Gomi H, Yoshida M, Mayumi T, Miura F, Gouma DJ, Garden OJ, Büchler MW, Kiriyama S, Yokoe M, Kimura Y, Tsuyuguchi T, Itoi T, Gabata T, Higuchi R, Okamoto K, Hata J, Murata A, Kusachi S, Windsor JA, Supe AN, Lee S, Chen XP, Yamashita Y, Hirata K, Inui K, Sumiyama Y; Tokyo Guidelines Revision Committee. TG13: Updated Tokyo Guidelines for the management of acute cholangitis and cholecystitis. J Hepatobiliary Pancreat Sci. 2013 Jan;20(1):1-7. doi: 10.1007/s00534-012-0566-y. PMID: 23307006.
31. Tarantino G, Magistri P, Ballarin R, Assirati G, Cataldo AD, Benedetto F. Surgery in biliary lithiasis: from the traditional «open» approach to laparoscopy and the «rendezvous» technique. Hepatobiliary Pancreat. Dis. Int. 2017;16:595-601. https://doi.org/10.1016/S1499-3872 (17)60031-6.
32. Trikudanathan G, Navaneethan U, Parsi MA. Endoscopic management of difficult common bile duct stones. World J Gastroenterol. 2013 Jan 14;19(2):165-73. doi: 10.3748/wjg.v19.i2.165. PMID: 23345939; PMCID: PMC3547556.
33. Troncone E, Mossa M, De Vico P, Monteleone G, Del Vecchio Blanco G. Difficult Biliary Stones: A Comprehensive Review of New and Old Lithotripsy Techniques. Medicina (Kaunas). 2022 Jan 13;58(1):120. doi: 10.3390/medicina58010120. PMID: 35056428; PMCID: PMC8779004.
34. Yasuda I, Itoi T. Recent advances in endoscopic management of difficult bile duct stones. Dig Endosc. 2013 Jul;25(4):376-85. doi: 10.1111/den.12118. Epub 2013 May 8. PMID: 23650878.
35. Zhou Y, Zha WZ, Wu XD, Fan RG, Zhang B, Xu YH, Qin CL, Jia J. Three modalities on management of choledocholithiasis: A prospective cohort study. Int J Surg. 2017 Aug;44:269-273. doi: 10.1016/j.ijsu.2017.06.032. Epub 2017 Jun 28.

Результати лікування складного холедохолітіазу за допомогою лапароскопічної холедохолітоекстракції та холедохоскопії. Досвід одного центру

Я. М. Сусак, М. В. Максименко, Л. Ю. Маркулан, Р. В. Гонза, І. І. Тюлюкін, В. В. Волковецький

Національний медичний університет імені О. О. Богомольця, Київ

Менеджмент складного холедохолітіазу (СХ), частота якого становить 10—15 % серед хворих із конкрементами жовчних проток, остаточно не визначений. Одним із можливих способів лікування СХ є лапароскопічна холедохолітоекстракція з холедохоскопією.

Мета — оцінити досвід одного центру в лікуванні складного холедохолітіазу за допомогою лапароскопічної холедохолітоекстракції та холедохоскопії.

Матеріали та методи. Проаналізовано результати лікування у 2018—2022 рр. 47 пацієнтів (16 (34 %) чоловіків та 31 (66 %) жінка) із СХ. Всіх пацієнтів оперовано методом лапароскопічної холедохолітоекстракції та холедохоскопії. Оцінювали причини СХ, відсоток повного очищення жовчних проток від конкрементів, тривалість оперативного лікування, загальний та післяопераційний ліжко-день, ускладнення і летальність.

Результати. Лапароскопічна холедохолітоекстракція з холедохоскопією виконана всім хворим. Причиною СХ були: особливості конкрементів — 27 (57,4 %), змінена анатомія органів гепатопанкреатобіліарної зони — 11 (23,6 %), особливості розташування конкремента у жовчних протоках — 9 (19,1 %). Після лапароскопічної холедохолітоекстракції з холедохоскопією конкременти у жовчних шляхах були відсутні у 95,7 % випадків. Середня тривалість операції — (130,0 ± 14,7) хв. Тривалість перебування в стаціонарі після операції становила у середньому (14,3 ± 1,7) дня. У 4 (8,5 %) хворих виникли ускладнення, які відповідають II (2 (4,2 %)) та III (2 (4,2 %)) класам за P. Clavien та D. Dindo (2009).

Висновки. Лапароскопічна холедохолітоекстракція з холедохоскопією може бути застосована як одна із технологій лікування складного холедохолітіазу.

Ключові слова: складний холедохолітіаз, лапароскопічна холедохолітоекстракція, лапароскопічна холедохоскопія.

FOR CITATION

Susak YM, Maksimenko MM, Markulan LY, Honza RV, Tiuliukin II, Volkovetskii VV. Results of laparoscopic choledocholithoextraction and choledochoscopy for difficult choledocholithiasis: a single centre experience. General Surgery (Ukraine). 2023:1;28-35. http://doi.org/10.30978/GS-2023-1-28.

UDC 617.51+617.53]:616.423-007]-053.2-08
DOI http://doi.org/10.30978/GS-2023-1-36

ISSN 2786-5584 print
ISSN 2786-5592 online

Life-threatening complications in patients with thoracic and abdominal lymphatic malformations

V. P. Prytula [1], Y. O. Rudenko [1], O. M. Gorbatiuk [2], A. Y. Nakonechnyi [3], Y. M. Susak [1]

[1] Bogomolets National Medical University, Kyiv
[2] Shupyk National Healthcare University of Ukraine, Kyiv
[3] Danylo Halytsky Lviv National Medical University

✉ Yevgen Rudenko: erudenko500@gmail.com

V. P. Prytula, http://orcid.org/0000-0001-9023-5898
Y. O. Rudenko, http://orcid.org/0000-0002-7532-1517
O. M. Gorbatiuk, http://orcid.org/0000-0003-3970-8797
Y. A. Nakonechnyi, http://orcid.org/0000-0003-1402-6642
Y. M. Susak, http://orcid.org/0000-0002-5102-485X

The term «lymphatic malformations» (LMs) refers to a wide spectrum of disorders with clinical manifestations that can vary from asymptomatic to life-threatening.

Objective — to analyze the factors and pathological conditions that necessitate the use of emergency surgical procedures in patients with thoracic and abdominal LMs.

Materials and methods. The retrospective study of medical charts of patients with LMs was performed for a period from 2012 to 2021. Among 240 patients with LMs, 55 (22.9%) were diagnosed with lesions of the abdominal or thoracic cavity. 5 (9.1%) required an emergency surgical procedure.

Results. Among 38 patients with abdominal LMs, only one (2.6%) required emergency surgery. This patient underwent laparotomy and subtotal bowel resection for total mesenteric thrombosis. The postoperative period was complicated by short bowel syndrome. Mediastinal LMs were diagnosed in 17 patients, 14 (73.7%) of whom had neck LM extension. In 4 cases, mediastinal LMs were complicated by intrathoracic tension syndrome. It was caused by a lymphatic leak into the pleural cavity in 1 case and by sudden enlargement of LMs, resulting from intracystic hemorrhage, in 3 other cases. A pleural drain with subsequent sclerotherapy was used in a patient with chylothorax. Patients with intracystic hemorrhage underwent thoracotomy and partial LM resection. They also received an injection of a sclerosing agent into the residual cysts. In uncomplicated cases, minimally invasive methods were preferred, with laparoscopic resections of abdominal LMs in 22 (78.6%) patients and sclerotherapy under ultrasound guidance in 7 (36.8%) patients with mediastinal LMs.

Conclusions. Intrathoracic tension syndrome and thrombotic complications are potentially dangerous and life-threatening conditions that pose a risk to patients with visceral LMs and require emergency interventions. Minimally invasive technologies were preferred in uncomplicated cases of thoracic and abdominal LMs, whereas open surgeries were the method of choice in complicated cases.

Keywords
lymphatic malformations, minimally invasive surgery, conversion, lymphorrhea, coagulopathy.

ARTICLE • Received 2023-02-01 • Received in revised form 2023-03-03
© 2023 Authors. Published under the CC BY-ND 4.0 license

The term «lymphatic malformations» (LMs) refers to a wide spectrum of disorders with clinical manifestations that can vary from asymptomatic to life-threatening.

LMs are most frequently found in the head and neck, accounting for up to 75% of all cases [1]. Head and neck LMs result in airway compression, a dangerous complication requiring a tracheostomy, and significant cosmetic deformities [16]. According to a Japanese group of authors, up to 14% of head and neck LMs can extend to the superior and anterior mediastinum, which increases the risk of airway obstruction [1, 16]. The incidence of abdominal and thoracic LMs is up to 20% [2], with

5 % and 6 % for each type [3], respectively. In some cases, they may be asymptomatic and incidentally diagnosed during a medical examination for other reasons. In 90 % of cases, LMs are diagnosed in pediatric patients by the age of 2 years due to clinical symptoms [3], some of which require urgent medical care. Other life-threatening complications of extensive vascular malformations may be associated with coagulation disorders [4].

Objective — to analyze the factors and pathological conditions that necessitate the use of emergency surgical procedures in patients with thoracic and abdominal LMs.

Materials and methods

The medical charts of pediatric patients with abdominal and thoracic cystic LMs were retrospectively reviewed, and the cases requiring emergency surgery were revealed. A cohort of 240 patients was studied between 2012 and 2021, and of those, 17 (30.9 %) had mediastinal LMs and 38 (69.1 %) had abdominal LMs. Gender, age of onset, primary clinical symptoms and signs, visualization options, complications, treatment options, and treatment outcomes were analyzed for all patients. Since MRI is the gold standard of pretreatment visualization of LMs, we performed it for all patients before and during treatment. D-dimer and fibrinogen blood tests were mandatory before treatment. The study was conducted according to guidelines implemented in consideration of GCP-ICH and the Declaration of Helsinki. All participants' parents or guardians gave written informed consent.

Results and discussion

LMs of the abdominal cavity were diagnosed in 38 (15.8 %) patients: 22 males and 16 females. In 15 of those patients, LMs were diagnosed before the age of one year; 6 of those LMs were detected during prenatal ultrasound screening. The diagnosis of LMs was made in 16 patients before the age of 18 months, and in 10 patients after the age of 5 years. Ultrasound was used as a screening method to establish the diagnosis of abdominal LM. We used MRI to confirm the diagnosis. According to retrospective analysis data, in most cases (n = 35; 92.1 %), patients received treatment within 6—18 months after the diagnosis of abdominal LMs was confirmed. An increased D-dimer level was detected in 5 (9.1 %) patients; 3 (5.5 %) of those patients had a decreased fibrinogen level. All patients with coagulopathy received low molecular weight heparin at a dose of 100 EM/kg /day before any intervention.

Four hours after the clinical presentation, urgent surgery for acute intestinal obstruction was performed in 3 (7.9 %) cases, and the diagnosis was confirmed in one of them. Treatment options used for abdominal cystic LMs were as follows: pure laparoscopic resections (n = 22; 57.9 %), including 11 (28.9 %) transumbilical segmental resections of the affected bowel; resections via laparotomy (n = 9; 23.7 %); and mTOR inhibitors systemic therapy (n = 1; 2.6 %). In one case, emergency surgery was performed on a child with prenatally diagnosed LM. A female patient was admitted within 22 days after birth with an antenatally identified intraabdominal cystic mass. The patient was born at a gestational age of 41 weeks with a birth weight of 3100 g and a length of 51 cm. A postnatal ultrasound confirmed a large multicystic lesion occupying much of the left side of the abdominal cavity. α-Fetoprotein and β-human chorionic gonadotrophin levels were not abnormally elevated.

The diagnosis was confirmed using an MRI. Afterwards, the newborn manifested a sudden deterioration of her condition, presenting with abdominal distention, marbled skin tone, arterial hypotension (50/30 mm Hg), bilious vomiting, and anxiety. After a short period of preoperative care (nasogastric decompression and intravenous fluid therapy), a laparotomy was performed to discover complete mesenteric thrombosis. The small bowel, affected by cystic LM, presented signs of necrosis, with its mesentery involved. Laparostomy was used to terminate the initial surgery. The planned relaparotomy performed in 48 hours revealed bowel necrosis caused by mesenteric thrombosis. Subtotal small bowel resection and resection of the LM were followed by jejuno-ileoanastomosis. The newborn has about 15 cm of residual small bowel. The patient required total parenteral nutrition for a long period of time due to the development of short bowel syndrome. This postoperative complication is characterized by massive loss of fluid and electrolytes in stool, thus requiring intravenous fluids and parenteral nutrition.

Mediastinal LMs were diagnosed in 19 (7.9 %) patients, with a predominance of head and neck LMs with mediastinal expansion (n = 14; 73.7 %). Other patients had an isolated mediastinal mass (n = 3; 15.8 %) or both mediastinal and abdominal LMs (n = 2; 10.5 %). According to retrospective analysis data, 7 (36.8 %) patients underwent sclerotherapy, which had a positive clinical result. 6 patients were prescribed combined treatment, including sclerotherapy and partial surgical LM resection. 2 (10.5 %) patients were treated using mTOR inhibitors. 4 (21.1 %) patients developed intrathoracic

tension syndrome that required emergency surgery. A lymphatic leak and chylothorax were diagnosed in an 8-month-old newborn. Sudden enlargement of LMs was reported in 3 patients, who were 4, 6, and 14 months old. 4 patients manifested acute respiratory failure (distress) as the first clinical sign that required mechanical ventilation in two of them. Pleural drainage was used to treat a patient with chylothorax. A chest tube was left inside the pleural cavity for two weeks. Then the patient underwent sclerotherapy for cystic LMs. The patient recovered. The follow-up period has lasted for 5 years so far. A thoracotomy with cystic LM resection was performed in 3 other cases, with one sclerosing agent injection into the residual LM cyst. Intraoperatively, it was found that LMs with a predominance of a microcystic component had occupied the entire right hemithorax, collapsed the lower and middle lobes of the right lung, and spread through the upper aperture of the chest into the tissue spaces of the neck. Cysts of a large diameter were filled with hemorrhagic content; fresh blood with clots was detected during aspiration, which was evidence of a sudden increase in the volume of the LM due to hemorrhage into the cyst cavity. The postoperative period was uneventful for all patients, and their follow-up period ranged from 18 to 48 months. 2 patients underwent repeated sclerotherapy for cystic LMs of the neck and superior mediastinum without experiencing any signs of respiratory disorders.

LMs are congenital malformations of the lymphatic system, which have two age peaks for clinical manifestations: before the age of two years and during puberty [3]. Superficial LMs can be initially suspected during the initial examination, and the primary diagnosis can be confirmed by ultrasound. Visceral LMs are the most challenging to diagnose [3, 5], and therefore, have a higher risk of complications. Thoracic LMs can cause airway compression and impaired lymph drainage that result in chylothorax or chyloperitoneum [8]. The enlargement of LMs due to intracystic hemorrhage or infection can elevate intraabdominal or intrathoracic pressure. The two most common causes of chylothorax in children are congenital pulmonary lymphangiectasia and lymphatic malformations of the thorax [15]. Other disorders that lead to chylothorax or pleural effusions include congenital absence or atresia of the thoracic duct, x-linked myotubular myopathy, Gorham-Stout disease, and generalized lymphatic anomaly (GLA) [3].

While formerly thought to be rather benign in their clinical course, the LMs' more recently recognized association with localized intravascular coagulation (LIC) explains many of their related symptoms and complications. LIC was first described in 2008 in patients with slow-flow vascular malformations [4]. It is well-known that extensive vascular malformations are commonly associated with systemic coagulation profile abnormalities [18]. The relative slow flow within the lesion results in thrombosis through the triggering of the fibrinolytic cascade. The extent of the activation and consumption of coagulation factors is characterized by the elevation of systemic D-dimer levels and decreased fibrinogen levels. In our study, an increase in D-dimer levels was observed in 5 patients with extensive LM, whereas acute thrombotic complications occurred in 1 patient. Although coagulation studies are useful for diagnosing LIC, there are not yet any published guidelines regarding its ongoing monitoring [18].

MRI is the gold-standard visualization option to confirm the diagnosis of LM [13]. In specific cases, histology verification is required to confirm it. Lymphatic vessels have a small internal diameter, so it makes the diagnostic process challenging. The effective imaging techniques are still being optimized and developed [14]. Treatment options of choice for LMs are surgical resection or sclerotherapy [7, 9]. Target therapy is used in complicated clinical cases when surgery or sclerotherapy are ineffective or bear a high risk of potential complications [11]. In most cases, treatment is planned and it starts after the patient is fully examined. Additional hemostasis tests help determine anatomical location and structure (mecro-, microcystic, or mixed form) of LMs [1]. It is crucial to order a coagulation panel with D-dimer and fibrinogen levels for all children, considering the potential risks of local coagulopathy, thrombosis, and afibrinogenemic bleeding in the postoperative period [12]. Emergency surgeries are rare anyway. At the same time, acute distress syndrome or intrathoracic tension syndrome resulting from intracystic hemorrhage or chylothorax, as well as thromboembolic complications, are life-threatening and therefore should be considered in treatment strategy planning [13]. Acute compartment syndrome developed in a newborn with giant abdominal LM is described as an indication for an emergency surgical procedure [6]. Abdominal LMs can also be complicated by obturation, intestinal obstruction, intestinal volvulus, constipation, and impaired urinary elimination [9]. Despite the fact that coagulation disorders are common in patients with vascular anomalies, we have not found any available research on acute mesenteric thrombosis as a complication of abdominal LMs. The low speed of blood flow in slow-flow vascular malformations can result in local intravascular coagulopathy that

is manifested by a high D-dimer level, a low thrombocyte count, and/or thrombocytopenia [11].

Minimally invasive methods are preferred for the treatment of uncomplicated LMs, in particular laparoscopic resections [5, 10], which were performed on 57.9 % of patients with abdominal LMs, and sclerotherapy under ultrasound or laparoscopic guidance, which was used in 36.8 % of patients with thoracic LMs. Multidisciplinary team care, minimally invasive techniques, and modern target technologies for patient examination must become an integral part of successful management of patients with LMs [17].

Critical and life-threatening complications require more aggressive surgical tactics, in particular laparotomy or thoracotomy. Despite the use of a sclerosant for sclerotherapy, swelling and enlargement of LMs are observed in the postoperative period [5, 6, 9]. Scleropathy may be dangerous when used in patients with intrathoracic tension syndrome due to the side effects of the sclerotic agents. A thoracotomy was preferred in such cases.

Conclusions

Intrathoracic tension syndrome resulting from intracystic hemorrhage or lymphatic leak (chylothorax) is a critical complication of mediastinal cystic LMs that requires emergency surgery.

Mesenteric and intestinal cystic LMs have the potential to cause total mesenteric thrombosis with subsequent short bowel syndrome.

The highest risk of complications is observed during the first year of life.

Considering the risk of potential critical life-threatening complications, the presence of both mediastinal and abdominal cystic LMs in one patient requires advanced attention and active treatment tactics with a minimal observation period.

Declaration of interests

The authors declare that they have no conflicts of interest.

Funding. No grants or funding were used in this study.

Authors contributions

V. P. Prytula: the conception and design of the study; the analysis of clinical data; Y. O. Rudenko: interpretation and statistical analysis of clinical data and literature review; O. M. Gorbatiuk: data collection and analysis; critical revision of the manuscript; A. Y. Nakonechnyi: the design of the study, a literature review, and data analysis; Y. M. Susak: drafting and critical revision of the manuscript.

All authors have read and approved the final version of the manuscript.

References

1. Бензар ІМ, Левицький АФ, Дегтярьова ДС, Годік ОС, Дубровін ОГ. Лікування лімфатичних мальформацій у дітей: 10-річний досвід. Хірургія дитячого віку. 2022;2(75):5-14. doi10.15574/PS.2022.75.5.
2. Benzar I., Levytskyi A., Diehtiarova D. et al. Vascular anomalies in newborns: clinical presentation, complications, and peculiarities of therapy. Wiad Lek. 2020;73(9 cz. 2):1934-9. doi:10.36740/WLek202009207.
3. Cooke-Barber J, Dasgupta R. Management of visceral vascular anomalies. Seminars in Pediatr Sur. 2020;29(5):150977. doi: 10.1016/j.sempedsurg.2020.150977.
4. Dompmartin A, Acher A, Thibon P, et al. Association of localized intravascular coagulopathy with venous malformations. Arch. Dermatol. 2008;144:873-7. Doi: 10.1001/archderm.144.7.873.
5. Francavilla ML, White CL, Oliveri B, Lee EY, Restrepo R. Intraabdominal lymphatic malformations: pearls and pitfalls of diagnosis and differential diagnoses in pediatric patients. AJR Am J Roentgenol. 2017;208(3):637-49. doi: 10.2214/AJR.16.17008.
6. Gasparella P, Singer G, Castellani C, Sorantin E, Haxhija EQ, Till H. Giant lymphatic malformation causing abdominal compartment syndrome in a neonate: a rare surgical emergency. J Surg Case Rep. 2020;26;2020(8):rjaa252. doi: 10.1093/jscr/rjaa252.
7. Ghaffarpour N, Burgos CM, Wester T. Surgical excision is the treatment of choice for cervical lymphatic malformations with mediastinal expansion. J Pediatr Surg. 2018;53(9):1820-4. doi: 10.1016/j.jpedsurg.2017.10.048.
8. Gurevich A, Hur S, Singhal S, DiBardino D, Haas AR, Hansen-Flaschen JH, Nadolski G, Itkin M. Nontraumatic chylothorax and chylopericardium: diagnosis and treatment using an algorithmic approach based on novel lymphatic imaging. Ann Am Thorac Soc. 2022; 19(5):756-62. doi: 10.1513/AnnalsATS.202103-262OC.
9. Kulungowski AM, Patel M. Lymphatic malformations. Semin Pediatr Surg. 2020 Oct;29(5):150971. doi: 10.1016/j.sempedsurg.2020.150971.
10. Liu Q, Fu J, Yu Q, Gong W, Li P, Guo X. Laparoscopic surgery of intra-abdominal lymphatic malformation in children. Exp Ther Med. 2022;19;24(3):581. doi: 10.3892/etm.2022.11519.
11. Mack JM, Verkamp B, Richter GT, Nicholas R, Stewart K, Crary SE. Effect of sirolimus on coagulopathy of slow-flow vascular malformations. Pediatr Blood Cancer. 2019;66(10):e27896. doi: 10.1002/pbc.27896.
12. Ricci KW, Brandão LR. Coagulation issues in vascular anomalies. Semin Pediatr Surg. 2020 Oct;29(5):150966. doi: 10.1016.
13. Scuglia M, Conforti A, Valfrè L, Totonelli G, Iacusso C, Iacobelli BD, Meucci D, Viggiano M, Fusaro F, Diociaiuti A, Morini F, El Hachem M, Bagolan P. Operative Management of Neonatal Lymphatic Malformations: Lesson Learned From 57 Consecutive Cases. Front Pediatr. 2021;18;9:709223. doi: 10.3389/fped.2021.709223.
14. Sun JD, Shum T, Behzadi F, Hammer MM. Imaging findings of thoracic lymphatic abnormalities. Radiographics. 2022;42(5):1265-82. doi: 10.1148/rg.220040.
15. Tutor JD. Chylothorax in infants and children. Pediatrics. 2014;133(4):722-33. doi: 10.1542/peds.2013-2072.
16. Ueno S, Fujino A, Morikawa Y, et al. Treatment of mediastinal lymphatic malformation in children: an analysis of a nationwide survey in Japan. Surg Today. 2018;48(7):716-25. doi: 10.1007/s00595-018-1640-0.
17. Zamora AK, Barry WE, Nowicki D, et al. A multidisciplinary approach to management of abdominal lymphatic malformations. J Pediatr Surg. 2021;56(8):1425-9. doi: 10.1016/j.jpedsurg.2020.10.007.
18. Zhuo KY, Russell S, Wargon O, Adams S. Localised intravascular coagulation complicating venous malformations in children: Associations and therapeutic options. J Paediatr Child Health. 2017;53(8):737-41. doi: 10.1111/jpc.13461.

Критичні хірургічні ускладнення у пацієнтів з лімфатичними мальформаціями грудної та черевної порожнини

В. П. Притула [1], Є. О. Руденко [1], О. М. Горбатюк [2], А. Й. Наконечний [3], Я. М. Сусак [1]

[1] Національний медичний університет імені О. О. Богомольця, Київ

[2] Національний університет охорони здоров'я України імені П. Л. Шупика, Київ

[3] Львівський національний медичний університет імені Данила Галицького

Лімфатичні мальформації (ЛМ) — це широкий спектр захворювань, перебіг яких варіює від безсимтомного до стану, який загрожує життю пацієнта.

Мета — проаналізувати чинники, що спричинили потребу в ургентному оперативному втручанні у пацієнтів з ЛМ грудної та черевної порожнини.

Матеріали та методи. Проведено ретроспективний аналіз історій хвороби пацієнтів з ЛМ, які перебували на лікуванні у 2012—2021 рр. Із 240 пацієнтів з ЛМ ураження грудної та черевної порожнини діагностовано у 55 (22,9 %). Потребували термінового оперативного втручання 5 (9,1 %) пацієнтів.

Результати. Із 38 пацієнтів з ЛМ черевної порожнини потреба в ургентному хірургічному втручанні виникла лише в одного. Оперативне лікування в обсязі лапаротомії та субтотальної резекції тонкої кишки проведено з приводу тотального тромбозу мезентеріальних судин. Перебіг післяопераційного періоду ускладнився розвитком синдрому тонкої кишки. Лімфатичні мальформації медіастинальної локалізації виявлено у 19 пацієнтів, з них у 14 (73,7 %) вони супроводжувалися ураженням шийної ділянки. Медіастинальні ЛМ ускладнилися синдромом внутрішньогрудного напруження у 4 пацієнтів, причиною якого в одному випадку було витікання лімфи в плевральну порожнину, у решті — раптове збільшення розмірів ЛМ на тлі крововиливу в порожнину кісти. Для купування хілотораксу проведено дренування плевральної порожнини з наступним склерозуванням ЛМ. У пацієнтів з крововиливом у порожнину кісти виконано торакотомію, часткове видалення ЛМ та введення склерозанта в резидуальні кісти. У неускладнених випадках перебігу ЛМ перевагу віддавали малоінвазивним методам лікування, зокрема лапароскопічному видаленню абдомінальних ЛМ (у 22 (78,6 %) випадках) і склерозуванню медіастинальних ЛМ під ультразвуковим контролем (у 7 (36,8 %)).

Висновки. Синдром внутрішньогрудного напруження та тромботичні ускладнення є потенційно небезпечними ускладненнями ЛМ вісцеральних порожнин, що потребують невідкладного хірургічного втручання. Для лікування неускладнених форм ЛМ грудної та черевної порожнини перевагу віддавали малоінвазивним технологіям, в ускладнених випадках проводили відкриті хірургічні втручання.

Ключові слова: лімфатичні мальформації, малоінвазивна хірургія, конверсія, лімфорея, коагулопатія.

FOR CITATION

Prytula VP, Rudenko YO, Gorbatiuk OM, Nakonechnyi AY, Susak YM. Life-threatening complications in patients with thoracic and abdominal lymphatic malformations. General Surgery (Ukraine). 2023;1;36-40. http://doi.org/10.30978/GS-2023-1-36.

UDC 616.37-002.1:616.34-089.819.2-056.25]-06
DOI http://doi.org/10.30978/GS-2023-1-41

ISSN 2786-5584 print
ISSN 2786-5592 online

Peculiarities of the use of enteral nutrition in patients with severe acute pancreatitis

I. V. Kolosovych, I. V. Hanol

Bogomolets National Medical University, Kyiv

✉ Ihor Hanol: ganoli@ukr.net

I. V. Kolosovych, ScD, MD, Prof., Head of the Department of Surgery N 2, http://orcid.org/0000-0002-2031-4897
I. V. Hanol, PhD, MD, Associate Professor of the Department of Surgery N 2, http://orcid.org/0000-0002-3470-2102

In the general structure of the disease, severe acute pancreatitis occurs in 20 % of cases, requires treatment in the intensive care unit, and is accompanied by a high risk of complications (up to 50 %) and death (40—70 %). In turn, early use of enteral nutrition in patients with severe acute pancreatitis significantly improves the condition of the intestinal wall and the course of the disease as a whole, reducing the number of complications and mortality.

Objective — to determine the timeframe for the restoration of intestinal absorptive function as one of the main criteria for the start of enteral nutrition in patients with severe acute pancreatitis and to improve the results of comprehensive treatment of patients by preventing its complications.

Materials and methods. The results of the evaluation and treatment of 67 patients with severe acute pancreatitis served as the basis for the study. Patients were divided into two groups depending on the specifics of the selected treatment strategies: a comparison group of 33 patients receiving standard enteral nutrition and a main group of 34 patients receiving standard enteral nutrition with the inclusion of antiflatulants in the mixture. Before the start of tube feeding, a test using unmetabolized disaccharides (lactulose/mannitol) and a sample containing a 3 % potassium iodide solution was conducted to determine the timeframe for the restoration of intestinal absorptive function.

Results. In 70.6 % of patients in the main group and 69.7 % of patients in the comparison group, the restoration of intestinal absorptive function was registered only after 48 hours from the beginning of treatment. After 7 and 14 days of enteral nutrition, a significant difference was obtained between total protein, albumin, cholesterol and serum K+ ($p < 0.05$). After 7 days of treatment, there was a significantly lower incidence of intestinal complications in patients of the main group by 21.5 % ($\chi^2 = 4.88$, 95 % CI 2.3—39.5, $p = 0.03$).

Conclusions. The method, which uses a 3 % potassium iodide solution, is quick and informative for determining the restoration of intestinal absorptive function in patients with severe acute pancreatitis. The inclusion of antiflatulants in the composition for enteral nutrition improved the laboratory parameters of blood serum and reduced the incidence of intestinal complications by 7 days and the duration of multiorgan failure from 11.5 ± 1.8 days to 10.5 ± 1.9 days ($p = 0.04$).

Keywords
acute pancreatitis, intestinal absorption, enteral nutrition, intestinal complications.

ARTICLE • Received 2022-08-30 • Received in revised form 2022-10-15
© 2023 Authors. Published under the CC BY-ND 4.0 license

Acute pancreatitis is a common disease that accounts for 5—10 % of urgent pathology of the abdominal cavity and ranks third (25 %) place, yielding to the incidence of acute cholecystitis (28 %) and acute appendicitis (26 %) [1]. In the general structure of the disease, severe acute pancreatitis (SAP) occurs in 20 % of cases, requires treatment in the intensive care unit, and is accompanied by a high risk of complications (up to 50 %) and death (40—70 %) [2]. Recent studies on the pathogenesis of SAP have focused on intestinal barrier disorders, which play an important role in the development of infectious complications during the course of the disease and exacerbate dysfunction of organs and systems [3]. According to the literature, even in the early period of SAP, there are changes in microcirculation and damage to the intestinal endothelium, leading to an increase in toxic products, mediators of inflammation and translocation of intestinal microflora into the bloodstream and surrounding tissues [4]. In turn, early use of enteral nutrition (EN) in patients with SAP significantly improves the

condition of the intestinal wall and the course of the disease as a whole, reducing the number of complications and mortality.

It should be noted that the effectiveness and safety of EN in patients with SAP depend on a number of factors, including the type of mixture used, the timeframe for the restoration of peristalsis and absorptive function of the intestinal wall, the method of introducing the mixture, and others. Thus, there are many studies that suggest that EN should be started as early as possible (24—48 hours after hospitalization) as compared to parenteral nutrition [6]. However, it is also known that early use of EN in patients with SAP can cause digestive and dynamic types of increased flatulence in the gastrointestinal tract, and compliance with these recommendations is dangerous for the development of intestinal complications in the form of large residual volumes — 39 %, diarrhea — 14.7 %, bloating — 13.2 %, vomiting — 12.2 %, and regurgitation — 5.5 % [7].

This is due to the fact that the EN is a violation of the balance between bacteria involved in the production of gases and their absorption, which explains the signs of flatulence in this category of patients. In turn, the combination of syndromes of maldigestion and malabsorption and reflex suppression of intestinal motility on the background of SAP leads to disorders of transport and absorption of nutrients.

It should be noted that guidelines for the care of patients with digestive disorders arising from the use of EN in the treatment of SAP as well as their prevention are insufficiently developed. Thus, according to the literature, enterosorbents, antidiarrheal drugs, and others are used to reduce gas formation in the intestine [8]. However, the therapeutic effect of these drugs is insignificant, so this issue needs further study.

Objective — to determine the timeframe for the restoration of intestinal absorptive function as one of the main criteria for the start of EN in patients with SAP and to improve the results of comprehensive treatment of patients by preventing its complications.

Materials and methods

The study was based on the results of the examination and treatment of 67 patients with SAP who were hospitalized in the clinic of the Department of Surgery No2 of Bogomolets National Medical University, and was approved by the Ethics Committee of Bogomolets National Medical University (15 December 2011, protocol #5). All patients were examined in the period from 2012 to 2021 and signed informed consent to participate in the study and /or treatment in the clinic. The diagnosis of SAP was established in the presence of two of the following three criteria: clinical (upper abdominal pain); laboratory (serum amylase or lipase level 3 times higher than the maximum normal value); and visualization (CT, MRI, or Ultrasound) criteria.

The study included patients with severe disease (the course of the disease was complicated by the presence of multiple organ failure lasting more than 48 hours) according to the acute pancreatitis classification proposed by the Acute Pancreatitis Classification Working Group (2012), who received EN. The APACHE II scale (severe course — 8 points or more) was used to predict the course of acute pancreatitis. The exclusion criteria were chronic somatic diseases in the decompensation phase and the patient's refusal to participate in the study.

Depending on the specifics of the selected treatment strategies, patients were divided into two groups: the comparison group (standard EN) — 33 patients, and the main group (standard EN+antiflatulants) — 34 patients. Semi-elemental and elemental mixtures were used for EN. Feeding was carried out during the day. A drip was given at a rate of 25 ml per hour using a dispenser. Before using EN, patients in the main group received additional injections of simethicone emulsion at a dose of 2 mL (80 mg) 3—5 times a day in order to prevent the development of diarrhea and flatulence.

Patients in the two groups did not differ significantly in age (50.8 ± 9.1 and 52.0 ± 9.5 years, $p > 0.05$, respectively), gender (men 57.6 % and 55.9 %, women 42.4 % and 44.1 %, $p > 0.05$, respectively) and the etiology of the disease (alcoholic 57.6 % and 55.9 %, biliary 30.3 % and 32.6 %, idiopathic 12.1 % and 11.8 %, %, $p > 0.05$, respectively). There was also no significant difference between the indicators (sum of points on the APACHE II scale) of disease severity of the comparison group and the main group at the time of hospitalization (12.9 ± 2.7 and 13.5 ± 3.1; $p > 0.05$, respectively).

Comprehensive conservative treatment of patients was performed in the intensive care unit in accordance with international treatment protocols. Surgical interventions, including minimally invasive ones, under general and local anesthesia were performed in 26 (78.9 %) patients in the comparison group and in 25 (73.5 %) patients in the main group.

A test using unmetabolized disaccharides (lactulose/mannitol) was performed before the start of EN to determine the timeframe for the restoration of intestinal absorptive function. Disaccharides were administered at the beginning of treatment after 12, 24, 36, and 48 hours [9]. In the feeding tube, 5.0 g of mannitol and 5.0 g of lactulose were dissolved in 100

ml of distilled water. Urine was collected within 6 hours after solution administration and analyzed by ion chromatography using a pulsed amperometric detector 945 Professional Detector Vario-Amperometry, Metrohm, Switzerland (the normal lactulose/mannitol ratio in urine is less than 0.03) [10].

As an alternative method for determining the onset of intestinal absorption, we used our own method, which included a 3 % potassium iodide solution (the sensitivity of the method is 87.36 %, while specificity is 81.5 %) [11]. The timeframe for the restoration of intestinal absorptive function was determined by monitoring the excretion of potassium iodide with saliva 10 minutes after its enteral probe administration (20 mL of a 3 % solution). The transparent secretion was taken in a test tube. In case of restoration of intestinal absorptive function, the color changed to blue upon addition of starch (2 mL of a 10 % of solution).

To analyze the effectiveness of EN in the study groups after 7 and 14 days after treatment, the levels of the following laboratory parameters were assessed: total protein, albumin, total bilirubin, creatinine, urea, fibrinogen, glucose, cholesterol, C-reactivae protein, Na^+ and K^+ serum. We also analyzed the incidence of intestinal complications (occurrence or intensification of epigastric pain, projection of the small and/or colon, vomiting, regurgitation, diarrhea) in the first 24 hours and 7 days after EN, and the occurrence of local complications during the disease, mortality, duration of multiple organ failure, and hospital stay of patients in the main group and the comparison group.

Statistical analysis. The normality of data distribution was determined by the Shapiro-Wilk test. The difference between the groups was established using the Student's t-test for independent samples in the case of parametric data distribution. Differences in sample distribution were assessed using the χ^2 test criterion. The results are presented as means and their standard deviation ($M \pm SD$). Differences between indicators were considered significant at $p < 0.05$.

Statistical analysis was performed using Statistica 10 (Serial Number: STA999K347150-W) and Medcalc® (open access Internet resource, https://www.medcalc.org/calc/).

Results and discussion

When comparing the mean levels of lactulose/mannitol in the urine and their standard deviation in the main group and the comparison group at the beginning of treatment (0.042 ± 0.001 and 0.041 ± 0.001; $p = 0.64$ respectively), after 12 hours (0.040 ± 0.002 and 0.041 ± 0.002; $p = 0.27$ respectively), 24 hours (0.039 ± 0.002 and 0.039 ± 0.003; $p = 0.92$ respectively), 36 hours (0.036 ± 0.003 and 0.037 ± 0.004; $p = 0.9$ respectively), 48 hours (0.033 ± 0.004 and 0.033 ± 0.004; $p = 0.9$ respectively), no significant difference was obtained.

Table 1. **The timeframe for the restoration of intestinal absorptive function in patients with severe acute pancreatitis depending on the duration of treatment in the hospital**

Duration of treatment, hours	Main group (n = 34)	Comparison group (n = 33)
24	3 (8.8 %)	4 (12.1 %)
36	10 (29.4 %)	9 (27.3 %)
48	24 (70.6 %)	23 (69.7 %)

The analysis of the timeframe for the restoration of intestinal absorptive function in patients with SAP depending on the duration of treatment was carried out (Table 1).

The vast majority of patients (70.6 % of patients in the main group and 69.7 % of patients in the comparison group), the restoration of intestinal absorptive function was registered only after 48 hours from the beginning of treatment (see Table 1). The specified time of the restoration of intestinal absorptive function was also confirmed when using a sample containing a 3 % potassium iodide solution.

The analysis and comparison of laboratory indicators of EN efficiency in patients of the main group and the comparison group were also performed. The evaluation of these indicators was performed before the start of the use of EN (Table 2), after 7 days (Table 3) and after 14 days from the beginning (Table 4).

According to the results of the analysis, 7 and 14 days after the use of EN, a significant difference was obtained between the total protein, albumin, cholesterol and K^+ serum ($p < 0,05$). The level of cholesterol, K^+ and Na^+ corresponded to the norm in both groups. It should be noted that the analysis of indicators after 14 days of EN also showed a significant difference between total bilirubin, creatinine, urea, and serum glucose ($p < 0.05$). The levels of glucose and creatinine in the main group were normal.

Analyzing the clinical symptoms associated with the use of EN, the following data were obtained: on the first day after the use of EN in the main group, complications occurred in 14 (41.2 %) patients (increased pain in 5 (14.7 %), vomiting — 4 (11.8 %), diarrhea — 4 (11.8 %), and regurgitation — one (2.9 %) patient) and in the comparison group, in 17 (51.5 %) patients (increased pain in 6 (18.8 %),

Table 2. **Baseline laboratory parameters of patients with severe acute pancreatitis**

Index	Rate	Main group (n = 34)	Comparison group (n = 33)
Total serum protein, g/L	65—85	47.4 ± 2.5 [43—50]	47.8 ± 1.9 [43—54]
Serum albumin, g/L	35—50	27.4 ± 1.1 [26—29]	27.6 ± 1.1 [25—30]
Total bilirubin, μmol/L	3.4—20.8	38.5 ± 13.1 [26.0 ± 61.2]	38.2 ± 13.8 [25.2 ± 68.9]
Creatinine, μmol/L	62—115	152.3 ± 13.0 [129.1—176.1]	151.3 ± 12.7 [121—176.2]
Urea, mmol/L	2.5—8.3	10.1 ± 0.9 [8.6—12.1]	10.1 ± 1.3 [8.9—12.1]
Glucose, mmol/L	3.5—5.5	8.2 ± 2.1 [5.5—12.6]	8.1 ± 1.9 [5.1—12.1]
C-reactive protein, mg/L	0.8—8.0	69.2 ± 20.6 [24—110]	69.8 ± 26.5 [28—120]
Serum cholesterol, mmol/L	2.9—5.17	5.0 ± 0.6 [4.0—6.1]	5.0 ± 0.6 [4.0—6.3]
Na^+ serum, mmol/L	130—149	136.9 ± 7.5 [128—150]	136.7 ± 7.5 [128—152]
K+ serum, mmol/L	3.5—5.4	3.4 ± 0.1 [3.1—3.6]	3.4 ± 0.2 [3.1—3.7]

The difference for all indexes between main and comparison group is statistically insignificant ($p > 0.05$).

Table 3. **Dynamics of laboratory parameters of patients with severe acute pancreatitis after 7 days of enteral nutrition**

Index	Rate	Main group (n = 34)	Comparison group (n = 33)
Total serum protein, g/L	65—85	52.9 ± 1.6 [50—56]	51.7 ± 2.5 [47—57]*
Serum albumin, g/L	35—50	29.8 ± 1.3 [27—31]	28.8 ± 1.6 [26—31]**
Total bilirubin, μmol/L	3.4—20.8	27.7 ± 7.5 [20.8 ± 51.0]	27.6 ± 8.2 [21.9 ± 54.0]
Creatinine, μmol/L	62—115	137.9 ± 16.5 [115.0—177.7]	141.2 ± 12.2 [121.0—166.0]
Urea, mmol/L	2.5—8.3	9.1 ± 1.0 [8.2—12.1]	9.3 ± 0.6 [8.4—10.9]
Glucose, mmol/L	3.5—5.5	6.1 ± 0.7 [5.1—7.7]	6.2 ± 0.6 [5.0—7.7]
C-reactive protein, mg/L	0.8—8.0	105.5 ± 49.7 [38—210]	106.2 ± 51.5 [38—250]
Serum cholesterol, mmol/L	2.9—5.17	4.6 ± 0.3 [3.8—5.2]	4.3 ± 0.5 [3.6—5.2]*
Na^+ serum, mmol/L	130—149	140.9 ± 3.1 [136—150]	140.6 ± 4.3 [133—153]
K+ serum, mmol/L	3.5—5.4	3.9 ± 0.2 [3.5—4.2]	3.7 ± 0.1 [3.5—4.3]**

The difference between the groups is statistically significant: * $p < 0.05$; ** $p < 0.01$.

Table 4. **Dynamics of laboratory parameters of patients with severe acute pancreatitis after 14 days of enteral nutrition**

Index	Rate	Main group (n = 34)	Comparison group (n = 33)
Total serum protein, g/L	65—85	58.4 ± 3.8 [52—64]	56.6 ± 3.1 [52—64]*
Serum albumin, g/L	35—50	32.7 ± 1.8 [27—35]	30.5 ± 1.6 [28—31]**
Total bilirubin, μmol/L	3.4—20.8	21.1 ± 2.1 [18.7 ± 31.2]	22.9 ± 3.4 [19.9 ± 44.2]
Creatinine, μmol/L	62—115	107.9 ± 10.8 [87.0—149.8]	120.7 ± 9.6 [98.8—149.9]***
Urea, mmol/L	2.5—8.3	8.1 ± 0.6 [6.4—9.9]	8.5 ± 0.5 [8—9.9]**
Glucose, mmol/L	3.5—5.5	5.4 ± 0.3 [4.6—6.6]	5.6 ± 0.4 [4.7—6.6]*
C-reactive protein, mg/L	0.8—8.0	101.6 ± 54.5 [23—220]	116.9 ± 63.1 [25—260]
Serum cholesterol, mmol/L	2.9—5.17	4.7 ± 0.3 [3.8—5.1]	4.0 ± 0.2 [3.0—4.9]***
Na^+ serum, mmol/L	130—149	142.2 ± 1.8 [137—146]	141.3 ± 2.1 [136—145]
K+ serum, mmol/L	3.5—5.4	4.1 ± 0.2 [3.5—4.5]	3.9 ± 0.1 [3.5—4.1]**

The difference between the groups is statistically significant: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

vomiting — 4 (12.1 %), diarrhea — 6 (18.8 %), and regurgitation — one (3 %) patient). Despite the fact that the incidence of intestinal complications on the first day after EN in the main group of patients was 10.3 % less, no significant difference between these indicators in the study groups was found ($\chi^2 = 0.23$; 95 % CI 12.9—32.1; p = 0.13). However, after 7 days, there was a significantly lower incidence of intestinal complications in patients of the main group by 21.5 % ($\chi^2 = 4.88$; 95 % CI 2.3—39.5; p = 0.03). Thus, in the main group, intestinal complications were registered in 3 (8.8 %) patients in the form of increased pain, and vomiting and diarrhea were observed in one patient. In the comparison group, intestinal complications were reported in 10 (30.3 %) patients, out of which 4 (12.1 %) patients showed increased pain in the epigastric region and projection of the colon, 5 (15.2 %) — diarrhea, and one (3 %) — vomiting.

The analysis and comparison of the frequency of local complications caused by SAP was also performed in the main group and the comparison group (41.2 % and 48.9 %, respectively) ($\chi^2 = 0.12$; 95 % CI 15.37—29.69; p = 0.5), duration of multiorgan failure (10.5 ± 1.9 [8—16] days and 11.5 ± 1.8 [6—15] days, respectively (p = 0.04)), length of hospital stay (50.7 ± 28.8 [23—124] days and 54.9 ± 32.6 [20—119] days, respectively (p = 0.5), and fatalities (11.8 % and 12.1 %, respectively ($\chi^2 = 0.11$; 95 % CI 16.25—17.07; p = 0.97).

Information on the timing of the start of EN in patients with SAP remains controversial. Thus, according to the recommendations of the experts of the European Society of Clinical Nutrition and Metabolism, in patients with SAP, EN should be started within 24—72 hours after hospitalization, while the early start of nutrition in patients of this category is associated with a decrease in the frequency of infectious complications by 24.2 % and mortality by 32.3 % compared to patients who started EN later [12]. However, in the literature, there are no clear criteria for the initiation of EN in patients with SAP, which is dangerous for complications and deterioration of the patient's condition [13]. Thus, according to experts of the American Gastroenterological Association, early enteral nutrition may not be effective in patients with SAP due to pain, vomiting or intestinal obstruction, so in such cases it is necessary to postpone the start of the introduction of the food mixture for 24 hours [14]. We believe that the restoration of the absorption function of the intestinal wall is one of the criteria for the prescription of EN in patients with SAP. We found that in the vast majority of patients with SAP (70.6 % of patients in the main group and 69.7 % of patients in the control group), recovery of intestinal absorption occurs in an average of 48 hours from the beginning of complex conservative therapy, so it is now optimal to start EN.

It should be noted that, according to the literature, in case of impaired carbohydrate tolerance and severe intestinal paresis when using a test with disaccharides, diagnostic errors may occur, leading to the development of gastrointestinal complications with EN in 15 % of patients [15]. There are also samples with a load of monosaccharides (1 g of fructose or glucose per 1 kg of body weight) and subsequent determination of fasting blood glucose within 2 hours after exercise. An increase in blood glucose concentration indicates the enzymatic activity of the corresponding intestinal disaccharides and is an indication for EN. A flat glycemic curve indicates a violation of glucose transport from the intestinal lumen to enterocytes. If the flattened curve is obtained after loading with disaccharide, and after glucose intake, the glycemic curve is not changed, it indicates a decrease in membrane digestion and is a contraindication to EN. However, the disadvantage of this method is fluctuations in glucose levels, which depend on a large number of factors (carbohydrate metabolism disorders that develop not only in diabetes but also in Itsenko-Cushing syndrome, pheochromocytoma, acromegaly, hyperthyroidism, etc.). For greater reliability and an accurate assessment of the shape of the glycemic curve, a binary test should be performed in which oral glucose is compared with intravenous bolus administration, which may worsen the condition of a patient with SAP.

Therefore, in addition to the application of the method described above, the onset of intestinal absorption was determined by an indicator method developed in our clinic and based on the registration of saliva color change to blue under the action of starch, indicating restoration of salivary excretion of potassium iodide after enteral probe injection. The obtained data on the restoration of intestinal absorption coincided with the data obtained by applying the sample with disaccharides.

In order to improve membrane digestion and absorption as well as reduce the incidence of complications with the use of EN in the treatment protocol of patients with SAP, we proposed the inclusion of simethicone emulsion mixture into the feeding tube at a dose of 2 mL (80 mg) 3—5 times a day. The use of this method made it possible to obtain a significant difference between the indicators of total protein, albumin, cholesterol and K+ serum in the study groups after 7 days and additionally between the indicators of total bilirubin, creatinine, urea and serum glucose after 14 days, although the

levels of glucose and creatinine in the main group corresponded to normal values. In addition, the use of antiflatulents reduced the incidence of intestinal complications after 7 days by 21.5 % ($\chi^2 = 4.88$; 95 % CI 2.3—39.5; p = 0.03) and the duration of multiorgan failure from 11, 5 ± 1.8 days to 10.5 ± 1.9 days, respectively (p = 0.04).

Conclusions

It is established that the restoration of intestinal absorptive function occurs on average after 48 hours from the beginning of complex conservative therapy in patients with SAP, so the use of EN at an earlier date does not make sense.

The method of determining the restoration of intestinal absorptive function in SAP patients using a 3 % potassium iodide solution is quick, safe, and informative.

The use of antiflatulants in the EN mixture improved the laboratory parameters of blood serum, reduced the incidence of intestinal complications by 7 days by 21.5 % ($\chi^2 = 4.88$; 95 % CI 2,3—39,5; p = 0,03), and decreased the duration of multiorgan failure from 11.5 ± 1.8 days to 10.5 ± 1.9 days (p = 0.04).

Declaration of interests

The Authors declare no conflicts of interest.

Funding. The work was performed in accordance with the plan of research work of the Department of Surgery No2 of Bogomolets National Medical University: «Development and implementation of methods for diagnosis and treatment of surgical pathology of the abdominal cavity and blood circulation». The authors did not receive additional financial support.

Ethics approval and written informed consents statements

The assessment and usage of all clinical data was approved and permitted before the study by the ethics committee of Bogomolets National Medical University. The study protocol conformed to the ethical guidelines of the «World Medical Association (WMA) Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects» adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 59th WMA General Assembly, Seoul, South Korea, October 2008.

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

Authors contributions

I. V. Kolosovych: conception or design of the work, drafting the aricle, critical revision of the article; I. V. Hanol: data collection, data analysis and interpretation, drafting the article.

References

1. Petrov MS, Yadav D. Global epidemiology and holistic prevention of pancreatitis. Nat Rev Gastroenterol Hepatol. 2019 Mar;16(3):175-84. doi: 10.1038/s41575-018-0087-5. PMID: 30482911; PMCID: PMC6597260.
2. Kolosovych IV, Hanol IV. Hemocoagulation factors of hemorrhagic complications in acute pancreatitis. Fiziol. Zh. 2022; 68(1): 56-61. DOI: https://doi.org/10.15407/fz68.01.056.
3. Schietroma M, Pessia B, Carlei F, Mariani P, Sista F, Amicucci G. Intestinal permeability and systemic endotoxemia in patients with acute pancreatitis. Ann Ital Chir. 2016;87:138-44. PMID: 27179282.
4. Patel BK, Patel KH, Bhatia M, Iyer SG, Madhavan K, Moochhala SM. Gut microbiome in acute pancreatitis: A review based on current literature. World J Gastroenterol. 2021 Aug 14;27(30):5019-36. doi: 10.3748/wjg.v27.i30.5019. PMID: 34497432; PMCID: PMC8384740.
5. Yang AL. Nutrition and Acute Pancreatitis. J Clin Med. 2021 Feb 18;10(4):836. doi: 10.3390/jcm10040836. PMID: 33670647; PMCID: PMC7922255.
6. Jabłońska B, Mrowiec S. Nutritional support in patients with severe acute pancreatitis-current standards. Nutrients. 2021 Apr 28;13(5):1498. doi: 10.3390/nu13051498. PMID: 33925138; PMCID: PMC8145288.
7. Yasuda H, Kondo N, Yamamoto R, et al. Monitoring of gastric residual volume during enteral nutrition. Cochrane Database Syst Rev. 2021 Sep 27;9(9):CD013335. doi: 10.1002/14651858.CD013335.pub2. PMID: 34596901; PMCID: PMC8498989.
8. Freitas LA, Fagundes AL, do Prado PR, et al. Factors associated with length of stay and death in tube-fed patients: A cross-sectional multicentre study. Nurs Open. 2021 Sep;8(5):2509-19. doi: 10.1002/nop2.774. Epub 2021 Jan 27. PMID: 33503335; PMCID: PMC8363365.
9. Calder N, Walsh K, Olupot-Olupot P, et al. Modifying gut integrity and microbiome in children with severe acute malnutrition using legume-based feeds (MIMBLE): A pilot trial. Cell Rep Med. 2021 May 18;2(5):100280. doi: 10.1016/j.xcrm.2021.100280. PMID: 34095882; PMCID: PMC8149470.
10. Generoso M, De Rosa M, De Rosa R, et al. Cellobiose and lactulose coupled with mannitol and determined using ion-exchange chromatography with pulsed amperometric detection, are reliable probes for investigation of intestinal permeability. J Chromatogr B Analyt Technol Biomed Life Sci. 2003 Jan 15;783(2):349-57. doi: 10.1016/s1570-0232(02)00766-3. PMID: 12482477.
11. Kolosovych IV, Hanol IV, Cherepenko IV. Enteral tube feeding in acute pancreatitis and its complications: World of Medicine and Biology. 2021;(4):75-9. doi: 10.26724/2079-8334-2021-4-78-75-79.
12. Arvanitakis M, Ockenga J, Bezmarevic M, et al. ESPEN guideline on clinical nutrition in acute and chronic pancreatitis. Clin Nutr. 2020 Mar;39(3):612-31. doi: 10.1016/j.clnu.2020.01.004. Epub 2020 Jan 22. PMID: 32008871.
13. Wanden-Berghe C, Patino-Alonso MC, Galindo-Villardón P, Sanz-Valero J. Complications associated with enteral nutrition: CAFANE Study. Nutrients. 2019 Sep 1;11(9):2041. doi: 10.3390/nu11092041. PMID: 31480563; PMCID: PMC6770113.
14. Crockett SD, Wani S, Gardner TB, Falck-Ytter Y, Barkun AN; American Gastroenterological Association Institute Clinical Guidelines Committee. American Gastroenterological Association Institute Guideline on Initial Management of Acute Pancreatitis. Gastroenterology. 2018 Mar;154(4):1096-101. doi: 10.1053/j.gastro.2018.01.032. Epub 2018 Feb 3. PMID: 29409760.
15. Chertishchev S. S. Udoskonalennya tekhnolohiy khirurhichnoho likuvannya uskladnenoyi vyrazkovoyi khvoroby dvanadtsyatypaloyi kyshky: avtoref. dys.... kand. med. nauk : 14.01.03 / Nats. med. un-t im. O. O. Bohomoltsya. K.; 2011. 20 p. [Ukr] http://www.irbis-nbuv.gov.ua/cgi.

Особливості застосування ентерального зондового харчування у пацієнтів з тяжким перебігом гострого панкреатиту

І. В. Колосович, І. В. Ганоль

Національний медичний університет імені О. О. Богомольця, Київ

У загальній структурі захворювання на частку гострого панкреатиту з тяжким перебігом припадає 20 %. Гострий панкреатит потребує лікування у відділенні інтенсивної терапії та реанімації. Супроводжується високим ризиком виникнення ускладнень (до 50 %) та летального наслідку (40—70 %). Раннє застосування ентерального зондового харчування у пацієнтів з гострим панкреатитом значно поліпшує стан кишкової стінки та перебіг захворювання в цілому, зменшуючи кількість ускладнень і знижуючи рівень летальності.

Мета — вивчити терміни відновлення кишкового всмоктування як одного з головних критеріїв початку ентерального зондового харчування у пацієнтів з тяжким перебігом гострого панкреатиту та поліпшити результати комплексного лікування шляхом профілактики його ускладнень.

Матеріали та методи. Дослідження ґрунтувалося на результатах обстеження та лікування 67 хворих на тяжкий гострий панкреатит. Залежно від лікувальної тактики хворих розподілили на дві групи: порівняння (стандартне ентеральне зондове харчування) — 33 пацієнти та основну (стандартне ентеральне зондове харчування з додаванням антифлатулентів у складі суміші) — 34 пацієнти. Для визначення термінів відновлення кишкового всмоктування перед початком ентерального зондового харчування виконували пробу з дисахаридами (лактулоза/манітол), які не метаболізуються, і тест із 3 % розчином калію йодиду.

Результати. У 70,6 % пацієнтів основної групи та 69,7 % — групи порівняння відновлення кишкового всмоктування зареєстрували лише через 48 год від початку лікування. Через 7 та 14 діб застосування ентерального зондового харчування виявлено статистично значущу різницю між групами за показниками загального білка, альбуміну, холестерину та K+ у сироватці крові ($p < 0,05$). Через 7 діб відзначено статистично значущо нижчу на 21,5 % частоту виникнення кишкових ускладнень у пацієнтів основної групи ($\chi^2 = 4,88$, 95 % довірчий інтервал 2,3—39,5; $p = 0,03$).

Висновки. Застосування методу із 3 % розчином калію йодиду для визначення відновлення кишкового всмоктування у хворих з гострим панкреатитом є швидким та інформативним. Використання антифлатулентів у складі суміші для ентерального зондового харчування дало змогу поліпшити лабораторні показники сироватки крові, зменшити частоту розвитку кишкових ускладнень на 7-му добу і тривалість поліорганної недостатності з (11,5 ± 1,8) до (10,5 ± 1,9) доби ($p = 0,04$).

Ключові слова: гострий панкреатит, кишкове всмоктування, ентеральне зондове харчування, кишкові ускладнення.

FOR CITATION

Kolosovych IV, Hanol IV. Peculiarities of the use of enteral nutrition in patients with severe acute pancreatitis. General Surgery (Ukraine). 2023;1;41-47. http://doi.org/10.30978/GS-2023-1-41.

UDC 616-001.4:576.72:617-089.844
DOI http://doi.org/10.30978/GS-2023-1-48

ISSN 2786-5584 print
ISSN 2786-5592 online

Keystone perforator island flaps in the reconstruction of lower limb defects resulting from shrapnel and mine-explosive combat injuries. Case series

S. V. Sliesarenko[1], P. A. Badiul[1,2], O. I. Rudenko[1,2], M. I. Romanshuk[1]

[1] Burns and plastic surgery Center, Municipal Hospital No 8, Dnipro
[2] Dnipro State Medical University

✉ Prof. Sergii Sliesarenko: slesarenko@yahoo.com

S. V. Sliesarenko, http://orcid.org/0000-0002-7113-3738
P. O. Badiul, http://orcid.org/0000-0001-8656-3143
O. I. Rudenko, http://orcid.org/0000-0002-7822-0228
M. I. Romanshuk, http://orcid.org/0000-0003-0633-8195

In the conditions of warfare in Ukraine, the question of providing medical services to injured civilian and military is especially relevant and severe. In plastic surgeons` professional activities, the task is to restore extensive and deep wound defects in a short term and with a high degree of damaged organ`s restoration, especially supporting function. In this article the authors describe their experience with local keystone perforator island flaps, which are used to reconstruct skin and soft tissue defects of the lower limbs caused by combat injuries.

Patients and methods. The authors conducted a retrospective review of 49 keystone perforator flaps for 28 patients (26 men and 2 women) who received treatment in the clinic for bullet, shrapnel, and mine-explosive injuries between 2014 and 2022.

Results. In all cases, extensive wound defects were completely closed during a single-stage surgical procedure, and the patients were discharged after recovery. Non-critical complications required secondary sutures in two cases (4 %), extending the duration of treatment by 6 days. The time spent in the operating room on the transposition of one flap ranged from 40 to 95 min (mean: 67 min).

Conclusions. The findings of the study show that local keystone perforator island flaps are highly effective in the successful reconstruction of lower limb defects caused by combat wounds. The keystone perforator island flap technique requires basic preoperative preparation of the patient, is easy-to-use, and exhibits a fairly high level of reliability at the same time. In most cases, keystone perforator island flaps provide primary and single-stage closure of a large defect in the thigh, in the area of the knee joint, and in the lower leg in the absence of secondary defects that are common at donor sites when alternative techniques are chosen.

Keywords
reconstructive surgery, perforator flap, combat injury, wounds, keystone flap.

ARTICLE • Received 2023-01-24 • Received in revised form 2023-03-03
© 2023 Authors. Published under the CC BY-ND 4.0 license

In the conditions of warfare in Ukraine, the question of providing medical services to injured civilians and military personnel is especially relevant and urgent. In the short term, plastic surgeons deal with restoring extensive and deep wound defects, which require a high degree of damaged organ restoration, especially supporting function [13, 20]. As the authors note, lower limb injuries range from 38.3 % to 91.0 % [9, 11, 14]. At the same time, surgical closure of wound defects is an urgent and rather difficult task, especially when specialists face the need to select a surgical method for closing deep and extensive wound defects [14, 16]. The ideal reconstruction for lower limb defects should be based on the following concept: replace «like to like» tissues and minimize donor-site morbidity, achieving the best possible aesthetic and functional outcome. In this regard, the demand for surgical

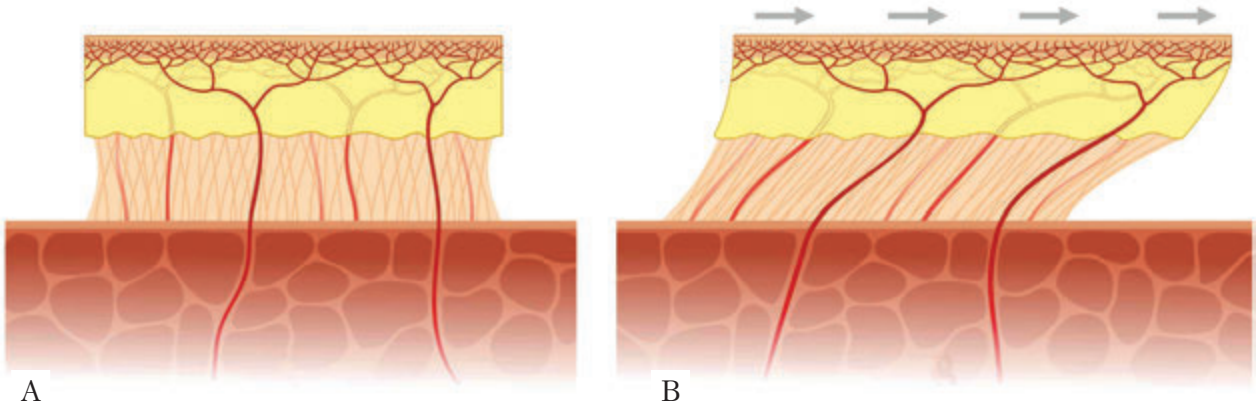

Figure 1. **Scheme of arterial and neurovascular connections of the raised keystone perforator island flap, based on the concept of angiotome: before (A) and after (B) displacement of the flap to the right. The remaining microvascular and axillary connections, along with arterial perforators, provide immediate vascular augmentation in the tissues after plastic surgery (IVA)**

transplantation of local flaps is growing. The technique provides a higher quality of single-stage wound defect closure than the transplantation of a skin graft, even if it includes the reconstruction of the dermal layer with a biomatrix [2, 18]. The keystone perforator island flap technique is an exclusive and effective method in reconstructive surgery [4, 5, 7]. The study presents the keystone perforator island flap technique and options for its clinical application in the reconstruction of lower limb defects resulting from shrapnel and mine-explosive combat injuries.

Objective — to provide the fastest and most effective closure of skin and soft tissue defects of lower limbs caused by combat injuries by using local donor resources according to the «like to like» reconstruction concept.

The keystone perforator island flap: description, design, and dissection technique

The method was developed by Behan et al. [4, 5, 7]. According to his studies on anatomical material and clinical practice, the majority of axillary perforating arteries have additional microscopic venous, neurovascular, and arterial plexuses closely connected to each other (Fig. 1). This fact indicates the potential for improving the nutrition of the marginal and adjacent territories of the skin and soft tissues, thereby significantly increasing the area and survival of the excised local keystone perforator island flap. The preserved arterial and neurovascular connections of the raised keystone perforator island flap can be seen without magnification intraoperatively (Fig. 2).

The classic keystone perforator island flap is planned according to the shape of the surface in the form of a trapezoid with a curved arch along the wound defect. Actually, the similarity between the shape of the flap and the stone arched blocks, which were mounted above the windows and passages by Roman architects, determined its name. The surgeon's clinical evaluation of the surrounding tissues is a sufficient condition for the formation of the flap geometry. It is not mandatory to confirm the functional validity of each perforator using CT with angiography or Doppler examination. It can be visualized intraoperatively and preserved during subsequent dissection.

After excision of the edges of the wound and radical debridement, it is necessary to give the wound defect an elliptical shape (Fig. 3). The marking of the flap is performed relative to the arc bordering the wound defect along its longest side.

The choice of donor site as well as its direction relative to the wound are determined by the

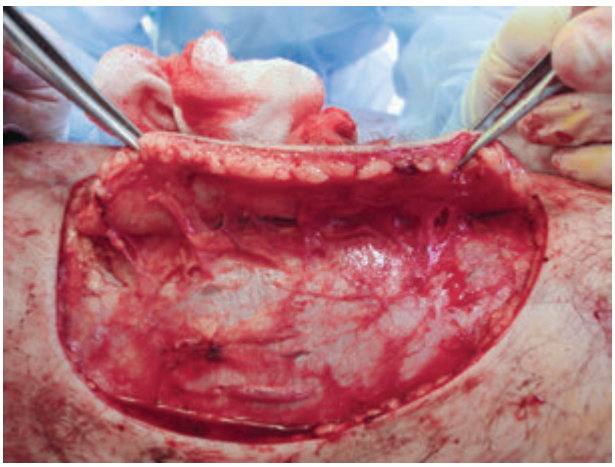

Figure 2. **Intraoperative view of the preserved arterial and neurovascular connections of the raised keystone perforator island flap in the thigh area**

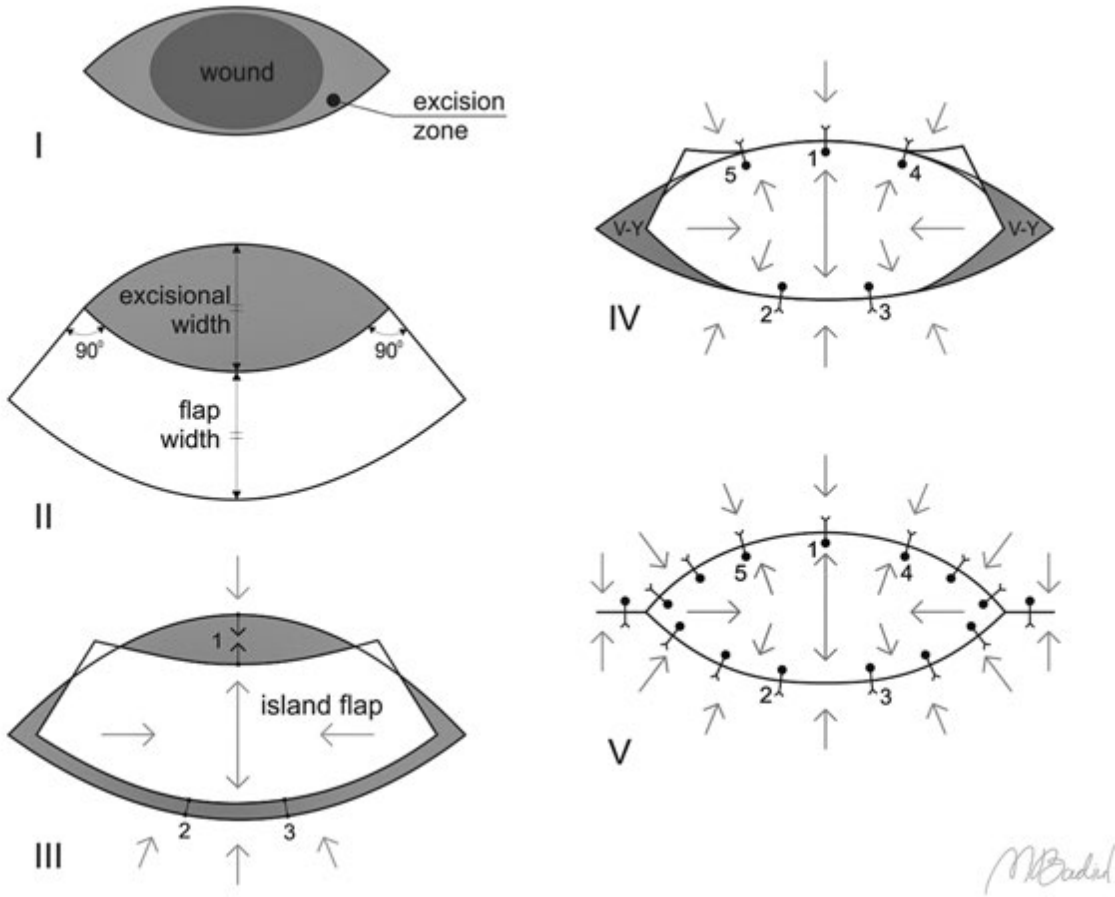

Figure 3. **Scheme of wound preparation techniques and plastic procedures for skin defect closure using the keystone perforator island flap:** I — surgical treatment of the wound with elliptical excision of the edges of the wound defect; II — the width of the excision of the wound defect must coincide with the width of the planned flap; III — the flap is cut out like an island with a complete crossing of the skin and subcutaneous tissues. The subsequent blunt preparation in the suprafascial space maximally preserves the available perforators and connected axillary plexuses, and at the same time makes it mobile, ready for spatial redistribution; IV — scheme of spatial redistribution of covering tissues without significant tension when moving the keystone island flap to the area of the wound defect and the sequence of applying key sutures; redistribution directions are indicated by arrows; V — the final stage of adaptation of the flap and suturing of the lateral fragments of the defect using the V-Y plastic maneuver without tissue tension

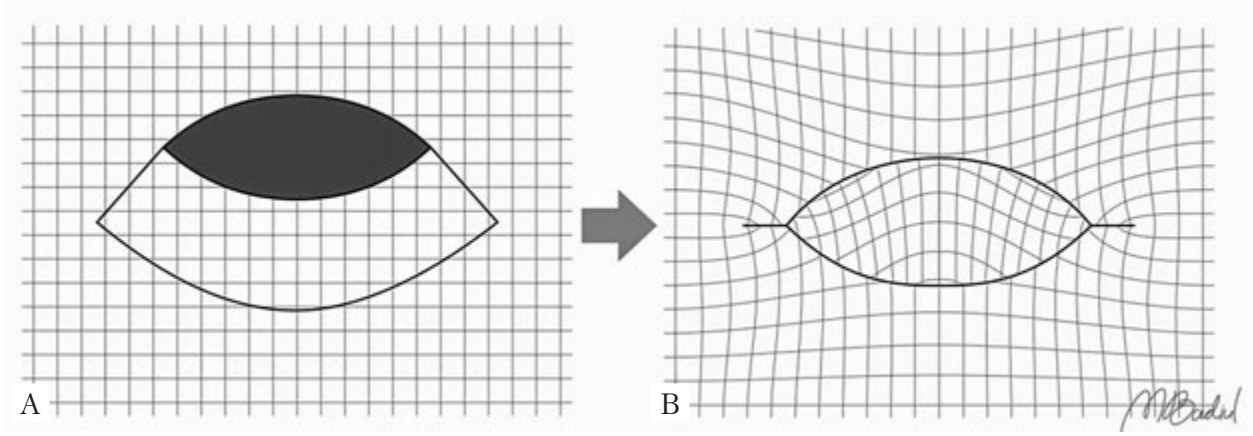

Figure 4. **Scheme of the distribution of covering tissues during plastic closure of wound defects with a keystone perforator island flap: A — before the flap is moved, the scale grid is not deformed; B — after moving and suturing the flap to the edges of the wound defect, deformations of the scale grid are visualized, which demonstrates a change in the geometry of various areas of the flap and surrounding tissues**

Table. **Patient characteristics**

PN	Age, years	Sex	FN	Aetiology	Localization	Wound size, cm	Flap size, cm	Complication
1	22	M	1	Mine shrapnel	Thigh	23×7	29×8	–
2	45	M	2	Mine shrapnel	Shin	15×8	13×4	–
			3	Mine shrapnel	Shin	24×5	27×8	–
3	36	M	4	Bullet	Shin	15×6	16×6	+
4	33	M	5	Bullet	Shin	8×7	17×7	–
			6	Bullet	Shin	5×3,5	9×3,5	–
5	28	M	7	Mine shrapnel	Thigh	14×7	23×7	–
			8	Mine shrapnel	Shin	17×6	35×6	–
6	35	M	9	Mine shrapnel	Shin	15×5	20×7	–
			10	Mine shrapnel	Shin	10×4	20×7	–
7	23	M	11	Mine shrapnel	Thigh	15×6	26×7	–
8	33	M	12	Mine shrapnel	Thigh	15×10	20×8	–
			13	Mine shrapnel	Thigh	15×10	13×9	–
9	47	M	14	Mine shrapnel	Knee joint	8×4	6 ×5	–
10	27	M	15	Mine shrapnel	Shin	10×4	12×5	–
			16	Bullet	Shin	6×3	11×3	–
11	29	M	17	Bullet	Thigh	15×5	18×6	–
			18	Bullet	Thigh	14×4	16×6	–
12	22	M	19	Mine shrapnel	Thigh	23×7	29×8	–
13	25	M	20	Mine shrapnel	Shin	15×7	16×7	–
			21	Mine shrapnel	Shin	12×7	12×7	–
14	21	M	22	Mine shrapnel	Shin	9×4	16×4	–
15	23	M	23	Mine shrapnel	Shin	9×4	15×5	–
16	43	M	24	Bullet	Thigh	7×4	13×5	–
			25	Bullet	Thigh	9×6	20×6	–
			26	Bullet	Thigh	11×6	18×7	–
17	25	M	27	Bullet	Thigh	10×5	13×5	–
18	19	M	28	Mine shrapnel	Thigh	7×6	9×6	–
			29	Mine shrapnel	Thigh	8×6	10×6	–
			30	Mine shrapnel	Shin	10×8	14×10	–
			31	Mine shrapnel	Shin	9×6	11×8	–
			32	Mine shrapnel	Thigh	12×6	14×7	–
			33	Mine shrapnel	Shin	8×6	10×6	–
			34	Mine shrapnel	Shin	16×8	18×9	–
19	38	M	35	Mine shrapnel	Shin	10×4	12×5	–
20	26	M	36	Mine shrapnel	Thigh	12×8	15×9	–
21	48	M	37	Mine shrapnel	Thigh	6×3	8×4	–
22	22	M	38	Mine shrapnel	Thigh	8×5	10×5	+
23	58	F	39	Mine shrapnel	Knee joint	10×4	12×6	–
24	21	M	40	Mine shrapnel	Shin	8×4	9×4	–
			41	Mine shrapnel	Shin	4×3	5×4	–
25	37	M	42	Mine shrapnel	Shin	8×5	10×5	–
			43	Mine shrapnel	Shin	5×4	7×4	–
26	20	M	44	Mine shrapnel	Shin	5×3	6×3	–
27	30	M	45	Mine shrapnel	Thigh	12×7	14×7	–
			46	Mine shrapnel	Thigh	9×4	11×6	–
			47	Mine shrapnel	Thigh	12×5	14×6	–
28	21	F	48	Mine shrapnel	Thigh	15×6	17×6	–
			49	Mine shrapnel	Thigh	14×7	18×7	–

Note. PN — patient number; FN — flap number.

mobility of the skin. For the lower limbs, the best choice is the formation of a flap behind the defect, where the most mobile fascial-muscular compartments are located. According to the figure (see Fig. 3; position II), the width of the excision of fthe wound defect must coincide with the width of the planned flap. However, the flap can differ considerably in size in terms of length. The step is caused by the fact that the flap expands in the form of a trapezoid to its edge, distant from the wound defect. A bordering incision along the perimeter forms an island-like flap with complete transection of the skin and subcutaneous tissues. The subsequent blunt preparation in the suprafascial space maximally preserves the available perforators and associated axillary plexuses (see Fig. 1, 2) and, at the same time, makes them mobile, ready for plastic distribution to the area of the wound defect. The sequence of stitching is also important. The flap is first adjusted in width with the application of key stitches in the central part, and then the displaced material is distributed and fixed on both sides of the center with subsequent stitches, with arrows indicating the directions of distribution of covering materials. The final stage of flap adaptation and suturing of the lateral fragments of the defect using the V-Y plastic maneuver is carried out without tissue tension. The diagram of the distribution of covering tissues during plastic closure of wound defects with a keystone island flap demonstrates the change in the geometry of the surface of various areas of the flap and surrounding tissues with the help of a scale grid (Fig. 4). When suturing the skin, tissue tension should not exceed 14.2 g/mm in order to prevent blood vessel spasm and thrombosis [17, 19]. Clinically, the skin tension should not cause paleness around the wound edges and the area where the skin is captured by a tool or suture.

Patients and methods

A clinical review of 28 patients (26 (93.0 %) men and 2 (7.0 %) women) was conducted from 2014 to 2022. Their ages ranged from 19 to 58. Patients suffered bullet or shrapnel injuries and mine-explosive injuries to the lower limbs. Initially, all patients received medical care at the mobile hospitals or local hospitals, and then they were transferred to a specialized center for the final plastic closure of wound defects. Patients underwent plastic surgery for reconstruction of the lost skin and soft tissues using a local perforator keystone flap. 49 flap surgeries were performed: 11 patients had 2 wounds that were closed instantly, 2 patients had 3 wounds, and 1 patient had 7 wounds. Concerning localization of defects, there were 23 (47.0 %) flaps on the thigh, 2 (4.0 %) flaps on the knee, and 24 (49.0 %) flaps on the tibia (Table).

Results

In all cases, significant lesion abnormalities were fully closed in one step and patients were discharged after convalescence. All flaps took root; post-operative flow complications were not critical and were eliminated. In two cases (4.0 %) of non-critical complications, secondary sutures were used, and treatment was prolonged by six days. The operating time spent on one flap transposition ranged from 40 to 95 minutes (the average time was 67 minutes). The displaced perforated local flaps were similar in structure and color to the surrounding tissue; they did not alter the contours of the donor and recipient zones. The absence of secondary defects that are common at donor sites when using alternative procedures was a feature of the aesthetic outcome of this method. Consequently, using perforator flaps in reconstructive surgery made it possible to simultaneously close the wound defect and the donor area without changing the contours of the body or limbs.

Case 1

Patient K., a 22-year-old civilian woman, was admitted to the clinic with a shrapnel and mine-explosive injury to her lower extremities. On the left side of the thigh there was a through-and-through wound, and on the right side of the wound, a blind canal ran

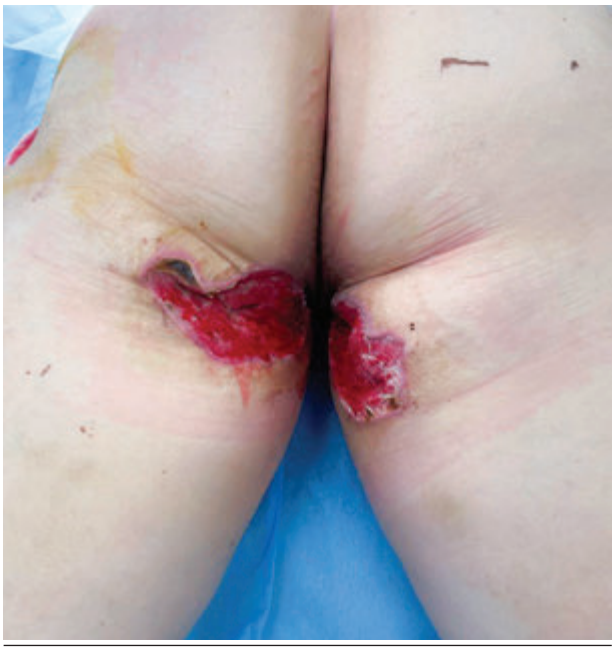

Figure 5. **View of shrapnel and mine-explosive injuries to the buttocks and lower extremities after NPWT**

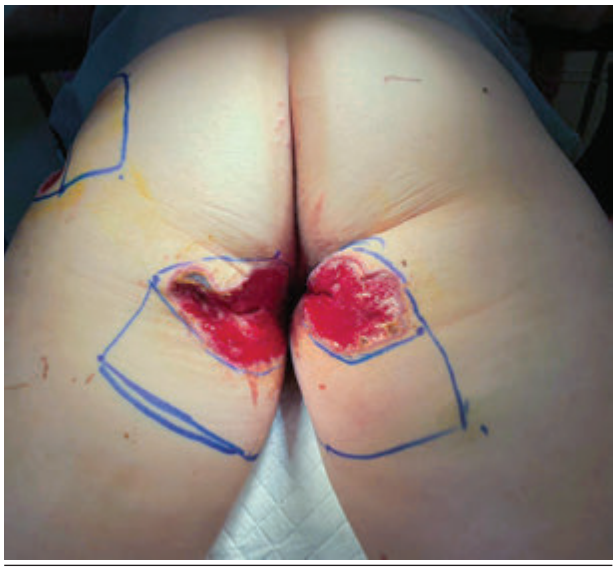

Figure 6. **Design and markup of the three planned keystone island flaps**

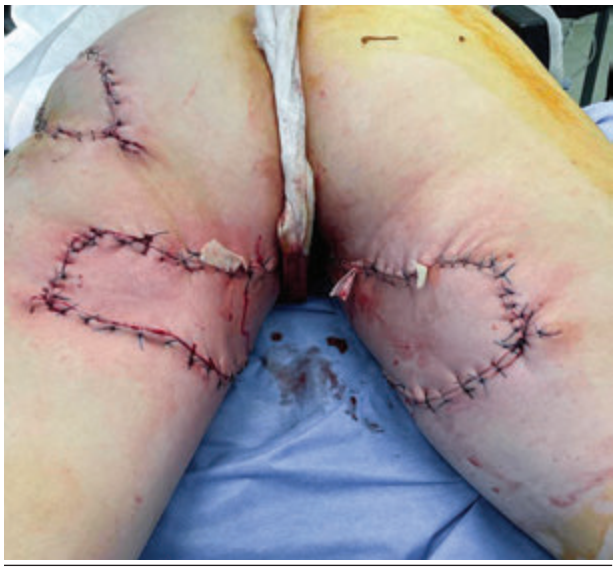

Figure 7. **Intraoperative digital photo. The flaps were adapted and sutured to the edges of the three wounds without tension**

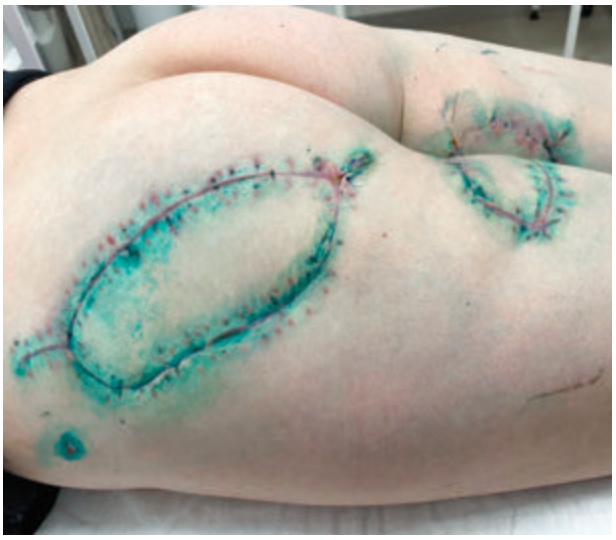

Figure 8. **Side view on the left. The result of treatment 18 days after surgery**

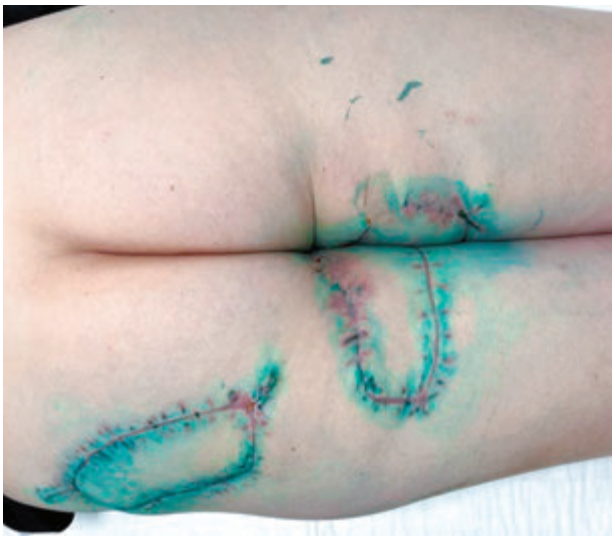

Figure 9. **View from the back. All wounds were closed without altering the contours of the buttocks and lower extremities**

along the medial surface in the upper 1/3. After the removal of non-viable tissues and negative pressure wound therapy (NPWT) for 5 days, deep and extensive defects located on the left side of the buttock and thighs were covered with granulations (Fig. 5). The keystone perforator island flap technique was chosen in order to close the wounds (Fig. 6). Three flaps were formed according to the island type, with a complete dissection of the skin along the perimeter and mobilizations that provided tissue mobility. The flaps were adapted to the edges of the wounds and fixed with tension-free sutures (Fig. 7). The postoperative course went smoothly; the sutures were removed on the 14th day, and the patient was discharged after recovery. The observation 18 days after surgery (Fig. 8, 9) demonstrates adequate restoration of the covering tissues without altering the contours of the buttocks and lower extremities. The newly formed covering tissue is quite elastic and mobile and exhibits sensitivity to various stimuli. The function of the lower extremities is fully restored.

Case 2

Patient L., a 61-year-old civilian woman, was admitted to the clinic with a shrapnel and mine-explosive injury to the knee area of her left lower extremity.

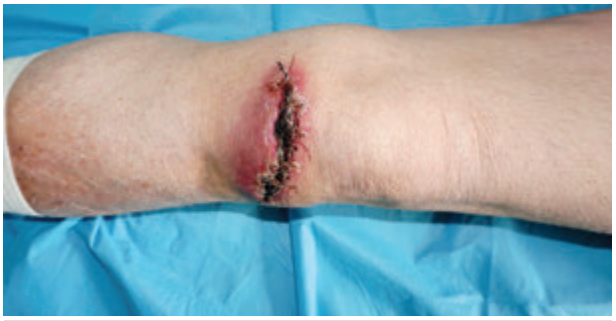

Figure 10. **View of the shrapnel and mine-explosive injury to the knee area of the left lower extremity. The wound did not heal for 6 weeks after simple suturing. The tissue surrounding the wound is inflamed**

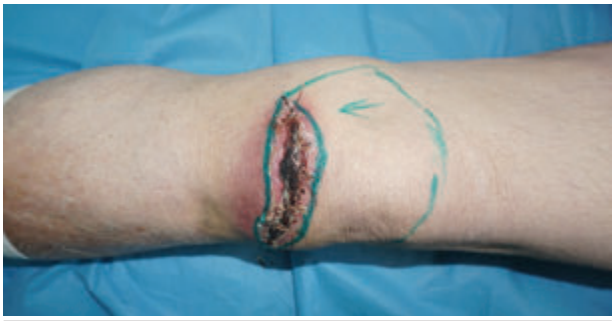

Figure 11. **Design and markup of the radical debridement area and planned keystone perforator island flap**

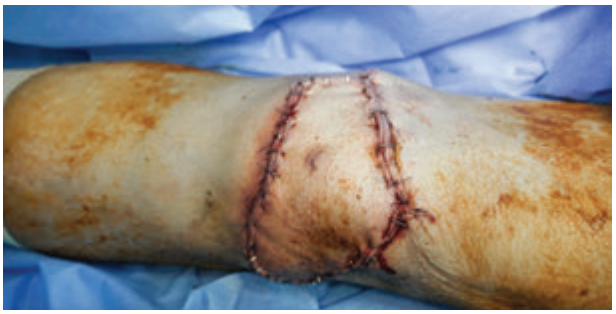

Figure 12. **Intraoperative digital photo. The flap was adapted and sutured to the edges of the wound without tension**

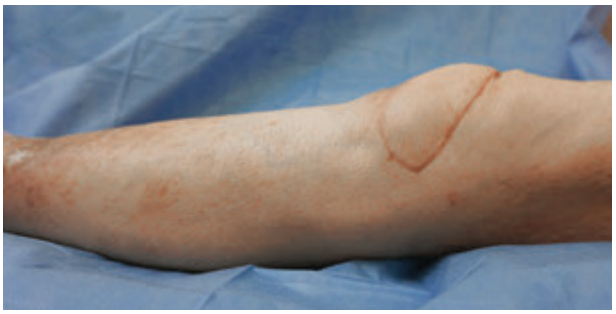

Figure 13. **Side view on the left. The result of treatment 61 days after surgery. The wound was closed without altering the contours of the knee area**

Previously, the wound was sutured at the local hospital without effect. The wound did not heal for 6 weeks (Fig. 10). It was planned to perform a radical debridement, revision of the wound, and its closure with a keystone perforator island flap, with the effect of revascularizing damaged structures in the functionally active zone of the joint (Fig. 11). The flap was formed as an island and moved to the area of the knee joint, where it was fixed with sutures to the edges of the wound defect without tension (Fig. 12). Immobilization of the lower limb in a splint for up to 4 weeks, the sutures were removed on the 14th and 20th days, and the patient was discharged after recovery. Two months of follow-up after surgery demonstrated adequate restoration of covering tissues without altering the contours of the lower limb (Fig. 13) and with complete restoration of the knee joint function (Fig. 14). The patient walks on his own with no special devices.

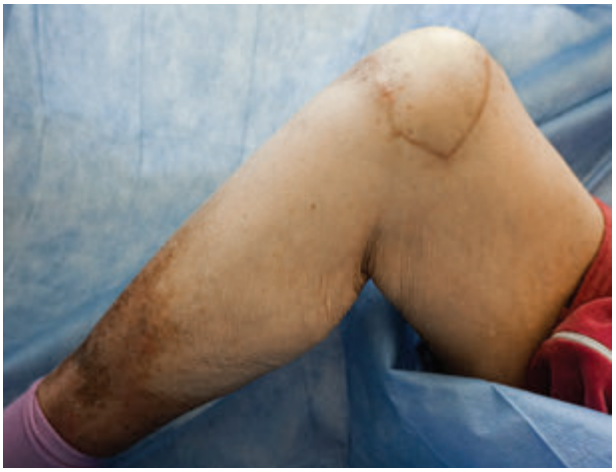

Figure 14. **The function of the lower extremities was fully restored**

Case 3

Patient M., a 38-year-old military man, was admitted to the clinic with a shrapnel and mine-explosive injury to the left shin (Fig. 15). It was planned to perform a radical debridement and wound closure with a perforator keystone island flap (Fig. 16).

After traditional mobilization with preservation of perforators and coaxial connections, a flap was adapted and sutured to the edges of the wound on the medial surface of the shin without tension (Fig. 17). The postoperative course went smoothly; the sutures were removed on the 14th day, and the patient was discharged after recovery. The observation 6 months after surgery (Fig. 18) demonstrates adequate

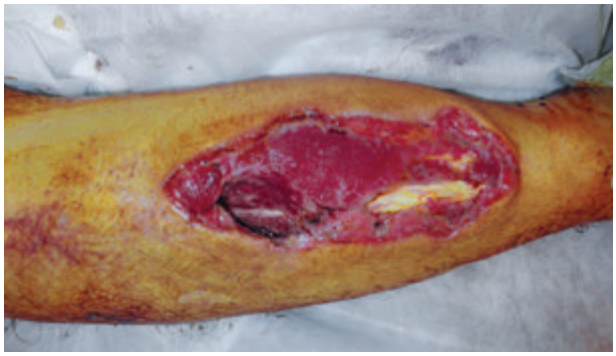

Figure 15. **View of the shrapnel and mine-explosive injury to the shin upon admission to the clinic**

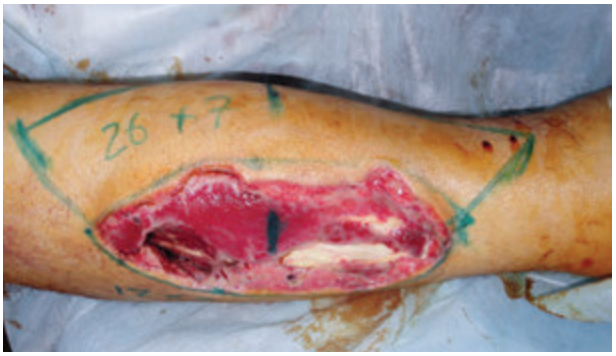

Figure 16. **Design and markup of the planned keystone perforator island flap**

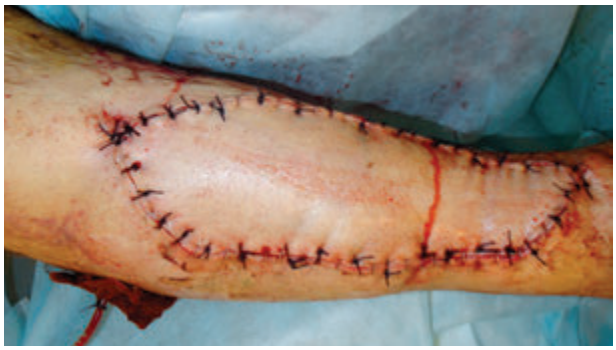

Figure 17. **Intraoperative digital photo. The flap was adapted and sutured to the edges of the wound on the medial surface of the shin without tension**

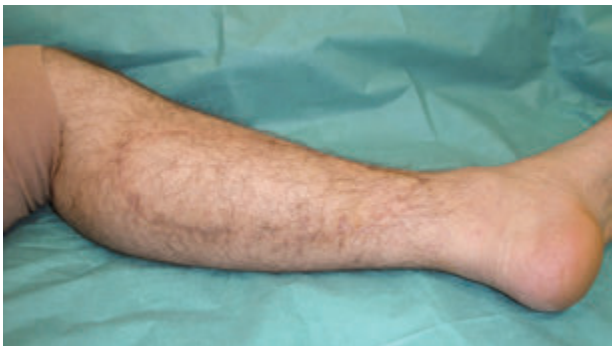

Figure 18. **Medial side view on the left shin. The result of treatment 6 months after surgery. The wound was closed without altering the contours, and the lower limb function was fully restored**

restoration of the covering tissues without altering the contours of the lower extremity. The newly formed covering tissue exhibits stability to various stimuli, is quite elastic and mobile, easy to fold, and has a hairline (Fig. 19), fulfilling the «like-to-like» principle.

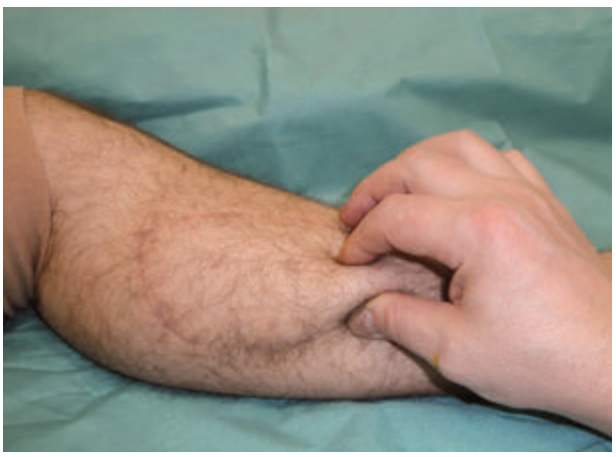

Figure 19. **The restored skin is elastic, easy to fold, exhibits stability to various stimuli, and has a hairline, fulfilling the «like-to-like» principle**

Discussion

Since 2014, combat injuries to the lower limbs have become a serious challenge for doctors of various specialties, including plastic surgeons [11, 13, 20]. Our preliminary results with regard to the reconstruction of lower limb defects caused by shrapnel and mine-explosive combat injuries using keystone perforator island flaps demonstrated a sufficiently high efficiency in the plastic closure of extensive wound defects in the injured areas of the thigh, knee joint, and lower legs. The accumulated experience allows us to affirm that the keystone perforator island flap is a priority method for one-step wound closure in the lower extremities. The use of alternative methods of plastic closure of wound defects in the lower extremities has been described in detail in previously published works [1, 15]. Local keystone perforator island flaps can be considered one of the primary methods for plastic closure of extensive combat wound defects at different anatomical locations, provided that the tissue surrounding the defect is intact and usable as a donor resource [3, 16].

One-stage reconstruction of extensive soft tissue defects is recognized by different authors as a priority in plastic surgery compared to multi-stage surgical interventions [16—18]. This reconstruction provides the fastest primary closure of the soft tissue defect. In order to increase the effectiveness of treatment in both the functional and aesthetic aspects, the keystone perforator island flap can become an alternative to skin autografts in terms of the quality of the restored covering and to two-stage cross-plastic methods or methods associated with the imposition of microvascular anastomoses, while significantly reducing the rehabilitation time and costs for hospitals [2, 5, 12, 14].

Some authors believe that the described technique is superior in efficiency to other local island flap methods, such as V-Y [12]. Compared to the transplantation of free flaps with microvascular anastomoses or perforator propeller flaps on the isolated artery, the presented method undoubtedly wins in terms of time spent in the operating room. According to our data, the average time to complete one case is 67 minutes. The research works of F. Behan et al. [4—6] and J. S. Khouri et al. [12] totally support this trend, although the authors note that the time spent in the operating room may also depend on the size of the defect itself. At the same time, plastic surgery using any other method, when perforator island flaps are used, takes at least 120 minutes. In cases of using the technique of microsurgical anastomoses for the transplantation of free flaps, this time increases occasionally [10, 17]. The relatively simple design and the absence of a directive need for invasive X-ray examinations at the stage of preparation for surgery enable us to recommend the keystone perforator island flap technique for adequate restoration of lost tissues with a complete fasciocutaneous covering with minimal surgical risk for the patient and excellent functional and aesthetic results [5—7, 17].

Other advantages of the described method include: a more stable blood supply with rapid postoperative restoration of perfusion in displaced tissues; minimal damage to the donor zone adjacent to the defect; a functionally and aesthetically acceptable final result of the lost skin restoration with a full-fledged skin-fascial flap; and a good indicator of the cost-effectiveness parameter [7, 8, 17].

Conclusions

The closure of lower limb defects caused by shrapnel and mine-explosive combat injuries with keystone perforator island flaps improves the efficiency of reconstructive surgery. The keystone perforator island flap technique requires basic preoperative preparation of the patient, is easy-to-use, and exhibits a fairly high level of reliability at the same time. In most cases, keystone perforator island flaps provide primary and single-stage closure of a large defect in the thigh, in the area of the knee joint, and lower leg in the absence of secondary defects that are common at donor sites when alternative techniques are chosen. The use of keystone perforator island flaps can be considered a priority technique for plastic closure of deep and extensive lower limb defects in the presence of intact and usable donor tissue resources adjacent to the defect.

Declaration of interests

The authors declare no conflicts of interest.

Funding. The authors did not receive any additional financial support.

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.

Authors contributions

Concept and design of the study: S. V. Sliesarenko; surgery in the clinic: S. V. Sliesarenko, P. A. Badiul, O. I. Rudenko, M. I. Romanshuk; Treatment of patients in the clinic: O. I. Rudenko, M. I. Romanshuk; literature review and discussion of the results P. A. Badiul, O. I. Rudenko, materials and research methods; carrying out research: S. V. Sliesarenko, M. I. Romanshuk.

References

1. Слесаренко СВ, Бадюл ПА, Hong JP и др. Основные принципы и алгоритм реконструкции при комбинированных повреждениях нижних конечностей. Пластична, реконструктивна і естетична хірургія, 2017;(3-4):49-73.
2. AlMugaren FM, Pak CJ, Suh HP, Hong JP. Best local flaps for lower extremity reconstruction. Plast Reconstr Surg. Glob Open. 2020;8(4):e2774. doi: 10.1097/GOX.0000000000002774. PMID: 32440438; PMCID: PMC7209892.
3. Badiul P, Sliesarenko S, Sliesarenko K. The local perforator flaps for plastic closure of extensive military wounds. Chirurgia Plastyczna i Oparzenia. 2015;2(3):59-60.
4. Behan F, Findlay M, Lo C. The keystone perforator island flap concept. Elsever, Australia; 2012. 227 p.
5. Behan F, Sizeland A, Porcedu S, Somia N, Wilson J. Keystone island flap: an alternative reconstructive option to free flaps in irradiated tissue. ANZ J Surg. 2006 May;76(5):407-13. doi: 10.1111/j.1445-2197.2006.03708.x. PMID: 16768705.
6. Behan F, Wilson I. The principle of the angiotome, a system of linked axial pattern flaps. Paper presented at the Sixth International Congress of Plastic and Reconstructive Surgery. Paris; 1975.
7. Behan FC, Lo CH, Sizeland A, Pham T, Findlay M. Keystone island flap reconstruction of parotid defects. Plast Reconstr Surg. 2012 Jul;130(1):36e-41e. doi: 10.1097/PRS.0b013e3182547f55. PMID: 22743953.
8. Behan FC, Lo CH, Sizeland A, Pham T, Findlay M. Keystone island flap reconstruction of parotid defects. Plast Reconstr Surg. 2012 Jul;130(1):36e-41e. doi: 10.1097/PRS.0b013e3182547f55. PMID: 22743953.

9. Geiger S, McCormick F, Chou R, Wandel AG. War wounds: lessons learned from Operation Iraqi Freedom. Plast Reconstr Surg. 2008 Jul;122(1):146-153. doi: 10.1097/PRS.0b013e3181773d19. PMID: 18594399.
10. Joon Pio Hong. The use of supermicrosurgery in lower extremity reconstruction: the next step in evolution. Plast. Reconsr Surg. 2009;123(1):230-5.
11. Kashtalyan MA, Herasymenko OS, Tertyshniy SV, Enin RV. New trends in the treatment of gunshot wounds. Kharkiv Surgical School. 2017;1 (82):112-5.
12. Khouri JS, Egeland BM, Daily SD, Harake MS, Kwon S, Neligan PC, Kuzon WM Jr. The keystone island flap: use in large defects of the trunk and extremities in soft-tissue reconstruction. Plast Reconstr Surg. 2011 Mar;127(3):1212-1221. doi: 10.1097/PRS.0b013e318205f36f. PMID: 21364423.
13. Kumar AR, Grewal NS, Chung TL, Bradley JP. Lessons from operation Iraqi freedom: successful subacute reconstruction of complex lower extremity battle injuries. Plast Reconstr Surg. 2009 Jan;123(1):218-229. doi: 10.1097/PRS.0b013e3181904da9. PMID: 19116556.
14. Levine JP Pu, Lee LQ, Wei Fu-Chan, editors. Reconstructive surgery of the lower extremity. Quality Medical Publishing, Incorporated; 2013. 1368 p.
15. Sliesarenko SV, Badiul PA, Nor NN, et al. Avoiding skin grafts: the local perforator flap in cutaneous defects covering. Eur J Burn Care, 2019;160:P099.
16. Sliesarenko SV, Badiul PO, Sliesarenko KS. Extensive mine-shrapnel and gunshot wound closure using keystone island perforator flaps. Plast Reconstr Surg Glob Open. 2016 May 26;4(5):e723. doi: 10.1097/GOX.0000000000000736. PMID: 27579247; PMCID: PMC4995696.
17. Sliesarenko SV, Badiul PO. Perforator flaps in reconstructive surgery. Atlas. Dnipro: ART-Press; 2021. 552 p.
18. Sliesarenko SV, Badyul PA, Cherednichenko NA, Fedorinchik MV. Combined use of local perforator transposition flaps in foot reconstruction. Klinicheskaia khirurgiia. 2012;11:31.
19. Stark HL. Directional variations in the extensibility of human skin. Br J Plast Surg. 1977 Apr;30(2):105-14. doi: 10.1016/0007-1226(77)90001-7. PMID: 870119.
20. Tsymbalyuk VI, ed. Gunshot wounds of soft tissues (Experience of an anti-terrorist operation/Operations of the united forces). Kharkiv: Kolegium; 2020. 400 p.

Закриття мінно-осколкових бойових дефектів нижніх кінцівок пластикою перфорантними keystone клаптями

С. В. Слєсаренко [1], П. О. Бадюл [1, 2], О. І. Руденко [1, 2], М. І. Романчук [1]

[1] Центр термічної травми та пластичної хірургії, міська клінічна лікарня № 8, Дніпро

[2] Дніпровський державний медичний університет

В умовах воєнних дій в Україні питання надання медичної допомоги постраждалим цивільним і військовим є особливо актуальним і гострим. У професійній діяльності пластичних хірургів стоїть завдання відновлення обширних і глибоких ранових дефектів в короткий термін і з високим ступенем відновлення пошкодженого органу, особливо опорної функції. Висвітлено досвід авторів щодо пластичної реконструкції бойових ушкоджень покривів і м'яких тканин нижніх кінцівок за допомогою локальних перфорантних keystone клаптів.

Матеріали та методи. Проведено ретроспективний огляд застосування 49 keystone клаптів у 28 пацієнтів (26 чоловіків і 2 жінки) з кульовими та мінно-осколковими пораненнями, які проходили лікування в клініці у період з 2014 до 2022 р.

Результати. У всіх випадках великі ранові дефекти були повністю закриті одноетапно. Пацієнти виписані з одужанням. При некритичних ускладненнях у 2 (4 %) випадках проведено накладення вторинних швів, що збільшило тривалість лікування на 6 днів. Час роботи в операційній, витрачений на транспозицію одного клаптя, становив від 40 до 95 хв (у середньому — 67 хв).

Висновки. Результати свідчать про високу частоту успішної реконструкції дефектів бойових поранень на нижніх кінцівках за допомогою локальних перфорантних keystone клаптів. Продемонстровано простоту доопераційної підготовки пацієнта і виконання операції та високу надійність запропонованої методики. У більшості випадків перфорантні keystone клапті дають змогу первинно та одномоментно закрити великий дефект на стегні, в ділянці колінного суглоба і гомілки за відсутності вторинних дефектів, характерних для донорських ділянок з вибором альтернативних методик.

Ключові слова: реконструктивна хірургія, перфорантний клапоть, бойове поранення, рани, keystone клапоть.

FOR CITATION

Sliesarenko SV, Badiul PA, Rudenko OI, Romanshuk MI. Keystone perforator island flaps in the reconstruction of lower limb defects resulting from shrapnel and mine-explosive combat injuries. Case series. General Surgery (Ukraine). 2023;1;48-57. http://doi.org/10.30978/GS-2023-1-48.

UDC 617.55-007.43-089.843(048.8)
DOI http://doi.org/10.30978/GS-2023-1-58

ISSN 2786-5584 PRINT
ISSN 2786-5592 ONLINE

Issues and challenges in the surgical treatment of anterior abdominal wall hernias. Review

T. V. Tarasiuk

Bogomolets National Medical University, Kyiv

✉ Tetiana Tarasiuk: tv.tarasiuk@gmail.com

T. V. Tarasiuk, http://orcid.org/0000-0001-6629-3908

The literature review discusses contentious issues and challenges that arise in the surgical treatment of anterior abdominal wall hernias. The author identified the causes of hernia formation and examined the dynamics of change in the pattern of hernia incidence. An analysis of the factors that contribute to the development of incisional ventral hernias was given special consideration. The causes of hernia recurrence were also studied. The entire spectrum of existing classifications of primary and incisional ventral hernias was reviewed, along with their advantages and disadvantages. Evaluation of current recommendations regarding the use of additional imaging methods for the examination of patients with ventral hernias was carried out. In the study, considerable attention was paid to surgical methods for hernia treatment. The advantages and disadvantages of "open" and minimally invasive laparoscopic hernioplasty techniques were critically evaluated. The difficulties in selecting an intervention method for certain types of hernias, including large ones, were highlighted, as was the importance of preventing hernia recurrence.

It has been established that there are still many unsolved problems in the surgical treatment of anterior abdominal wall hernias. The author justified the need for a standardized approach to determining the characteristics of anterior abdominal wall hernias and their further classification. It is necessary to study the effectiveness of using imaging methods (ultrasound, computed tomography) for ventral hernias, depending on their size and location. There is a need for wider implementation of laparoscopic hernioplasty techniques, and the degree of the hernial defect should be taken into account when determining the indications for surgical intervention. The possibility of using laparoscopic hernioplasty for large hernias, as well as for hernias associated with rectus abdominis diastasis, requires further investigation. Improving management strategies for patients with anterior abdominal wall hernias is critical in order to reduce the risk of hernia recurrence and complications.

Keywords
ventral hernia, incisional hernia, hernioplasty, mesh.

ARTICLE • Received 2023-02-09 • Received in revised form 2023-03-04
© 2023 Author. Published under the CC BY-ND 4.0 license

Anterior abdominal wall hernias are one of the most common pathologies in surgical practice. About a quarter of the global population is either born with a ventral hernia or may develop it during life [25, 26].

Etiology and epidemiology of anterior abdominal wall hernias

The reasons for hernia development include evolutionary anatomical weakness of certain areas of the abdominal wall (umbilical area, midline of the abdomen, inguinal areas), predisposition to the formation of a defect in the abdominal wall (operative interventions in the anamnesis), and increased intra-abdominal pressure [41]. However, such social factors as a decreased birth rate, a lack of physical activity, increased life expectancy, and higher obesity rates can have an impact on the pattern of hernia incidence [35].

According to epidemiological studies, inguinal hernias (70—75 %) predominate among abdominal wall hernias [35, 56, 67]. And while 30 years ago femoral hernias were the second most prevalent (6—17 %), the situation has changed [56, 67]. According to N. Dabbas et al., midline abdominal wall hernias became the most common among ventral hernias. Hernias of the umbilical area (umbilical and paraumbilical — 19 %) are currently the second most common, followed by midline abdominal wall hernias, including epigastric (8.6 %) and incisional (4.8 %) hernias, femoral hernias (2.6 %) and hernias of rare locations, including Spiegelian hernias (less than 1 %) [35]. However, the prevalence of incisional ventral hernias varies widely

(2—23 %), according to various authors, and is dependent on the technique used to suture the surgical wound, the presence of concomitant diseases, wound infection, and other factors. Incisional hernias occur in 1—15 % of patients operated on by the traditional «open» method for various types of abdominal pathology. Their frequency increases to 20 % 10 years after surgery [16, 19, 21, 23, 29, 39, 53, 57, 63, 64, 68, 71, 80, 82]. At 12 months of follow-up, a meta-analysis based on 24 randomized controlled trials (a total of 3,490 patients) demonstrated a significant difference in the incidence of incisional ventral hernias after laparoscopic (4.3 %) and open (10.1 %) surgery [54]. Incisional hernias can occur in up to 69 % of high-risk patients [59].

S. G. Parker et al. identified 5 groups of important prognostic factors for the development of ventral hernia recurrence based on a meta-analysis of the results of the treatment of 12,423 patients. Female sex, age 65 years or less, a body mass index greater than 25 kg/m^2 (patient factors), as well as the presence of such concomitant diseases as diabetes, chronic obstructive pulmonary disease, III—IV ASA degree, smoking, and use of steroids, significantly increase the risk of hernia recurrence. Two factors associated with hernias (incisional/primary, recurrent/primary), six intraoperative factors (use of biological mesh, bridging, open vs. laparoscopic surgery, hernia suture vs. synthetic mesh, onlay mesh placement technique vs. retrorectus, intraperitoneal mesh placement compared with retrorectus), and six postoperative factors (any complication, surgical-site occurrence, wound infection, seroma, hematoma, and wound opening) were also identified as important prognostic factors for hernia recurrence [62]. In the study, the authors aimed to determine the factors that influenced the risk of recurrence of ventral hernias but did not concentrate on assessing the importance of each of the factors. In a number of analyzed studies, for example, a body mass index greater than 25 kg/m^2 increased the rate of hernia recurrence, but the indicator of 30 kg/m^2 was the threshold for most studies. However, J. S. Jolissaint et al. noted that surgical site occurrences, not body mass index, increased the risk of ventral hernia recurrence in the long term [50].

After surgery, recurrences of small and large umbilical hernias are observed in 15—20 % and 30—40 % of cases, respectively [16]. The frequency of recurrence of incisional ventral hernias is on average 18—21 % after 12 months of observation, but it can reach 37 % after 48 months of observation [52]. At the same time, the difference in the data on the development of recurrence after laparoscopic and open hernioplasty is controversial.

Classification of anterior abdominal wall hernias

The goal of developing a hernia classification is to standardize an approach to identifying the type of hernia, processing and presenting statistical data, determining examination tactics, and selecting the type of surgical treatment based on the hernia's characteristics [38, 61]. The literature review demonstrates the absence of a single approach to the classification of anterior abdominal wall hernias. Primary ventral and incisional hernias are distinguished by different factors that contribute to their occurrence. Some authors propose categorizing them separately [33, 51, 61, 70, 78] based on different indicators, while others combine these types of hernias into a single classification [20, 38].

In 2000, J. P. Chevrel and A. M. Rath proposed the SWR classification of incisional hernias. They chose three criteria: the location of the hernia «S» (medially or laterally located, with further division into 4 subgroups according to the localization zone on the abdominal wall), the width of the defect «W» (4 subgroups with a step of 5 cm) and the number of hernia recurrences «R» [33]. However, the classification did not include the length of the hernial defect or the number of defects, and had shortcomings in the distribution according to the site of the defect, which made it difficult to determine surgical tactics.

V. Schumpelick proposed to divide incisional hernias into 5 classes, taking into account the maximum size of the hernial defect, the number of defects, their localization, symptoms, the presence of recurrence, and the repairability of the hernia. However, his classification was not widely used in surgical practice [61, 70].

In 2001, M. Korenkov et al. proposed their version of the classification of incisional hernias, modifying the Chevrel classification. They grouped hernias according to their location, which was defined as vertical, transverse, oblique, or combined. They also proposed to determine the size of the hernia not only by its width but also by its length, dividing it into three subgroups while leaving a step of 5 cm and defining a large hernia as a hernia with a width or length of more than 10 cm. M. Korenkov et al. focused on the need to determine the «real» size of the hernial defect by measuring the distance between the muscle-aponeurotic structures and not the edges of the scar tissue of the defect, which cannot serve as a frame when suturing the defect. It was proposed to take into account the presence of hernia symptoms and their reducibility [51]. However, the risk factors for the development of hernia recurrence and the number of defects were not taken into

consideration. Moreover, when assessing the size of the defect, the width and length were compared as equally important, which negatively affects the adequacy of the choice of surgical tactics. It is the width of the hernial defect that influences the degree of tissue tension after suturing and determines the need to separate the components of the abdominal wall in order to prevent compartment syndrome [22].

In 2007, U. A. Dietz et al. proposed a classification of incisional hernias [37], which later received the name of the Wuerzburg classification of ventral and incisional hernias [38]. It is based on the determination of the patient's body type, localization (hernia morphology), and size of the hernia, the presence of previous attempts at hernioplasty, and risk factors for hernia recurrence [37, 38].

There were attempts to supplement the hernia classification with additional indicators, including the ratio of the area of the anterior abdominal wall to the area of the hernial defect. As the indicator of this ratio increases, the risk of high tension in the anterior abdominal wall and compartment syndrome increases [22].

All of these above-mentioned classifications have not been widely used in practice. For example, in 2008, a method for collecting statistical data on the basis of which hernias were classified was presented in the Swedish Register of Hernias of the Anterior Abdominal Wall. In addition to the generally defined parameters, including hernia localization, their number, and size, it was supposed to take into account additional preoperative indicators such as the patient's body mass index, causes of incisional hernia formation, the presence of a pre-installed mesh, and the type and location of the previous incision [61].

In order to develop a common language and create a practically oriented and widely supported classification of hernias, the European Hernia Society (EHS) formed a working group that included the authors of the above classifications. In 2009, they introduced the classification of primary and incisional hernias of the anterior abdominal wall. Primary hernias of the anterior abdominal wall are classified according to their location, with medial (epigastric, umbilical) and lateral (Spiegelian, lumbar) hernias distinguished, as well as their size, with small (less than 2 cm), medium (from 2 to 4 cm), and large (4 cm and more) hernias defined. Depending on their location, incisional hernias are classified as middle (subxiphoid M1, epigastric M2, umbilical M3, subumbilical M4, suprapubic M5) and lateral (subcostal L1, flank L2, iliac L3, lumbar L4). It is suggested that the length and width of the hernial defect be measured in centimeters and that the type of hernia be classified as W1 (< 4 cm), W2 (from 4 to 10 cm), and W3 (10 cm and more). In addition, it is necessary to indicate whether the hernia is recurrent (yes/no). However, it is not necessary to indicate the number of hernial defects. In the case of their multiplicity, it is proposed to define the width as the distance between the lateral edges of the most laterally located defects and the length as the distance between the upper edge of the most cranially located defect and the lower edge of the most caudally located defect [61].

Despite the wide range of hernia characterization criteria and ease of use, the EHS classification is still criticized and competes for use with other developed classifications [20, 27, 30, 38, 44, 75]. Since one of the goals of developing a hernia classification was to facilitate the selection of surgical tactics and predict the risk of complications, the working group from the United States proposed a hernia grading system (hernia grading system: assessment of risk for surgical site occurrences) [78]. It is based on the determination of risk factors for postoperative wound healing (4 degrees), depending on the infection of the operative field or the presence of concomitant diseases that worsen the reparative processes. The use of this grading system assists in determining surgical tactics and selecting the type of mesh (synthetic or biological), but it is fundamentally different from the proposed EHS principles of stratification of hernias and is not a hernia classification [38, 78]. Another attempt was made to categorize ventral hernias into 4 degrees based on clinical manifestations and imaging results (ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI)). However, this classification is also fundamentally different from the EHS classification, and the results of its implementation are still being studied [20].

As a result, the EHS classification of anterior abdominal wall hernias remains the most standardized and used [27, 49, 60], though it is subject to changes when different professional associations reach a consensus. Thus, the joint working group of EHS and the American Hernia Society (AHS) suggested changing the size parameters of umbilical and epigastric hernias, dividing them into small (0—1 cm), medium (1—4 cm), and large (more than 4 cm) [49]. It should be noted that all the above classifications do not take into account the association of hernias with rectus abdominis diastasis, which can significantly influence the choice of surgical tactics [28].

In Ukraine, there is no single approach to the classification of anterior abdominal wall hernias. K. D. Toskin and V. V. Zhebrovskyi (1984) proposed a classification of abdominal hernias that takes into

account the location, size of the defect, and clinical signs of the hernia. But excessive detailing and a lack of clearly defined criteria for the size of the defect contributed to the limitation of its implementation in surgical practice. The leading hernia centers in Ukraine have used the EHS classification in publications to present the results of their research [15, 17, 18], but it is still not widely used among herniological surgeons. Some authors use domestic and foreign classifications of previous years [6, 12, 14] or do not describe the hernia's characteristics at all [10]. Implementing a unified approach to ventral hernia classification will allow us to develop an optimal treatment algorithm, compare comparable treatment results, and evaluate them in the distant postoperative period, regardless of the place of surgical treatment.

Diagnosis of anterior abdominal wall hernias

The clinical examination of the patient (examination, palpation, percussion, auscultation of the abdomen and areas of localization of the hernial defect) allows for the assessment of the location, size, and contents of the hernial sac. In most cases, a clinical examination is sufficient to diagnose an anterior abdominal wall hernia [49]. According to S. Halligan et al., preoperative methods of hernia visualization are used in only 12 % of cases, while in the postoperative period this indicator increases to 29 % [48], which may be due to the need for timely diagnosis of complications in the early postoperative period. CT is preferred over ultrasound as a procedure for hernia visualization. MRI and other X-ray imaging methods (herniography, abdominal X-ray) are very rarely or never used [48].

Although ultrasound examination of the anterior abdominal wall has long been used to detect hernias [73], it is not a required routine practice. If the clinical examination is complicated by obesity or severe pain syndrome, ultrasound is a non-invasive, accurate, reliable, relatively inexpensive, and easily accessible method for diagnosing hernias in patients [83]. Ultrasound is also recommended for excluding, confirming, or measuring rectus abdominis diastasis [27].

In the guidelines for surgical treatment of primary ventral and incisional hernias, data on imaging and instrumental diagnostics are either absent [30] or represented by limited recommendations based on insufficient evidence (grade D, level 4, level 5) to draw any conclusions regarding the use of CT and MRI in special cases [27, 29]. Thus, according to the 2014 ENS guidelines, CT and MRI are recommended for the diagnosis of ventral hernias in patients who are obese, as well as in cases of giant (loss of domain), post-traumatic, lumbar, or Spiegelian hernias [29]. A small number of publications support the use of CT for the diagnosis of rare types of ventral hernias [46, 47, 66, 72]. In order to better plan the surgical strategy and inform the patient, the 2019 EHS guidelines recommend considering CT in patients with large or incarcerated hernias (Grade D) [27]. CT can help predict wound complications and anterior abdominal wall tension caused by the use of separation techniques in the treatment of patients with large ventral hernias [27, 43]. There is a need to define radiological criteria for the detection of hernia recurrence because there are inconsistencies in the findings regarding the detection of ventral hernias when a CT scan is performed in the postoperative period [27].

According to D. V. Cherla et al., there is a moderate correlation between the results of a clinical examination, a CT scan, and an intraoperative laparoscopic assessment when evaluating the extent of ventral hernia defects. However, differences in measurements can have an impact on the hernia classification and the choice of mesh size in 58 % and 56 % of cases, respectively [32].

According to the EHS and AHS guidelines, umbilical and linea alba hernias should be diagnosed clinically. Ultrasound or CT are recommended when the diagnosis is unclear [49].

The limited use of imaging methods for detecting anterior abdominal wall hernias can result in an underestimation of the hernia's characteristics, an increased risk of recurrence [48], and an irrational selection of the surgical procedure. More research into the effectiveness of ultrasound and CT in hernia patients is required.

Types of surgical treatment of hernias and their features

Prior to the development of modern minimally invasive technologies and meshes, the only surgical treatment option for anterior abdominal wall hernias was «open» suturing of the hernial defect, which included the formation of various types of aponeurotic duplications to strengthen the suturing zone and prevent recurrence. However, this technique had a high risk of complications and relapses, which significantly increased with large hernial defects [29]. The situation changed with the introduction of minimally invasive technologies and meshes. Their use in surgical practice when performing various types of hernioplasty significantly improved hernia treatment outcomes [27, 29]. J. W. Burger et al.

discovered that suturing an incisional ventral hernia up to 6 cm in size with a mesh reduced the rate of recurrence from 63 % to 32 % [31]. And, while the use of a mesh reduces the rate of recurrence by three times when compared to autoplasty, the location of the mesh does not allow for a significant reduction in the frequency of recurrence, but does affect the overall rate of complications [24, 77, 79]. According to the EHS and AHS recommendations, a mesh should be placed for ventral hernias larger than 1 cm to prevent recurrence of the disease [27, 49].

«Open» hernioplasty with mesh placement in the thickness of the anterior abdominal wall (sublay, onlay, or inlay) is still one of the most common surgical treatments for ventral hernias of various localizations [16, 79]. This technique is used to treat both small umbilical (mainly sublay mesh placement) and large incisional ventral hernias [4, 16, 27, 34]. The technique of surgical intervention involves wide dissection of tissues for adequate placement of the implant, which causes a large intraoperative trauma, the development of a pronounced pain syndrome in the postoperative period, a long period of rehabilitation, and the social adaptation of patients [36]. And, if these open surgery methods are justified for the treatment of giant incisional hernias with the need to model the anterior abdominal wall, their use for small ventral hernias becomes debatable.

Open, non-tension surgery using mesh and the sublay technique has taken the lead in the surgical treatment of umbilical hernias in Ukraine. There is a 2 % to 16.9 % reccurence rate when using this technique [16]. However, even small umbilical hernias require extensive mobilization of soft tissues, which, when associated with rectus abdominis diastasis, causes significant traumatization of anterior abdominal wall tissues, contributing to prolonged surgical wound healing and patient rehabilitation. As a result, there is no consensus on the criteria for selecting the best surgical intervention technique for umbilical hernias associated with rectus abdominis diastasis.

Laparoscopic technologies for the treatment of hernias are currently in the implementation stage in Ukraine. They are primarily used in specialized medical centers and clinics of university surgical departments [1, 2, 4, 5, 7—9, 13, 15, 16]. The use of an intraperitoneal mesh (IPOM) during laparoscopic hernioplasty prevents tissue trauma and eliminates the need for abdominal wall component separation [29, 76]. Laparoscopic hernioplasty can decrease the rate of postoperative complications, reduce the length of stay, and promote rehabilitation [27, 29, 40, 58, 81]. The IPOM technique is the most widely used and researched method of ventral hernioplasty. Other laparoscopic hernioplasty methods with mesh placement preperitoneally, retrorectally, or retromuscularly are still being studied and are technically more traumatic [28].

The requirement for specialized equipment and surgeon skills, the high cost of modern mesh implants, and the lack of a clear diagnostic and treatment algorithm all make it difficult to incorporate minimally invasive technologies into general surgical practice [55]. Treatment strategies are frequently determined by the surgeon's personal preferences for one type of surgical intervention or another, the clinic's capabilities, and the patient's requests. Laparoscopic hernioplasty is the optimal treatment option for the hernial defects up to 10 cm in size [29]. If the size of the hernial defect is more than 10 cm, it can be challenging to suture the defect in the anterior abdominal wall without tension. In such cases, «open» hernioaloplasty with various modifications of the Ramirez technique is preferred. This is a traumatic procedure that increases the risk of developing postoperative complications, including complications in the area of the postoperative wound [16, 42].

Laparoscopic surgery does not always involve suturing the hernial defect. In their study, K. Suwa et al. indicate the availability of a limited number of publications that compare the results of IPOM with and without suturing of the hernial defect before mesh placement. Suturing the hernial defect prior to IPOM yields better results [74]. However, A. M. Gonzalez et al. presented the research, which included 134 patients. The study's findings revealed a higher recurrence rate of 7.5 % in the group that did not have hernial defect suturing prior to IPOM, compared to 1.5 % in the group that had hernial defect suturing [45]. The availability of the results of mostly comparative studies and a limited sample of patients do not allow determining the reliability of performing IPOM without hernial defect suturing with a high degree of certainty.

A number of authors report a higher rate of hernia recurrence after minimally invasive laparoscopic procedures when compared to «open» techniques. However, the rate of recurrence varies significantly depending on the length of the postoperative observation period [40, 81]. According to S. Olmi et al., after 24 months of follow-up, hernia recurrence was found in 2.3 % of patients after laparoscopic surgery and in 1.1 % of patients after «open» hernioplasty in a prospective randomized study of 170 cases [81]. In a multicenter randomized controlled study including 206 patients, H. H. Eker et al. noted that after 35 months of observation, the frequency of hernia recurrence in the group after

laparoscopic surgery was 18 %, while in the group after open surgery it was 14 % [40]. Y. Zhang et al. found no significant difference in the frequency of hernia recurrence after laparoscopic and open hernioplasty for ventral hernias in their systematic review and meta-analysis of the results of 11 randomized controlled trials, including 1,003 patients [84]. The study, however, had several limitations, including the heterogeneity of the data collected and the hernioplasty techniques used. The analysis of 10 randomized controlled trials, which included 880 patients, shows that there is no significant difference in the frequency of hernia recurrence after laparoscopic and «open» hernioplasty [69].

The lack of a single systematic approach to selecting a method of treatment for anterior abdominal wall hernias results in a high frequency of complications and relapses of the disease with an unjustified preference for one of the treatment methods [3, 11].

Conclusions

Evaluation of the effectiveness of surgical treatment for anterior abdominal wall hernias requires a standardized method for recording hernia incidence and consensus on a classification approach.

The issue of introducing laparoscopic operations in herniology is extremely relevant and promising. The problem of preventing hernia recurrence after surgery and the use of minimally invasive technologies in the treatment of large hernias require special attention.

The optimization of the diagnostic and treatment algorithms for patients with anterior abdominal wall hernias will be possible through the investigation and analysis of current techniques for treating ventral hernias, the frequency and structure of postoperative complications, and the recurrence rate.

Declaration of interests

The author has no conflicts of interest to declare.

References

1. Вансович ВЄ, Осадчий ДМ. Лапароскопічна герніопластика післяопераційних вентральних гриж із застосуванням політетрафлуороетиленової сітки з нітиноловим каркасом (Rebound System). Шпитальна хірургія. 2012;(3):120-3.
2. Грубнік ВВ, Парфентьєв РС, Аскеров Є, Воротинцева КО. Перспективні методи лікування вентральних гриж. Acta Medica Leopoliensia. Львівський медичний часопис. 2009;XV(3):47-9.
3. Жебровский ВВ, Косенко АВ, Воронов НВ. и др. Особенности оперативного лечения осложненных форм послеоперационных грыж брюшной стенки. Клінічна хірургія. 2010;(3):31-4.
4. Іоффе ОЮ, Стеценко ОП, Тарасюк ТВ, Цюра ЮП, Прадош ІМ. Формування пупка при лапароскопічній герніопластиці за методикою IPOM з приводу неускладнених пупкових гриж. Хірургія України. 2013;(3):51-4.
5. Каштальян МА, Шаповалов ВЮ. Использование биоматериала политетрафторэтилен в ходе лапароскопической аллогерниопластики вентральных грыж. Хірургія України. 2011;(3):59.
6. Кравченко БС, Клименко АВ, Клименко ВМ, Сергєєва ЛН. Порівняльний аналіз оперативних втручань з приводу післяопераційної вентральної грижі в пацієнтів з ожирінням. Медичні перспективи. 2021;26(3):78-84. doi: 10.26641/2307-0404.2021.3.241958.
7. Криворучко ИА, Сивожелезов АВ, Тесленко СН, Чугай ВВ. Лапароскопические пластики вентральных грыж. Сучасні медичні технології. 2012;(4):30-2.
8. Лерчук ОМ, Гавриш ЯІ, Лерчук МО, Маркевич ЮО, Павловський МП. Лапароскопічна герніопластика рубцевих вентральних гриж. Галиц. лікар. вісн. 2002;9(3):179-80.
9. Литвиненко ОМ, Лукеча ІІ. Лапароскопічна герніопластика післяопераційної вентральної кили. Хірургія України. 2014;(3):34.
10. Lutkovskyi R. Алопластика післяопераційних вентральних гриж живота з використанням наномодифікованої поліпропіленової сітки. Актуальні проблеми сучасної медицини. 2019;3:61-6. doi: 10.26565/2617-409X-2019-3-09.
11. Милица НН, Милица КН. Выбор метода открытой герниопластики с использованием аллотрансплантата. Харківська хірургічна школа. 2012;1(52):152-4.
12. Пак ВЯ, Березний ТВ, Ситнік ОЛ, Мелеховець ЮВ, Перерва ОО. Протирецидивна пластика гриж передньої черевної стінки. Харківська хірургічна школа. 2022;(4-5):38-41. doi: 10.37699/2308-7005.4-5.2022.08.
13. Пепенин АВ, Иоффе ИВ, Алексеев АВ, Пепенин НА. Лапароскопическая коррекция IPOM троакарных параумбиликальных грыж. Хірургія України. 2014;(3):42-3.
14. П'ятночка ВІ. Невирішені питання хірургічного лікування хворих на післяопераційну вентральну грижу за умов коморбідності. Вісник наукових досліджень. 2017;(1):11-5. doi: 10.11603/2415-8798.2017.1.7348.
15. Tarasiuk TV. Перший досвід використання ботулотоксину типу А при хірургічному лікуванні вентральних гриж. Шпитальна хірургія. Журнал імені Л. Я. Ковальчука. 2020;(2):102-5. doi: 10.11603/2414-4533.2020.2.10775.
16. Фелештинський ЯП. Післяопераційні грижі живота. К.: Бізнес-Логіка; 2012. 200 р.
17. Фелештинський ЯП, Лерчук ОМ, Сміщук ВВ. Оптимізація вибору лапароскопічної та відкритої алопластики при післяопераційних вентральних грижах. Клінічна та експериментальна патологія. 2021;20(2):80-7. doi: 10.24061/1727-4338. XX.2.76.2021.12.
18. Фелештинський ЯП, Лерчук ОМ, Сміщук ВВ, Гудима ЯМ. Лапароскопічна преперитонеальна алопластика післяопераційних вентральних гриж. Klinichna khirurhiia. 2020;87(5-6):50-4. doi: 10.26779/2522-1396.2020.5-6.50.
19. Adotey JM. Incisional hernia: a review. Niger J Med. 2006;15(1):34-43. doi: 10.4314/njm.v15i1.37113.
20. Alghamdi F. Ventral hernia: an innovative grading system. International Journal of Clinical Medicine. 2022;13:204-211. https: // doi.org/10.4236/ijcm.2022.135017.
21. Alnassar S, Bawahab M, Abdoh A, Guzman R, Al Tuwaijiri T, Louridas G. Incisional hernia postrepair of abdominal aortic occlusive and aneurysmal disease: five-year incidence. Vascular. 2012;20(5):273-7. doi: 10.1258/vasc.2011.oa0332.
22. Ammaturo C, Bassi G. The ratio between anterior abdominal wall surface/wall defect surface: a new parameter to classify abdominal incisional hernias. Hernia. 2005;9(4):316-21. doi: 10.1007/s10029-005-0016-8.
23. Andersen LP, Klein M, Gögenur I, Rosenberg J. Incisional hernia after open versus laparoscopic sigmoid resection. Surg Endosc. 2008;22(9):2026-9. doi: 10.1007/s00464-008-9924-x.
24. Andersen LP, Klein M, Gögenur I, Rosenberg J. Long-term recurrence and complication rates after incisional hernia repair with the open onlay technique. BMC Surg. 2009;9:6. doi: 10.1186/1471-2482-9-6.
25. Beadles CA, Meagher AD, Charles AG. Trends in emergent hernia repair in the United States. JAMA Surg. 2015;150(3):194-200. doi: 10.1001/jamasurg.2014.1242.
26. Bedewi MA, El-Sharkawy MS, Al Boukai AA, Al-Nakshabandi N. Prevalence of adult paraumbilical hernia. Assessment by high-resolution sonography: a hospital-based study. Hernia. 2012;16(1):59-62. doi: 10.1007/s10029-011-0863-4.
27. Bittner R, Bain K, Bansal VK, et al. Update of Guidelines for laparoscopic treatment of ventral and incisional abdominal wall hernias (International Endohernia Society (IEHS))-Part A [published correction appears in Surg Endosc. 2019 Jul 12]. Surg Endosc. 2019;33(10):3069-139. doi: 10.1007/s00464-019-06907-7.

28. Bittner R, Bain K, Bansal VK, et al. Update of Guidelines for laparoscopic treatment of ventral and incisional abdominal wall hernias (International Endohernia Society (IEHS)): Part B. Surg Endosc. 2019;33(11):3511-49. doi: 10.1007/s00464-019-06908-6.
29. Bittner R, Bingener-Casey J, Dietz U, et al. Guidelines for laparoscopic treatment of ventral and incisional abdominal wall hernias (International Endohernia Society (IEHS)-part 1. Surg Endosc. 2014;28(1):2-29. doi: 10.1007/s00464-013-3170-6.
30. Bougard H, Coolen D, de Beer R, et al. HIG (SA) Guidelines for the Management of Ventral Hernias. South African Journal of Surgery. 2016;54(4):S1-S32.
31. Burger JW, Luijendijk RW, Hop WC, Halm JA, Verdaasdonk EG, Jeekel J. Long-term follow-up of a randomized controlled trial of suture versus mesh repair of incisional hernia. Ann Surg. 2004;240(4):578-85. doi: 10.1097/01.sla.0000141193.08524.e7.
32. Cherla DV, Lew DF, Escamilla RJ, et al. Differences of alternative methods of measuring abdominal wall hernia defect size: a prospective observational study. Surg Endosc. 2018;32(3):1228-33. doi: 10.1007/s00464-017-5797-1.
33. Chevrel JP, Rath AM. Classification of incisional hernias of the abdominal wall. Hernia. 2000;4:7-11. https://doi.org/10.1007/BF01230581.
34. Cobb WS, Warren JA, Ewing JA, Burnikel A, Merchant M, Carbonell AM. Open retromuscular mesh repair of complex incisional hernia: predictors of wound events and recurrence. J Am Coll Surg. 2015;220(4):606-13. doi: 10.1016/j.jamcollsurg.2014.12.055.
35. Dabbas N, Adams K, Pearson K, Royle G. Frequency of abdominal wall hernias: is classical teaching out of date? JRSM Short Reports. 2011;2(1):1-6. doi: 10.1258/shorts.2010.010071.
36. Davies SW, Turza KC, Sawyer RG, Schirmer BD, Hallowell PT. A comparative analysis between laparoscopic and open ventral hernia repair at a tertiary care center. Am Surg. 2012;78(8):888-92.
37. Dietz UA, Hamelmann W, Winkler MS, et al. An alternative classification of incisional hernias enlisting morphology, body type and risk factors in the assessment of prognosis and tailoring of surgical technique. J Plast Reconstr Aesthet Surg. 2007;60(4):383-8. doi: 10.1016/j.bjps.2006.10.010.
38. Dietz UA, Winkler MS, Härtel RW, et al. Importance of recurrence rating, morphology, hernial gap size, and risk factors in ventral and incisional hernia classification. Hernia. 2014;18(1):19-30. doi: 10.1007/s10029-012-0999-x.
39. Edmiston CE Jr, Leaper DJ. Intra-operative surgical irrigation of the surgical incision: What does the future hold-saline, antibiotic agents, or antiseptic agents? Surg Infect (Larchmt). 2016;17(6):656-64. doi: 10.1089/sur.2016.158.
40. Eker HH, Hansson BM, Buunen M, et al. Laparoscopic vs. open incisional hernia repair: a randomized clinical trial. JAMA Surg. 2013;148(3):259-/63. doi: 10.1001/jamasurg.2013.1466.
41. Elango S, Perumalsamy S, Ramachandran K, Vadodaria K. Mesh materials and hernia repair. Biomedicine (Taipei). 2017;7(3):16. doi: 10.1051/bmdcn/2017070316.
42. Faylona JM. Evolution of ventral hernia repair. Asian J Endosc Surg. 2017;10(3):252-8. doi: 10.1111/ases.12392.
43. Franklin BR, Patel KM, Nahabedian MY, Baldassari LE, Cohen EI, Bhanot P. Predicting abdominal closure after component separation for complex ventral hernias: maximizing the use of preoperative computed tomography. Ann Plast Surg. 2013;71(3):261-5. doi: 10.1097/SAP.0b013e3182773915.
44. García-Ureña MÁ, López-Monclús J, Cuccurullo D, et al. Abdominal wall reconstruction utilizing the combination of absorbable and permanent MESH in a retromuscular position: a multicenter prospective study. World J Surg. 2019;43(1):149-58. doi: 10.1007/s00268-018-4765-9.
45. Gonzalez AM, Romero RJ, Seetharamaiah R, Gallas M, Lamoureux J, Rabaza JR. Laparoscopic ventral hernia repair with primary closure versus no primary closure of the defect: potential benefits of the robotic technology. Int J Med Robot. 2015;11(2):120-5. doi: 10.1002/rcs.1605.
46. Gough VM, Vella M. Timely computed tomography scan diagnoses spigelian hernia: a case study. Ann R Coll Surg Engl. 2009;91(8):W9-W10. doi: 10.1308/147870809X450629.
47. Habib E, Elhadad A. Spigelian hernia long considered as diverticulitis: CT scan diagnosis and laparoscopic treatment. Computed tomography. Surg Endosc. 2003;17(1):159. doi: 10.1007/s00464-002-4237-y.
48. Halligan S, Parker SG, Plumb AAO, et al. Use of imaging for pre- and post-operative characterisation of ventral hernia: systematic review. Br J Radiol. 2018;91(1089):20170954. doi: 10.1259/bjr.20170954.
49. Henriksen NA, Montgomery A, Kaufmann R, et al. Guidelines for treatment of umbilical and epigastric hernias from the European Hernia Society and Americas Hernia Society. Br J Surg. 2020;107(3):171-90. doi: 10.1002/bjs.11489.
50. Jolissaint JS, Dieffenbach BV, Tsai TC, et al. Surgical site occurrences, not body mass index, increase the long-term risk of ventral hernia recurrence. Surgery. 2020;167(4):765-71. doi: 10.1016/j.surg.2020.01.001.
51. Korenkov M, Paul A, Sauerland S, et al. Classification and surgical treatment of incisional hernia. Results of an experts' meeting. Langenbecks Arch Surg. 2001;386(1):65-73. doi: 10.1007/s004230000182.
52. Köckerling F. Recurrent incisional hernia repair-an overview. Front Surg. 2019;6:26. Published 2019 May 14. doi: 10.3389/fsurg.2019.00026.
53. Köckerling F, Hoffmann H, Mayer F, et al. What are the trends in incisional hernia repair? Real-world data over 10 years from the Herniamed registry. Hernia. 2021;25(2):255-65. doi: 10.1007/s10029-020-02319-y.
54. Kössler-Ebs JB, Grummich K, Jensen K, et al. Incisional hernia rates after laparoscopic or open abdominal surgery-a systematic review and meta-analysis. World J Surg. 2016;40(10):2319-30. doi: 10.1007/s00268-016-3520-3.
55. LeBlanc KA. Current considerations in laparoscopic incisional and ventral herniorrhaphy. JSLS. 2000;4(2):131-9.
56. Morris PJ, Malt RA. Oxford Textbook of Surgery. Vol. 1. Oxford: Oxford Medical Publications, Oxford University Press; 1994.
57. Mudge M, Hughes LE. Incisional hernia: a 10 year prospective study of incidence and attitudes. Br J Surg. 1985;72(1):70-1. doi: 10.1002/bjs.1800720127.
58. Müller-Riemenschneider F, Roll S, Friedrich M, et al. Medical effectiveness and safety of conventional compared to laparoscopic incisional hernia repair: a systematic review. Surg Endosc. 2007;21(12):2127-36. doi: 10.1007/s00464-007-9513-4.
59. Muysoms FE, Antoniou SA, Bury K, et al. European Hernia Society guidelines on the closure of abdominal wall incisions. Hernia. 2015;19(1):1-24. doi: 10.1007/s10029-014-1342-5.
60. Muysoms F, Campanelli G, Champault GG, et al. EuraHS: the development of an international online platform for registration and outcome measurement of ventral abdominal wall hernia repair. Hernia. 2012;16(3):239-50. doi: 10.1007/s10029-012-0912-7.
61. Muysoms FE, Miserez M, Berrevoet F, et al. Classification of primary and incisional abdominal wall hernias. Hernia. 2009;13(4):407-14. doi: 10.1007/s10029-009-0518-x.
62. Parker SG, Mallett S, Quinn L, et al. Identifying predictors of ventral hernia recurrence: systematic review and meta-analysis [published correction appears in BJS Open. 2021 May 7;5(3):]. BJS Open. 2021;5(2):zraa071. doi: 10.1093/bjsopen/zraa071.
63. Pérez-Köhler B, Bayon Y, Bellón JM. Mesh infection and hernia repair: a review. Surg Infect (Larchmt). 2016;17(2):124-37. doi: 10.1089/sur.2015.078.
64. Poelman M, Apers J, van den Brand H, et al. The INCH-Trial: a multicentre randomized controlled trial comparing the efficacy of conventional open surgery and laparoscopic surgery for incisional hernia repair. BMC Surg. 2013;13:18. Published 2013 Jun 7. doi: 10.1186/1471-2482-13-18.
65. Ponten JE, Leenders BJ, Charbon JA, et al. Mesh Or Patch for Hernia on Epigastric and Umbilical Sites (MORPHEUS trial): study protocol for a multi-centre patient blinded randomized controlled trial. BMC Surg. 2014;14:33. doi: 10.1186/1471-2482-14-33.
66. Rose M, Eliakim R, Bar-Ziv Y, Vromen A, Rachmilewitz D. Abdominal wall hernias. The value of computed tomography diagnosis in the obese patient. J Clin Gastroenterol. 1994;19(2):94-6.
67. Russell RCG, Williams NS, Bulstrode CJK. Bailey and love's short practice of surgery. 23rd Edition. Hodder Arnold, London; 2000.
68. Rutkow IM. Demographic and socioeconomic aspects of hernia repair in the United States in 2003. Surg Clin North Am. 2003;83(5):1045-vi. doi: 10.1016/S0039-6109(03)00132-4.
69. Sauerland S, Walgenbach M, Habermalz B, Seiler CM, Miserez M. Laparoscopic versus open surgical techniques for ventral or incisional hernia repair. Cochrane Database Syst Rev. 2011;(3):CD007781. Published 2011 Mar 16. doi: 10.1002/14651858.CD007781.pub2.
70. Schumpelick V. Narbenhernie. In: Schumpelick V (ed). Hernien. Thieme, Stuttgart; 2000. P. 266-269.
71. Seiler CM, Bruckner T, Diener MK, et al. Interrupted or continuous slowly absorbable sutures for closure of primary elective midline abdominal incisions: a multicenter randomized trial (INSECT: ISRCTN24023541). Ann Surg. 2009;249(4):576-82. doi: 10.1097/SLA.0b013e31819ec6c8.

72. Skrekas G, Stafyla VK, Papalois VE. A Grynfeltt hernia: report of a case. Hernia. 2005;9(2):188-91. doi: 10.1007/s10029-004-0278-6.
73. Spangen L. Ultrasound as a diagnostic aid in ventral abdominal hernia. J Clin Ultrasound. 1975;3(3):211-3. doi: 10.1002/jcu.1870030311.
74. Suwa K, Okamoto T, Yanaga K. Closure versus non-closure of fascial defects in laparoscopic ventral and incisional hernia repairs: a review of the literature. Surg Today. 2016;46(7):764-73. doi: 10.1007/s00595-015-1219-y.
75. Torregrosa-Gallud A, Sancho Muriel J, Bueno-Lledó J, et al. Modified components separation technique: experience treating large, complex ventral hernias at a University Hospital. Hernia. 2017;21(4):601-8. doi: 10.1007/s10029-017-1619-6.
76. Van Hoef S, Tollens T. Primary non-complicated midline ventral hernia: is laparoscopic IPOM still a reasonable approach?. Hernia. 2019;23(5):915-25. doi: 10.1007/s10029-019-02031-6.
77. Venclauskas L, Silanskaite J, Kanisauskaite J, Kiudelis M. Long-term results of incisional hernia treatment. Medicina (Kaunas). 2007;43(11):855-60.
78. Ventral Hernia Working Group, Breuing K, Butler CE, et al. Incisional ventral hernias: review of the literature and recommendations regarding the grading and technique of repair. Surgery. 2010;148(3):544-58. doi: 10.1016/j.surg.2010.01.008.
79. de Vries Reilingh TS, van Geldere D, Langenhorst B, et al. Repair of large midline incisional hernias with polypropylene mesh: comparison of three operative techniques. Hernia. 2004;8(1):56-9. doi: 10.1007/s10029-003-0170-9.
80. Walming S, Angenete E, Block M, Bock D, Gessler B, Haglind E. Retrospective review of risk factors for surgical wound dehiscence and incisional hernia. BMC Surg. 2017;17(1):19. doi: 10.1186/s12893-017-0207-0.
81. Wells JM, Pring C, Olmi S, Scaini GC, Erba L, Croce E. Laparoscopic versus open incisional hernia repair. Surg Endosc. 2007;21:555-9. Surg Endosc. 2008;22(1):266. doi: 10.1007/s00464-007-9590-4.
82. Wiegering A, Sinha B, Spor L, et al. Gentamicin for prevention of intraoperative mesh contamination: demonstration of high bactericide effect (in vitro) and low systemic bioavailability (in vivo). Hernia. 2014;18(5):691-700. doi: 10.1007/s10029-014-1293-x.
83. Young J, Gilbert AI, Graham MF. The use of ultrasound in the diagnosis of abdominal wall hernias. Hernia. 2007;11(4):347-51. doi: 10.1007/s10029-007-0227-2.
84. Zhang Y, Zhou H, Chai Y, Cao C, Jin K, Hu Z. Laparoscopic versus open incisional and ventral hernia repair: a systematic review and meta-analysis. World J Surg. 2014;38(9):2233-40. doi: 10.1007/s00268-014-2578-z.

Проблемні питання в хірургічному лікуванні гриж передньої черевної стінки. Огляд

Т. В. Тарасюк

Національний медичний університет імені О. О. Богомольця, Київ

Розглянуті дискусійні питання, які виникають при хірургічному лікуванні гриж передньої черевної стінки. Висвітлено чинники розвитку гриж. Проаналізовано динаміку зміни структури захворюваності на грижі. Особливу увагу приділено аналізу причин розвитку післяопераційних вентральних гриж. Також проаналізовано причини рецидиву гриж. Наведено класифікації первинних та післяопераційних вентральних гриж. Проаналізовано їхні переваги та недоліки. Проведено оцінку актуальних рекомендацій щодо застосування додаткових візуалізаційних методів обстеження у пацієнтів з вентральними грижами. Велику увагу приділено хірургічним методам лікування гриж. Критично оцінено переваги та недоліки «відкритих» та малоінвазивних лапароскопічних технік герніопластики. Наголошено на складності вибору методу втручання при окремих видах гриж, зокрема великих, і важливості профілактики рецидиву грижі.

Установлено, що в хірургічному лікуванні гриж передньої черевної стінки є багато невирішених питань. Обґрунтовано потребу в стандартизованому підході до визначення характеристик гриж передньої черевної стінки та вдосконаленні їхньої класифікації, зокрема в Україні. Необхідно вивчити ефективність застосування візуалізаційних методів (ультразвуку, комп'ютерної томографії) при вентральних грижах різного розміру та локалізації. Є потреба у ширшому впровадженні лапароскопічних методів герніопластики, визначенні показань до оперативного втручання залежно від розміру грижового дефекту. Потребує оцінки можливість використання лапароскопічної герніопластики при грижах великого розміру, а також при поєднанні гриж із діастазом прямих м'язів живота. Нагальною є потреба у вдосконаленні тактики ведення пацієнтів з грижами передньої черевної стінки для мінімізації ризику появи рецидивів та ускладнень.

Ключові слова: вентральна грижа, післяопераційна грижа, герніопластика, сітка.

FOR CITATION

Tarasiuk TV. Issues and challenges in the surgical treatment of anterior abdominal wall hernias. Review. General Surgery (Ukraine). 2023:1;58-65. http://doi.org/10.30978/GS-2023-1-58.

General Surgery has specific **instructions and guidelines for submitting manuscripts**. The instructions and guidelines comply with the requirements of the Ministry of Education and Science of Ukraine for publications presenting the results of dissertations for obtaining Doctor of Sciences, Candidate of Sciences or Doctor of Philosophy degree and published in the scientific professional editions of Ukraine (orders of the Ministry of Education and Science of Ukraine No 32 of Jnuary 15, 2018, No 1437 of November 18, 2020), as well as with the requirements of the International Committee of Medical Journal Editors for manuscripts submitted to the biomedical editions. The Editorial Board will not consider submissions that do not adhere to the Author Guidelines.

General Surgery accepts manuscript submissions through the journal website or via email **office.generalsurgery@gmail.com**.

MANUSCRIPT COMPONENTS

To submit a manuscript, authors must check off their submission's compliance with all of the following items.

Title page

· Index of the Universal Decimal Classification (UDC).

· Full name of each author (first name, middle initial and last name) followed by each author's highest academic degree(s). Name of institution(s) with which each author is affiliated (if the work should be attributed to different institutions, it is necessary to personify each author with numbers 1, 2, 3), address and ORCID id.

· Full name, academic degree and academic title, telephone number, and e-mail of the author responsible for correspondence concerning the manuscript.

Note. The Ukrainian authors must provide the above-mentioned data both in Ukrainian and English. Please note that names and last names are not corrected by the editorial staff and, therefore, are published exactly as they appear in the manuscript.

· For the collective paper, the signatures of all authors are required.

· The paper must be submitted with the official assignment from the institution where the research was carried out.

· A copy of the form of article licensing terms must be completed and submitted with the manuscript.

· All submitted manuscripts must be written in English.

Formatting

The length of the manuscript, including references, tables, illustrations and figures is up to 15 pages for an empirical paper and up to 20 pages for a review paper.

Tables, illustrations, figures, diagrams and formulas should be included in the text and cited consecutively in the manuscript.

Tables should be designed using the Microsoft Word format. Each table must have a title and a number. Number them in the order in which they are discussed.

Other illustrations (photographs, figures, graphs, diagrams etc.) must be marked as «Fig.». Number them in the order in which they are discussed.

Photographs, echograms must be submitted in the original or digital format. The digital artwork must be saved at a resolution of 300 dpi as JPG or TIFF files and additionally submitted as a separate file. Each figure should have a concise caption describing accurately what it depicts. Tags and symbols should be clear and readable after diminution. If photographs of patients are used, they must be accompanied by written permission to use the photograph, or the subjects must not be identifiable.

Abstract. The abstract should not be less than 1800 characters, including spaces. The structure of the abstract must follow the structure of the article. The abstract for original research manuscript should contain the same sections as the article. *The Ukrainian authors must provide the abstract both in Ukrainian and English. Both abstracts should be identical.*

Keywords. 3—7 keywords or phrases that capture the most important aspects of the paper. The keywords must be relevant to a subject of research and included into the Medical Subject Headings 2021 (MeSH) thesaurus, which is available online at https://meshb.nlm.nih.gov/search; https://www.ncbi.nlm.nih.gov/mesh.

Article structure for original research section. The article should contain the next sections: Introduction (summarize the relevance of the study or rationale for it, providing the scientific context for the research. Do not review the subject exhaustively); Objective; Materials and methods; Results and discussion; Conclusions. Other types of manuscripts (clinical observations, lectures and reviews, etc.) could be drafted in another way.

The requirements for other types of manuscripts (review papers, case reports, meta-analysis, lectures, history of surgical science, and etc.) can be found at: https://www.care-statement.org/ for clinical case reports; http://www.consort-statement.org/ for CONSORT's randomized research and execution standards; https://www.equator-network.org/ for all types of medical research in all fields of medicine.

Acknowledgements (not obligatory). Acknowledge those who contributed to the manuscript providing technical help or writing assistance, or who provided general support.

Author contributions. Participation of each author in the manuscript writing (concept and design of the study; material collection, material processing, statistical data processing, writing text, and etc.)

Declaration of interests. Declare the presence or absence of a financial/personal interest or belief, consultant, institutional and other relationships that might affect the objectivity of the research.

Funding. All sources of funding must be acknowledged in the manuscript.

References. References must be numbered in alphabetical order with the literature sources in the Ukrainian or Russian language (Cyrillic letters) followed by the literature sources in the foreign languages (Latin letters). Use the AMA style: https://www.enago.com/academy/unique-characteristics-of-the-ama-style-guide/. Specify a unique numeric identifier for the DOI article. Check the availability of the DOI identifier at http://search.crossref.org or http://www.citethisforme.com. For information on DOI, you need to enter the English title in the search box.

Ethical policies

In studies, involving human subjects, the authors must indicate if the experiments were conducted in accordance with the ethical standards of the Helsinki Declaration of 1964 that were revised by the 59th General Assembly of the Military Medical Academy, Seoul, October, 2008. Confirmation should be provided that the patient's informed consent has been obtained. The authors should note that the procedures were duly approved by the local ethics committee. The protocol details, issued by the local ethics committee, must be provided.

The experiments with animal subjects must comply with the principles of the European Convention for the Protection of Vertebrate Animals Used for Research and Other Scientific Purposes (Strasbourg, 1986) and the Law of Ukraine «On the Protection of Animals from Cruelty». It is necessary to indicate the type and number of experimental animals, methods of anaesthesia and euthanasia.

Editorial Policies

The Editorial Board will consider the papers meeting the high standards of the journal and significantly contributing to the advancement of surgical science.

All forms of plagiarism and data fabrication are unethical and unacceptable.

The Editorial Board will not consider manuscripts that were previously published in other journals.

For all articles, the scientific originality of a paper is measured by means of software developed for determining the level of originality.

The editors reserve the right to change the style of the article formatting. The article may be returned to the authors with the request to revise or to answer queries.

The proof-sheet will not be sent to the authors. Pre-publishing preparation of the author's manuscript is completed by the editors.

All articles are published under a Creative Commons Attribution-NoDerivatives 4.0 International License (CC BY-ND 4.0).