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KOLOPROKTOLOGIA

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Общероссийская общественная организация «Ассоциация колопроктологов России», созданная 3 октября 1991 г. по инициативе врачей-колопроктологов РФ, является уникальной в своей сфере и одной из старейших общественных медицинских ассоциаций. На данный момент в Ассоциации состоит более 800 колопроктологов практически из всех субъектов РФ

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- издание научно-практического медицинского журнала «Колопроктология», входящего в перечень рецензируемых журналов и изданий ВАК Министерства образования и науки РФ;
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ПРЕИМУЩЕСТВА ЧЛЕНСТВА В АССОЦИАЦИИ

- **более низкие регистрационные взносы на участие в Общероссийских научно-практических мероприятиях;**
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НАУЧНО-ОБРАЗОВАТЕЛЬНЫЙ ОТДЕЛ:
123423, г. Москва, ул. Саляма Адиля, д. 2,
каб. №2 (цокольный этаж),
Заведующая учебной частью – Шадина Наталья Евгеньевна
тел.: +7(499)642-54-41 доб. 500
e-mail: edu@gnck.ru, info@gnck.ru

АДРЕС АССОЦИАЦИИ
123423, г. Москва, ул. Саляма Адиля, д. 2

Тел.: 8 (499) 642-54-41 доб. 1215
Факс: 8 (499) 199-04-09
E-mail: info@akr-online.ru

Главный бухгалтер:
Артамонова П.Ю.
polinav@mail.ru

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«Ассоциация колопроктологов России»

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том 21, № 2, 2022

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Ответственный секретарь:
Рыбаков Е.Г.
E-mail: proctologia@mail.ru

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EDITORIAL OFFICE

Salyama Adilya St., 2, Moscow, Russia, 123423

Phone & fax: +7 (499) 199-00-68

E-mail: **proctologia@mail.ru**
koloproktologia@akr-online.ru

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ЦЕЛИ И ЗАДАЧИ

Целью журнала «Колопроктология» является освещение современных тенденций и научно-практических достижений в колоректальной хирургии.

Заболевания толстой кишки, заднего прохода, тазового дна и промежности являются одними из наиболее распространённых, а колопроктология — наиболее динамично развивающейся хирургической специальностью.

Колоректальный рак занимает одну из ведущих позиций в структуре онкологических заболеваний, наблюдается неуклонный рост воспалительных заболеваний кишечника, дивертикулярной болезни. Постоянно изменяются диагностические и лечебные подходы при лечении геморроидальной болезни, свищей заднего прохода, анальной трещины, анальной инконтиненции.

Колопроктологи в России, как и во всем остальном мире, интенсивно взаимодействуют с онкологами, гастроэнтерологами, общими хирургами, эндоскопистами, патофизиологами и специалистами других научно-практических направлений врачебной деятельности.

Целевой аудиторией журнала являются колопроктологи, а также врачи других специальностей, интерес которых сконцентрирован на заболеваниях толстой кишки, заднего прохода, тазового дна и промежности.

Журнал «Колопроктологии» объединяет колопроктологов России в тесном сотрудничестве с профессиональными объединениями мира и ведущими международными экспертами в области колоректальной хирургии.

В журнале публикуются оригинальные статьи, результаты фундаментальных исследований, направленные на изучение общепатологических процессов с целью улучшения лечения больных, описание клинических наблюдений, мета-анализы и обзоры литературы по широкому спектру вопросов колопроктологии, а также результаты клинических и экспериментальных исследований.

AIM AND SCOPE

The purpose of the journal *Koloproktologia* (Russian Journal of Coloproctology) is to highlight current trends and scientific achievements in colorectal surgery.

Diseases of the colon, anus, pelvic floor, and perineum are among the most common; and coloproctology is the most dynamically developing surgical specialty.

Colorectal cancer occupies one of the leading positions in the structure of oncological diseases. There is a steady increase in inflammatory bowel diseases, diverticular disease, stoma patients.

Diagnostic and treatment options for hemorrhoid disease, anal fistula, anal fissure, and anal incontinence are constantly changing.

Coloproctologists in Russia, as in the rest of the world, intensively interact with oncologists, gastroenterologists, general surgeons, endoscopists, pathophysiologists, and specialists in other scientific and practical areas of medical activity.

The target audience of the journal is coloproctologists, as well as doctors of other specialties, whose interest is focused on diseases of the colon, rectum, anus, pelvic floor and perineum.

The journal *Koloproktologia* (Russian Journal of Coloproctology) unites coloproctologists of Russia in close cooperation with professional associations of the world and leading international experts in the field of colorectal surgery.

The journal publishes original articles, the results of basic research aimed at studying general pathological processes in order to improve the treatment of patients, clinical cases, meta-analyses, and literature reviews on a wide range of coloproctology issues, as well as the results of clinical and experimental studies.

Журнал включен в перечень рецензируемых научный изданий, рекомендуемых ВАК, для публикации основных научных результатов диссертационных исследований на соискание ученой степени кандидата наук, на соискание ученой степени доктора наук по научным специальностям (по состоянию на 29.03.2022):

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Doctor of Medical Sciences Alexey S. Tsukanov,
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CLINICAL GUIDELINES
Adenomatous Polyposis Syndrome

Yuri A. Shelygin, Evgeny N. Imyanitov, Sergey I. Kutsev, Sergey I. Achkasov, Sergey V. Vasiliev, Sergey A. Frolov, Vladimir N. Kashnikov, Alexander M. Kuzminov, Evgeny G. Rybakov, Vladimir V. Strelnikov, Dmitry V. Vyshegorodtsev, Alexey S. Tsukanov, Alexey I. Moskalev, Dmitry Yu. Pikunov

Developers of Clinical Recommendations:
Association of Coloproctologists of Russia;
Association of Medical Geneticists

Coding according of the International Statistical Classification of Diseases and Health-Related Problems: **D12**

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LIST OF ABBREVIATIONS

APS — adenomatous polyposis syndrome
ROA — rectal occlusion apparatus (anal sphincter)
CRC — colorectal cancer
CT — computed tomography
MAP — *MutYH*-associated polyposis
MRI — magnetic resonance imaging
TRUSE — transrectal ultrasound examination
Ultrasound — ultrasound examination
EGDS — esophagogastroduodenoscopy

TERMS AND DEFINITIONS

The autosomal dominant type of inheritance is a type of inheritance characterized by the following signs: each sick descendant has a sick parent; the disease occurs in persons of both sexes; the risk of inheritance of the disease for the children of the affected parent is 50%; in healthy descendants of the patient, all children should be healthy.

An autosomal recessive type of inheritance is a type of inheritance of a trait characterized by the following signs: the disease occurs in persons of both sexes; there are breaks in the pedigree; sick children can be born to healthy parents; if both parents are sick, then all their children will also be sick.

Proband is a person from whom the compilation of a pedigree begins to study the process of inheritance of a disease among members of the same family.

The family tree is a graphical representation of family history data, in addition to the nature of family ties between family members, reflects information about the manifestation of a trait, health status or pathology among relatives, provides visual information about the nature of inheritance of the trait.

Germinal (hereditary) mutations are any genetic changes that take place inside the progenitor cells of germ cells; they are determined in all cells of the body.

Adenoma is a benign tumor originating from the glandular epithelium.

Polyp is a collective term used to refer to various pathological tissue growths over the mucous membrane.

Dentate adenoma is a variant of a polyp that occupies an intermediate position between adenomas and hyperplastic polyps, a characteristic feature of which is a pronounced expansion of the basal sections and horizontal growth of crypts along the muscular plate of the mucous membrane.

Hyperplastic polyp is a polyp formed as a result of focal hyperplasia and morphologically unrelated to benign intestinal tumors.

Desmoid tumor (desmoid, desmoma, aggressive fibromatosis) is a rare, locally invasive, non-metastatic tumor that develops from musculoaponeurotic structures and occupies an intermediate position between benign and malignant neoplasms. The most common localization is the anterior abdominal wall, upper and lower extremities, mesentery of the small intestine.

1. BRIEF INFORMATION ON THE DISEASE OR CONDITION (GROUP OF DISEASES OR CONDITIONS)

1.1 Definition of a Disease or Condition (Group of Diseases or Conditions)

Adenomatous polyposis syndrome is a rare hereditary disease characterized by the development of multiple (more than 20) colon adenomas at a young age with their inevitable malignant transformation in case of untimely surgical treatment [1–2].

1.2 Etiology and Pathogenesis of a Disease or Condition (Group of Diseases or Conditions)

The etiological cause of the development of the APS is the presence of a germinal mutation in one of the genes encoding proteins that regulate intercellular adhesion and apoptosis (*APC, MutYH*).

The *APC* (adenomatous polyposis coli) gene was identified and mapped by two independent groups of researchers in 1986–1991 [3–5]. It is located on the long arm of chromosome 5 in the 5q22 region, and includes 16 exons, of which 15 encode a protein containing 2,843 amino acids [6]. The *APC* gene is responsible for the synthesis of a specific protein that functions as a tumor suppressor, ensuring normal proliferation in the cells of the gastrointestinal mucosa. Mutations in the *APC* gene lead to the synthesis of a 'shortened' protein, which loses the function of suppressing increasing epithelial dysplasia, and are the cause of the development of an autosomal dominant hereditary syndrome — familial adenomatosis of the colon, which is characterized by the development of multiple adenomas with their subsequent malignant transformation in 100% of cases [7,8]. The most common types of mutations in the *APC* gene are deletion, insertion with a reading frame shift and nonsense mutation. Deletion is characterized by the loss of one or more nucleotides, the number of which is not a multiple of 3, from a normal DNA chain; insertion is the insertion of one or more nucleotides, the number of which is not a multiple of 3, into a DNA molecule; and nonsense mutation is a type of mutation in which the formation of a premature stop codon occurs [9].

To date, more than 2,000 unique pathogenic hereditary mutations in the *APC* gene have been described; but new mutations are regularly found in ongoing studies, which is due to both the heterogeneous population affiliation of the probands and the nature of the gene itself [8,9]. An autosomal dominant type of inheritance is characteristic for the transmission of mutations in the *APC* gene, which has a number of features:

- The trait occurs, as a rule, in each generation, which is called vertical inheritance;
- Male and female individuals are affected with the same frequency;
- Sick men and women equally transmit the trait to offspring — boys and girls;
- A sick family member, as a rule, has a sick parent (less often parents);
- The probability of having a sick child if both parents are sick is 75%, if one of them is sick — 50%.

In 2002, biallelic mutations in the *MutYH* gene located on the first chromosome in the 1p34 region were described for the first time [10]. This gene encodes a DNA excision repair protein involved in the reduction of oxidative damage to guanine. ***MutYH*-associated polyposis** is an autosomal recessive disease characterized by the development of multiple colon adenomas and the risk of CRC on their background, reaching 80% in case of late diagnosis and treatment. A characteristic feature of APS caused by mutation in the *MutYH* gene is the presence in the colon, along with adenomatous polyps, also creeping **dentate adenomas**, hyperplastic polyps, mixed polyps (hyperplastic and adenomatous) [11,12]. An autosomal recessive type of inheritance is characteristic of the *MutYH* gene mutation transmission, which has a number of features:

- The trait is rare, not in every generation;
- Sick children are born, as a rule, to healthy parents;
- Mostly siblings (brothers, sisters) are sick;
- Healthy children may be born to a sick parent;
- Male and female individuals are affected with the same frequency;
- The probability of having a sick child in a marriage of two heterozygotes is 25% for each subsequent child, regardless of the number of already existing sick children.

At the birth of a child, clinical signs of APS do not appear. In the future, as the body grows, the appearance of small polyps on the mucous membrane of the colon is detected [13,14].

1.3 Epidemiology of a Disease or Condition (Group of Diseases or Conditions)

In 2018, more than 74,000 new cases of CRC were detected in the Russian Federation [15]. About 5–10% occur in cases of cancer with a known molecular genetic cause, while up to 1% of cases are caused by APS [16], which is

the second most common genetically determined syndrome after Lynch syndrome [17,18]. The prevalence of mutations in the *APC* gene in Europeans, according to various estimates, is from 1:6,850–1:31,250 [19,20].
The frequency of occurrence of allelic mutations in the *MutYH* gene, according to various estimates, is 1:20,000–1:60,000 [19,21].

1.4 Features of Coding a Disease or Condition (Group of Diseases or Conditions) According to the International Statistical Classification of Diseases and Health-Related Problems

ICD-10 codes

Class — Neoplasms (C00-D48) (II).
Block — Benign neoplasms (D10-D36).
Code — D12 — Benign neoplasm of the colon, rectum, anus, and anal canal:
D12.0 — Caecum
D12.1 -Vermiform process
D12.2 — Ascending colon
D12.3 — Transverse colon
D12.4 — Descending colon
D12.5 — Sigmoid colon
D12.6 — Colon of unspecified part, including:
- Adenomatosis of the colon
- Large intestine
- Polyposis (congenital) of the colon

D12.7 — Rectosigmoid compound
D12.8 — Rectum
D12.9 — Anus and anal canal

1.5 Classification of a Disease or Condition (Groups of Diseases or Conditions)

Polyposis syndromes include situations when 20 or more colon polyps are detected. All of them are united by the concept of "adenomatous polyposis syndrome".
APS is classified according to the clinical course and variant of the genetic mutation. The classification is used to determine the severity of the disease and the choice of treatment tactics [1,2]. The following clinical forms of the disease are distinguished:
1. The classical form is the most common form, which is characterized by the presence of hundreds or thousands (i.e. more than 100) polyps in the colon, and their malignant transformation occurs at the age of 18–40 years. The first symptoms of the disease may appear already in childhood. In addition, patients with the classical form of the disease may develop severe metabolic disorders and anemia, which often cause children to lag behind in physical development [2,23]. In the classical form of APS, mutations in the *APC* gene are detected in about 80% of observations. In other cases, the presence of the wild-type *APC* gene is detected.
In the classical form of APS, Gardner syndrome and Turco syndrome are additionally distinguished.
- *Gardner syndrome* is a combination of APS with soft tissue tumors, osteomas of the skull bones. Most often there are desmomas — highly differentiated connective tissue tumors localized in the anterior abdominal wall, mesentery of the small or large intestine, sometimes in the intermuscular layers of the back and shoulder girdle. By their structure, tumors are not malignant, do not metastasize, but are prone to aggressive locally destructive growth and frequent recurrence.
- *Turcot syndrome* is APS in combination with malignant tumors of the central nervous system — medulloblastomas.

2. The weakened form is characterized by the presence of 20 to 100 polyps in the large intestine, localized mainly in the proximal parts. Clinical manifestations occur at the age of 40–45 years, and polyp malignancy occurs at the age of over 50 years. The weakened form occurs in about 8% of patients with APS. With a weakened form of APS, mutations in the *APC* gene are detected in about 20% of observations. In other cases, when 20–99 polyps are detected, the presence of the wild-type *APC* gene is detected.
3. *MutYH*-associated polyposis (MAP) caused by the presence of 2 non-allelic mutations in the *MutYH* gene, in contrast to the classical and weakened forms, in which mutations occur in the *APC* gene [24–27].
Despite the localization of mutations in different genes, MAP can manifest itself as a classical form of APS (100 or more polyps) and weakened form (20–99 polyps). Unlike the classical and weakened forms of APS, MAP **always** reveals 2 mutations in the *MutYH* gene.
4. Preclinical Form. This variant of the disease includes clinical situations when a relative of a patient with APS had a characteristic mutation, but colonoscopy did not reveal colon polyps.

1.6 Clinical Picture of a Disease or Condition (Group of Diseases or Conditions)

The most frequent manifestations of the disease *in the classical form of APS* are changes in the frequency and consistency of stool — diarrheal syndrome, metabolic disorders, as well as the presence of blood and mucus

impurities in the stool, abdominal pain. In addition, the characteristic symptoms are also general weakness, dizziness, which develop against the background of anemia. The first symptoms appear at the age of 14–16 years, and malignant degeneration of polyps occurs at the age of 18–40 years. With late treatment, there may be signs of intestinal patency disorders.

With a weakened form of APS, the main complaints in patients are the discharge of blood, mucus from the anus. At the same time, the first symptoms of the disease appear at the age of 20–45 years, and malignant degeneration of polyps often occurs at the age of over 40 years. Most often, the diagnosis of a weakened form of APS is established as a result of examination for clinical symptoms characteristic of the presence of a malignant tumor of the colon.

MutYH-associated polyposis is similar in clinical picture to the weakened form of APS.

In addition, patients with APS have a high risk of developing malignant neoplasms of extra-intestinal localization: duodenal, stomach, thyroid, brain cancer, hepatoblastomas (may occur in children), tumors of the hepatobiliary system [23].

2. DIAGNOSIS OF A DISEASE OR CONDITION, MEDICAL INDICATIONS AND CONTRAINDICATIONS TO THE USE OF DIAGNOSTIC METHODS

Diagnosis of APS is based on the clinical picture of the disease, family history data, endoscopic picture and molecular genetic study.

When establishing the diagnosis of APS, it is necessary to carry out differential diagnosis with other diseases and hereditary syndromes:

- Colon cancer
- Lynch syndrome
- Peitz-Jaegers syndrome
- Juvenile polyposis

Diagnosis Principles

The diagnosis of APS is established on the basis of the clinical picture (the presence of 20 or more colon polyps) and the results of genetic studies indicating the presence and localization of mutations in the gene. The last two criteria are especially important for a clinical geneticist, whose participation in the APS diagnosis is necessary as part of the multidisciplinary team work.

In the presence of 100 or more colon polyps, a diagnosis of the classical form of APS is established. When a mutation is detected in the *APC* gene, the localization of the mutation is indicated. For example:

"Adenomatous polyposis syndrome, classical form. Mutation in the *APC* gene c.2730-2737del8."

If a mutation in the *APC* gene is not detected in the patient, then the presence of the wild-type *APC* gene is established. In this case, the diagnosis is formulated as follows:

"Adenomatous polyposis syndrome, classical form. The wild-type *APC* gene."

With the classical form of APS and the detection of a soft tissue tumor, a diagnosis of Gardner syndrome is established, and also the nature, localization and size of the soft tissue tumor are indicated, for example:

"Adenomatous polyposis syndrome, classical form. Mutation in the *APC* gene c.2730-2737del8. Gardner syndrome, desmoma of the anterior abdominal wall 6 × 13 cm."

With the classical form of APS and the detection of a tumor of the posterior cranial fossa, the diagnosis of Turko syndrome is established. This part of the diagnosis is formed by a neurosurgeon, for example:

"Adenomatous polyposis syndrome, classical form. Mutation in the *APC* gene c.2730-2737del8. Turko syndrome, medulloblastoma of the cerebellum."

When 20–99 colon polyps are detected, the weakened form of APS is diagnosed. With the weakened form, the number and size of the identified polyps must be indicated, as well as the localization of the mutation in the *APC* gene, for example:

"Adenomatous polyposis syndrome, weakened form (52 colon polyps, 3–28 mm). Mutation in the *APC* p.Arg405X gene."

If in the presence of 20–99 colon polyps a mutation in the *APC* gene is not detected, then the wild type of the *APC* gene is stated, for example:

"Adenomatous polyposis syndrome, weakened form (34 colon polyps, 8–34 mm), wild-type *APC* gene."

If a mutation in the *APC* gene is detected in the patient's relatives, then even in the absence of colon polyps, it is necessary to diagnose APS, while the localization of the mutation is necessarily indicated, for example:

"Adenomatous polyposis syndrome, preclinical form. Mutation in the *APC* gene c.2730-2737del8."

If a patient has 2 biallel mutations in the *MutYH* gene, the diagnosis of MAP is established, while the number and size of polyps are indicated, as well as the localization of mutations in the *MutYH* gene, for example:

"Adenomatous polyposis syndrome. *MutYH-associated* polyposis (14 polyps, 6–25 mm). Mutations in the *MutYH* p.R231H and p.G382D gene."

With MAP, if the number of polyps is more than 100, then the exact number and size of polyps are not indicated, for example:

"Adenomatous polyposis syndrome. *MutYH-associated* polyposis (more than 100 polyps). Mutations in the *MutYH* p.R231H and p.G382D gene."

If 2 mutations in the *MutYH* gene are detected in the patient's relatives, even in the absence of polyps during colonoscopy, the diagnosis of APS is established, for example:

"Adenomatous polyposis syndrome. *MutYH*-associated polyposis. Mutations in the *MutYH* p.R231H and p.G382D gene. Preclinical stage."

When a malignant tumor of the colon is detected in APS, a cancer diagnosis should be the first in the diagnosis establishment, for example:

"Cancer of the ascending intestine T4N0M0. Adenomatous polyposis syndrome, the classical form. Mutation in the *APC* gene c.2730-2737del8."

2.1 Complaints and Anamnesis

Patients with APS are most characterized by complaints of frequent, loose stools, abdominal pain, the presence of pathological impurities in the stool (blood, mucus). Some patients may complain of general weakness, weight loss, bloating, nausea.

• For all patients who, according to their anamnesis and instrumental examination, have (had) a total of more than 20 colon polyps, as well as those who have a family history of APS or a history of having any number of polyps in the colon had extra-intestinal manifestations of APS (multiple duodenal/gastric adenomas, desmoid tumors, papillary thyroid cancer, epidermal cysts, osteomas), it is **recommended** to compile a pedigree with subsequent analysis of the type of inheritance characteristic of this family (autosomal dominant, autosomal recessive) [24,28–30].

Category of recommendations — A (Level of evidence — 1)

2.2 Physical Examination

All patients with suspected APS should undergo a physical examination:

- *General examination;*
- *Examination and palpation of the abdomen;*
- *External examination of the perineum and anus;*
- *Digital rectal examination.*

During the general examination of the patient, attention is paid to the body mass index, pallor and dryness of the skin, the presence/absence of extra-intestinal manifestations (soft tissue tumors, sebaceous glands). The examination and palpation of the abdomen is carried out in order to identify tumors of the abdominal organs, desmoid tumors and to assess the condition of the inguinal lymph nodes.

The examination of the perianal area is carried out on a gynecological chair in the position of the patient on his back with his legs maximally brought to the abdomen, and if impossible — in the side position.

During an external examination of the perineum and anus, attention is paid to changes in the perianal skin, the shape of the anus, its gaping, the presence of any changes and deformities. Digital rectal examination assesses the presence or absence of polyps in the lower ampullary rectum and their size, as well as the presence or absence of malignant neoplasms on their background. Attention should be paid to the tone and volitional contractions of the anal sphincter to assess the condition of the rectal occlusion apparatus(ROA).

2.3 Laboratory Diagnostic Tests

- All patients with suspected APS are **recommended** to undergo a molecular genetic blood test for the presence of mutations in the *APC/MutYH* genes [31–36].

Category of recommendations — C (Level of evidence — 4)

Comments: *This method allows to establish not only the presence of the disease in the patient, but also to determine the probability of its development in a still healthy child. All patients with more than 20 adenomatous polyps in the colon need to perform DNA diagnostics of the entire coding sequence of APC/MutYH genes. Moreover, if a patient has more than 100 polyps, then in order to save time, it is advisable to start the study with the APC gene, and if their number is from 20 to 100, then with the MutYH gene [19,21,22,34].*

Technique: blood is taken from a patient with APS, the coding regions of the APC/MutYH genes are examined. If a mutation is detected, blood is taken from his/her blood relatives. Since mutations in blood relatives are localized in the same parts of the gene as in the patient, a targeted study of the identified affected part of the gene is carried out. If the presence of a mutation is confirmed, the patient under study is diagnosed with APS and an endoscopic examination is prescribed.

• All blood relatives of the patient with a confirmed presence of a mutation in the *APC/MutYH* genes (children, siblings, nephews and nieces) are recommended to undergo a molecular genetic study to search for a similar mutation, in case of detection of which they should undergo lifelong clinical monitoring and timely surgeries to avoid malignant transformation of polyps [31–33].

Category of recommendations — C (Level of evidence — 5)

In the absence of mutations in the APC and MutYH genes in patients with a clinical picture of APS, the expediency of genetic testing of all his/her blood relatives disappears. But all these relatives are potentially at risk of developing colon cancer and need lifelong monitoring.

In addition, iron deficiency anemia can be diagnosed in patients with suspected APS according to the results of a general (clinical) blood test, and a biochemical blood test can reveal electrolyte and metabolic disorders, hypoproteinemia (in particular, hypoalbuminemia).

2.4 Instrumental Diagnostic Examinations

• It is **recommended** for all patients with suspected APS to undergo a total colonoscopy with multiple biopsy (if necessary) [17,19,26, 28].

Category of recommendations — C (Level of evidence — 5)

Comments: *Colonoscopy is the main and most accurate method of diagnosing APS. In this study, the extent of lesion on various parts of the colon by polyps is determined, which directly influences the choice of treatment tactics. With the help of a biopsy, data on the malignant transformation of polyps in various parts of the colon are obtained.*

• It is **recommended** for all patients with APS to undergo EGDS to determine the presence/absence of polyps in the stomach, duodenum and their malignant transformation [37–41].

Category of recommendations — C (Level of evidence — 4)

• CT of the abdominal cavity and pelvis is **recommended** for all patients with APS in order to exclude tumors of extra-intestinal localization and desmoid tumors of intraabdominal localization [35,36,42,43].

Category of recommendations — C (Level of evidence — 4)

Comments: *In the presence of malignant tumors against the background of APS, CT scans of the chest organs are additionally performed to determine the prevalence of the malignant process and diagnose distant tumor metastasis.*

• When planning a surgery with the formation of a small intestinal reservoir in a patient with APS, it is **recommended** to conduct a physiological study of the functions of the sphincter occlusion apparatus of the rectum to exclude the initial incontinence of the anal sphincter, which may negatively affect the functional results of the surgery [44,45].

Category of recommendations — C (Level of evidence — 5)

• In the presence of malignant rectal tumors against the background of APS, it is **recommended** to perform magnetic resonance imaging of the pelvis to assess the presence of malignant transformation and the depth of invasion [35,51,59].

Category of recommendations — B (Level of evidence — 3)

Comments: *If a patient with APS has a neoplasm with suspected malignancy or a malignant tumor of the colon, it is necessary to conduct additional examination methods provided for by Clinical Recommendations for the diagnosis and treatment of colon cancer, rectal cancer.*

2.5 Other Diagnostic Tests

They are not available.

3. TREATMENT, INCLUDING DRUG AND NON-DRUG THERAPY, DIET THERAPY, ANESTHESIA, MEDICAL INDICATIONS AND CONTRAINDICATIONS TO THE USE OF TREATMENT METHODS

3.1 Conservative Treatment

There are no methods of non-surgical treatment of APS [1,2,35,47].

3.2 Surgical Treatment

Currently, the main method of treating APS is surgical. At the same time, the APS treatment should be performed in specialized hospitals, since the incidence of complications and the functional outcome significantly depend on the qualifications of the surgeon (in particular, on the number of similar surgeries performed) [48].

• When performing surgeries in patients with APS, it is **recommended** to use laparoscopic technologies if technically possible [49,50,83,84].

Category of recommendations — A (Level of evidence — 2)

Comments: *The use of laparoscopic technologies reduces surgical trauma, reduces the level of perioperative*

complications, provides the possibility of early activation of the patient, as well as shortening the rehabilitation period [50]. In addition, in patients with APS the use of laparoscopic technologies reduces the risk of infertility by 90% [83].

3.2.1 Classical Form of APS

Taking into account the genetically determined nature of the disease (hence, the lack of conservative treatment options), as well as the obligate-precancerous status of the disease, the only possible method of surgical treatment is the removal of the target organ — the colon.

- With the confirmed classical form of APS, all patients are **recommended** to undergo coloproctectomy with the formation of a small intestinal reservoir, reservoir-anal anastomosis, preventive ileostomy [52,53, 86].

Category of recommendations — C (Level of evidence — 4)

Comments: *Taking into account the young age of patients (in the classical form of the disease, manifestation occurs in 2–3 decades of life), with the potential purpose of social adaptation after removal of the colon, a plastic stage of surgery is performed — the formation of a reservoir from the distal loop of the ileum, the reduction of the resulting structure into the pelvic cavity with the imposition of a reservoir-anal anastomosis and a preventive double-barreled ileostomy [53].*

To improve the quality of life of patients, during surgery it is possible to preserve 1–2 cm of the rectal wall in the supra anal area for the formation of an anastomosis by hardware. If it is impossible to form an anastomosis using a stitching device, abdominal-anal resection of the rectum should be performed and a manual reservoir-anal anastomosis should be applied. Despite the fact that a small fragment of the mucous membrane is preserved when using a stitching device, the risk of cancer in this area is low and corresponds to that in the formation of a manual anastomosis [54].

Reconstructive surgery to restore intestinal continuity — closure of the ileostomy — is performed not earlier than 1.5–2 months after the initial surgery, provided that the sutures of the small intestine reservoir are consistent, as well as reservoir-anal anastomosis (according to the results of retrograde radiological examination with contrast — reservoir imaging) [2].

- A patient with the classical form of APS, in the presence of contraindications to the formation of a small intestinal reservoir and a reservoir-anal anastomosis, is **recommended** to undergo a coloproctectomy with the formation of a terminal ileostomy [35].

Category of recommendations — C (Level of evidence — 5)

Comments: *Contraindications to performing coloproctectomy with the formation of a small intestinal reservoir and reservoir-anal anastomosis are: the presence of a desmoid tumor involving the mesentery of the small intestine, as well as anatomical features of the mesentery of the small intestine, excluding the possibility of relegation to the pelvic cavity; the presence of low-lying rectal cancer with germination into surrounding tissues and infiltration of pelvic floor elements; as well as the patient's refusal of the plastic component of the surgery in favor of the formation of a permanent ileostomy (due to personal preferences or malfunction of the rectal occlusion apparatus) [35].*

3.2.2 Weakened form of APS

The choice of the method of surgical treatment of the weakened form of APS depends on the age of the manifestation of the disease, the number, type, size and localization of the identified colon polyps, as well as the results of genetic research.

- A patient with the weakened form of APS, with the possibility of complete endoscopic colon sanitation and the presence of no more than 10 polyps > 1 cm in size, is **recommended** to undergo endoscopic removal of colon polyps [55,87].

Category of recommendations — C (Level of evidence — 5)

Comments: *It should be remembered that regardless of the results of endoscopic polypectomy, patients require regular dynamic monitoring, since this method is exclusively supportive and cannot replace radical surgery [55]. Contraindications to endoscopic polypectomy are: suspicion of the presence of malignancy in any of the polyps, the presence of high-grade dysplasia in the polyp tissue according to the results of biopsy, a significant increase in the number and size of polyps in the period between the two nearest colonoscopies [55].*

- With the weakened form of APS and the detection of a biallel mutation in the *MutYH* gene, as well as with the detection of an insignificant number of polyps in the rectum, colectomy with the formation of an ileorectal anastomosis is **recommended** [35,56,57].

Category of recommendations — C (Level of evidence — 4)

Comments: *The clinical picture of APS caused by the mutation in the MutYH gene is characterized by a predominant lesion of the right colon and an insignificant number*

of polyps in the rectum, and therefore its preservation is possible during surgical treatment [56]. If the weakened form of APS is detected in patients over 45 years of age with no signs of polyp malignancy and a predominant lesion of the right colon, it is also possible to preserve the rectum and form an ileorectal anastomosis. After performing this surgery, patients need annual endoscopic monitoring with the removal of newly formed polyps in the rectum [57].

3.2.3 MAP

- A patient with MAP in the presence of 20–99 polyps and the possibility of complete endoscopic colon sanitation (in the presence of no more than 10 polyps > 1 cm in size) is **recommended** to undergoendoscopic removal of colon polyps [12, 87].

Category of recommendations — C (Level of evidence — 5).

- When detecting a biallel mutation in the *MutYH* gene, as well as when detecting a small number of polyps in the rectum, it is **recommended** to perform a colectomy with the formation of an ileorectal anastomosis [35,56,57].

Category of recommendations — C (Level of evidence — 5).

- With MAP with the number of polyps of 100 or more, all patients are **recommended** to undergo coloproctectomy with the formation of a small intestinal reservoir, reservoir-anal anastomosis, preventive ileostomy [12,86].

Category of recommendations — C (Level of evidence — 4).

3.3 Treatment of CRC on the Background of APS

In most cases, the diagnosis of APS reveals the presence of single or synchronous multiple malignized tumors of the colon. At the same time, the symptoms of CRC often play a leading role in the clinical picture.

When detecting a malignant colon tumor in a patient with APS, it is advisable to conduct neoadjuvant /adjuvant treatment (if necessary) for CRC (see clinical recommendations 'Malignant neoplasms of the colon and rectosigmoid department' and 'Rectal cancer') [58,59]. With the development of CRC against the background of APS, the priority is the treatment of oncological disease according to its localization and degree of prevalence [58,59].

- In the surgical treatment of a patient with CRC on the background of APS, it is **recommended** to perform surgery according to the oncological principles set out in the 'Clinical guidelines for the diagnosis and treatment of colon and rectal cancer' [58,59], supplementing it with the removal of the remaining parts of the colon.

Category of recommendations — C (Level of evidence — 5).

3.4 Treatment of Desmoid Tumors in Patients with APS

Desmoid tumors are histologically benign, but potentially locally aggressive neoplasms that affect about 15% of patients with APS. Unlike other desmoid tumors, APS-associated desmoids are usually located in the abdominal cavity and involve the mesentery of the small intestine. Most of them occur after surgery. Risk factors for the development of desmoids are considered to be the presence of such tumors in the family history, intra-abdominal surgeries, as well as the location of the pathogenic mutation in the range from 148 to 1,800 codons in the *APC* gene [60]. If these factors coincide, the risk of developing an intra-abdominal desmoid tumor reaches 65% [61].

There are no proven predictors of desmoid tumor growth. Some of them may spontaneously stop growing, some regress, and others continue to grow nonstop. In a small number of patients, this growth may be rapid and uncontrolled.

- When a desmoid tumor located in the thickness of the abdominal wall or in the abdominal cavity is detected in patients with APS, conservative therapy with high-dose drugs of the antiestrogen group in combination with a nonsteroidal anti-inflammatory drug from the group of acetic acid derivatives and related compounds is **recommended** [35,88].

Category of recommendations — C (Level of evidence — 5).

Comments: *Due to the insignificant quantity and quality (retrospective, uncontrolled) of the studies conducted, there is no convincing data on priority methods of treatment of desmoid tumors. However, in a prospective cohort study involving 64 patients with desmoid intraperitoneal tumors that occurred against the background of APS, after treatment with high-dose estrogen receptor modulators in combination with a nonsteroidal anti-inflammatory drug from the group of acetic acid derivatives, a tumor response (in the form of stabilization or regression) was demonstrated in 85% of cases after at least 1 year of treatment with high-dose estrogen receptor modulators in combination with a nonsteroidal anti-inflammatory drug*

from the group of acetic acid derivatives. After achieving a positive response, the dose of drugs was reduced in 60% of patients, against this background, only one recurrence of the tumor was noted after 10 years [62]. Thus, the role of surgical treatment of desmoid tumors should be limited to the correction of secondary changes due to the local nature of tumor growth — obstruction of the gastrointestinal tract, urinary tract, etc.

4. MEDICAL REHABILITATION AND SPA TREATMENT, MEDICAL INDICATIONS AND CONTRAINDICATIONS TO THE USE OF REHABILITATION METHODS, INCLUDING THOSE BASED ON THE USE OF NATURAL THERAPEUTIC FACTORS

There are no specific rehabilitation measures for patients with APS. In a number of patients in whom surgeries for APS resulted in the formation of a small intestinal reservoir and a reservoir-anal anastomosis, a decrease in the holding function is possible. Medical rehabilitation measures are aimed at the fastest possible recovery in the postoperative period, achieving a socially acceptable degree of adaptation of patients in society after surgical treatment. At the same time, rehabilitation of such patients is carried out in three stages: the 1st stage (early rehabilitation) is carried out immediately after surgery on the 14th day. The main tasks are: restoration of normal functioning of the gastrointestinal tract, control of homeostasis, relief of postoperative pain syndrome, activation of the patient, healing of postoperative wounds. The second stage of rehabilitation begins after 15 days and continues as necessary in the future, aimed at the final healing of postoperative wounds with monitoring of the activity of the gastrointestinal tract and the other body systems. This stage can be carried out both on an outpatient basis and in a day- or 24-hourhospital. The third stage of rehabilitation is carried out in the late postoperative period in patients with both permanent ileostomy and before reconstructive and recovery surgery.

The main rehabilitation actions at this stage are compensation of the gastrointestinal tract function, as well as measures aimed at identifying and correcting the function of the rectal occlusion apparatus.

Patients with APS who have undergone surgery with the formation of a temporary/permanent ileostomy need to use colostomy bags and stoma care products [63]. To care for the stoma in the early postoperative period, a special postoperative colostomy bag is used, which is glued immediately after the surgery. A hole corresponding to the size of the stoma is cut out in the plate. A transparent bag and a removable lid allow to monitor the condition of the stoma in the early postoperative period. For further care of the stoma, a one- or two-component system is selected for the patient, taking into account the functional features of the stoma, the relief of the peristomal area, individual preferences and the patient's training opportunities.

- In patients with APS, before performing reconstructive and recovery surgery, it is recommended to examine the sphincter (occlusion) apparatus functions of the rectum (sphincterometry, profilometry, a study of conduction along the sacral nerve), with the followed consultations with a doctor of functional diagnostics when functional disorders are detected [45].

Category of recommendations — C (Level of evidence — 5).

Comments: *In a number of patients whose surgeries for APS resulted in the formation of a small intestinal reservoir, there may be a decrease in the holding function due to the removal of an ampoule of the rectum and intraoperative traumatization of the occlusion apparatus due to the formation of a reservoir-anal anastomosis [64,85].*

- If a patient with APS who underwent coloproctectomy with the formation of a small-intestinal reservoir and reservoir-anal anastomosis is found to have 2–3 degree anal sphincter incontinence before reconstructive surgery, it is **recommended** to conduct a 10-day cycle of electrostimulation using biofeedback therapy and tibial neuromodulation in a day or 24-hourhospital in order to improve the expected quality of life of patients [46, 65].

Category of recommendations — C (Level of evidence — 4).

Comments: *In the rehabilitation of patients with anal sphincter incontinence, according to the literature, a treatment method based on biofeedback (BFB) has found wide application aimed at improving the contractility of the muscles of the external sphincter and pelvic floor by increasing both the strength and duration of arbitrary compression [46, 65]. This method involves the body's own resources in the rehabilitation process with the development of the right skills at the level of creating new conditioned reflex connections. The method of tibial neuromodulation is also effective, in which an electric current along one nerve pathway modulates pre-existing activity in other nerve pathways or centers. Percutaneous electrical stimulation of the posterior tibial nerve is used for functional*

diseases of the pelvic organs, since fibers from the II and III sacral segments of the spinal cord pass through the posterior tibial nerve, which play a significant role in the innervation of the rectum, bladder and their sphincters. It has been proved that the muscle structures of the disabled occlusion apparatus can respond to biofeedback therapy and tibial neuromodulation with an increase in both tone and strength of volitional contractions [46, 65]. Stimulation of the tibial nerve is carried out using a cutaneous stimulating electrode, which allows the patient to continue the course of treatment independently at home after a course of preliminary training. In this case, the course of treatment with daily stimulation sessions can be extended up to 1–3 months.

The effectiveness of the BFB therapy is monitored before and after each course of procedures by a comprehensive physiological study of the function of the rectal occlusion apparatus (sphincterometry + physiological study of the reservoir function of the formed reservoir). With an improvement in the tone and contractility of the anal sphincters, the question of performing reconstructive and recovery surgery aimed at resuming the natural passage through the gastrointestinal tract can be raised [46].

5. PREVENTION AND DISPENSARY SUPERVISION, MEDICAL INDICATIONS AND CONTRAINDICATIONS TO THE USE OF PREVENTION METHODS

Taking into account the fact that APS is a hereditary disease, there is no specific prevention of it [1,2].

Despite this, there is evidence of the study of the use of nonsteroidal anti-inflammatory drugs as chemoprophylactic agents in patients with APS. At the same time, it was demonstrated that the administration of nonsteroidal anti-inflammatory drugs from the group of acetic acid derivatives, as well as from the group of coxibs, reduces the number and size of polyps in the short term [66–69]. However, long-term cancer prevention as an endpoint was not achieved in large randomized trials [70–72].

Considering APS as an obligate precancerous disease, it is important to clarify that the only way to prevent CRC is timely surgical treatment described in paragraph 3. Preventive measures also include careful collection of a family history of a patient with APS, conducting the necessary genetic research and a comprehensive examination of the closest blood relatives for timely detection of patients with APS before the onset of clinical symptoms.

APS is often accompanied by the development of multiple polyps also in the upper gastrointestinal tract (stomach, duodenum). At the same time, fundal gland polyps are detected in 80% of patients with APS [73] and are completely benign formations without malignant potential, without increasing the risk of developing stomach cancer [74]. At the same time, the presence of adenomatous polyps in the duodenum in APS is associated with the risk of cancer in 5% of cases [75].

- Patients with APS are **recommended** to undergo esophagogastroduodenoscopy from the age of 25 years, and in those patients diagnosed with APS at a later age — from the moment of diagnosis of APS [35, 41].

Category of recommendations — C (Level of evidence — 5).

Comments: *Given the incidence of duodenal cancer reaching 5%, preventive removal of the organ is not used. At the same time, for those patients whose duodenal cancer was diagnosed during dynamic follow-up, an advantage in survival was demonstrated compared to those who went to the doctor already with clinical symptoms [76]. Currently, it is customary to use Spigelman, A.D.'s classification for stagingduodenal lesions and determining observation intervals (Table 1).*

- All patients with APS who have undergone coloproctectomy with the formation of ileorectal/reservoir-anal anastomosis are **recommended** to undergo an annual endoscopic examination of the remaining part of the rectum, the small intestine reservoir [12,35,36].

Category of recommendations — C (Level of evidence — 5).

Comments: *In the part of the rectum remaining after surgery, new polyps may appear, which, in the absence of the necessary control, are prone to malignancy. In addition, 12–18 months after the closure of the ileostomy, morphological changes of the epithelial lining develop in the reservoir, characterized by flattening and reduction of the number of villi, leading to their atrophy ("colonic metaplasia"), which potentially leads to the risk of malignant transformation of the mucous membrane of the reservoir [79,80]. Thus, out of 212 patients observed within the framework of the Netherlands Polyposis Registry, the cumulative risk of developing adenoma in the small intestine reservoir at 10-year follow-up was 45%: twenty-five patients (11.8%) developed adenoma with severe dysplasia, and four patients (1.9%) developed carcinoma. The cumulative risk of developing cancer in the reservoir at 10-year follow-up was 1% [81].*

Table 1. *Classification of duodenal lesions in APS and appropriate management tactics (according to Spigelman A.D. [77,78]).*

	Number of points		
	1	**2**	**3**
Number of polyps	1-4	5-20	> 20
Polyp size, mm	1-4	5-10	> 10
Histological structure	Tubular	Tubular-villous	Villous
Degree of dysplasia	Weak	Moderate	Severe

Total points	**Stage**	**Recommended tactics**
0	0	EGDS after 5 years
1-4	I	EGDS after 5 years
5-6	II	EGDS after 3 years
7-8	III	EGDS after one year, endoscopic intervention is possible
9-12	IV	EGDS after 6–12 months or endoscopic/surgical treatment

- All patients who have undergone surgery for APS are **recommended** to undergo an annual comprehensive ultrasound/CT of the abdominal cavity and pelvic organs for timely detection of possible desmoid tumors [89,90].

Category of recommendations — A (Level of evidence — 1).

Comments: *APS-associated desmoids, as a rule, are located in the abdominal cavity, involve the mesentery of the small intestine and occur after surgery. Risk factors for the development of desmoids are considered to be the presence of such tumors in the family history, surgeries in the abdominal cavity, as well as the location of a pathogenic mutation from 148 to 1,800 codon in the APC gene [60]. If these factors coincide, the risk of developing an intra-abdominal desmoid tumor reaches 65% [61,82].*

6. ORGANIZATION OF MEDICAL CARE

Medical care, with the exception of medical care within the framework of clinical approbation, in accordance with Federal Law No. 323-FZ of 21.11.2011 (ed. of 47 25.05.2019) 'On the basics of protecting the health of citizens in the Russian Federation' is organized and provided:

1) In accordance with the regulations on the organization of medical care by type of medical care, which is approved by the authorized federal executive authority.
2) In accordance with the procedures for providing assistance in the "Coloproctology" profile, which is mandatory for all medical organizations on the territory of the Russian Federation.
3) Based on these clinical recommendations.
4) Taking into account the standards of medical care approved by the authorized federal executive authority.

Primary specialized medical and sanitary care for APS patients is provided by a coloproctologist, oncologist, gastroenterologist, and other specialist doctors in medical organizations licensed to provide appropriate types of medical activities.

In case of suspicion or detection of APS in a patient, internists, district internists, general practitioners (family doctors), specialist doctors, secondary medical workers, in accordance with the established procedure, refer the patient for consultation to a medical organization that has a coloproctologist's office and/or an outpatient coloproctology center (unit) to provide him/her with primary specialized health care. Consultation in the specified structural units of the medical organization must be carried out no later than 15 working days from the date of issuance of the referral for consultation.

The coloproctologist organizes a timely qualified examination of the patient, including determining the severity of clinical symptoms, endoscopic examination, taking biopsy material and consulting a geneticist. The geneticist finds out the family history, draws up a pedigree and prescribes DNA diagnostics in the genetics laboratory.

If treatment and in-depth examination in inpatient conditions are necessary, the patient is referred by the attending physician to the coloproctology unit or other medical organization providing inpatient medical care to patients in the "Coloproctology" profile.

A coloproctologist of a medical organization that includes a coloproctologist's office, an outpatient coloproctology center (unit), directs the patient to

medical organizations that have a coloproctology unit and a genetic laboratory in their structure to provide medical care in inpatient conditions (in case it is impossible to establish a diagnosis when providing primary specialized medical care), to provide specialized, including high-tech, medical care. The deadline for the start of specialized, with the exception of high-tech, medical care is determined by the decision of the commission for the selection of patients for hospitalization, depending on the severity of clinical symptoms; the period should not exceed 30 calendar days from the date of issuance of the referral for hospitalization.

Specialized, including high-tech, medical care for APS is provided by coloproctologists in medical organizations that have a coloproctology unit, have a license, the required material and technical base, certified specialists in inpatient and day hospital conditions, and includes diagnostics and treatment of APS that require the use of special methods and complex unique medical technologies as well as medical rehabilitation.

Indications for hospitalization in a 24-houror day hospital of a medical organization providing specialized, including high-tech, medical care for APS are determined by a coloproctologist with, if necessary, a multidisciplinary consultation.

The indication for hospitalization of a patient to a medical organization in an emergency or urgent form is:

1) The presence of complications of APS that require specialized medical care in an emergency and urgent form.
2) The presence of complications of the APS treatment that require specialized medical care in an emergency and urgent form.

The indication for hospitalization to a medical organization in a planned form is:

1) The need to perform complex diagnostic medical interventions that require follow-up in a 24-hour or day hospital.
2) The presence of indications for specialized treatment of APS (surgery), requiring observation in a 24-houror day hospital.

The indication for the patient discharge from the medical organization is:

1) Completion of a course of treatment or one of the stages of providing specialized, including high-tech, medical care, in a 24-houror day hospital, provided there are no complications of treatment requiring medication correction and/or medical interventions in a hospital setting.
2) Refusal by the patient or his/her legal representative from specialized, including high-tech, medical care in a 24-houror day hospital, established by the consultation of the medical organization providing APS treatment, provided there are no complications of the underlying disease and/or treatment requiring medication correction and/or medical interventions in inpatient conditions.

The need to transfer the patient to another medical organization according to the appropriate profile of medical care. The conclusion on the expediency of transferring the patient to a specialized medical organization is carried out after a preliminary consultation on the provided medical documents and /or a preliminary examination of the patient by specialist doctors of the medical organization to which the transfer is planned.

7. ADDITIONAL INFORMATION (INCLUDING FACTORS AFFECTING THE OUTCOME OF THE DISEASE OR CONDITION)

It is not available.

Criteria for assessing the quality of medical care

№	Quality criteria	Category of recommendations	Level of evidence
1.	All patients with suspected APS underwent colonoscopy	A	2
2.	All patients with APS underwent EGDS	B	3
3.	All patients with APS underwent CT of the abdominal cavity and pelvis	C	4
4.	All patients with suspected APS underwent a molecular genetic blood test for the presence of mutations in the *APC/MutYH* genes	A	2
5.	Sphincterometry was performed in patients who are planning to form a small intestinal reservoir	C	4
6.	Coloproctectomy was performed in the classical form of APS	C	5
7.	Colectomy was performed with the formation of an ileorectal anastomosis with the weakened form of APS	C	4

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Juvenile polyposis in a family with «familial adenomatous polyposis» — an accidental find or a natural phenomenon?

Dmitry Yu. Pikunov, Anna N. Loginova, Alexander M. Kuzminov, Margarita Kh. Toboeva, Alexey A. Barinov, Alexey S. Tsukanov

Ryzhikh National Medical Research Center of Coloproctology (Salyama Adilya str., 2, Moscow, 123423, Russia)

ABSTRACT *Hereditary polyposis syndromes are genetically determined conditions characterized by multiple polyps observed in patients throughout the gastrointestinal tract. The most common is familial adenomatous polyposis. At the same time, the juvenile polyposis syndrome found under it can be considered the most common in hamartomous polyposis syndromes, however, according to the endoscopic picture, it often causes one of the forms of adenomatous polyposis. A clinical case of the family with suspected familial adenomatous polyposis for years, and only complete exome sequencing revealed juvenile polyposis syndrome. A previously unknown pathogenic mutation in the SMAD4 gene was detected — c .705dupA (p.Gly236ArgfsTer28).*

KEYWORDS: *juvenile polyposis, adenomatous polyposis syndrome, familial adenomatous polyposis, hamartomatous polyposis syndrome, SMAD4, whole-exome sequencing*

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ADDRESS FOR CORRESPONDENCE: *Pikunov D.Yu., Ryzhikh National Medical Research Center of Coloproctology, Salyama Adilya str., 2, Moscow, 123423, Russia, + 7 (916)182-32-28, e-mail: pikunov.gnck@mail.ru*

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INTRODUCTION

Hereditary polyposis syndromes are a whole group of genetically determined conditions characterized by the development of multiple polyps in patient throughout the gastrointestinal tract. In addition, patients with this pathology have an increased risk of developing both colorectal cancer and tumors of extra-intestinal sites. Thus, malignant tumors of the large intestine caused by the presence of hereditary polyposis syndrome account for up to 2–3% in the general statistics of colorectal cancer [1,2]. According to the nature of polyps formed in the gastrointestinal tract, polypous syndromes are divided into adenomatous and hamartomic [3]. The most common and most studied in this group of diseases is familial adenomatosis poliposis (FAP) — a syndrome with an autosomal dominant type of inheritance due to the presence of a mutation in the *APC* gene and characterized by the appearance of multiple (from several tens to several thousands) adenomatous polyps in the colon. According to generally accepted data, the risk of developing colorectal cancer in FAP reaches 70–100% [2], thus familial colon adenomatosis can be considered an obligately precancerous condition.

It is important to note that according to various authors, the frequency of detection of mutations in the *APC* gene in FAP is 70–85% [4, 5]. At the same time, in some cases, with a peculiar clinical picture, a genetic study indicates the absence of mutations in the *APC* and *MutYH* genes responsible for the manifestations of adenomatous polyposis syndrome.

Such a situation requires the continuation of the diagnostic search with the inclusion of other rare hereditary polyposis syndromes in the differential series. One of

the diseases masquerading as the FAP can be considered juvenile polyposis syndrome (JPS), which refers to hamartomic polyposis syndromes; however, according to the endoscopic picture, it often resembles one of the forms of adenomatous polyposis syndrome [6].

Juvenile polyposis syndrome (OMIM # 174900) is a rare disease with an autosomal dominant type of inheritance, which is characterized by the presence of multiple juvenile polyps in the gastrointestinal tract. Polyps are found mainly in the large intestine (98%), stomach (14%), duodenum (7%), jejunum and ileum (7%) [7]. The number of detected polyps is very variable: in some patients, there may be only four or five of them in their entire life; in the other members of the same family, it can reach 100 or more [8]. In addition to juvenile polyps, patients may have adenomatous polyps, which greatly complicates the diagnosis of the disease [6]. At the same time, the term 'juvenile polyp' defines its histological structure, and not the age of appearance of polyps. Thus, the presence of single juvenile polyps is not considered as belonging to a hereditary JPS and can be detected in 2–3% of children and adolescents [9]. Another peculiar feature of the JPS is an increased risk of developing malignant neoplasm of the large intestine and stomach cancer in patients, which reaches 40–50% and 20%, respectively [9,10].

The prevalence of the JPS ranges from 1:100,000 to 1:160,000 people [11]. In 60% of cases, the molecular genetic cause of the JPS is the presence of a hereditary mutation in one of the genes: *SMAD4*, localized on chromosome 18q21, or *BMPR1A*, located on chromosome 10q22.

Both genes are involved in the signaling cascade of the TGFß family, which plays a key role in suppressing cell growth and apoptosis [12]. At the same time, about 25% of newly diagnosed cases are sporadic and are associated with *de novo* mutations [7,12]. According to one of the most comprehensive databases on mutations in the human genome, HGMD Professioanal 2021.1, only 141 pathogenic variants in the *SMAD4* gene and 160 in the *BMPR1A* gene have been described in the world.

Due to the highly variable clinical picture and the rare occurrence, the diagnosis of the JPS is often difficult. In this paper, we present a clinical case of a family in which the presence of familial adenomatosis polyposis was suspected for several years, and only a full-exome study helped to reveal a juvenile polyposis syndrome, while a new pathogenic variant in the *SMAD4* gene, not previously described in the literature, was identified in the patients.

Clinical Case

The first member of R.'s family who applied to the RNMRCof Coloproctology was patient III.1 (Fig. 1).

In 2019, at the age of 59, she was consulted in an outpatient unit of the Center. From the history of the disease it became known that from the age of 13 she noted the blood in stools, she was examined at the place of residence, a large polyp of the sigmoid colon was detected during colonoscopy, as a result of which a resection of the sigmoid colon was performed in 1975. During a control examination 3 years after the surgery, in the patient polyps in the right colon were detected. She was sent to the RNMRC of Coloproctology, where, based on the presence of multiple polyps in the large intestine with a predominant location in the right colon, the young age of the patient who applied, she was diagnosed with FAP. Due to the treatment approach applied at that time, based on the clinical picture of the disease, in 1980 the patient underwent a right hemicolectomy. Follow-up at the place of residence showed new polyps in the remaining parts of the large intestine, as well as growth of polypoid tumors in the stomach, in connection with which in 1986, 1996, 2006, 2007, 2011, their endoscopic removal was performed.

In 2012 due to the uncontrolled growth of polyps in the patient's stomach, laparoscopically assisted Billroth Ire section of

2/3 of the stomach was done. Follow-up showed the growth of polyps in the stump of the stomach, and in 2014 the removal of the stomach stump with Roux-en-Y anastomosis was done.

Colonoscopy in 2019 in the RNMRC of Coloproctology, revealed 2 polyps of 1.5cm and 2.5cm without endoscopic signs of malignancy in the remaining part of the large intestine. Taking into account the patient's history, the previously established diagnosis of FAP (however, without genetic verification due to the lack of technical feasibility of the study), the patient's family history was carefully reassembled, and a molecular genetic study was done, in which mutations in the *APC* and *MutYH* genes were not detected.

Taking into account the peculiarities of the family history, as well as the clinical picture of the disease in the patient herself, which is somewhat unusual for FAP, it was decided to make a full-exome sequencing. As a result of the test, the variant c.705dupA (p.Gly236ArgfsTer28) in exon 6 of the *SMAD4* gene, previously not described in the world literature, was found.

The presence of the detected mutation was confirmed by sequencing using the Sanger method (Fig. 2). No mutations were detected in the other genes, changes in which led to the polyps in the gastrointestinal tract. Thus, the genetic test made it possible to detect in patient III.1 the juvenile polyposis syndrome.

The patient underwent endoscopic removal of the neoplasms, according to histology, the polyps had the structure of tubular and tubulo-villous adenoma of the large intestine with low grade dysplasia. No complications occurred in the postoperative period, in the future regular follow-up was recommended.

The patient has a 41-year-old son (IV.1). Given the hereditary nature of the disease in the mother, he also underwent a genetic study aimed at finding a mutation in the *SMAD4* gene. According to the results of the study, the sought-for mutation was not detected.

The conducted comprehensive endoscopy (gastro-, colonoscopy) also revealed no lesions in the stomach and large bowel.

With careful collection of the family history, the closest relatives of the patient with a similar clinical picture were identified (Fig. 1).

So, her own older sister (patient III.2) underwent gastric resection twice at the age of 35 and 39 due to uncontrolled growth of

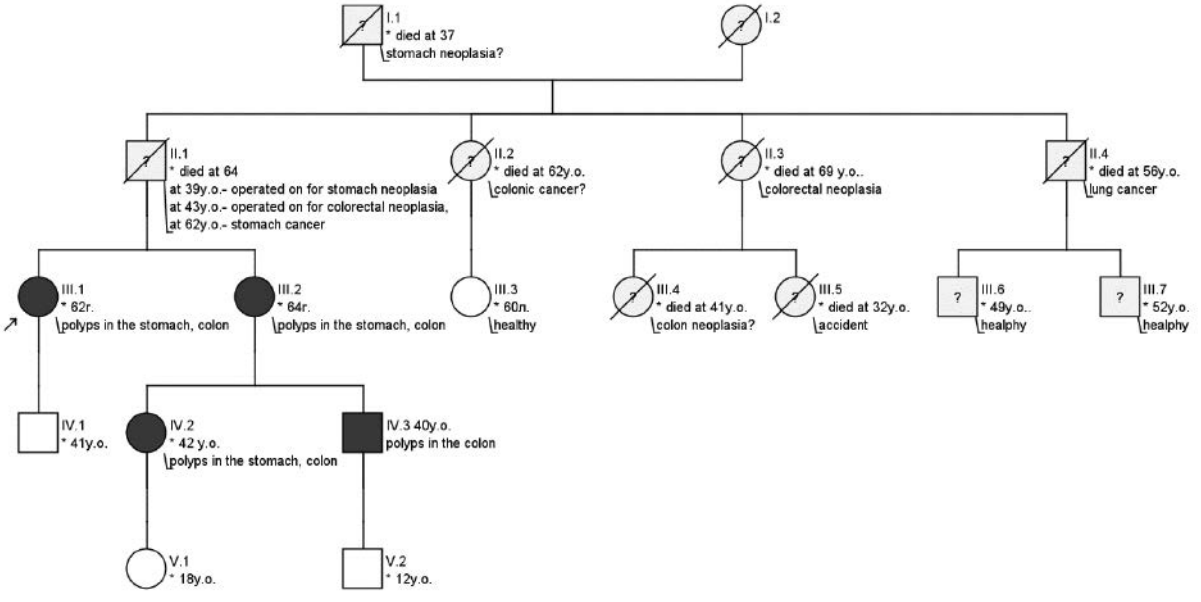


Figure 1. *The R. family tree*

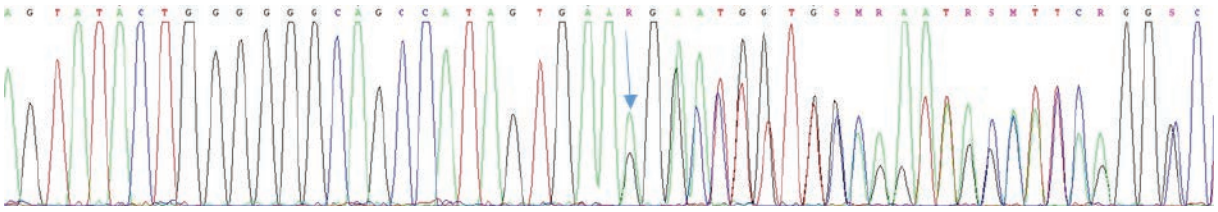


Figure 2. *Sanger sequencing of SMAD4 gene. The beginning of c.705dupA mutation is indicated by an arrow*

polyps in the stomach. Subsequently, 4 polyps of up to 3.5 cm in length were found in the large intestine; an endoscopic polypectomy was done at the age of 46. The histology of the removed polyps, unfortunately, are unknown. The patient was invited to the RNMRC of Coloproctology for examination. The endoscopy of the upper gastrointestinal tract revealed no growth of polyps. Colonoscopy revealed a 10 polyps 0.3–1.0 cm in the large intestine throughout, on broad bases, with a fibrin on the surface (Fig. 3), with an endoscopic picture corresponding to juvenile polyps. As planned, the largest polyps were endoscopically removed. The histology showed juvenile polyps.

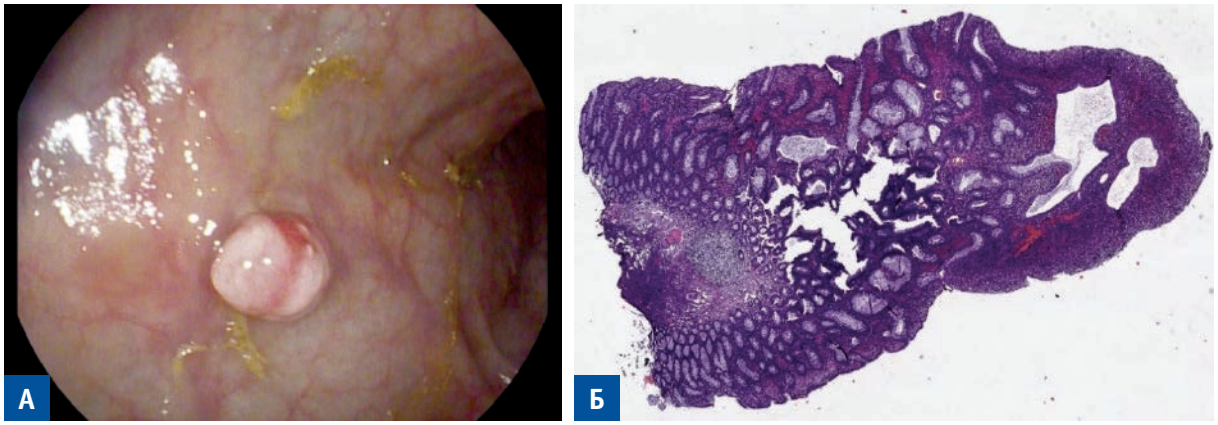
A genetic study confirmed the mutation in the *SMAD4* gene.

In turn, patient III.2 has two children, who were invited for examination within the framework of the Register of patients with hereditary forms of colorectal cancer, functioning in the RNMRCof Coloproctology [13]. It should be noted that in both children, a genetic study also revealed the presence of a mutation in the *SMAD4* gene. When analyzing history of the disease, it turned out that the daughter (patient IV.2) at the age of 16 underwent endoscopic removal of 6 colon polyps of up to 1.5 cm in length (the histology is unknown). At the age of 18, multiple gastric polyps, detected with gastroscopy, were not amenable to endoscopic removal, as a result of which subtotal resection of the stomach was performed. Further, no significant changes were detected during the periodic check-up. A colonoscopy in the Center showed several polyps in the large intestine: in the descending colon — a polypoid neoplasm 0.5 cm in length with an indeterminate pit pattern (Fig. 4.a), in the sigmoid colon — 3 polypoid neoplasms up to 1.0 cm, on a one infiltrated pedicle, with a pit pattern corresponding to type IIIL-IV by Kudo (Fig. 4.b).

Endoscopic removal of the identified polyps was done. The histology showed the morphological picture of a juvenile polyp in the descending colon and a tubular-villous adenoma with low grade epithelial dysplasia in the sigmoid colon (Fig. 5).

Gastroscopy revealed two polyps of up to 1.0 cm in the area of gastro-jejunal anastomosis, subjected to endoscopic removal.

In the son of patient III.2 (patient IV.3) at the age of 14 years old, 15 polyps of up to



Fugure 3. *Juvenile colon polyp of patient III.2: А — endoscopic picture, Б — micro-specimen (staining with hematoxylin and eosin, ×40)*

3.5 cm were detected in the colon at the place of residence; their endoscopic removal was performed (histological structure is unknown). In the future, for more than 20 years, the patient was not checked-up anywhere. Colonoscopy in the Center revealed 4 polyps of up to 0.4 cm in the caecum with an endoscopic picture corresponding to juvenile polyps (Fig. 6). No pathological formations were detected during gastroscopy. Given the small size of the colon polyps, it was decided to refrain from their endoscopic removal; follow-up was recommended to the patient.

It should be noted that in the children of patients IV.2 and IV.3 (aged 18 and 12 years old, respectively) no mutation of the *SMAD4* gene was detected.

It also follows from the family history that the father of proband (patient II.1) at the age of 39 underwent a sigmoid resection (the reason for the surgery is unknown), and at the age of 43, he underwent a Billroth II resection (the reason for the surgery is also unknown). At the age of 64, stomach stump cancer with distant metastases was detected, which was the cause of his death. In addition, in his own 2 sisters and 1 brother (subjects II.2, II.3 and II.4) according to his relatives, presumably malignant tumors of various sites (colorectal cancer, lung cancer) were found, which caused the death of the patients aged 62, 69 and 56 years old, respectively.

In addition, Proband's paternal grandfather (subject I.1) at the age of 37 underwent

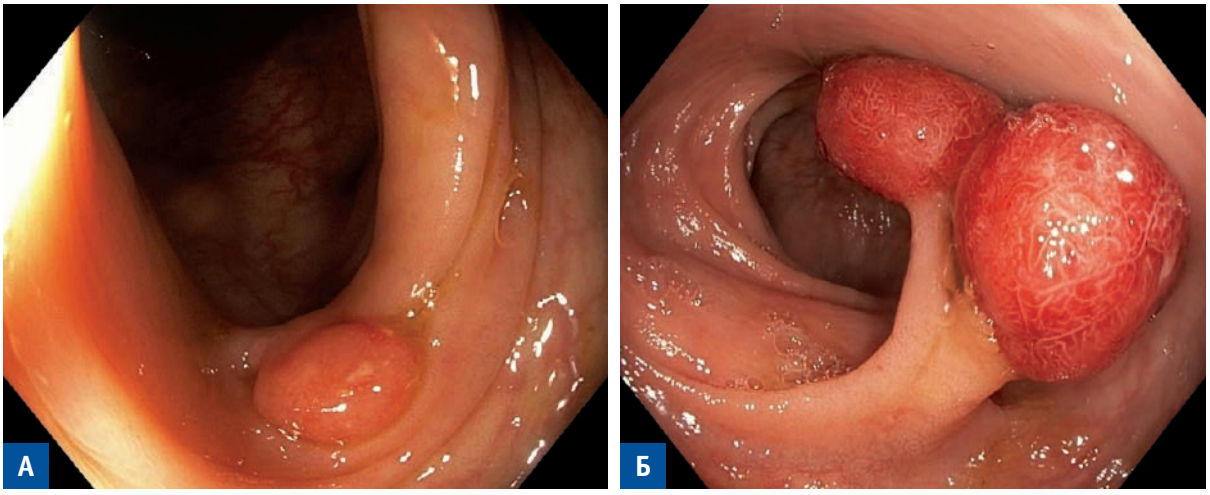


Figure 4. *Colonoscopy in patient IV.2: А — juvenile polyp of 0.5 cm in the descending colon; Б — adenomatous polyps of the sigmoid colon*

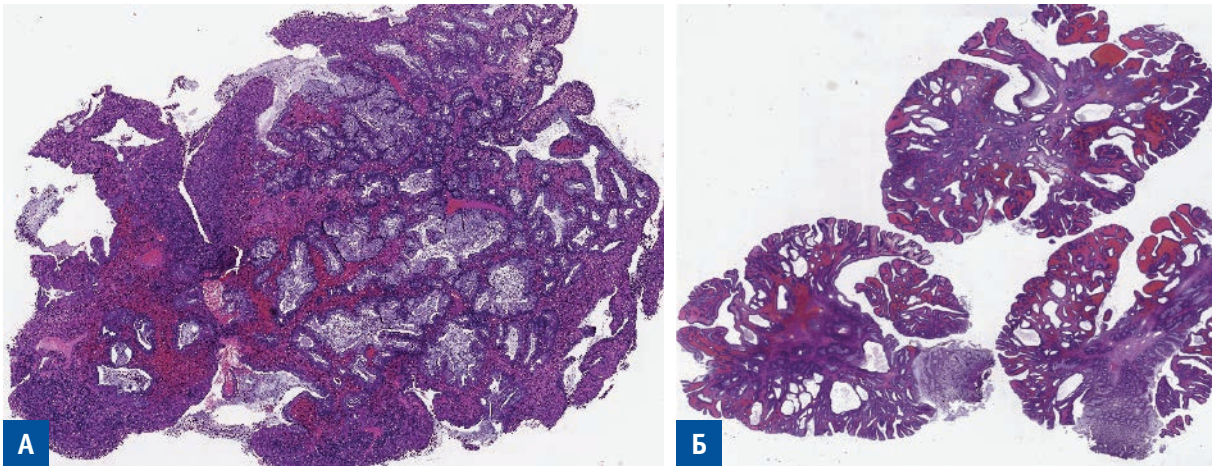


Figure 5. *Micro-specimens of patient IV.2: А — juvenile polyp of the descending colon (×40); Б — tubular villous adenomas of the sigmoid colon (×20). Stained with hematoxylin and eosin*

gastric surgery, the cause of which was presumably a tumor (the removal extent is unknown). A few months after the surgery, he died (the cause of the death also remained unknown).

DISCUSSION

Juvenile polyposis syndrome is a rare disease. In accordance with generally accepted criteria, the diagnosis can be established when patient confirms one of the following signs: 1) the presence of 5 or more juvenile polyps in the large intestine; 2) the presence of multiple juvenile polyps throughout the gastrointestinal tract; 3) any number of juvenile polyps in the presence of the JPS in a family history [7,14]. According to these criteria, patient III.1, who applied to the Center, had no reasons for the diagnosis of the JPS: the 2 large neoplasms identified at that time in the large intestine had the structure of tubular and tubulo-villous adenoma; there were no indications of the presence of juvenile polyps throughout the gastrointestinal tract, as well as accurate information about the JPS in the family history. Moreover, the clinical data could well correspond to the previously established diagnosis of the FAP. And only a genetic study, which made it possible to exclude the presence of mutations in the *APC* and *MutYH* genes in patient III.1, as well as to identify a pathogenic variant in the *SMAD4* gene, made it possible to establish a diagnosis of juvenile polyposis in the family. Despite the fact that the variant c.705dupA (p.Gly236ArgfsTer28) in exon 6 of the *SMAD4* gene has not been previously described in the literature, its pathogenicity is not in doubt, since the mutation is represented by a duplication of one nucleotide, which leads to a shift in the reading frame, causing the formation of a premature stop codon. The phenotypic picture of the carriers of the mutation in R.'s family confirms the data of various authors testifying to a significantly more often lesion with juvenile polyps of the upper gastrointestinal tract when a mutation in the *SMAD4* gene is detected compared with carriers of mutations in the *BMPR1A* gene [6,9,15].

So, Blatter, R. et al., as a result of a retrospective assessment of literature data on over 600 patients with juvenile polyposis syndrome, state about 39% vs.13% (p = 0.001) of the detection rate of juvenile polyps in the stomach, as well as a more clinically severe manifestation of the disease in carriers of the mutation in the *SMAD4* gene compared with carriers of the mutation in the *BMPR1A* gene, respectively [16]. And indeed, in R.'s family almost each patient with a confirmed mutation had a stomach lesion, which led primarily to the need for its resection, and only after that there were indications for surgeries in the other parts of the gastrointestinal tract. At the same time, the checked-up members of R.'s family did not have another symptom most characteristic of carriers of the mutation in the *SMAD4* gene — the presence of hereditary hemorrhagic teleangioectasias [17], which can manifest only when *SMAD4* is affected (they are detected in 34% of patients) and are not described in the presence of the mutation in the *BMPR1A* gene [16].

By the nature of neoplasms formed in the gastrointestinal tract, juvenile polyposis refers to hamartomic polyposis syndromes [18]. Wherein, hamartomic intestinal polyps are formed from normal intestinal wall tissues in their unusual combination with a violation of the ratio of tissue elements and the predominance of stroma, while in adenomatous polyps, the pathological process affects only the epithelial layer [18,19]. In R.'s family we are observing, colorectal adenomatous polyps prevailed checked-up patients at the time of endoscopy, which made diagnosis complicated. When analyzing literature data, the unusual,at first glance, presence of adenomatous polyps in patients with the JPS found its explanation. Back in 1994, Subramony, S. et al. noted that juvenile polyps of less than 1 cm in size had a

morphology of a hamartomic polyp; however, with an increase in size from 1 to 2.9 cm, the occurrence of epithelium with mild or moderate dysplasia increased, and with a polyp size exceeding 3 cm, most juvenile polyps were covered mainly with dysplastic epithelium, visually masquerading as an adenoma [20]. In addition, a number of authors confirm the fairly often occurrence of other types of polyps in patients with the JPS [21]; some even single out a separate type of polyposis syndrome — hereditary mixed polyposis syndrome (HMPS), while noting its conditionality by mutations in the *BMPR1A* gene [22,23]. For example, Blatter R. et al. have given data on 37.6–82.2% of patients with the JPS, who had the presence of other types of polyps (mainly adenomas and hyperplastic polyps), however, with relatively the same incidence of mutations in the *SMAD4* and *BMPR1A* genes [16].

In R.'s family we have presented, three relatives allegedly had colorectal cancer, which caused the death at the ages of 41, 62 and 69, and two family members were diagnosed with stomach cancer at the ages of 37 and 64. Among the 8 family members checked-up in the Center (4 of whom are carriers of the first detected mutation in the *SMAD4* gene) at the age of 12–64 years, none of them had malignant tumors. According to literature data, the risk of colorectal cancer in patients with the JPS is 17–22% by the age of 35, and the lifetime risk of stomach and duodenal cancer is 10–21% [3]. Unlike FAP, which is an obligate precancerous disease, the JPS does not have such a high oncological risk, as a result of which less invasive methods are used as treatment, depending on the degree of clinical manifestations. Thus, the main method of treatment is endoscopic removal of detected polyps, and the reason for surgery is only uncontrolled growth of polyps and/or their malignancy [7,8].

CONCLUSION

The study of the unusual disease in a family with a previous diagnosis of FAP, a pathogenic mutation c.705dupA (p.Gly236ArgfsTer28) in exon 6 of the *SMAD4* gene, previously not described in world literature, was revealed. Thanks to this, it became possible to diagnose juvenile polyposis syndrome, which nominally refers to hamartomic hereditary polyposis syndromes and has a wide phenotypic variability. At the same time, the probability of detection in the large intestine, in addition to juvenile polyps, also adenomatous and hyperplastic polyps mask the disease and creates prerequisites for diagnostic errors. This indicates the possibility of including in the diagnostic search in patients with a clinical picture of adenomatous polyposis syndrome, genetic study not only for the presence of mutations in the *APC* and *MutYH* genes, but also *SMAD4* and *BMPR1A*.

AUTHORS CONTRIBUTION

Concept and design of the study: *Dmitry Yu. Pikunov, Alexey S. Tsukanov*

Collection and processing of materials: *Anna N. Loginova, Margarita Kh. Toboeva, Alexey A. Barinov*

Text writing: *Dmitry Yu. Pikunov*

Editing: *Alexey S. Tsukanov, Alexander M. Kuzminov*

INFORMATION ABOUT THE AUTHORS (ORCID)

Dmitry Yu. Pikunov — 0000-0001-7040-6979;
Anna N. Loginova — 0000-0002-7248-111X
Alexander M. Kuzminov — 0000-0002-8489-1853
Margarita Kh. Toboeva — 0000-0002-2956-805X
Alexey A. Barinov — 0000-0002-1443-960X
Alexey S. Tsukanov — 0000-0001-8571-7462

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CT and MRI diagnostics of desmoid-type fibromatosis in familial adenomatous polyposis

Irina V. Zarodnyuk, Denis M. Belov, Alexander M. Kuzminov, Dmitry V. Vyshegorodtsev, Vyacheslav Yu. Korolik, Dmitry Yu. Pikunov, Tatiana A. Savelyeva

Ryzhikh National Medical Research Center of Coloproctology (Salyama Adilya str., 2, Moscow, 123423, Russia)

ABSTRACT *AIM: to study of the features of computed tomography (CT) and magnetic resonance imaging (MRI) for desmoid-type fibromatosis (DF) in familial adenomatous polyposis (FAP).*

PATIENTS AND METHODS: the study included 35 patients with desmoid-type fibromatosis (DF) with familial adenomatous polyposis of the colon (FAP). All patients were examined using CT and MRI with intravenous contrast. The site, size, growth pattern, prevalence of DF, features of contrasting and the intensity of the MR signal on T2-weighted and post-contrast T1-weighted were assessed. Twenty-five (71.4%) patients were followed-up, including systemic therapy.

RESULTS: In 21 (60%) patients, only one anatomical zone was involved, when 14 (40%) showed lesions in different anatomical zones. In most cases (33/35, 94.4%), desmoid-type fibromatosis was detected in the mesentery and in root of the small bowel mesentery, including those with combined involvement. Most patients (24/35, 68.6%) were diagnosed with a combination of infiltrative and mass-like form of growth; in 13 (37.1%) mass-like form and in 6 (17.1%) infiltrative form. Twenty-five patients (71.4%), repeatedly re-examined using CT (13/35, 37.1%) and MRI (12/35, 34.3%), in particular during systemic therapy.

CONCLUSION: CT and MRI are the basic methods for detecting DF in FAP, making it possible to determine the pattern of tumor growth, assess its extent of the tumor and the involvement of adjacent organs and structures. In follow-up and evaluation of the response of a desmoid-type fibromatosis to systemic therapy, MRI has greater diagnostic capabilities compared to CT, since it takes into account not only the size of the desmoid tumor, but also the MR signal intensity on T2-weighted and the pattern of the accumulation of a contrast agent on post-contrast T1-weighted with fat saturation.

KEYWORDS: *desmoid-type fibromatosis, desmoid tumor, familial adenomatous polyposis, Gardner's syndrome, computed tomography, magnetic resonance imaging*

CONFLICT OF INTEREST: *the authors declare no conflict of interest*

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ADDRESS FOR CORRESPONDENCE: *Zarodniyk I.V. Ryzhikh National Medical Research Center of Coloproctology, Salyama Adilya str., 2, Moscow, 123423, Russia,, e-mail: 89104420581@mail.ru*

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INTRODUCTION

Desmoid fibroids (desmoids, desmoid tumors) are a special variant of mesenchymal tumors that do not metastasize, but are prone to aggressive local growth and recurrence [1,2]. A combination of familial adenomatous polyposis (FAP) and desmoid fibroids (DF), known as Gardner's syndrome, occurs in 10–20% of patients with FAP while one or more desmoid tumors may develop during their lifetime [3–6]. In FAP, desmoids are most often intraabdominal, and with multifocal growth they are often combined with extraabdominal tumors located usually in the anterior abdominal wall [7,8]. Over the past decade, approaches to the DF have changed and include follow-up ('watch and wait'), surgical treatment, systemic therapy (steroids, chemotherapy,

targeted therapy) [9–14]. Imaging, primarily CT and MRI, are important in identifying desmoids determining the extent of the process and the involvement of adjacent organs and structures [11,15–19]. When planning a surgery, this information plays a key role in assessing the resectability of the tumor at the preoperative stage. Radiation methods are of no less importance in detecting relapses of DF, as well as in assessing the tumor response to systemic therapy [14,20,21]. In most publications, the main attention is paid to the imaging of sporadically occurring DF, mainly extraabdominal location (limbs, head, neck, chest, anterior abdominal wall), and the issues of CT and MRI diagnostics of desmoid tumors in FAP are covered only in some works [11,22–25].

AIM

The aim was to study the features of CT and MRI diagnostics of desmoid fibroids in familial adenomatous polyposis.

PATIENTS AND METHODS

The study included 35 patients with confirmed FAP in combination with desmoid tumors of the anterior abdominal wall and mesentery of the small intestine (Gardner's syndrome), in 2009–2021. There were 23 females and 12 males aged 37.3 ± 7.2 (23–57) years. All patients underwent colectomy with J-pouch in 27 cases and excision of the anterior abdominal wall desmoids in 3 cases. After surgical treatment, all patients were checked-up with abdominal CT and MRI with intravenous contrast. In 25 (71.4%) of them the follow-up ranged 2–10 years after surgery. A total of 98 studies were performed on 35 patients: 50 CT and 48 MRI. The desmoid tumors in most cases (30/35, 85.7%) were detected after 2–4 years after surgery. Only in 5 (14.3%) of them desmoids were detected during the initial examination before surgery.

Computed tomography was performed on a "CT Philips Brilliance 64". It included scanning of the abdominal cavity and pelvic organs with a slice thickness of 2 and 3 mm after intravenous bolus injection of a nonionic contrast agent in a volume of 80–100 ml at a rate of 2.5–3 ml/ sec.

Magnetic resonance imaging was performed on a 'Philips Achieva' with a magnetic field strength of 1.5 T. A 16-channel receiving and transmitting coil for the Sense XL Torso body was used for scanning. Abdominal and pelvic organs were scanned with intravenous gadolinium containing contrast agent 0.1 mmol/kg.

Bowel cleansing for CT and MRI studies included a diet with the exclusion of gas-forming products 2–3 days before the diagnostic procedure, with the last meal taken at least 6 hours before the procedure.

When analyzing the CT and MRI images obtained, the site, growth pattern, prevalence of desmoid tumor, involvement of adjacent organs and structures were determined. The structure of the DF and the degree of accumulation of contrast agent were evaluated with CT on native (contrast–free) tomograms and after intravenous contrast; with MRI — on T2-WI images and post-contrast T1-WI images with adipose suppression.

RESULTS

In 21 (60.0%) patients, only one anatomical area was affected (mainly the mesentery of the small intestine), and in 14 (40.0%) cases, desmoid tumors were located in different anatomical zones: the mesentery of the small intestine and the anterior abdominal wall, the mesentery of the small intestine and the pelvis (Fig. 1). In the majority of patients (33/35, 94.4%), DF was detected in the mesentery, including simultaneous lesions (Table 1).

Two thirds of patients (24/35, 68.6%) showed *infiltrative-nodal form* of growth of desmoid tumors located in the mesentery of the small intestine and pelvis, in 8

Table 1. *Location and pattern of growth of desmoid tumors according to CT and MRI (n = 35)*

Location	Form of growth				Total
	Infiltrative-nodal form	Infiltrative	Nodal form	Infiltrative-nodal + nodal form*	
Mesentery of the small intestine	11 (31.4%)	5 (14.3%)	3 (8.7%)		19 (54.4%)
Anterior abdominal wall			1 (2.8%)		1 (2.8%)
Retroperitoneal space			1 (2.8%)		1 (2.8%)
Mesentery of the small intestine + anterior abdominal wall				8 (22.9%)	8 (22.9%)
Mesentery of the small intestine + small pelvis	5 (14.3%)	1 (2.8%)			6 (17.1%)
Total	16 (45.7%)	6 (17.1%)	5 (14.3%)	8 (22.9%)	35 (100%)

** In the mesentery of the small intestine, there is an infiltrative-nodal form of growth, in the anterior abdominal wall –nodal form*

of them — in combination with desmoids of the anterior abdominal wall (Table 1). During CT and MRI, this form was characterized by infiltrative growth, without clear margins, tumor spread in the mesentery of the small intestine and/or pelvic cavity with the involvement of small intestine loops (23/35, 65.7%), mesenteric vessels (19/35, 54.4%), pelvic peritoneum (5/35, 14.3%), ureters (3/35, 8.6%), J-pouch

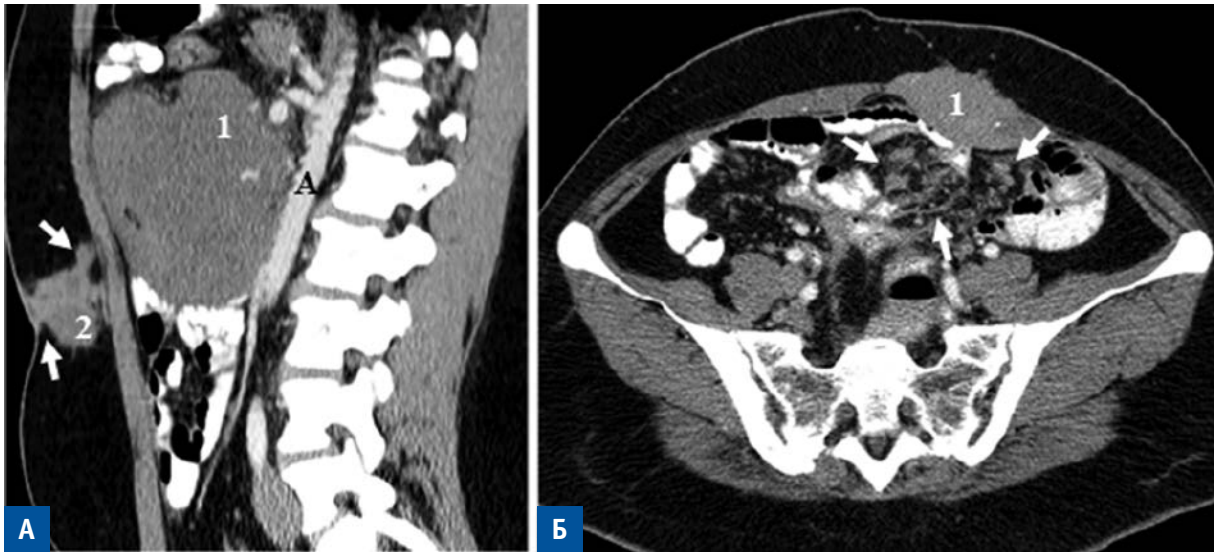

Figure 1. *Computed tomography with contrast enhancement. Combined lesion of the abdominal cavity and anterior abdominal wall. A — tomogram in the sagittal projection of the patient L., 28 years old; 1 — DF of the mesentery of the small intestine with dimensions of 11 × 9.5 cm, adjacent to the abdominal aorta; the structure is homogeneous with a slight accumulation of a contrast agent (A); 2 — DF of the anterior abdominal wall with infiltration of subcutaneous adipose tissue and skin; the structure is heterogeneous with moderate accumulation of the contrast agent (arrows). Б — tomogram in the axial projection of the patient K., 50 years old; 1 — DF of the anterior abdominal wall; diffuse infiltration of the mesentery of the small intestine (arrows)*

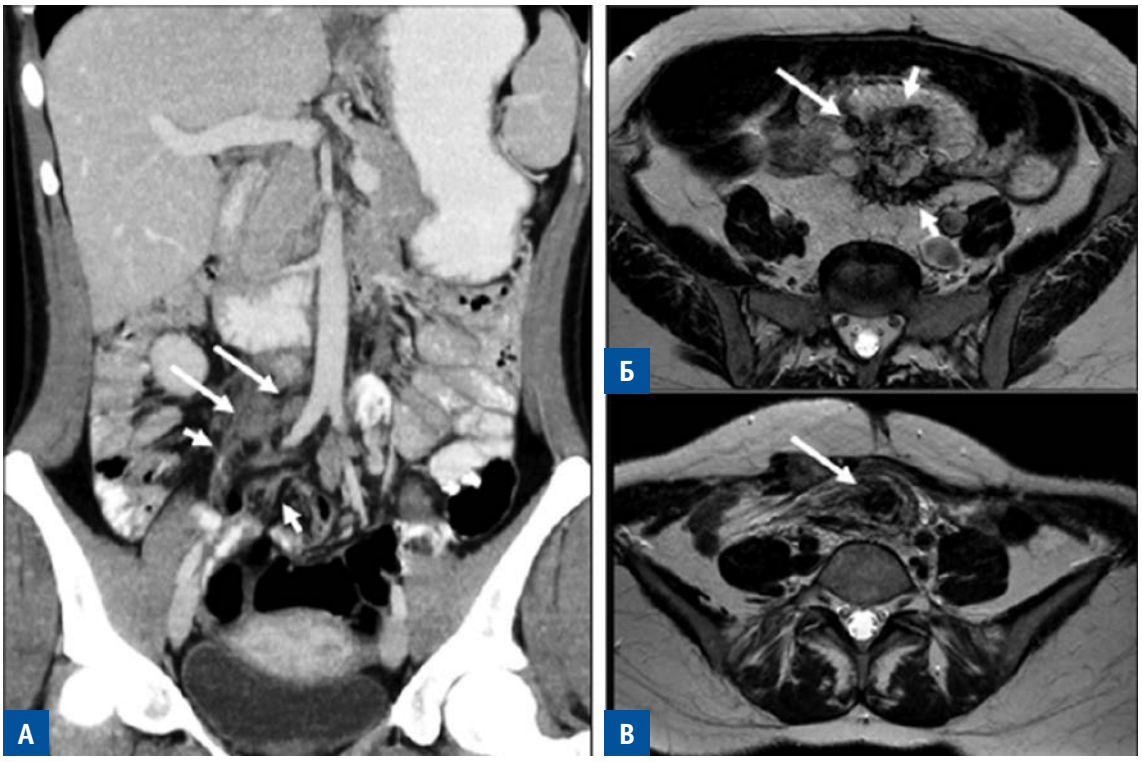

Figure 2. *Combination of infiltrative and nodal form of desmoid-type fibromatosis of the small intestine mesentery. А — CT in the coronal projection of patient Sh., 26 years old; infiltrative (short arrows) and nodal (long arrows) DF components. Б, В — MRI in the axial projection, T2-WI; Б — tomogram of patient S., 47 years old; a mass up to 1 cm (long arrow) against the background of diffuse infiltration of the mesentery involving the loop of the small intestine (short arrows); В — tomogram of patient X, 37 years old; a hypointense mass up to 1.5 cm against the background of diffuse infiltration of the root of the small intestine mesentery*

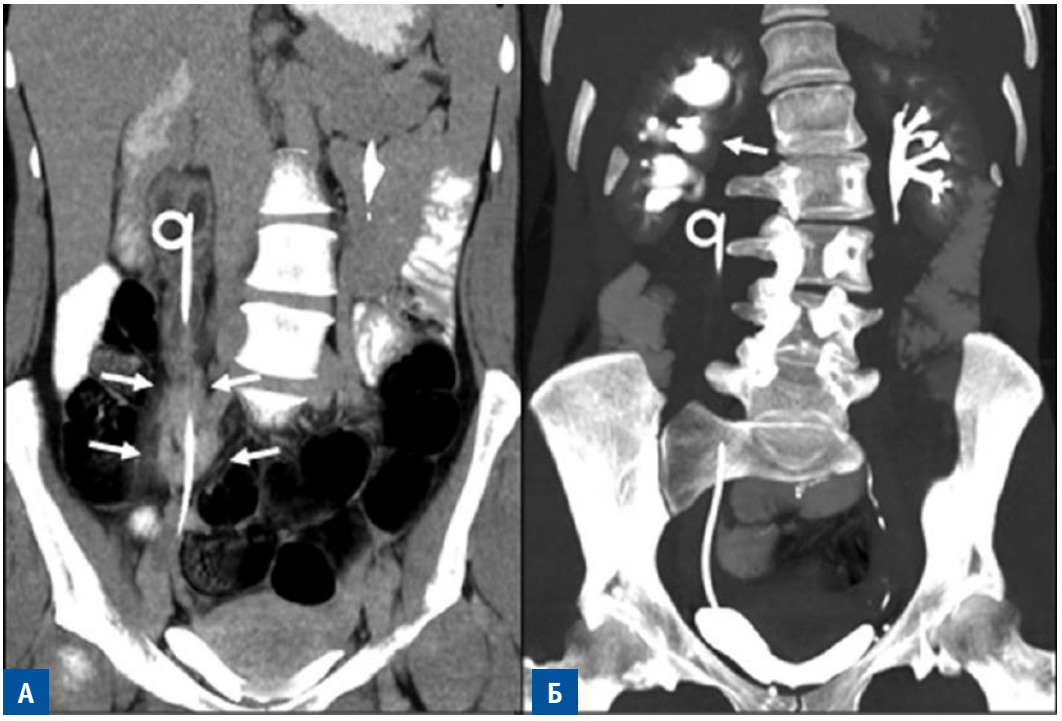

Figure 3. *CT with intravenous contrasting, patient Ch, 36 years old. А — coronal projection; infiltrative growth of DF (arrows) involving the right ureter with a stent placed inside; Б — MIP-reconstruction; hydronephrotic transformation of the pyelocaliceal system of the right kidney (arrow)*

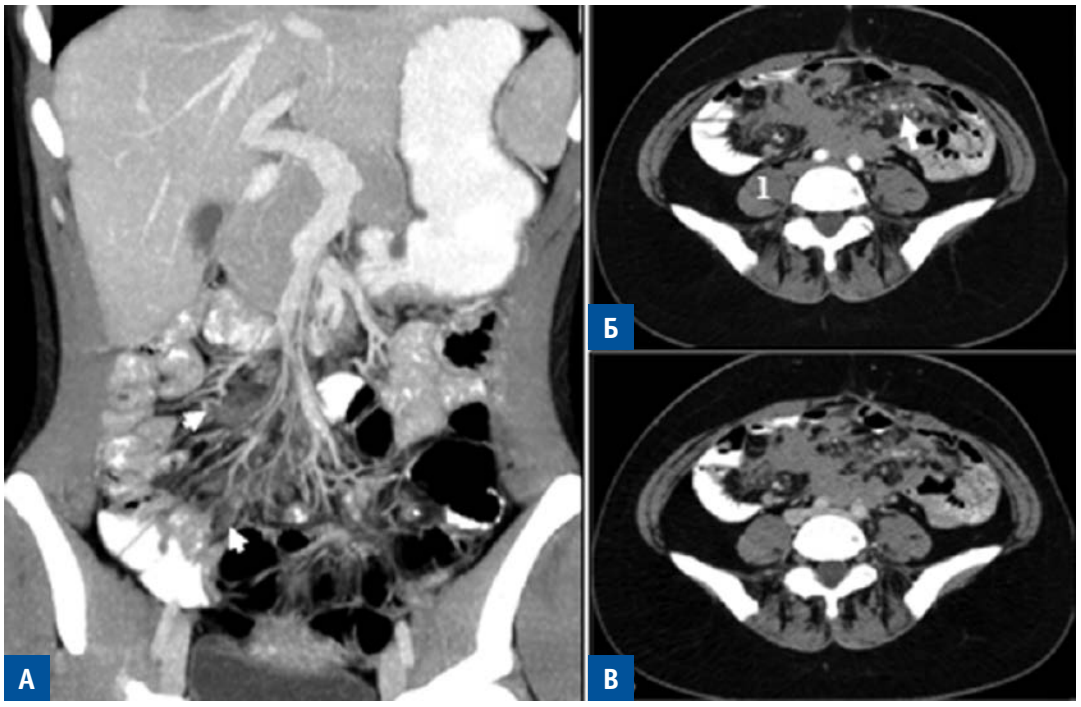

Figure 4. *Infiltrative form of desmoid-type fibromatosis of the small intestine mesentery. CT with contrast enhancement. A — coronary tomogram of patient. K., 26 years old, VIP-reconstruction; infiltrative growth of DF (arrows) along the mesenteric vessels. Б, В — axial tomograms of patient Ts., 50 years old; DF of the mesentery and the root of the small intestine mesentery with the involvement of small intestine loops and mesenteric vessels (arrow); Б — arterial phase; no accumulation of contrast agent, DF density close to muscle density (1); C — venous phase; slight accumulation of contrast agent*

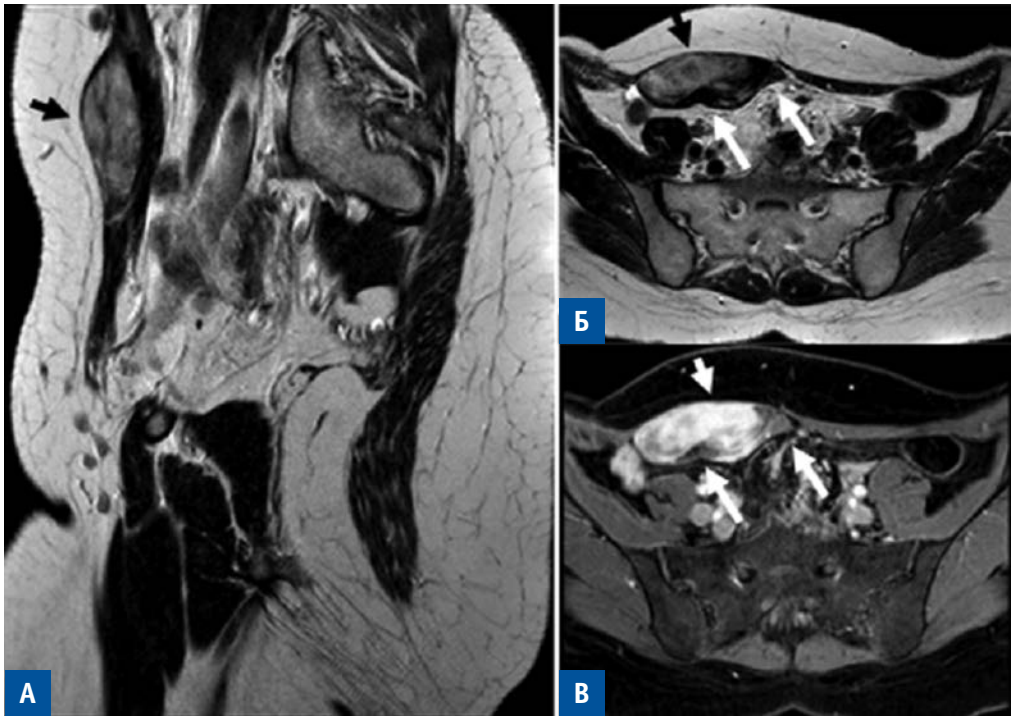

Figure 5. *Nodal form of desmoid-type fibromatosis of the anterior abdominal wall. Magnetic resonance imaging with intravenous contrasting, patient Kh., 37 years old. А, Б — T2-WI in sagittal (А) and axial (Б) projections; the tumor is clearly delimited from the surrounding tissues; the structure is heterogeneous; the hyperintense signal relative to muscle tissue predominates (black arrows) with areas of hypointense signal (white arrows). В — post-contrast T1-WI with adipose suppression; axial projection; clear enhancement of contrast agent in the zone of hyperintense T2-WI signal (short white arrow) and insignificant in the zone of hypointense T2-WI signal (long white arrows)*

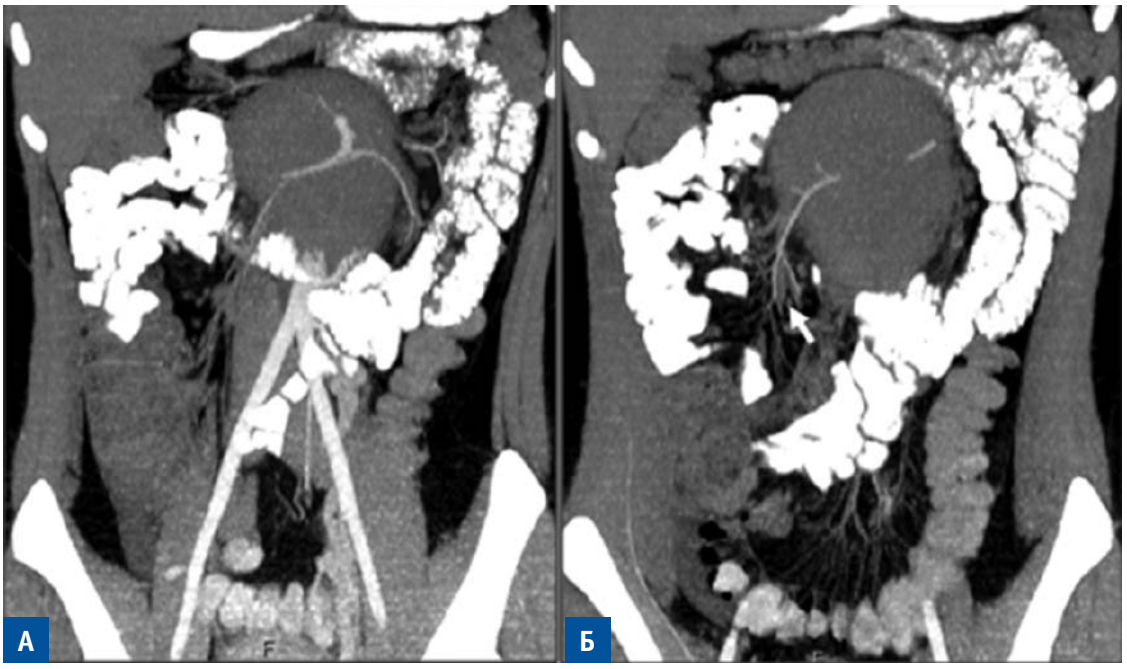

Figure 6. *Nodal form of desmoid-type fibromatosis of the small intestine mesentery. Computed tomography with intravenous contrast enhancement of the patient A., 38 years old, MIP-reconstruction in the coronal projection. А — mesenteric vessels are pushed forward and 'flattened' on the tumor; Б — infiltrative tumor growth along the vessels (arrow)*

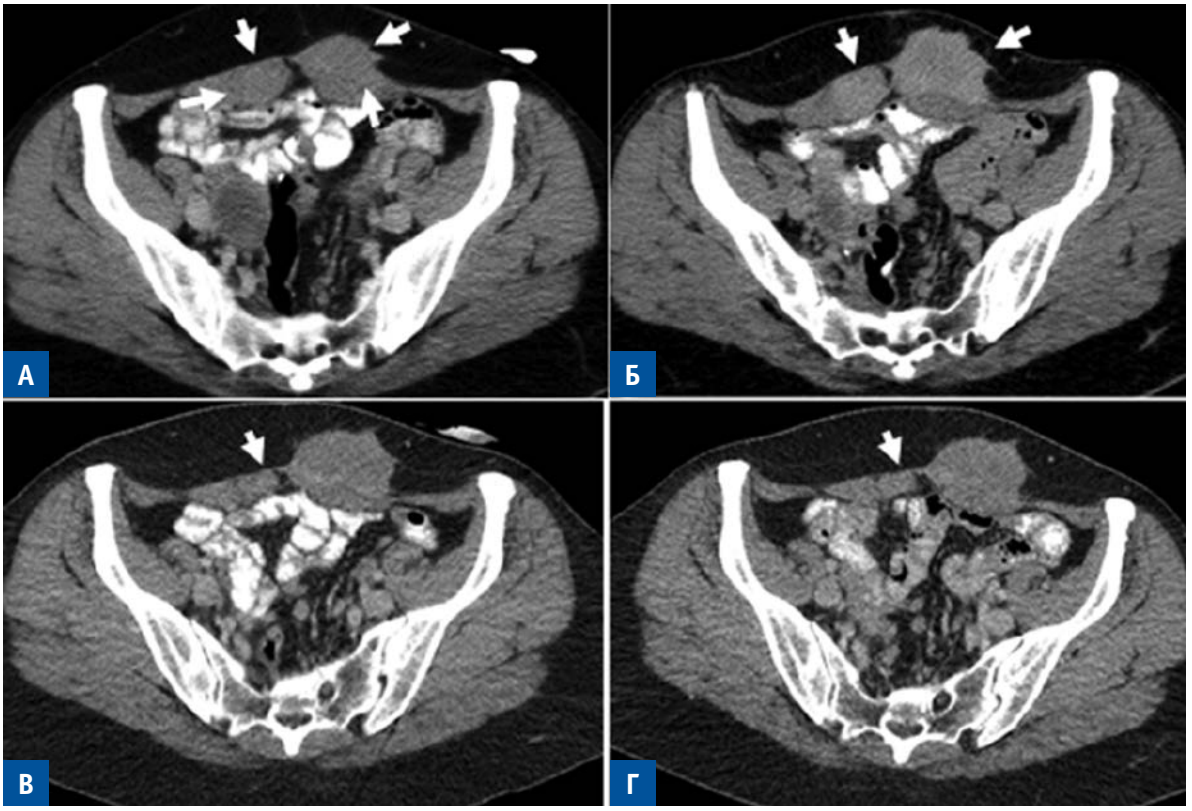

Figure 7. *Desmoid-type fibromatosis of the anterior abdominal wall. CT with intravenous enhancement in patient Y., 36 years old. А — Tumors of the anterior abdominal wall in the area of the postoperative scar (arrows) with dimensions of 3.5 × 2.0 cm and 2.0 × 1.8 cm, 'merging' in density with muscle tissues. Б — after 6 months, there was an increase in the size of the masses up to 4.9 × 3.1 cm and 3.0 × 2.2 cm, respectively, and increased accumulation of the contrast agent compared to the muscles. В — 6 months after chemotherapy (methotrexate, vinorelbine), the tumor on the right (arrow) decreased by more than two times; the size of the second tumor did not change. Г — after 6 months of CT images did not change significantly*

(2/35, 6.7%), uterus (2/35, 6.7%), ovaries (1/35, 2.8%) (Fig. 2). Involvement of the ureters required stenting in two cases due to the hydronephrosis (Fig. 3). Against the background of infiltrative changes, nodal formations were detected in the amount from 1 to 9, with sizes from 1.5 to 5 cm.

The infiltrative form was detected in 6 (17.1%) patients and was located in the mesentery of the small intestine, accompanied by infiltrative involvement of the loops of the small intestine (6/35, 17.1%), mesenteric vessels (2/35, 6.7%) and pelvic peritoneum (1/35, 2.8%) in combination with infiltrative pelvic desmoid (Fig. 4).

The nodal form of desmoid tumor growth was revealed in 13 (37.1%) patients, in 8 of these cases in combination with infiltrative and nodal DF of the mesentery of the small intestine. In 9 (25.7%) cases, nodal formations were detected in the anterior abdominal wall, in 3 (8.6%) cases — in the mesentery of the small intestine and in 1 (2.8%) — in the retroperitoneal space. The number of nodal formations ranged from 1 to 4, sizes from 2 cm to 25 × 10 cm (Fig. 5). Two-thirds of the patients had tumor invasion into adjacent tissues, in the remaining patients the tumor nodes were clearly separated from the surrounding tissues. In one case, a large (12 × 10 × 9.5 cm) desmoid tumor with displacement and compression of mesentery vessels was detected in the mesentery of the small intestine, which required removal of the tumor (Fig. 6).

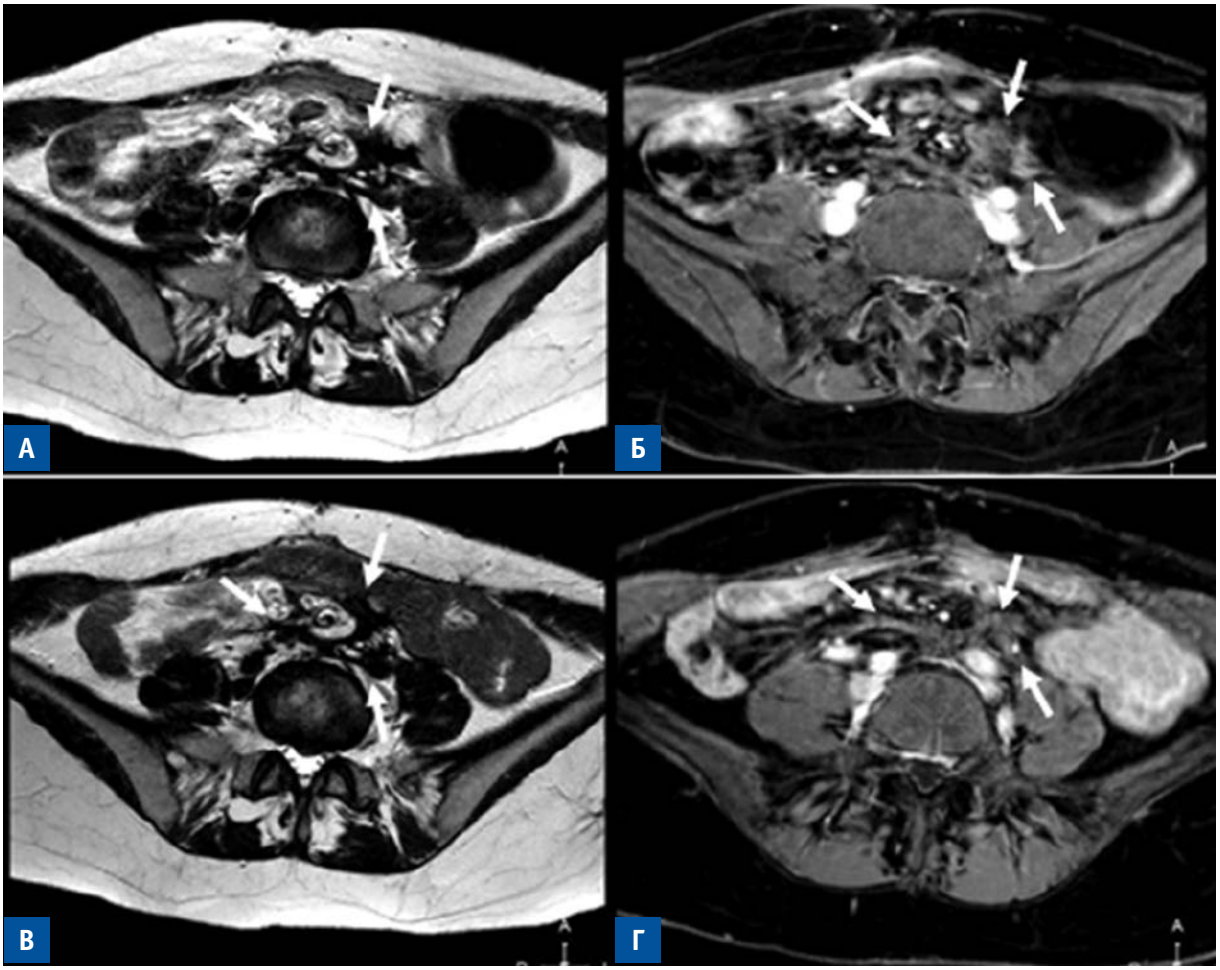

Figure 8. *MRI with intravenous enhancement in patient D., 33 years old. Axial projections. A, B — T2-WI; Б, Г — post-contrast T1-WI with adipose suppression. Infiltrative DF of the root of the small intestine mesentery; hypointense MR signal (A) with a slight accumulation of contrast agent (Б) (arrows). When examining 12 months later, the area of the lesion, the intensity of the MR signal on T2-WI (B) and post-contrast T1-WI (Г) did not change (arrows)*

Twenty-five patients (25/35, 71.4%) were re-examined using CT (13/35, 37.1%) and MRI (12/35, 34.3%), including after systemic therapy or during treatment.

Computed tomography revealed an increase in the size of desmoid formations in 5 patients (with the appearance of a new node in one case), and subsequent imaging during systemic therapy showed downsizing of tumors in three of them (Fig. 7). In the remaining 8 patients, under follow-up, the size of the DF remained the same (5 patients) or smaller (3 patients). CT density and structure of formations, the nature and degree of accumulation of contrast medium did not change throughout the follow-up in most patients. Only in two patients, the increase in desmoid tumor size was accompanied by the appearance of heterogeneity of the structure and a moderate increase in the accumulation of contrast agent.

With MRI in 7 patients, the picture remained the same throughout the entire follow-up: the size of the DF did not change, which was accompanied by the preservation of a hypointensive signal on T2-WI, the absence of contrast or a slight accumulation of contrast agent on T1-WI with adipose suppression (Fig. 8). In two cases, the size of the DF decreased, which was combined with a decrease in the intensity of the MR signal on T2-WI and on post-contrast T1-WI with adipose suppression. In three cases, an increase in the size of the tumor was revealed, while an inhomogeneous structure

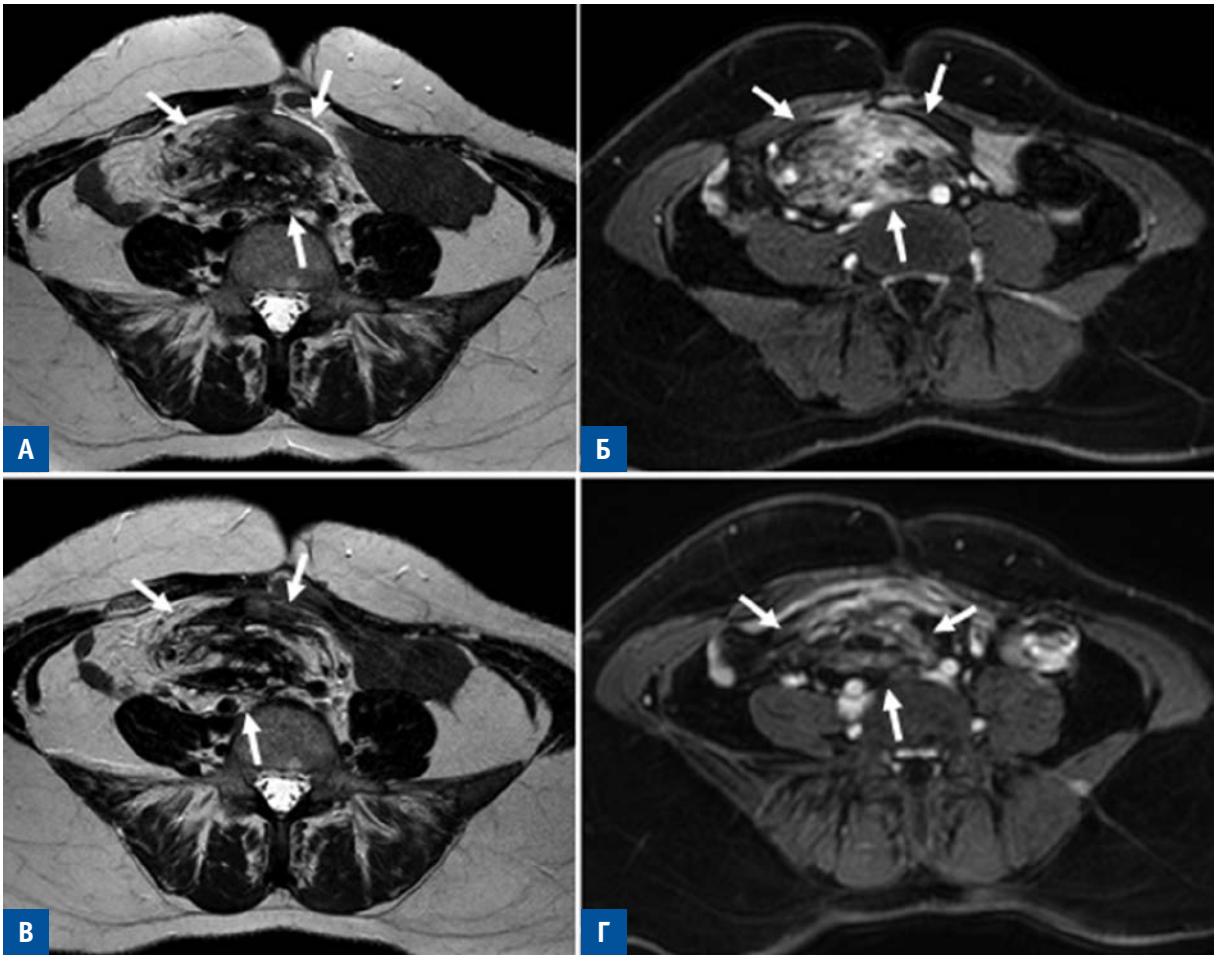

Figure 9. *MRI with intravenous contrasting in patient Y., 39 years old. Axial projections. А, В — T2-WI; Б, Г — post-contrast T1-WI with adipose suppression. Infiltrative DF root of the small intestine mesentery; heterogeneous MR signal (А) with pronounced accumulation of contrast agent (Б) (arrows). In the study 12 months after chemotherapy, the area of the lesion did not change, there was a predominance of a hypointense MR signal (В) with a slight accumulation of a contrast agent (Г) (arrows)*

of the formation was revealed with a predominance of a hyperintensive signal on T2-WI compared to the previous study and a pronounced accumulation of a contrast agent. With further follow-up, two of these three patients showed a positive response to the therapy: the size of the desmoids remained the same, but a decrease in the intensity of the MR signal on T2-WI was determined with the appearance of hypointensive zones, the accumulation of contrast agent was moderate, insignificant in some areas (Fig. 9).

DISCUSSION

The risk of desmoid tumors in patients with FAP may be associated with a number of factors, such as female gender, abdominal surgery, the family history of desmoid fibroids, mutations in the *APC* gene of a certain location [3,5,26–31]. FAP-associated DFs in most cases develop within 5 years after surgery [27]. In this study, two-thirds of the patients were women and, in the majority of cases (30/35, 85.7%) desmoids were revealed in 2–4 years after colectomy. In most cases (33/35, 94.4%) with CT and MRI, desmoid tumors were detected in the mesentery and mesentery root of the small intestine, and in every fourth there was a combination of intra-abdominal site of desmoids with lesion to the anterior abdominal wall.

This coincides with the literature data on predominantly intraabdominal site of desmoid tumors in FAP, as well as their often combination with extraabdominal DF [3,4,8,11].

When the mesentery of the small intestine was affected, infiltrative-nodal (24/35) and infiltrative (6/35) forms of DF prevailed, with infiltrative growth to adjacent organs and structures, primarily to the small intestine and mesenteric vessels. A number of papers inform that such changes can lead to intestinal obstruction and compression of vascular structures [11,16,21]. When the ureters are involved in the tumor, hydronephrosis may develop [14,15,23]. In the study, the spread of DF from the mesentery root to the ureter in two cases required ureter stenting due to the hydronephrotic transformation of the kidney. The nodal form of desmoids was revealed in 13 (37.1%) patients, including 8 cases in combination with infiltrative-nodal DF of the mesentery of the small intestine. In most cases, nodal formations were located in the anterior abdominal wall. The presence of a large nodal DF in the mesentery of the small intestine developed displacement and compression of the mesentery vessels, which required surgical removal of the tumor.As for the diagnostic capabilities of CT and MRI in detecting DF in FAP, some authors believe that both methods can be used to determine the location and extent of the tumor [3, 11], others prefer MRI, especially in young patients to exclude radiation, and consider it appropriate to use CT only to detect complications [16,24]. According to the data obtained, both methods made it possible to visualize desmoid formations both in the mesentery of the small intestine and in the anterior abdominal wall, enabled to assess the extent of the process and the nature of the involvement of adjacent organs and structures. When the infiltrative form of DF was located in the pelvis, MRI had an advantage in differential diagnosis between the tumor and postoperative fibrous changes. Given the predominantly intra-abdominal location of DF in FAP, from our point of view, it is advisable to use CT for the primary detection of desmoids in these patients. This is due to the short scanning time (30–60 seconds), the ability to simultaneously visualize the organs of the peritoneal cavity and pelvis, vessels, as well as intestinal obstruction and excretory function of the kidneys when the ureter is involved in the process. MRI requires a longer time (20–40 min.) and, as a rule, separate scanning of the abdominal cavity and pelvic organs.

In addition to detecting DF and determining the extent of changes, imaging methods are used for dynamic control and evaluation of the tumor response to systemic therapy. It is believed that in CT to determine the changes of the tumor process, two parameters are important — the size of the DF and its density (densitometric indicators in the study without intravenous contrast) [11]. In a follow-up of 13 patients using CT, only in two patients an increase in DF was accompanied by a change in the density of formation and a moderate increase in the accumulation of contrast agent. In all other cases, the density indicators did not change when increasing, decreasing or maintaining the same dimensions of the DF. As for the accumulation of contrast agent in the tumor during intravenous contrast, it was insignificant in most patients and did not change significantly during repeated imaging, with the exception of two cases.
Thus, the main parameter for assessing the changes of the tumor in CT in the study was the size of the tumor.
MRI has great capabilities in determining the DF structure due to the high soft-tissue contrast. The signal intensity on T2-WI and post-contrast T1-WI reflect the ratio of cellular and fibrous components of the tumor [11,22]. Most often, in MRI images, desmoids have an inhomogeneous structure with an isointensive or slightly hyperintensive relative to muscle tissue signal on T2-WI. A decrease in the signal intensity on T2-WI is associated with a decrease in the number of spindle cells and an increase in the number of collagen fibers [11]. Thus, the intensity of the MR signal on T2-WI is an important characteristic of DF [11,21,22,24,32,33]. A tumor downsizing and the hyperintensivity of the signal on T2-WI indicate a positive response to systemic therapy [14,20]. It is also believed that desmoids with a high content of spindle-shaped cells actively accumulate a contrast agent with intravenous gadolinium-containing contrast agents [11,16]. A correlation was revealed between the hyperintensivity of the T2-WI signal and the degree of accumulation of contrast agent by a desmoid tumor [24]. These parameters, along with the size of the tumor, allow a more detailed assessment of the changes of the tumor process during repeated imaging, including during systemic therapy. In the study, dynamic control using MRI was performed in 12 patients. At the same time, in a number of patients, during the first and subsequent imaging, a homogeneous hypointensive signal was detected on T2-WI, which was accompanied by a lack of contrast or a slight accumulation of contrast agent on post-contrast T1-WI with adipose suppression. The revealed MR indicators, in our opinion, show a clear predominance of the fibrous component of the tumor and clinically corresponded to the stabilization phase. In two patients during treatment, a decrease in the size of the DF was noted in combination with a decrease in the intensity of the MR signal on T2-WI and on post-contrast T1-WI with adipose suppression, which was regarded as a positive response to the therapy. The progression in three cases was accompanied by an increase in the size of the DF, with a predominance in comparison with the previous study of the hyperintensive signal on T2-WI and a clear accumulation of the contrast agent. It should be said that MRI, unlike CT, allows us to judge the changes of the tumor process even in the absence of size changes in DF [11]. Thus, during further follow-up, two out of three patients with DF progression showed a positive response to the therapy: the size of desmoids remained the same, but there was a decrease in the intensity of the MR signal on T2-WI with the appearance of hypointensive zones, and the accumulation of contrast agent became moderate, insignificant in some areas.

CONCLUSION

CT and MRI are the basic imaging methods for detecting desmoid fibroids in familial adenomatous polyposis, allowing to determine the nature of tumor growth, assess the extent of the tumor process and the involvement of adjacent organs and structures. In dynamic control and evaluation of the response of a desmoid tumor to systemic therapy, MRI has greater diagnostic capabilities compared to CT, since it takes into account not only the size of the desmoid, but also the intensity of the MR signal on T2-WI and the nature of the accumulation of contrast agent on post-contrast T1-WI with adipose suppression.

AUTHORS CONTRIBUTION

Concept and design of the study: *Irina V. Zarodnyuk, Alexander M. Kuzminov, Dmitry Yu. Pikunov*
Collection and processing of materials: *Irina V. Zarodnyuk, Denis M. Belov, Dmitry V. Vyshegorodtsev, Vyacheslav Yu. Korolik, Tatiana A. Savelyeva*
Textwriting: *Irina V. Zarodnyuk*
Editing: *Alexander M. Kuzminov, Dmitry V. Vyshegorodtsev*

INFORMATION ABOUT THE AUTHORS (ORCID)

Irina V. Zarodnyuk — 0000-0002-9442-7480
Denis M. Belov — 0000-0003-2545-7966
Alexander M. Kuzminov — 0000-0002-8489-1853
Dmitry V. Vyshegorodtsev — 0000-0001-6679-1843
Vyacheslav Yu. Korolik — 0000-0003-2619-5929
Tatiana A. Savelyeva — 0000-0001-9934-3596
Dmitry Yu. Pikunov — 0000-0001-7040-6979

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КРАТКАЯ ИНСТРУКЦИЯ ПО ПРИМЕНЕНИЮ ЛЕКАРСТВЕННОГО ПРЕПАРАТА ДЛЯ МЕДИЦИНСКОГО ПРИМЕНЕНИЯ ПОСТЕРИЗАН® СУППОЗИТОРИИ РЕКТАЛЬНЫЕ. Регистрационный номер: П N012331/02. **Торговое наименование:** Постеризан®. **Международное непатентованное название (МНН): –. Лекарственная форма:** суппозитории ректальные. **Состав.** В 1 суппозитории содержится действующее вещество: стандартизированная суспензия культуры бактерий (СКБ) E.coli 387,10 мг микр. кл. E.coli, инактивированных и законсервированных в 6,6 мг сниженного фенола. **Фармакотерапевтическая группа:** противогеморроидальные препараты для местного применения. **Код АТХ:** C05AX. **Показания к применению:** назначают взрослым (с 18 лет) при следующих заболеваниях: анальный зуд, выделения и жжение в анальной области вследствие геморроидальных заболеваний. **Противопоказания:** повышенная чувствительность к фенолу. **Применение при беременности и в период грудного вскармливания:** может без риска применяться во время беременности и в период кормления грудью. **Способ применения и дозирования:** вводят в анальный проход по одному суппозиторию утром и вечером по возможности после дефекации. Рекомендуемая суточная доза – 2 суппозитория. Курс лечения составляет 2–3 недели. **Побочное действие:** Постеризан® не обладает побочными явлениями даже при длительном применении. В качестве консерванта в препарате используется фенол, поэтому возможны аллергические реакции у пациентов с повышенной чувствительностью к этому компоненту, при развитии которых применение препарата следует прекратить. Условия хранения: в сухом, защищенном от света месте при температуре от 0 °С до 25 °С. Хранить в недоступном для детей месте. **Срок годности:** 3 года. **Условия отпуска:** без рецепта.

КРАТКАЯ ИНСТРУКЦИЯ ПО ПРИМЕНЕНИЮ ЛЕКАРСТВЕННОГО ПРЕПАРАТА ДЛЯ МЕДИЦИНСКОГО ПРИМЕНЕНИЯ ПОСТЕРИЗАН® МАЗЬ ДЛЯ РЕКТАЛЬНОГО И НАРУЖНОГО ПРИМЕНЕНИЯ. Регистрационный номер: П N012331/01. **Торговое наименование:** Постеризан®. **Международное непатентованное название (МНН): –. Лекарственная форма:** мазь для ректального и наружного применения. **Состав.** В 1 г мази содержится действующее вещество: стандартизированная суспензия бактерий E.coli 166,70 мг микр. кл. E.coli, инактивированных и законсервированных в 3,3 мг сниженного фенола. **Фармакотерапевтическая группа:** противогеморроидальные препараты для местного применения. **Код АТХ:** C05AX. **Показания к применению:** назначают взрослым при следующих заболеваниях: анальный зуд, выделения и жжение в анальной области вследствие геморроидальных заболеваний; анальные трещины; экземы. **Противопоказания:** повышенная чувствительность к фенолу. **Применение при беременности и в период грудного вскармливания:** может без риска применяться во время беременности и в период кормления грудью. **Способ применения и дозирования:** мазь наносится тонким слоем на пораженный участок кожи и слизистой оболочки утром и вечером, а также после каждой дефекации. Для более глубокого введения мази в прямую кишку можно использовать навинчивающийся аппликатор, прилагаемый к упаковке. Курс лечения составляет 2–3 недели. **Побочное действие:** Постеризан® не обладает побочными явлениями даже при длительном применении. В качестве консерванта в препарате используется фенол, поэтому возможны аллергические реакции у пациентов с повышенной чувствительностью к этому компоненту, при развитии которых применение препарата следует прекратить. **Условия хранения:** в сухом, защищенном от света месте при температуре от 0 °С до 25 °С. Хранить в недоступном для детей месте. **Срок годности:** 3 года. **Условия отпуска:** без рецепта. Полная информация представлена в инструкции по медицинскому применению.

КРАТКАЯ ИНСТРУКЦИЯ ПО ПРИМЕНЕНИЮ ЛЕКАРСТВЕННОГО ПРЕПАРАТА ДЛЯ МЕДИЦИНСКОГО ПРИМЕНЕНИЯ ПОСТЕРИЗАН® ФОРТЕ МАЗЬ ДЛЯ РЕКТАЛЬНОГО И НАРУЖНОГО ПРИМЕНЕНИЯ, СУППОЗИТОРИИ РЕКТАЛЬНЫЕ. Регистрационный номер: П N014065/01 от 14.05.2010, П N014065/02 от 12.01.2010. **Торговое наименование:** Постеризан® форте. **Международное непатентованное н азвание (МНН): –. Лекарственная форма:** мазь для ректального и наружного применения, суппозитории ректальные. **Состав.** В 1 г мази содержатся инактивированные фенолом микробные клетки кишечной палочки (500 млн), гидрокортизон 2,5 мг. В 1 суппозитории содержатся инактивированные фенолом микробные клетки кишечной палочки (1000 млн), гидрокортизон 5 мг. **Фармакотерапевтическая группа:** противогеморроидальные препараты для местного применения, комбинация. **Код АТХ:** C05AX03. **Показания к применению:** мазь назначают взрослым при следующих заболеваниях: упорное течение геморроя; перианальный дерматит; анальный зуд, особенно устойчивый к другим лекарственным средствам; анопапиллит; анальная трещина. Суппозитории назначают взрослым при следующих заболеваниях: упорное течение геморроя; анальный зуд, особенно устойчивый к другим лекарственным средствам, анопапиллит; анальная трещина. **Противопоказания:** повышенная чувствительность к гидрокортизону или другим компонентам препарата. Бактериальные заболевания в области лечения (например, туберкулез, сифилис, гонорея). Грибковые заболевания в области лечения. **Применение при беременности и в период грудного вскармливания:** нет указания на то, что гидрокортизон из мази или суппозитория Постеризан® форте попадает в плаценту или в материнское молоко. До настоящего времени не обнаружено никаких сведений, указывающих на повреждающее действие препарата на плод. Вместе с тем мазь или суппозитории Постеризан® форте, как и все медикаменты, должны применяться при беременности и в период лактации только при строгом контроле врача. **Способ применения и дозирования:** мазь наносят тонким слоем на пораженный участок кожи и слизистой оболочки утром и вечером, а также после каждой дефекации. Для более глубокого введения мази в анальный канал можно использовать навинчивающийся аппликатор, прилагаемый к комплекту. Суппозитории ректальные применяют утром и вечером, а также после каждой дефекации. Возможно комбинированное использование мази и суппозиториев. Курс лечения продолжается 2–3 недели. **Побочное действие:** в качестве консерванта в препарате используется фенол, поэтому возможны аллергические реакции у пациентов с повышенной чувствительностью к этому компоненту. **Условия хранения:** в сухом, защищенном от света месте при температуре от 0 °С до 25 °С. Хранить в недоступном для детей месте. **Срок годности:** мазь – 3 года, суппозитории – 2 года. **Условия отпуска:** без рецепта. Полная информация представлена в инструкциях по медицинскому применению.

Перед применением необходимо ознакомиться с полной инструкцией по применению лекарственного препарата.

1. Адаптировано: Нехрикова С.В., Титов А.Ю., Веселов А.В. Влияние препарата Постеризан® на заживление послеоперационных ран анального канала и промежности // Доказательная гастроэнтерология. – 2017. – Т. 6.– № 2. – С. 59–65. 2. Инструкция по медицинскому применению лекарственного препарата Постеризан® мазь (регистрационный номер П N012331/01) 3. Инструкция по медицинскому применению лекарственного препарата Постеризан® суппозитории (регистрационный номер П N012331/02). 4. Инструкция по медицинскому применению лекарственного препарата Постеризан® форте мазь (регистрационное удостоверение П N014065/01).
5. Инструкция по медицинскому применению лекарственного препарата Постеризан® форте суппозитории (регистрационное удостоверение П N014065/02).

* Мазь и суппозитории Постеризан® могут без риска применяться во время беременности и в период лактации, мазь и суппозитории Постеризан® форте должны применяться только при строгом контроле врача.

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ИНФОРМАЦИЯ ИСКЛЮЧИТЕЛЬНО ДЛЯ МЕДИЦИНСКИХ И ФАРМАЦЕВТИЧЕСКИХ РАБОТНИКОВ

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Surgery for familial adenomatous polyposis

Oleg I. Kit, Yury A. Gevorkyan, Natalia V. Soldatkina, Evgeny N. Kolesnikov, Vladimir E. Kolesnikov, Olga K. Bondarenko, Eldar K. Khabzhokov

National Medical Research Centre for Oncology (Line 14 str., 63, Rostov-on-Don, 344037, Россия)

ABSTRACT *AIM: to analyze the results of surgery for familial adenomatous polyposis (FAP).*
PATIENTS AND METHODS: the case series study included 20 patients with FAP, 85% of procedures with anastomosis and 15% with a permanent ileostomy. Laparoscopic approach was used in 35%.
RESULTS: the mean time of operation time was 243 minutes, the mean intraoperative blood loss was 244 ml, and the mean hospital stay was 17.2. Three (15.0%) patients developed postoperative complications. Laparoscopic procedures were advantageous in terms of intraoperative blood loss and faster recovery. The first polyps were detected in the rectal stump within 6–8 months after surgery, desmoid tumors within 24.3 months. Most patients had an acceptable quality of life with an mean number of stools per day 11.1.
CONCLUSIONS: FAP is a complex problem of modern medicine requiring the teamwork of various medical specialists. Minimally invasive interventions for FAP have advantages over open procedures.

KEYWORDS: *familial adenomatous polyposis, examination, surgical treatment, polyposis, desmoid tumors*

CONFLICT OF INTEREST: *the authors declare no conflict of interest*

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ADDRESS FOR CORRESPONDENCE: *Soldatkina N.V., National Medical Research Centre for Oncology, Line 14 str., 63, Rostov-on-Don, 344037, Россия, 8-918-545-3004, e-mail: snv-rnioi@yandex.ru*

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INTRODUCTION

Familial adenomatous polyposis (FAP) is a genetic autosomal dominant type disease, occurring in 1 out of 6,800–29,000 people and characterized by multiple colorectal adenomas with progressive growth and mandatory malignancy [1,2]. In most patients, colorectal adenomas develop in the second decade of lifetime, and colorectal cancer develops in the third or fourth decade [3]. Recently, the only treatment method for FAP is preventive surgery on the colon and rectum. Surgery for FAP include: proctocolectomy with J-pouch, colectomy with ileorectal anastomosis and proctocolectomy with permanent ileostomy [4]. Colectomy with ileorectal anastomosis is associated with better functional results and quality of life. However, the remaining rectum requires lifetime control due to the risk of polyposis progression and the development of rectal cancer [5]. When choosing a surgical method for FAP, the age of the patient, the severity of rectal adenomatosis, genetic mutations and, of course, the choice of the patient him/herself are taken into account [6].

AIM

to analyze the results of surgery for familial adenomatous polyposis (FAP).

PATIENTS AND METHODS

Twenty patients with FAP were included in the retrospective study (November, 2015 — October, 2021). There were 11 men (55.0%), 9 women (45.0%). The patients were aged 42.2 (21–74) years. The BMI was 24.7 kg/m^2. The clinical characteristics of the patients are presented in Table 1. All the patients were checked-up including colonoscopy with multiple adenoma

Table 1. *Clinical features of patients with FAP*

Indicator	FCAP (*n* = 20) M; Me (Q1; Q3); *n* (%)
Age, years	42.2; 39 (32.5; 49.5)
BMI	24.7; 26.2 (22.1; 26.8)
Gender: Females Males	9 (45%) 11 (55%)
Family history	13 (65%)
Hereditary mutations	20 (100%)
Classical form of FAP	20 (100%)
Colorectal cancer	12 (60%)

Table 2. *Types of operations in patients with FAP*

Indicator	Open, n (%)	LS, n (%)	Total, n (%)	*p*
Colectomy with rectal resection, J-pouch, preventive ileostomy	1 (7.7%)	7 (100%)	8 (40%)	< 0.001
Colectomy with rectal resection, small intestine rectal anastomosis, preventive ileostomy	7 (53.7%)	0 (0.0%)	735.0%	0.044
Proctocolectomy with J-pouch, preventive ileostomy	2 (15.4%)	0 (0.0%)	2 (10.0%)	0.52
Proctocolectomy with permanent ileostomy	3 (23.1)	0 (0.0%)	3 (15.0%)	0.47
Total	13 (100%)	7 (100%)	20 (100%)	

Note: the exact bilateral Fisher test

biopsy (Fig. 1), proctoscopy, genetics, gastroduodenoscopy, X-ray.

To perform a molecular genetic test, genomic DNA was isolated from peripheral blood leukocytes according to a standard technique. The concentration of the obtained DNA specimens was measured on a Qbit 2.0 fluorimeter (Invitrogen, USA) using a set of Quant-iTTMdsDNA. 15 coding exons of the *APC* gene with adjacent parts of introns (50–100 nucleotide pairs) were amplified by polymerase chain reaction using 23 pairs of primers. Further, the obtained DNA fragments were sequenced along two complementary chains using the ABI PRISM 3500 device (8 capillaries; Applied Biosystems).

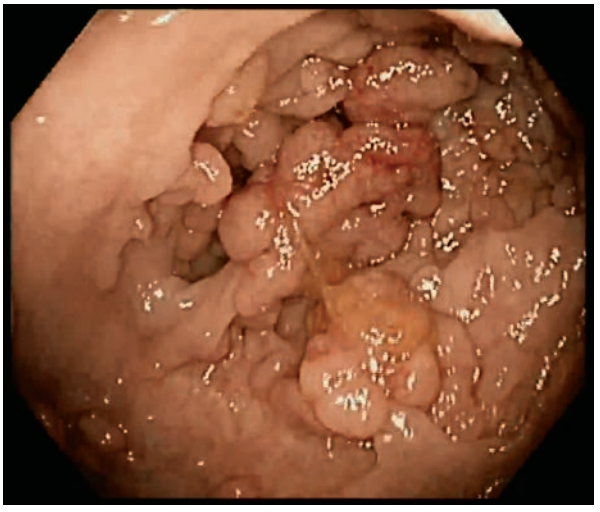

Figure 1. *Endoscopic picture of FAP*

Table 3. *Characteristics of procedure and the postoperative period in FCAP*

Indicators	Laparoscopic (*n* = 7)		Open (*n* = 13)		
	M N (%)	Me (Q1;Q3)	M N (%)	Me (Q1;Q3)	*p*
Operation time, min.	307	310 (310; 315)	208	160 (160; 260)	0.045*
Intraoperative bloodloss, ml	207	200 (200;200)	264	250 (200; 300)	0.057*
The appearance of intestinal peristalsis, day	1,6 1.6	2 (1; 2)	2.5	3 (2; 3)	0.013*
Recovery of motor activity, day	1.6	2 (1; 2)	3.5	3 (3; 4)	0.0007*
Postoperative complications	2 (28.6%) *n* = 7		1 (7.7%) *n* = 13		0.27**
Postoperative hospital stay	20.1	17 (13; 24)	15.6	16 (15; 17)	0.66*

*Note: * significance of differences between open and laparoscopic surgeries, Mann-Whitney test; ** significance of the differences between open and laparoscopic surgeries, the exact bilateral Fisher test*

All the patients had a classical form of FAP with the presence of specific complaints. Complaints of general weakness were in 8 (40%) patients, admixture of blood and mucus in the feces — 7 (35.0%) patients, abdominal pain — in 7 (35.0%) patients, frequent liquid stools — in 6 (30.0%) patients, constipation — in 5 (25.0%) patients, discomfort in the rectum — in 3 (15.0%) patients, weight loss — in 3 (15.0%) patients. Thirteen (65.0%) patients had a family history. Hereditary mutations were found in all patients. Histologically, 13 (65.0%) patients showed tubular intestinal adenomas, 7 (35%) patients had tubulo-villous adenomas, 5 (25.0%) had low-grade epithelial dysplasia, 3 (15.0%) had low- and high-grade intraepithelial neoplasia.

Colorectal cancer was revealed in 12 (60.0%) patients: primary multiple tumors were found in 5 (41.7%) patients, rectal cancer — in 5 (41.7%), colon cancer — in 2 (16.6%) patients. One patient with rectal cancer had distant liver metastases.

The average age of the patients with FAP without colorectal cancer was 33.3 years, the average age of the patients who developed colorectal cancer on the background of FAP was 48.2 years ($p = 0.003$).

The time from diagnosis to surgical treatment was 3.9 months. All the patients underwent curative surgery (Table 2): 17 (85.0%) procedures with anastomosis and 3 (15.0%) with permanent ileostomy. Seven (35.0%) procedures were performed laparoscopically. Two patients underwent curative surgery after previous colon resections.

The stages of operations for FAP were standard. The J-pouch, the and the removed specimen are shown in Figures 2–4.

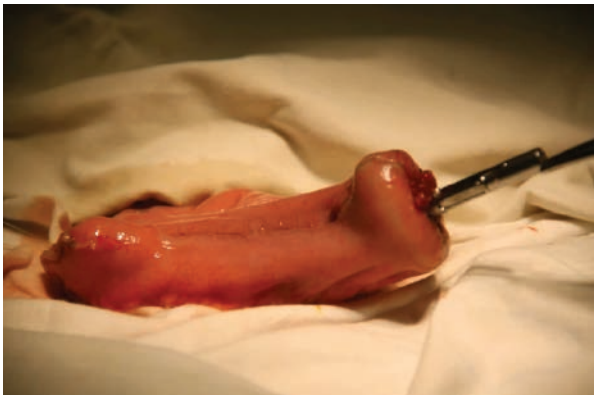

Figure 2. *J-pouch*

The operation time, intraoperative blood loss, postoperative complications, and postoperative hospital stay were assessed.

After surgery, patients were under the control of a gastroenterologist to ensure adequate digestion and defecation by conservative treatment. The follow-up included endoscopy of the rectum and J-pouch, imaging of the abdominal cavity.

Functional results of surgery were evaluated by the GIFO scale [7].

Statistical data processing was carried out using the STATISTICA 12.0 statistical package. Quantitative indicators are represented by the mean (M), median (Me) and quartile values Q1 and Q3 in the format M, Me (Q1; Q3). The numerical values of the two groups were compared using the nonparametric Mann-Whitney test.

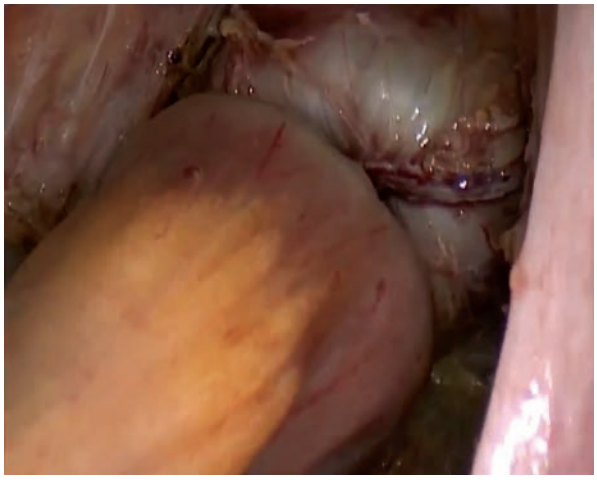

Figure 3. *Pouch-anal anastomosis*

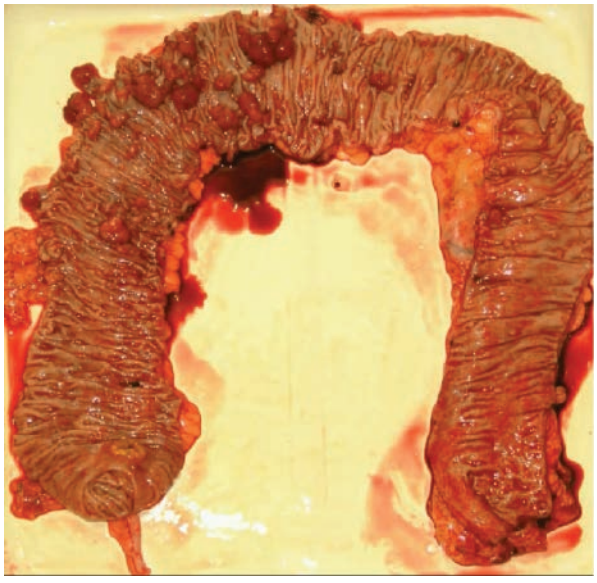

Figure 4. *Removed specimen in FAP*

Categorical data were presented in the form of absolute and relative incidence (%). Comparison of feature incidence was carried out using the exact bilateral Fisher test, the threshold level of significance of p was assumed to be 0.05. The patients' survival rate was assessed using the Kaplan-Meyer test.

RESULTS

The results showed that the mean operation time for FAP was 243 minutes, the mean intraoperative blood loss was 244 ml, and the mean hospital stay was 17.2 days. There were no intraoperative complications.

Postoperative complications developed in 3 (15.0%) patients. In the early postoperative period, complications were detected in 2 (10.0%) patients only after laparoscopic colectomy with rectal resection, the formation of J-pouch and preventive ileostomy: one patient developed a pouch leakage on the 5th day after surgery. Another patient developed a pouch leakage on the 4th day. Both complications required re-operation: relaparoscopy, peritoneal washout and additional peritoneal drainage.

In the late postoperative period, complications developed in 1 (5.0%) patient after colectomy with rectal resection, J-pouch and preventive ileostomy: on the 65th day after surgery rectovaginal fistula developed, transanal fistulectomy was performed.

A comparative analysis showed (Table 3) that laparoscopic procedures have advantages relative to intraoperative blood loss (1.3 times less, $p = 0.057$), intestinal motility (by 1.9 days faster, $p = 0.0007$). The advantage of laparoscopic approach was also the cosmetic effect due to the absence of large incisions of the anterior abdominal wall. Open procedures were faster (1.5 times, $p = 0.047$).

The preventive ileostomy takedown was performed in all cases. In the patients without postoperative complications, ileostomy closure was performed after 3 months; in the patients with postoperative complications, ileostomy closure was performed after 14 months. No

Table 4. *Functional results of colectomy with rectal resection and J-pouch 1 year after ileostomy closure (n = 8)*

Indicator	M,Me (Q1;Q3); *n* (%)
Scale GIFO, M, Me (Q1; Q3)	70.3 70 (65; 77)
Daily stool incidence, M, Me (Q1; Q3)	11.1 9 (6.5; 14)
Incidence of daytime stool, M, Me (Q1; Q3)	8.1 7 (4; 10)
Incidence of night stool, M, Me (Q1; Q3)	3.03 (1; 5)
Laundry contamination, *n* (%) Daytime, *n* (%) Night time, *n* (%)	4 (50%) 4 (50%) 4 (50%)
Episodes of intestinal discomfort, *n* (%)	7 (87.5%)
Taking antidiarrheal medications, *n* (%)	4 (50%)
Gas incontinence, *n* (%)	7 (87.5%)
Ability to distinguish gases/feces, *n* (%)	7 (87.5%)
Perianal skin irritation, *n* (%)	6 (75%)
Stool consistency: Liquid, *n* (%) Mixed, *n* (%) Dense, *n* (%)	 3 (37.5%) 5 (62.5%) 0%
Dietary restrictions, *n* (%)	6 (75%)

postoperative complications were noted after ileostomy takedown.

The functional results of colectomy with rectal resection, J-pouch in 8 patients 1 year after the closure of the ileostomy are presented in Table 4.

As can be seen from the table, most patients have an acceptable quality of life with stool on average 11.1 times a day, gas incontinence, the ability to distinguish gases/feces, and a mixed stool. At the same time, most patients reported dirty under wear, episodes of abdominal discomfort and irritation of the perianal skin. Also, most patients are forced to limit their diet, half of the patients take antidiarrheal medications.

After preventive colorectal surgery, eight patients returned to work within 8 to 12 months after treatment; the remaining patients were not employed before the surgery, but returned to their former lives.

During follow-up after surgery, the first polyps of the rectal stump were detected within 6–8 months after surgery in 5 (33.3%) of 15 patients; in 4 (80.0%) of these patients, a stapler iliac-rectal/anal anastomosis was peformed. All the patients underwent endoscopic removal of revealed new polyps. Gastroduodenal polyps were detected within 10 to 14 months after surgery in 2 (10.0%) patients (their endoscopic removal was also performed); ileum polyps were not detected in our patients during the follow-up.

Desmoid tumors of the abdomen or abdominal wall were detected on average in 24.3 months after surgery in 3 (15.0%) patients, all of which developed after laparoscopic procedures (42.9%). All the patients with desmoid tumors

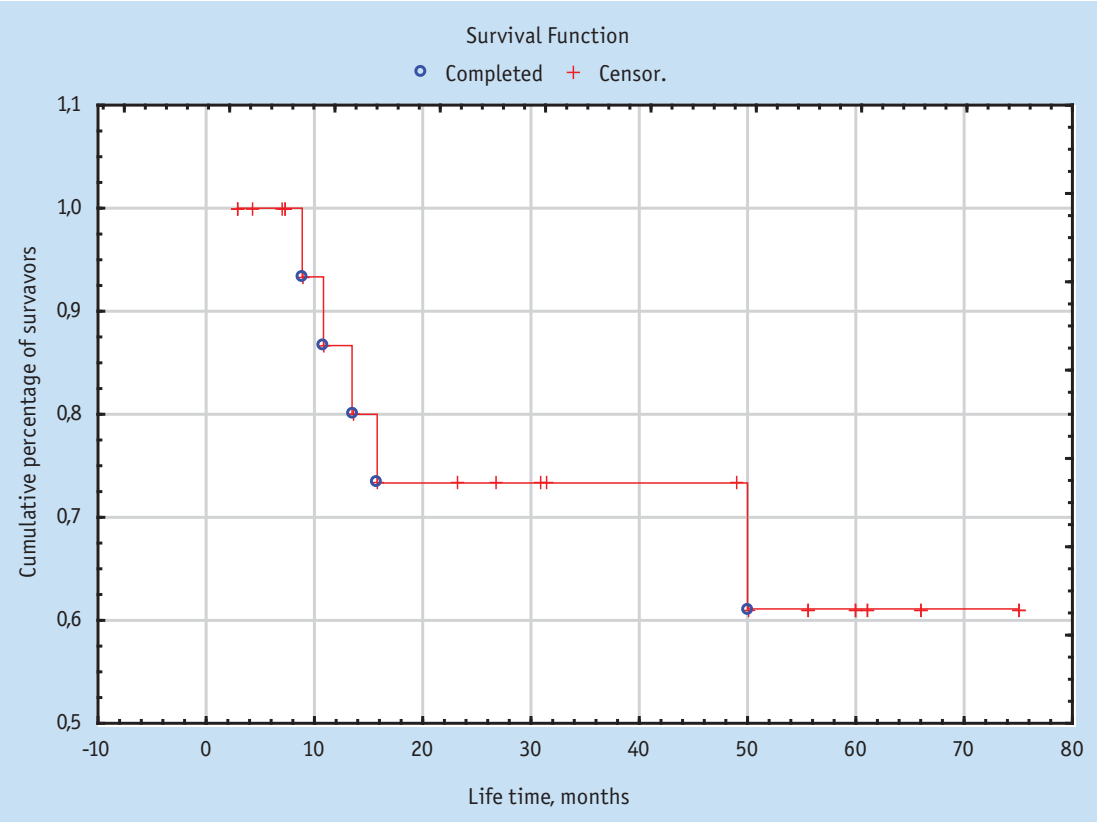

Figure 5. *Survival of patients with FAP, months (75% survival -14.2 months)*

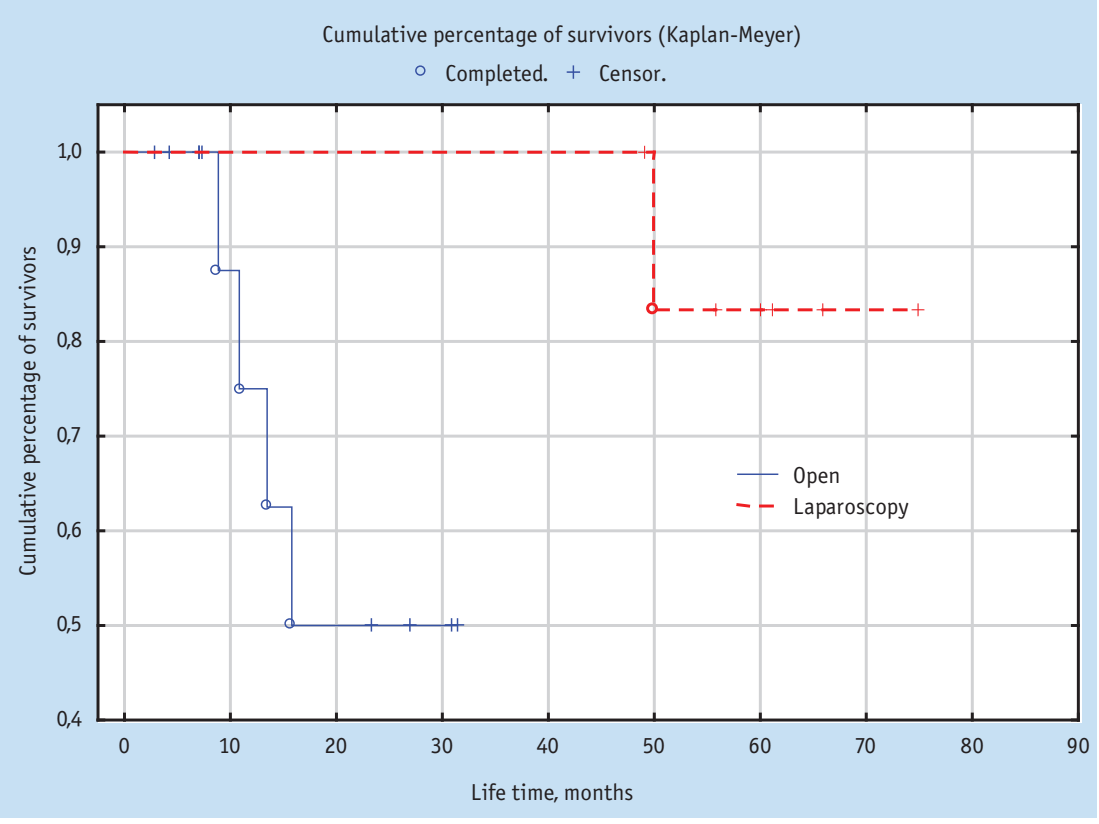

Figure 6. *Survival of patients with FAP after open and laparoscopic surgeries*

Note: significance of differences between survival p = 0.045, Log-rank criterion

were operated on. In two of these patients, abdominal desmoid tumors originated from the mesentery root of the small intestine with involvement of the main vessels and the inability to remove them. Then the patients received conservative treatment. One patient had a desmoid tumor located in the abdominal wall; after its removal, surgery was performed twice with an interval of six months for newly identified desmoid tumors of the abdominal wall.

During the follow–up, 5 (25.0%) patients died, of whom 4 (20.0%) patients died due to the colorectal cancer progression, 1 (5.0%) patient died due to an aggressive abdominal desmoid tumor (Fig. 5).

The analysis showed significant better survival of patients with minimally invasive access (Fig. 6).

DISCUSSION

According to the literature, the average age of patients with FAP during surgery was 28–33.5 years [4,8,9] with a gender ratio (male / female) of 0.93. On average, 60% of patients had a family history of FAP. Colorectal cancer was detected in 31–60% of patients with an average age of 34.6 years [8,10].

The data obtained in the study are generally consistent with the literature data: the gender ratio (male/female) was also about one — 1.2. Family history was observed in 65% of patients. 60% of patients with FCAP were diagnosed with colorectal cancer at an average age of 48.2 years. The differences relate to the average age of patients at the time of surgical treatment: our patients were older, with an average age of 42.2 years. Apparently, this is due to the peculiarities of the diagnosis of FAP in different countries, in particular, the presence or absence of registers of patients with FAP, as well as current clinical guidelines for the treatment of FAP [11,12].

We performed 75% of colectomies with rectal resection and 25% of proctocolectomies. When choosing surgery for FAP, we took into account the choice of the patient. Currently, there is no ‘gold’ standard of surgery in FAP, since many factors influence the choice of surgery. In some studies, the main surgery for FAP was colectomy with rectal resection [13], in others — proctocolectomy [8].

There are studies indicating that colectomy with rectal resection has a risk of rectal cancer of 13% with a mortality rate of 7%. Therefore, it can be a first-choice surgery only with weakened variants of FAP [13]. Proponents of performing proctocolectomy in FAP also appeal to the data that almost a third of patients with colectomy and rectal resection will have rectal incontinence and the need for secondary proctectomy within 20 years after surgery and more than half — after 30 years. Approximately 10% will develop rectal cancer after 20 years and 20% after 30 years of follow-up, resulting in a cumulative mortality of 8% over 20 years [13].

In this study, the overall incidence of postoperative complications was 15%; all of them required re-operations. These data are consistent with other studies in which the incidence of postoperative complications was from 5.3% to 26.2%, with the incidence of re-operations up to 14.3% [14,15,16].

A comparison of laparoscopic and open procedures for FAP revealed the following advantages of minimally invasive access: less intraoperative blood loss (by 1.3 times), rapid recovery of intestinal motility (by 0.9 days) and motor activity (by 1.9 days). However, at the same time, operation time was longer (1.5 times).

Campos, F, et al. [10] compared the results of 38 laparoscopic and 25 open procedures for FAP and found that the duration of laparoscopic procedure was longer than open (374 min. vs. 281 minutes, $p = 0.003$). The incidence of early postoperative complications (28% vs. 28.9%), the postoperative hospital stay (10.9 vs. 8.9 days) and re-operation rate (28% vs. 21%) in the groups of patients did not differ statistically. However, the greater number of late postoperative complications (16% vs. 2.6%; $p < 0.001$) and the incidence of late re-operations (16% vs. 5.2%; $p < 0.05$) were higher after open surgeries.

In general, laparoscopic proceduresfor FAP are becoming a standard surgery in many institutions [4].

To date, the functional results of surgery for FAP are one of the main factors for decision making in choosing one or another approach. Studies show that the functional results of colectomy with rectal resection are significantly better than proctocolectomy in terms of stool incidence during the day and at night, underwear soil, gas and stool incontinence, stool consistency and the need for antidiarrheal drugs [11]. The study confirmed the data on good functional results of colectomy with rectal resection, since most patients had an acceptable quality of life with a stool on average 11.1 times a day; employed patients were able to return to work.

According to the literature, endoscopic control of the pouch and the remaining part of the rectal mucosa after surgery should be carried out for life due to the risk of developing adenomas and their further malignancy. Thus, in the study by Zahid, A. et al. [17] adenomas were found in 12 (44.0%) of 27 patients with an average time till the formation of the first polyp — 88 months. An interesting fact is that in this study, none of the five patients who underwent manual ileo-anal anastomosis developed adenomas at follow-up, compared with 12 (55.0%) of 22 patients with stapler anastomosis ($p = 0.047$).

In the study, the first adenomas of the rectal stump were detected earlier — within 6–8 months after surgery in 5 (33.3%) of 15 patients; in 4 (80.0%) of these patients, a stapler ileo-rectal/anal anastomosis was formed. Adenomas of the small intestine J-pouch were not detected.

Another problem that arises in the treatment of FAP is the occurrence of aggressive desmoid tumors.

Literature data indicate that the overall risk of desmoid tumors during life in patients with FAP reaches 21% [18]. In most patients, desmoid tumors develop after surgery, so surgical trauma is considered a potential risk factor for their development through the activation of an abnormal wound healing process caused by somatic *APC* mutations. Other risk factors for the development of desmoid tumors include family history, female gender and location of mutation in the *APC* gene. However, until the end, the cause of desmoid tumors after surgery for FAP has not been established at the moment.

As for the risk of developing desmoid tumors depending on surgical access, the literature data are ambiguous: some studies do not find a difference in the incidence of desmoid tumors with laparoscopic and open access, other studies report a lower incidence of desmoid tumors after laparoscopic surgery (4% vs. 16.3%) [9]. In the patients included in our study, desmoid tumors developed in 15% of cases during follow-up; all of them were observed after laparoscopic surgery.

The literature data unanimously indicate that the main causes of death of patients with FCAP are colorectal cancer and aggressive desmoid tumor. In our study, 20% of patients died from the progression of colorectal cancer, 5% of patients died from an aggressive desmoid tumor, which is consistent with other studies. Thus, in the study by Sahakitrungruang, C, et al. [16] out of 29 patients, 7 (24.1%) patients died from colorectal cancer and 2 (6.9%) from desmoid tumor.

CONCLUSION

Despite the rarity of the disease, FAP is a complex problem of modern medicine, including the MDT of different specialties: gastroenterologists, geneticists, endoscopists, radiologists, surgeons, oncologists, and others. Diagnostic problems with determining the type of FAP and examining relatives are intertwined with traumatic surgery that changes the patient's quality of life and requires diet and drug support, but does not always guarantee the absence of progression of polyposis with the development of cancer, as well as aggressive desmoid tumors. Minimally invasive surgeries in FCAP have advantages over open surgeries and can become standard surgeries.

INFORMATION ABOUT THE AUTHORS (ORCID)

Oleg I. Kit — ORCID 0000-0003-3061-6108, SPIN:*1728-0329*

Yury A. Gevorkyan — ORCID 0000-0003-1957-7363, SPIN:*8643-2348*

Natalia V. Soldatkina — ORCID 0000-0002-0118-4935, SPIN:*8392-6679*
Evgeny N. Kolesnikov — ORCID 0000-0003-1957-7363
Vladimir E. Kolesnikov — ORCID 0000-0002-9979-4095
Olga K. Bondarenko — ORCID 0000-0002-9543-4551
Eldar K. Khabzhokov — ORCID 0000-0001-6162-2346

AUTHORS CONTRIBUTION

Concept and design of the study: *Oleg I. Kit, Yury A. Gevorkyan*
Collection and processing of materials: *Olga K. Bondarenko, Eldar K. Khabzhokov*
Text writing: *Natalia V. Soldatkina, Evgeny N. Kolesnikov, Vladimir E. Kolesnikov*
Editing: *Oleg I. Kit, Yury A. Gevorkyan*

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Комментарии редколлегии к статье

«Результаты хирургического лечения семейного аденоматоза толстой кишки», авторы: Кит О.И., Геворкян Ю.А., Солдаткина Н.В., Колесников Е.Н., Колесников В.Е., Бондаренко О.К., Хабжоков Э.К.

Представленная статья «Результаты хирургического лечения семейного аденоматоза толстой кишки» посвящена одной из актуальных проблем колопроктологии — лечению больных с наиболее часто встречающимся видом наследственного полипозного синдрома — семейным аденоматозом толстой кишки (САТК). Известно, что в большинстве случаев причиной развития САТК служит наличие патогенной мутации в гене *APC*, который является геном-супрессором опухолевого роста и участником WNT-пути. В настоящее время описано более двух тысяч патогенных мутаций в гене *APC*, однако обнаружить наличие мутации даже при современном уровне развития молекулярной генетики удается лишь у 75-80% пациентов с классической формой САТК и 20-25% больных с ослабленной формой САТК. В представленной статье авторы обнаружили мутации у всех пациентов. Однако, к сожалению, они не приводят список выявленных мутаций, что заставляет думать о возможном принятии непатогенных структурных вариантов в гене *APC* за патогенные.

В отношении хирургической тактики у больных с *классической* формой САТК в современных отечественных и зарубежных клинических рекомендациях единственно возможным вариантом является *полное* удаление всей толстой кишки (включая прямую!) с формированием тонкокишечного резервуара и резервуаро-анального анастомоза, а при наличии противопоказаний — концевой илеостомы. В связи с этим, нельзя согласиться с выбором хирургической тактики авторами представленной статьи, при которой у 15 из 20 больных с классической формой САТК в результате лечения оказались сохраненными те или иные отделы прямой кишки. Доказательством нерадикальности выбранного объема операции стали данные о появлении полипов в оставшейся прямой кишке уже через 6–8 месяцев после операции у трети больных. При этом не возникает сомнений, что со временем часть этих пациентов могут стать кандидатами на выполнение повторной операции с удалением оставшейся части прямой кишки и уже формированием постоянной илеостомы.

Считаем важным отметить, что, учитывая редкую встречаемость больных с семейным аденоматозом толстой кишки в клинической практике, детальная диагностика (включая современные методы молекулярно-генетического обследования) и лечение этой непростой категории больных, а также последующий мониторинг и скрининг среди ближайших родственников должны осуществляться в крупных специализированных медицинских центрах, а накопление полученных данных — в рамках территориальных регистров.

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Molecular-genetic profiling in patients with adenomatous polyps of the gastrointestinal tract

Tatiana S. Lisitsa[1], Anastasia M. Danishevich[2], Anastasia O. Khakhina[1], Amina S. Ibragimova[1], Anastasia D. Shagina[1], Alexandra E. Valeeva[2], Natalya A. Bodunova[2], Ivan S. Abramov[1], German A. Shipulin[1]

[1]Federal State Budgetary Institution "Centre for Strategic Planning and Management of Biomedical Health Risks" of the Federal Medical Biological Agency (Pogodinskaya street, 10 bild. 1, Moscow, 119121, Russia)
[2]State budgetary healthcare institution «The Loginov Moscow Clinical Scientific Center under the Health department of Moscow» (Shosse Entuziastov, 86, Moscow, 111123, Russia)

ABSTRACT *AIM: to reveal hereditary mutations in patients with adenomatous polyps of the gastrointestinal tract*
PATIENTS AND METHODS: a retrospective cohort study included 8 patients with adenomatous polyps of the gastrointestinal tract (ranging from 4 to several hundred). The APC, AXIN2, BMPR1A, BRCA2, CDH1, CHEK2, EPCAM, GALNT12, GREM1, MLH1, MLH3, MSH2, MSH3, MSH6, MutYH, NTHL1, PMS2, POLD1, POLE, SMAD4, STK11 genes were studied using new generation sequencing.
RESULTS: five patients were found to have pathogenic mutations in the genes APC (3 patients with > 100 polyps), POLE (1 patient with < 10 polyps), MutYH (1 patient with 2 mutations with > 28 polyps; 1 patient with monoallelic mutation in combination with a mutation in the APC gene with a number of polyps > 100).
CONCLUSION: the probability of detecting a pathogenic mutation increases with an increase in the number of polyps in a patient.

KEYWORDS: *adenomatous polyps, gastric polyps, colon polyps, familial adenomatous polyposis, NGS, targeted sequencing*

CONFLICT OF INTEREST: *The authors declare no conflict of interest*

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ADDRESS FOR CORRESPONDENCE: *Lisitsa T.S., Centre for Strategic Planning and Management of Biomedical Health Risks, Pogodinskaya street, 10 bild. 1, Moscow, 119121, Russia, e-mail: TLisitsa@cspmz.ru*

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INTRODUCTION

Colorectal polyps (CP) are neoplasms protruding above the surface of the mucous layer into the lumen of the bowel [1]. According to the classification of the World Health Organization (WHO), polyps can be divided into four types: adenomatous, inflammatory, hyperplastic and hamartomic [2].
According to the World Gastroenterological Society, during colonoscopy as part of screening, adenomatous polyps are diagnosed in 18–36% of patients [3].
Gastric polyps are found in 1–4% of patients after gastroscopy. Hyperplastic and adenomatous polyps are often found against the background of *H.Pylori* infection, but they can also manifest in hereditary tumor syndromes (HTS), such as Lynch syndrome, familial colon adenomatosis (FCA). The recognition of gastric syndromic polyps is important for the management of patients [4].
There are classical and attenuated FAP. The classical form of FAP is characterized by the development of one hundred to thousands of adenomas of the rectum and colon during the second to third decade of life. The incidence of FAP is approximately 1 in 8,300 cases. This disease is the cause of about 1% of cases of colorectal cancer (CRC) [5]. Classical FAP is inherited by autosomal dominant

type and occurs as a result of germinal mutation in the *APC* gene. APC protein is a classical tumor suppressor that plays a central role in the signaling of the Wnt cascade, partly by regulating the degradation of β-catenin. In about 10% of patients, mutations in the *APC* gene occur *de novo*, mosaicism is often found [5,6].

Attenuated FAP (AFAP) is characterized by a smaller number of adenomatous colorectal polyps (usually less than 100) and a later age of their appearance [7]. Patients with AFAP also have an increased risk of developing malignant neoplasms [8]. AFAP is caused by mutations in the *APC* gene in codons 1–157, 1595–2843 and exon 9 [9]. At the same time, a similar clinical picture is in the presence of mutations in the *MutYH* and *POLD1/POLE* genes.

MutYH -associated polyposis (MAP) is characterized by the development of 20 to 100 adenomatous colorectal polyps; however, hyperplastic, dentate polyps and mixed (hyperplastic and adenomatous) polyps can occur. Duodenal adenomas are common. In some cases, patients may have a phenotype similar to the classical form of FAP [10]. In patients with MAP, the risk of developing CRC at the age of 60 ranges from 43% to 100%. In some patients, CRC develops in the absence of polyposis [11,12].

The cause of MAP is the presence of a homozygous or compound heterozygous mutation in the *MutYH* gene, which encodes DNA glycosylase involved in excisional DNA repair.

Another form of familial polyposis associated with germinal mutations in the *POLE* and *POLD1* genes (Polymerase Proofreading-Associated Polyposis, PPAP), encoding the exonuclease domain of DNA polymerases epsilon and delta, respectively. In this case, the exonuclease activity of the DNA polymerase is lost, while the polymerase activity remains. Tumors of such patients have an MSS phenotype, but accumulate missense mutations [12].

NTHL1, as well as *MutYH*, is a DNA glycosylase gene underlying autosomal recessive polyposis with high penetrance. *NTHL1* encodes DNA glycosylase of the excision repair pathway [13]. Recessive inheritance of adenomatous polyposis associated with mutations in the *MSH3* gene has been described in a number of patients [14].

AIM

Identification and analysis of molecular genetic characteristics of patients with adenomatous polyps of the gastrointestinal tract (GIT).

PATIENTS AND METHODS

The study included peripheral blood samples from 8 patients who underwent check-up and treatment in 2020–2021. Half of the patients (n = 4) had no gastrointestinal complaints; polyps were diagnosed during a routine check-up. In 4 patients, polyposis was accompanied by pain in the epigastric region, bloating, frequent liquid stools or constipation. The average age at the time of diagnosis of polyps was 39 ± 13 years. In most cases (n = 7) isolated colorectal polyposis was detected, one patient had synchronous gastric lesion.

Total polyposis was diagnosed in 2 patients. Four patients had a history of malignant neoplasms (MN) of various locations. Detailed clinical data of patients are described in Table 1. This study was approved by the local Ethics Committee of the SBHI LMCSC; and informed consent was obtained from each patient.

DNA isolation from peripheral blood lymphocytes was carried out using the QIAamp DNA Blood Mini Kit (Qiagen), on the QIAcube automated DNA, RNA and protein isolation system.

DNA libraries were prepared using the KAPA Hyper Prep Kit (Roche) according to a standard protocol with enzymatic fragmentation of nucleic acids. Hybridization selective enrichment was carried out using a custom panel of probes using the standard Hyper (Roche) protocol. The design of the probe panel was carried out using the Hyper Design (Roche) online service, included coding sites, splicing sites and UTR regions related to genes associated with the development of the HTS, including *APC, AXIN2, BMPR1A, BRCA2, CDH1, CHEK2, EPCAM, GALNT12, GREM1, MLH1, MLH3, MSH2, MSH3, MSH6, MutYH, NTHL1, PMS2, POLD1, POLE, SMAD4, STK11,* disorders in which are associated with the development of gastrointestinal polyps, as well as gastric cancer and CRC.

The MiSeq system (Illumina) was used as a sequencing platform. The sequencing data were

Table 1. *Clinical characteristics of the examined group of patients*

№	Gender	Clinical symptoms	Age	Location of polyps	Number of polyps	MN in history (AD)	Familial history (relatives of I/II degree of kinship)
1	Female	None	39	Colon	4	GC(39)	GC/none
2	Male	Bloating, frequent, loose stools	23	Colon + Gastric	Totally	None	None/ None
3	Female	Epigastric pain	21	TK Colon	< 10	PTK (21) CC(21)	None/ None
4	Female	None	59	TK Colon	> 15	None	PC/PC, GITC
5	Male	None	60	Colon	> 100	None	AP/none
6	M Male	Blood impurities in the stool	50	Colon	> 28	Synchronous CC (50)	None/ None
7	M Male	None	23	Colon	Totally	Hepatoblastoma (1)	AP/none
8	M Male	Blood impurities in the stool	37	Colon	> 10	None	Leukemia/none

Abbreviations: AD — age at the time of diagnosis, GC — gastric cancer, PC — prostate cancer, GITC — cancer of the gastrointestinal tract, AP — adenomatous polyposis, CC — colon cancer, MN — malignant neoplasm, C — colon, G — gastric.

analyzed in accordance with the recommendations of GATK Best Practices (Broad Institute) to search for germinal and somatic mutations according to the algorithm we described earlier [15].

RESULTS AND DISCUSSION

The hereditary nature of the disease was established in 5 patients (Table 2). In one patient with a clinical picture of total colorectal polyposis and synchronous gastric polyposis and another patient with total colorectal polyposis and hepatoblastoma, the previously described germinal pathogenic variants of the nucleotide sequence (VNS) were identified c.3927_3931del, p.Glu1309 AspfsTer, rs121913224 and c.3183_3187del, p.Gln1062Ter, rs587779352 in the *APC* gene in heterozygous form accordingly, associated with the classical form of FCA (OMIM# 175100). A 60-year-old patient with more than 100 adenomatous polyps, who has a relative with adenomatous polyposis, revealed the previously described VNS c.1192_1193del, p.Lys398GlufsTer, rs387906238 in the *APC* gene in heterozygous form, as well as c.1187G > A, p.Gly369Asp, rs36053993 in the *MUTYH* gene in heterozygous form.

Taking into account the clinical picture and the presence of pathogenic VNS in the 398 codon of the *APC* gene, we can talk about the presence of an attenuated form of AFCA in this patient.

In a 50-year-old patient with the presence of more than 28 adenomatous polyps, synchronous CRC and the absence of MN in a family history in the *MUTYH* gene, VNS c.1187G > A, p.Gly369Asp, rs36053993 in heterozygous form, described in the Varsome, InSight databases as pathogenic, and c.548G > A, p.Gly183Asp, rs587781864 is registered in the Varsome database as probably pathogenic.

Taking into account the characteristic clinical picture and autosomal recessive type of inheritance, this disease should be regarded as *MUTYH*-associated colon polyposis (OMIM # 608456).

The most interesting case is a 21-year-old patient with less than 10 polyps and adenocarcinoma of the rectosigmoid part with liver metastases. The patient revealed a previously undescribed VNS

Table 2. *Germline pathogenic variants of nucleotide sequence*

№	Gene	VNS	rsID	Pathogenic variant class
1	Not revealed			
2	*APC*	chr5:112839515delAAAAG c.3927_3931del, p.Glu1309AspfsTer	rs121913224	Class 5 (Pathogenic)
3	*POLE*	chr12:132676655T > C c.802-2A > G	–	Class 5 (Pathogenic)
4	Not revealed			
5	*MutYH*	chr1:45331556C > T c.1187G > A, p.Gly369Asp	rs36053993	Class 5 (Pathogenic)
	APC	chr5:112819224 delAA c.1192_1193del, p.Lys398GlufsTer	rs387906238	Class 5 (Pathogenic)
6	*MutYH*	chr1:45331556C > T c.1187G > A, p.Gly369Asp	rs36053993	Class 5 (Pathogenic)
	MutYH	chr1:45332791C > T c.548G > A, p.Gly183Asp	rs587781864	Class 4 (LikelyPathogenic)
7	*APC*	chr5:112838774delAAAAC c.3183_3187del, p.Gln1062Ter	rs587779352	Class 5 (Pathogenic)
8	Not revealed			

c.802-2A>G in the *POLE* gene, which is located in the highly conserved region of the gene and is represented by the replacement of one nucleotide in the canonical splicing site. According to ACMG criteria [16], this VNS can be regarded as pathogenic clinically significant, associated with PPAP and predisposition to CRC, type 12 (OMIM # 615083). According to the study of Bellido et al, in patients with pathogenic VNS in the *POLE* gene, more than 2 colon adenomas occur in 81.8% of cases, the average number of colorectal adenomas is 19.3 (1–68), and the incidence of CRC in carriers of the *POLE* mutation is 63.8%, the average age at the time of diagnosis is 40.7 years. It should be noted that in this study only patients with the missense variant c.1270C > G, p.Leu424Val, rs483352909 were considered, and for patients with nonsense variants or mutations of the splicing site, the clinical picture may differ. The authors propose criteria for selecting patients for genetic testing for the presence of mutations in the *POLE* gene: the presence of 20–100 adenomatous colorectal polyps, or compliance with the criteria of Amsterdam I, or the presence of CC and 5–20 adenomatous colorectal polyps under the age of 50, or the presence of CRC and 5–20 adenomatous polyps and a relative of the 1st degree of kinship with CC diagnosed at the age of 50, or the presence of CRC and 5–20 adenomatous colorectal polyps and more than two relatives of 1–2 degrees of kinship with CRC diagnosed at any age [17].

CONCLUSION

Recently, several dominant and recessive HTS have been described, the clinical manifestation of which are adenomatous colorectal and/or gastric polyps.

In this regard, there is a need to work out a strategy for molecular genetic testing, approve the necessary minimum list of genes and the sequence of tests. Also, one of the important steps towards determining the optimal treatment approach,

prevention, early diagnosis, further support of patients with polyposis may be the organization of follow-up of patients carrying the mutation.

AUTHORS CONTRIBUTION

Sample collection and clinical and anamnestic characteristics: *Anastasia M. Danishevich, Alexandra E. Valeeva*

Experimental part: *Anastasia O. Khakhina, Amina Sh. Ibragimova, Anastasia D. Shagina*

Research concept and design, data processing, writing and reviewing articles: *Ivan S. Abramov, Tatiana S. Lisitsa, Natalya A. Bodunova, German A. Shipulin*

INFORMATION ABOUT THE AUTHORS (ORCID)

Tatiana S. Lisitsa — 0000-0002-6212-7627
Anastasia M. Danishevich — 0000-0002-3573-8342
Anastasia O. Khakhina — 0000-0002-0723-9765
Amina Sh. Ibragimova — 0000-0003-0485-7450
Anastasia D. Shagina — 0000-0002-0673-4908
Alexandra E. Valeeva –0000-0002-6228-5756
Natalya A. Bodunova — 0000-0002-3119-7673
Ivan S. Abramov — 0000-0002-6954-1564
German A. Shipulin — 0000-0002-3668-6601

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Опыт лечения полипоза толстой кишки у детей

Ионов А.Л.[1], Пичугина М.В.[1], Мызин А.В.[1], Лука В.А.[1], Костомарова Т.Д.[1], Сулавко Я.П.[2]

[1]РДКБ ФГАОУ ВО РНИМУ им. Н.И. Пирогова Минздрава России (ул. Островитянова, д. 1, г. Москва, 117997, Россия)

[2]РДКБ ФГАОУ ВО РНИМУ им. Н.И. Пирогова Минздрава России, кафедра детской хирургии (ул. Островитянова, д. 1, г. Москва, 117997, Россия)

РЕЗЮМЕ *ЦЕЛЬ: проанализировать опыт лечения пациентов детского возраста с полипозом толстой кишки.*
ПАЦИЕНТЫ И МЕТОДЫ: в публикации представлен опыт лечения детей с полипами толстой кишки в возрасте от 1 до 17 лет. Описаны клиника, методы диагностики и тактика ведения пациентов. Детально представлены результаты лечения пациентов с аденоматозным (n = 38) и ювенильным полипозом толстой кишки (n = 16).
РЕЗУЛЬТАТЫ: описаны варианты оперативного вмешательства с учетом результатов морфологического анализа и данных обследования (колэктомия и формирование наданального илеоректального анастомоза с формированием серозно-мышечного цилиндра (n = 8), колпроктэктомии с формированием тонкокишечного резервуара, илеоанального анастомоза (n = 10) и результаты лечения.
ЗАКЛЮЧЕНИЕ: выявление полипов толстой кишки у детей требует широкого спектра обследований и тактика лечения зависит от четкого представления о нозологической форме полипоза толстой кишки, что позволяет определить оптимальный срок и вариант оперативного лечения.

КЛЮЧЕВЫЕ СЛОВА: *дети, полипы толстой кишки, аденоматоз толстой кишки, ювенильный полипоз толстой кишки*

КОНФЛИКТ ИНТЕРЕСОВ: *авторы заявляют об отсутствии конфликта интересов*

ДЛЯ ЦИТИРОВАНИЯ: Ионов А.Л., Пичугина М.В., Мызин А.В., Лука В.А., Костомарова Т.Д., Сулавко Я.П. Опыт лечения полипоза толстой кишки у детей. *Колопроктология*. 2022; т. 21, № 2, с. 64–71. https://doi.org/10.33878/2073-7556-2022-21-2-64-71

Colon polyps in children

Andrey L. Ionov[1], Marina V. Pichugina[1], Artem V. Myzin[1], Viktor A. Luka[1], Tatiana D. Kostomarova[1], Yakov P. Sulavko[2]

[1]Pirogov Russian National Research Medical University (Ostrovitianova st., 1, Moscow, 117997, Russia)

[2]Pirogov Russian National Research Medical University, Department of Pediatric Surgery (Ostrovitianova st., 1, Moscow, 117997, Russia)

ABSTRACT *AIM: to evaluate the results of bowel polyposis in children.*
PATIENTS AND METHODS: the retrospective study included children, aged 1 to 17 years. The clinic manifestations, diagnostics and treatment approach are described. Patients with adenomatous polyposis (n = 38) and juvenile polyposis (n = 16) are presented in details.
RESULTS: options for surgical procedure are described due to early and late results, morphological data and diagnostic findings (colectomy with ileorectal anastomosis and formation of seromuscular cylinder, n = 8; colproctectomy with ileal pouch, n = 10).
CONCLUSIONS: the detection of colorectal polyps requires a wide range of diagnostic and treatment approaches depends on a clear understanding of the nosological form of polyposis, which allows to determine the optimal period and method of surgical treatment.

KEYWORDS: *children, colon polyps, colon adenomatosis, juvenile polyposis*

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АДРЕС ДЛЯ ПЕРЕПИСКИ: *Сулавко Я.П., РДКБ ФГАОУ ВО РНИМУ им. Н.И. Пирогова Минздрава России, кафедра детской хирургии, ул. Островитянова, д. 1, Москва, 117997, Россия; e-mail: mishutka_sno@mail.ru*

ADDRESS FOR CORRESPONDENCE: *Sulavko Ya.P., Pirogov Russian National Research Medical University, Ostrovitianova st., 1, Moscow, 117997, Russia; e-mail: mishutka_sno@mail.ru*

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ВВЕДЕНИЕ

Одной из актуальных проблем в детской клинической практике является лечение полипоза толстой кишки. Наиболее часто полипы выявляются у больных в возрасте от 5 до 14 лет. Основным симптомом, с которым дети поступают в стационары, является примесь крови в стуле, кровотечение после акта дефекации. В некоторых случаях отмечается выпадение полипа из анального отверстия, может наблюдаться болевой абдоминальный синдром. Также полипоз у детей может проявляться более широкой гаммой симптомов. К ним относятся анемия, энтеропатия, гипопротеинемия, нарушение питания и в ряде случаев рецидивирующие эпизоды инвагинации кишечника. Выраженность этих проявлений зависит от числа, локализации и размеров полипов [1–8].

В настоящее время с развитием эндоскопии диагностика полипов толстой кишки не представляет трудностей. Колоноскопия под наркозом позволяет выявить имеющиеся патологические изменения, а также разработать дальнейший ход диагностических мероприятий и определить тактику ведения пациента [9,10].

Пациенты с аденоматозным и ювенильным полипозом требуют дифференциального хирургического подхода, и тактика их ведения является предметом дискуссий.

У пациентов детского возраста остается открытым вопрос о сроках и вариантах хирургического лечения. [1,11–16]. В настоящее время в детской отечественной практике при аденоматозном полипозе толстой кишки широко используется колэктомия и формирование наданального илеоректального анастомоза. Несмотря на хорошие функциональные результаты лечения, эта операция имеет существенный недостаток, а именно, сохранение дистального отдела прямой кишки с продолжающемся ростом полипов и их неизбежной малигнизацией. Это ставит перед хирургами задачу повторного оперативного вмешательства. В то же время, выполнение колпроктэктомии с формированием тонкокишечного резервуара и илеоанальным анастомозом позволяет исключить вероятность продолженного роста и малигнизации полипов [15,17–34]. По данным зарубежных авторов, этот вариант оперативного вмешательства у пациентов детского возраста имел преимущества перед формированием «прямого» наданального анастомоза и в функциональном аспекте [34–36].

ЦЕЛЬ

Целью настоящей публикации является проанализировать опыт лечения пациентов детского возраста с полипозом толстой кишки.

ПАЦИЕНТЫ И МЕТОДЫ

В публикации представлен опыт лечения 62 пациентов, у которых по данным эндоскопического обследования выявлены множественные полипы, что позволило выделить их в отдельную группу — детей с полипозом толстой кишки. На первом этапе диагностики проводилась колоноскопия. Помимо этого выполнялась эзофагогастродуоденоскопия. Видеокапсульная эндоскопия проведена у одного пациента. Морфологическая оценка удаленных в ходе колоноскопии полипов или полученных биоптатов позволила выделить 2 группы: аденоматоз толстой кишки выявлен у 38 пациентов (из них 2 — с синдромом Тюрко, 3 — с синдромом Гарднера), ювенильный полипоз — в 16 случаях.

Характеристика данной категории больных представлена в таблицах 1 и 2.

У большинства пациентов с аденоматозом дебют заболевания отмечен в подростковом возрасте (у 50% — от 8 до 14 лет, старше 15 лет — 45%), первые проявления заболевания у пациентов с ювенильным полипозом у 37% отмечались до 7 лет, у 56% — до 14 лет. Основным клиническим проявлением заболевания явилось кишечное кровотечение. А в сочетании с болями в животе — у 13% больных. В 30% случаев проведение колоноскопии у детей с бессимптомным течением аденоматоза толстой кишки было обусловлено наличием семейного анамнеза, указывающего на наличие полипоза у родственников.

Распределение пациентов с учетом количества и размеров полипов представлено в таблице 3.

Обращает на себя внимание, что при аденоматозе толстой кишки наибольшую группу составили пациенты с числом более 100 полипов. У большинства больных размеры полипов были до 10 мм. При ювенильном полипозе толстой кишки, преимущественно, встречаются крупные полипы (более 10 мм).

По данным морфологического исследования удаленных полипов или биоптатов, у подавляющего большинства пациентов с аденоматозом толстой кишки

Таблица 1. *Пациенты с полипозом толстой кишки*
Table 1. *Patients with colon polyposis*

Клинические группы	Распределение по полу		Дебют (возраст выявления заболевания)			
	мужской	женский	1–3 года	4–7 лет	8–14 лет	Старше 15 лет
Аденоматоз толстой кишки (*n* = 38)	20	18	1	1	19	17
Ювенильный полипоз толстой кишки (*n* = 16)	7	9	4	2	9	1

Таблица 2. *Пациенты с полипозом толстой кишки (клиническая характеристика)*
Table 2. *Patients with colon polyposis (clinical characteristic)*

Клинические группы	Клинические проявления (на момент выявления заболевания)			
	Кишечное кровотечение	Кишечное кровотечение в сочетании с болевым абдоминальным синдромом	Болевой абдоминальный синдром	Бессимптомное течение
Аденоматоз толстой кишки (*n* = 38)	16	5	5	11
Ювенильный полипоз толстой кишки (*n* = 16)	11	2	2	1

Таблица 3. *Распределение пациентов с учетом количества и размеров полипов*
Table 3. *Distribution of patients taking into account the number and size of polyps*

Клинические группы	Количество полипов			Размер полипов			
	до 20	от 20 до 100	более 100	до 5 мм	от 6 до 10 мм	от 11 до 30 мм	более 30 мм
Аденоматоз толстой кишки (*n* = 38)	7 (18,5%)	5 (13,0%)	26 (68,5%)	17 (45,0%)	7 (18,%)	9 (24%)	5 (13%)
Ювенильный полипоз толстой кишки (*n* = 16)	5 (31,0%)	2 (13,0%)	9 (56,0%)	0	3 (19,0%)	6 (37,0%)	7 (44,0%)

выявлены признаки дисплазии низкой степени (79% пациентов), у 3 (7,9%) больных — дисплазия высокой степени. У 3 пациентов отмечено формирование аденокарцином, причем у 2 больных — с дебютом заболевания до 14 лет (синдром Тюрко). При ювенильном полипозе, диплазия отмечена только в 37,5% случаев. У одного больного с ювенильным полипозом выявлен аденоматозный полип с высокой степенью дисплазии наряду с наличием большого количества ювенильных полипов.

В представленной группе больных генетические исследования проведены лишь у нескольких пациентов, что представляется недостаточным для какой-либо оценки этих данных.

РЕЗУЛЬТАТЫ

При выявлении нескольких полипов, как правило, на первом этапе диагностики в ходе колоноскопии проводилось поэтапное их удаление (46 пациентов). При этом полипы небольшого размера удалялись без технических трудностей, по границе ножки полипа, тогда как крупные образования резецировались фрагментами с использованием петли в режимах последовательной электрокоагуляции и резки. У одного пациента после полипэктомии возникла перфорация сигмовидной кишки, потребовавшая проведения лапаротомии и ушивания дефекта. Не подлежали удалению полипы на широком основании, но проводилась их биопсия (11 больных).

Совокупность результатов морфологического анализа и данные обследования, а также данные семейного анамнеза и клинические проявления позволили определить показания к оперативному лечению**.**

У пациентов с аденоматозом толстой кишки показанием к хирургическому лечению стал высокий риск развития злокачественного процесса, по данным морфологического исследования удаленных полипов при колоноскопии (у 6 больных).

В 12 случаях показанием к проведению колэктомии были: частые кишечные кровотечения с падением уровня гемоглобина, гипопротеинемия (3 больных с ювенильным полипозом, 9 пациентов с аденоматозом толстой кишки). Большое количество полипов **(более 100 полипов)** не позволяло провести эндоскопическую санацию толстой кишки.

Возраст оперированных пациентов был от 4 до 17 лет. В среднем, возраст проведения колэктомии составил 14 лет.

Полипоз толстой кишки у детей в ряде случаев требовал тщательной предоперационной подготовки, направленной на коррекцию анемии и водно-электролитных нарушений. При стабилизации состояния ребенка проводилось хирургическое вмешательство.

В хирургическом лечении полипоза толстой кишки в детской отечественной практике была предложена и широко использовалась колэктомия и формирование наданального илеоректального анастомоза. Эта операция выполняется в 2 этапа: 1 этапом — колэктомия с последующим низведением подвздошной кишки с избытком. Во время первого этапа после колэктомии проводится формирование

Таблица 4. *Варианты тактики при полипозах толстой кишки*
Table 4. *Tactic variants in patients with colon polyposis*

Клинические группы	Варианты тактики ведения пациентов и оперативных вмешательств				
	колоноскопия с биопсией	колоноскопия с полипэктомией	Колэктомия и формирование наданального илеоректального анастомоза (2 этапа)	Колпроктэктомия с формированием тонкокишечного резервуара, илеоанального анастомоза	Резекция толстой/прямой кишки
Аденоматоз толстой кишки (n = 38)	9	12	5	10	1
Ювенильный полипоз толстой кишки (n = 16)	1	11	3	0	1

серозно-мышечного цилиндра прямой кишки со стороны малого таза от уровня переходной складки брюшины до уровня на 3–5 см выше зубчатой линии прямой кишки. Во время второго этапа осуществлялось отсечение избытка кишки и формирование наданального анастомоза. При этом зона анастомоза, сформированного в ходе 2 этапа данной операции после резекции избытка низведенного терминального отдела подвздошной кишки, располагается на 3–5 см выше зубчатой линии (наданальный илеоректальный анастомоз). Эта методика позволяет избежать в будущем анальной инконтиненции (зона сфинктерного аппарата и инервация прямой кишки остаются интактными), но остается дистальный участок прямой кишки с сохраненной слизистой оболочкой, где в последующем появляются полипы. Данная методика была применена в 5 случаях у больных с аденоматозом, в 3 — подобные операции проведены по поводу ювенильного полипоза толстой кишки.

Дети после проведения подобной операции достаточно быстро, в течение 1–1,5 лет, адаптировались в социальном плане. Частот дефекации была 6–8 раз, эпизоды недержания кала были редки и возникали, как правило, в ближайшем послеоперационном периоде, а в последующем функция анального держания не страдала. Хорошие функциональные результаты по данным клинического обследования отмечались у всех оперированных пациентов. Учитывая отсутствие клинических признаков анальной инконтиненции, функциональные исследования запирательного аппарата прямой кишки не проводились.

Также одним из вариантов оперативного лечения полипоза выбрана резекция различных отделов толстой кишки с формированием межкишечных анастомозов. Одному пациенту с ювенильным полипозом выполнена резекция илеоцекального угла. Также одному больному с аденоматозом проведена резекция прямой кишки, осложнившейся частичной несостоятельностью анастомоза, что в последующем потребовало формирования илеостомы и этапных реконструктивных вмешательств. Данные операции проведены у пациентов с локализацией полипов в одном из отделов — в начальном отделе толстой кишки и в прямой кишке, соответственно.

В рамках катамнестического обследования после проведенного оперативного вмешательства с формированием наданального илеоректального анастомоза на первом плане стоит проведение эндоскопической оценки с биопсией или удалением оставшихся полипов и обязательным морфологическим исследованием. У 5 пациентов с аденоматозом после формирования прямого наданального илеоректального анастомоза выявлены полипы с низкой степенью дисплазии. У 2 больных с аденоматозом после формирования илеоректального анастомоза в прямой кишке отмечен продолженный рост полипов с малигнизацией.

С 2019 года у пациентов с аденоматозным полипозом толстой кишки проводилось выполнение колпроктэктомии с формированием тонкокишечного резервуара, илеоанального анастомоза (10 пациентов). У всех пациентов при операции создания резервуара с илеоанальным анастомозом также формировалась временная двуствольная илеостома. Восстановление кишечного транзита с ликвидацией илеостомы проводилось через 1,5–3 месяца после эндоскопического и рентгеноконтрастного контрольного обследования зоны илеанального анастомоза и резервуара. Одному пациенту в связи с выявленным стенозом анастомоза потребовалось проведение бужирования, другому больному в связи с диагностированной детрузорношеечной диссенергией для восстановления самостоятельного мочеиспускания проведена трансуретальная электроинцизия шейки мочевого пузыря.

ОБСУЖДЕНИЕ И ВЫВОДЫ

Семейный аденоматозный полипоз толстой кишки является наследственным заболеванием и в большинстве случаев обусловлен мутациями в гене *APC*. В настоящее время установлено, что среди больных аденоматозным полипозом российского происхождения отмечается большая частота герминальных мутаций в этом гене и отсутствует

четкая генетико-фенотипическая корреляция [37]. Генетическое обследование является очень важной частью диагностической программы и требует дальнейшего внедрения в клиническую практику. Однако имеются ограничения организационного порядка, а также невозможность использования генетического анализа в детском возрасте в рамках программы государственных гарантий бесплатного оказания медицинской помощи.

Обязательным является морфологическая оценка строения полипа. Выделяют аденоматозные полипы, строение которых повторяет структуру слизистой и подслизистого слоя. Принципиальным является оценка степени дисплазии клеток полипа.

Аденоматозные полипы имеют тенденцию в последующем переходить в стадию малигнизации.

Ювенильные и гамартомные полипы по структуре имитируют все слои стенки кишки, их озлокачествление менее вероятно, но, тем не менее, риск существует за счет возможных диспластических изменений слизистой. Эти данные определяют тактику динамического наблюдения за пациентами с последующей эндоскопической полипэктомией оставшихся полипов.

Если характер морфологической картины одиночных образований соответствует ювенильному полипу, считаем целесообразным проведение динамического эндоскопического наблюдения за пациентами с обязательным контрольным обследованием в сроки от 6 до 12 месяцев. По-видимому, необходим скрининг таких пациентов с учетом дальнейшего развития клинической картины кишечного кровотечения, а также решение вопроса о генетическом обследовании при бессимптомном течении с учетом семейного анамнеза.

При выявлении нескольких полипов морфологическая оценка позволяет определить характер полипозного синдрома. Дальнейший план обследования, помимо выполнения эзофагогастродуоденоскопии может включать видеокапсульную эндоскопию у больных с ювенильным полипозом и синдромом Пейтца-Егерса. Данное исследование, преимущественно, показано для выявления полипов тонкой кишки. Также для оценки пассажа по кишечнику и планирования оперативного вмешательства может проводиться рентгенконтрастное исследование. Ирригография диагностической значимости не имеет и проводится при возникновении трудностей при выполнении ФКС, невозможности осмотра вышележащих отделов толстой кишки вследствие имеющихся деформаций и сужений.

Именно гистологическая картина и результаты генетического обследования позволяют адекватно определить дальнейшую тактику ведения таких больных и решить вопрос о вариантах оперативного вмешательства и сроках радикального хирургического лечения.

Существуют разногласие в отношении сроков проведения операции при семейном аденоматозе толстой кишки. Как правило, показаниями к операции являются появление симптомов (кишечное кровотечение, боли в животе), увеличение размеров или количества полипов, выявленное при контрольной колоноскопии, наличие дисплазии высокой степени, а также пожелания родителей и пациента. Однако нет единого мнения о возрасте пациента, размере или количестве полипов, при которых следует проводить тот или иной вариант операции. Некоторые рекомендуют колэктомию сразу после выявления аденом, в то время как другие рекомендуют колэктомию в тот период, когда она меньше будет мешать психологическому, социальному развитию ребенка. Также считается, что у пациентов с мутацией, характерной для более легкого течения и меньшим количеством полипов (менее 500 полипов толстой кишки и менее 20 полипов прямой кишки) целесообразно отложить операцию или провести колэктомию с формированием илеоректального анастомоза [22,35].

Наиболее распространенной операцией в хирургическом лечении семейного аденоматоза толстой кишки у взрослых является выполнение профилактической колпроктэктомии с формированием тонкокишечного резервуара [38]. Анализ результатов широко используемой в нашей стране в детской практике двухэтапной операции с формированием серозно-мышечного цилиндра и созданием анастомоза на 3–5 см выше зубчатой линии позволяет утверждать, что, несмотря на хорошие функциональные результаты, продолжающийся рост полипов в данной зоне и их малигнизация диктуют в будущем необходимость проведения повторного оперативного вмешательства: резекции оставшегося участка прямой кишки. При этом при повторной операции создание резервуара из подвздошной кишки и его анастомозирования с анальным каналом после удаления оставшейся слизистой прямой кишки в ряде случае затруднено, в связи с изменением топографо-анатомических взаимоотношений органов малого таза и архитектоники сосудов брыжейки тонкой кишки в ходе низведения при первой операции. Таким образом, выполнение таких операций у пациентов с аденоматозом толстой кишки нецелесообразно.

В случае высокого риска развития аденокарцином, по прогностическим данным морфологии и генетического обследования (семейный аденоматоз, синдром Тюрко и т.д.), считаем обоснованным проведение колпроктэктомии с мукозэктомией и формированием илеоанального анастомоза с резервуаром. По данным зарубежных авторов, выполнение этой операции в детском возрасте является

обоснованным и имеет преимущества перед операциями с наложением прямого илеоанального анастомоза. Наложение прямого илеоанального анастомоза чревато развитием выраженной недостаточности сфинктерного аппарата с развитием тяжелой степени недержания кала, перианального дерматита, что, безусловно, значительно снижает качество жизни пациента [25,34–36].

Анализ результатов широко используемой в нашей стране в детской практике двухэтапной операции с формированием серозно-мышечного цилиндра и созданием анастомоза на 3–5 см выше зубчатой линии позволяет утверждать, что, несмотря на хорошие функциональные результаты, вероятность продолженного роста полипов в данной зоне и их малигнизации не исключена. То есть в будущем возникает необходимость проведения повторного оперативного вмешательства: резекции оставшегося участка прямой кишки.

При этом создание резервуара из подвздошной кишки при повторной операции и его анастомозирования с анальным каналом после удаления оставшейся слизистой прямой кишки в ряде случае затруднено, в связи с изменением топографо-анатомических взаимоотношений органов малого таза и архитектоники сосудов брыжейки тонкой кишки в ходе низведения при первой операции. Таким образом, выполнение таких операций у пациентов с аденоматозом толстой кишки нецелесообразно.

Проведения радикального оперативного вмешательства рекомендуем в случае выявления дисплазии полипов высокой степени, а также при наличии выраженного кишечного кровотечения и невозможности санации толстой кишки в ходе колоноскопии из-за большого количества полипов. Возраст пациентов не является определяющим фактором. Минимальный возраст, когда была выполнена радикальная операция у пациента с аденоматозом толстой кишки, в наших наблюдениях составил 4 года.

При ювенильном полипозе показаниями к хирургическому лечению являются такие клинические проявления как анемия, гипотрофия, частые эпизоды кишечного кровотечения. Если отсутствуют признаки дисплазии и риск ранней малигнизации, а также есть возможность последующего удаления полипов в прямой кишке с учетом их количества, оптимальным вариантом, по нашему мнению, может быть колэктомия с формированием илеоректального анастомоза. Целесообразным для удобства выполнения возможных будущих радикальных оперативных вмешательств может быть предложено формирование анастомоза в 3–5 см над переходной складкой брюшины. Важно подчеркнуть, что указанное вмешательство редко сопровождается осложнениями и сводит к минимуму развитие функциональных нарушений в послеоперационном периоде. При наличии большого количества полипов в прямой кишке, наличии признаков дисплазии этих полипов показано выполнение радикальной операции, как при аденоматозе толстой кишки — ***колпроктэктомии*** с формированием илеоанального анастомоза с тонкокишечным резервуаром, как при аденоматозе толстой кишки. Оперативное лечение показано в любом возрасте и является единственным методом коррекции вышеописанных патологических состояний, наблюдаемых при полипозе [7,21,22,35,36].

Оперативное лечение показано в любом возрасте и является единственным методом коррекции вышеописанных патологических состояний, наблюдаемых при полипозе [7,21,22,35,36].

Оперативное лечение целесообразно проводить в специализированных детских колопроктологических учреждениях.

В заключении стоит отметить, что выявление полипоза толстой кишки требует широкого спектра обследований и тактика лечения зависит от четкого представления о нозологической форме полипоза толстой кишки.

СВЕДЕНИЯ ОБ АВТОРАХ (ORCID)
Яков Сулавко — 0000-0001-6135-2729

INFORMATION ABOUT THE AUTHORS (ORCID)
Yakov P. Sulavko — 0000-0001-6135-2729

УЧАСТИЕ АВТОРОВ
Концепция и дизайн исследования: *Ионов А.Л., Сулавко Я.П.*
Сбор и обработка материалов: *Пичугина М.В., Мызин А.В.*
Написание текста: *Костомарова Т.Д., Сулавко Я.П.*
Редактирование: *Ионов А.Л., Лука В.А.*

AUTHORS CONTRIBUTION
Concept and design of the study: *Andrei L. Ionov, Yakov P. Sulavko*
Collection and processing of materials: *Marina V. Pichugina, Artem V. Myzin*
Text writing: *Tatiana D. Kostomarova, Yakov P. Sulavko*
Editing: *Andrei L. Ionov, Viktor A. Luka*

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Genotype-phenotypic correlation of Peutz-Jeghers syndrome

Tatiana I. Yanova[1], Natalya A. Bodunova[1], Igor E. Khatkov[1], Alexey S. Tsukanov[2], Nikita G. Khodos[1], Ivan A. Pavlov[1], Ivan Yu. Nedoluzhko[1], Tatiana A. Savelyeva[2], Anastasia M. Danishevich[1], Vera V. Polyakova[1]

[1]GBUZ Moscow Clinical Scientific Center named after Loginov MHD (Shosse Entuziastov, 86, Moscow, 111123, Russia)

[2]Ryzhikh National Medical Research Center of Coloproctology (Salyama Adilya str., 2, Moscow, 123423, Russia)

ABSTRACT *INTRODUCTION: Peutz-Jeghers syndrome (PEUTZ-JEGHERS SYNDROME; PJS; OMIM#175200) is hereditary tumor syndrome and is characterized by the occurrence of hamartomatous polyps of gastrointestinal tract, melanocytic pigmentation of the skin and mucous membranes, as well as a high predisposition to malignant tumors of various locations. Despite the fact that the clinical features of PJS are currently well understood, the nature of the variability in the phenotypic manifestations of the disease has not been fully described.*

AIMS: to determine the phenotypic and clinical features in patients with PJS depending on the type of mutation in the STK11 gene.

PATIENTS AND METHODS: the clinical and genetic data of 3 patients aged 21, 28 and 39 years with clinical signs of PJS are presented. All patients underwent medical genetic counseling and molecular genetic diagnostics of the STK11 gene using NGS and MLPA methods.

RESULTS: large deletions of ex2-8 and ex1 in the STK11 gene were revealed in two patients, and one patient showed a splice site variant c.921-1G > A. The identified variant ex2-8 has not previously been described in international databases. When evaluating the clinical and genetic features, the most severe picture of the disease was in a patient with an extended deletion of exons 2-8, large number of polyps and surgical procedures in history. However, in this case, melanocytic pigmentation became less with age, in contrast to patients with a splice site mutation and a single exon deletion. No cancers were detected in the patients.

CONCLUSION: the molecular genetic test made it possible to confirm the clinical diagnosis of PJS, based on various phenotypic features, and to work out the personalized plan for follow-up. Evaluation of the genotype-phenotype correlations will be possible with the development of a unified register of mutation carriers.

KEYWORDS: *Peutz-Jeghers syndrome, gastrointestinal polyposis, hamartoma polyps, melanocytic hyperpigmentation, splicing site mutation, deletion, STK11 gene*

CONFLICT OF INTEREST: *The authors declare no conflict of interest.*

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ADDRESS FOR CORRESPONDENCE: *Yanova T. I., Center for Personalized Medicine, GBUZ Moscow Clinical Scientific Center named after Loginov MHD, 86, Shosse Entuziastov, Moscow, 111123, Russia, e-mail: t.yanova@mknc.ru*

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INTRODUCTION

Peutz-Jeghers syndrome(PJS, PEUTZ-JEGHERS SYNDROME; OMIM# 175200) is a rare hereditary autosomal dominant syndrome characterized by the occurrence of tens to hundreds of hamartomic polyps in the small intestine (60%-90%), stomach (15%-30%), and large intestine (50%-64%), melanocytic pigmentation of the skin and mucous membranes (95% of cases), as well as an increased risk of malignant neoplasms (MN). The prevalence of the syndrome in the population ranges from 1:25,000 to 1:200,000 newborns [1]. To date, the criteria for making a clinical diagnosis include [2,3]: — The presence of three or more hamartomic polyps of the gastrointestinal tract (GIT); — Melanocytic pigmentation of the face skin and/or mucous

membranes; — Burdened family history of diseases from the PJSrange.

The diversity of these criteria and the variability of the clinical picture of PJS do not always allow to establish a diagnosis without a molecular genetic study. The peculiarities of this syndrome are caused by disorders in the *STK11* gene, which encodes the protein serine-threonine kinase 11, which participates in the regulation of cellular metabolism, cell polarization and response to DNA lesion. The *STK11* gene is located at 19p13.3, includes 9 coding exons. Germinal mutations in the *STK11* gene lead to loss of gene product function, in particular, activation *pik3A/AKT/* of the target of the mTOR signaling pathway and carcinogenesis [4]. Identification of the pathogenic variant in the *STK11* gene allows to confirm the diagnosis, as well as to establish a carrier among the patient's relatives, to reduce the incidence of emergency surgery and the risk of MN [5]. In general, the risk of MN of various sites is 15 times higher in patients with PJSin comparison with the general population, and by the age of 65 years old it can reach 93% [6,7]. Currently, there is no pathogenetically based treatment for Peitz-Jaegers syndrome. The main approach is dynamic control and prevention of severe complications.

Often, the diagnosis of PJS is established at the stage of surgical complications, such as intussusception of the small intestine, intestinal obstruction, bleeding, and others, which emphasizes the importance of early diagnosis of the disease [8,9]. Recently, the lack of reliable data on phenotype-genotypic correlation does not allow predicting the course of the disease and the risk of MN [10–11]; further study of this issue may lead to an improvement in the prognosis for such patients.

PATIENTS AND METHODS

The paper presents the clinical and genetic data of 3 patients aged 21, 28 and 39 years with clinical signs of PJSin 2021. All patients underwent medical and genetic counseling, as a result of which it was recommended to make DNA test of the *STK11* gene using NGS (next generation sequencing) methods on the Illumina MiSeq sequencer. The MLPA (Multiplex Ligation-dependent Probe Amplification) method was performed using the MRC Holland kit, SALSA MLPA Probemix P101-B4 STK11.

This study was approved by the local ethics committee and informed consent was received from each patient.

RESULTS

Clinical Observation 1

Patient A., aged 21, consulted a geneticist to clarify the hereditary nature of polyposis. It is known from the history that for the first time at the age of 11 months after an episode of prolapse of the rectal mucosa during defecation, a tumor of the rectum was revealed, which was removed; during histology, it was a villous adenoma. From the age of 7, the patient had episodes of bloodin the stool, iron deficiency anemia. At the age of 14, multiple diffuse polyps in the stomach, smalland large intestine were detected, and the diagnosis of PJS was clinically approved.

In this regard, elective endoscopic polypectomies from the stomach, small and large intestine were repeatedly performed. At the age of 21, an enterography revealed an invaginate with polyps of 1.6 and 2.0 cm in the middle third of the jejunum, a polyp up to 3.5 cm in the proximal loops of the ileum.Shadows of small polyps up to 0.3–0.8 cm were also detected throughout the small intestine. However, it should be noted that the lumen of the small intestine was uniform throughout. Due to the threat of small intestine obstruction, the patient underwent elective surgery. Laparotomy was performed, the invaginate was straightened, 3 enterotomies were performed and 7 of the largest polyps with a diameter of up to 3.5 cm were removed. According to the morphology of the removed polyps, hamartomas were revealed. When examining the patient, attention is drawn to the light brown pigmentation of the lips, which was more pronounced in childhood. In the family history, attention is drawn to multiple operations for small intestine obstruction in the father at the age of 16, 20 and 45 years; taking into account clinical data, he was diagnosed with PJS without confirmation by molecular genetic diagnosis.

Table 1. *Clinical characteristics and results of check-up*

Patients/ Examples	А.	Б.	В.
Melanocytic pigmentation	Lipmucosa	The mucous part of the lips, cheeks, skin around the lips, periorbital, back surface of the hands and palms	Periorbital
Age of detection of polyposis	11 months	28 years old	24 years old
Location of polyps	S, SI, C	S, SI, C	S, SI, C
Total number of hamartomic polyps during life	> 70	> 40	> 20
Variant in the *STK11* gene (NM_000455.5)	ex2-8 del [g.(?_001169421)_ (001174101_?)del]	ex1 del [g.(?_001156776)_ (001157954_?)del]	chr19:1222984G > A, c.921-1G > A
Clinical significance of the variant	Pathogenic	Pathogenic	Pathogenic
MN in relatives of I-II degree of kinship	None	CC (II-2), MN in B (I-2), BC (II-3)	None
The number of operations in the history	15	1	3

ABBREVIATIONS: S — stomach, SI — small intestine, C — colon, BC — breast cancer, CRC — colorectal cancer, B — brain; (II-2) — mother of patient B, (I-2) — paternal grandmother of patient B, (II-3) — maternal aunt.

In his half-siblings (his brothers aged 6 and 9 on his father's side), hamartomicgastric polyps were revealed.

Taking into account the results of endoscopy and histology (multiple hamartomic polyps), complicated family history, phenotype data (the patient and half-siblings had pigmentation of the skin and oral mucosa from the age of two years), a presumptive diagnosis was established — PJS. The patient's phenotypic data and family history are presented in Fig. 1.

The patient provided data from a molecular genetic test of the siblings: no causative variants were detected in the coding part of the *STK11* gene. The proband was searched for extended deletions/duplications in the *STK11* gene by MLPA, which allowed to determine the mutation ex2-8 del [g.(?_001169421)_(001174101_?)del] and confirm the diagnosis of Peitz-Jaegers syndrome (Table 1).

Clinical Observation 2

Patient B., aged 28 years old, when complaints of spastic pain in the epigastrium appeared, a check-up was performed (esophagogastroduodenoscopy, colonoscopy, abdominal CT), as a result of which invagination of the vermiform appendix into the lumen of the cecum and multiple invaginates in the small intestine caused by multiple hamartomic polyps of the small intestine, as well as an exophytic villous tumor of the splenic flexureof 8 × 3 × 5 cm and 3 polyps of the sigmoid colon up to 4, 5 and 7 cm in diameter on long legs were revealed (Fig. 2, 3).

The patient underwent elective surgery. The intraoperative revision revealed invaginates of the small intestine at 100 and 110 cm from the Treitz ligament and one invaginate at 100 cm from the ileocecal valve. The procedure includedstraightening of the jejunum invaginates, enterotomy, removal of two polyps up to 3 cm in diameter on long pedicle, segmental resection of the ileum with the hand-sewn ileo-ileoanastomosis "side-to-side", resection of the dome of the cecum with an appendix and resection of the left colon with the hand-sewn transverso-sigmoid anastomosis "side-to-side" due to the impossibility of endoscopic removal of tumors of the descending and sigmoid colon. The morphology revealed a tubulovillous adenoma with low grade epithelial dysplasia. Polyps of the vermiform appendix of the small intestine were hamartomas.

Taking into account the pigmentation characteristic of the PJS in the proband, the family history (Fig. 1) and the results of the check-up, the patient was referred to the consultation of a geneticist. Based on the available facts, it was decided to search for mutations in the *STK11* gene by the NGS method.

As a result, pathogenic and probably pathogenic variants were not identified. In order to search for extended deletions/duplications, the *STK11* gene was further analyzed by the MLPA method. The mutation ex1 del [g.(?_001156776)_(001157954_?)del]was detected. The detailed clinical and anamnestic data and the results of the patient's DNA diagnosis are given in Table 1. Based on the result of the molecular genetic test, the diagnosis of PJS was confirmed.

Clinical Observation 3

Patient V., aged 39 years old, consulted a geneticist to clarify the prognosis of the disease (Fig. 1). It is known from the history that since 2006 she has been observed by a gastroenterologist for iron deficiency anemia, gastric polyposis. The patient repeatedly has undergone endoscopic removal of gastric polyps. In November 2019, the patient was hospitalized by an ambulance team with a clinical picture of small intestine obstruction, for which laparotomy, resection of the small intestine invaginate was urgently performed. With control esophagogastroduodenoscopy in 2020 diffuse gastric polyposis, multiple duodenal polyps were

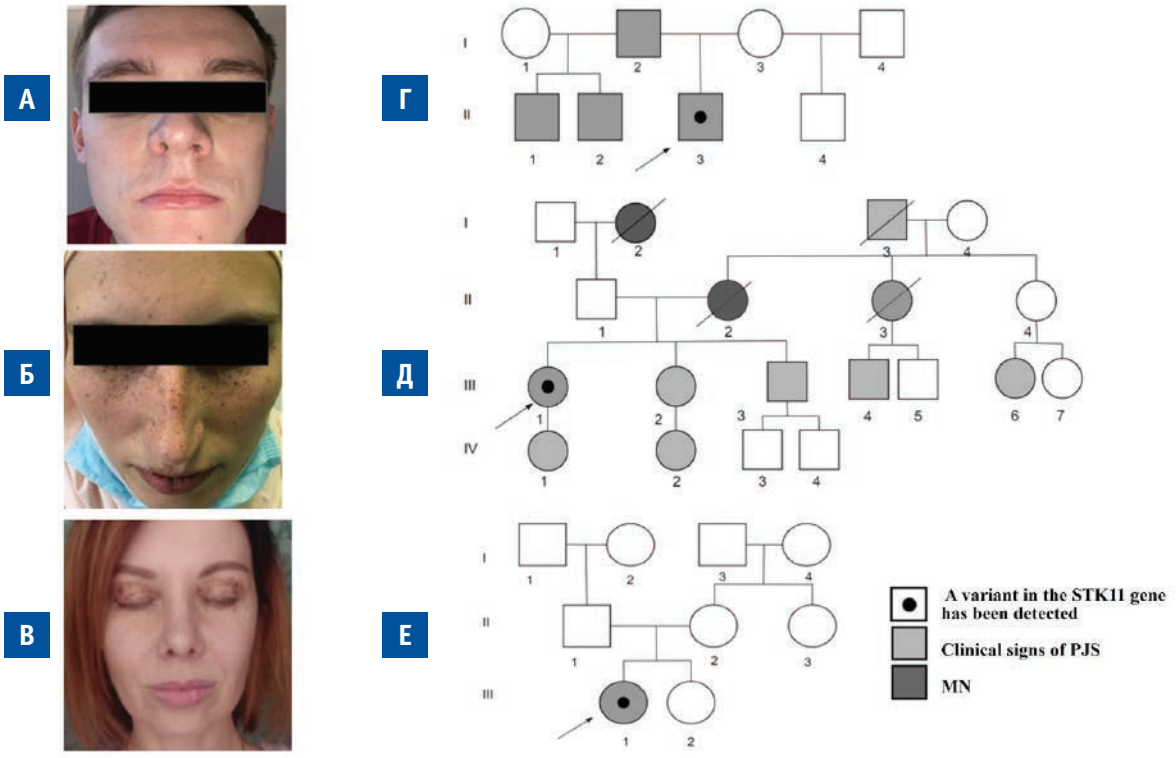

Figure 1. *А — Light brown lip pigmentation of patient A, Г — Pedigree of patient A; Б — Hyperpigmentation of the facial skin of patient B; Д — Pedigree of patient B; В — Hyperpigmentation of the skin around the eyes of patient B, Е — Pedigree of patient B.*

revealed. Histology revealed fragments of a glandular polyp of the stomach, hyperplastic polyps of the duodenum. Colonoscopy showed a sigmoid colon polyp with a diameter of 4–5 mm on a narrowed base, according to the histology — an adenomatous polyp.

The search for pathogenic and likely pathogenic mutations in genes associated with hereditary tumor syndromes and hereditary polyposes, and in particular the study of the coding sequence of the genes *STK11, MutYH, APC* were performed. A mutation c.921-1G>A was detected in the *STK11* gene (Table 1). Based on genetic testing, the patient was diagnosed with PJS, and regular intestinal control was recommended to exclude the growth of new polyps.

DISCUSSION

The study included the clinical data of three patients with a molecular-genetically confirmed PJS with identified mutations in the *STK11* gene.

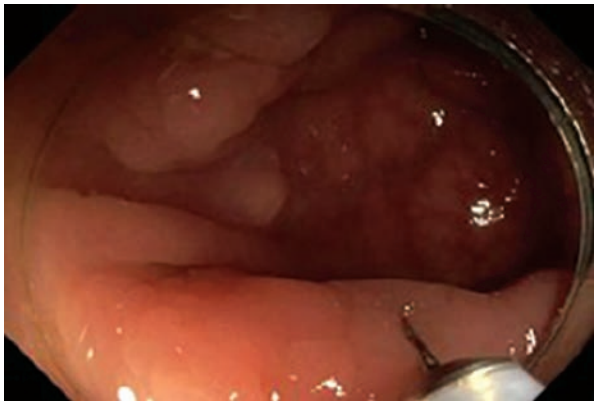

Figure 2. *Endoscopy of colorectal polyposis (patient B)*

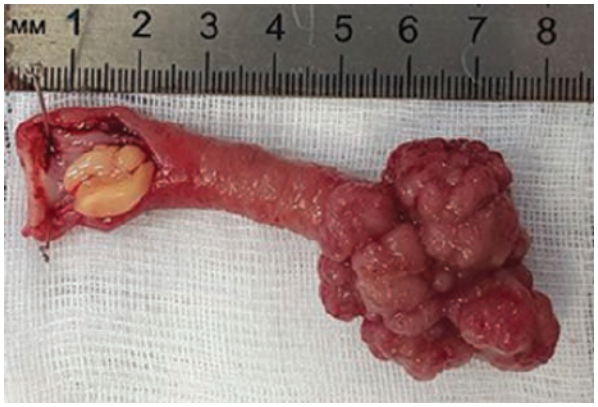

Figure 3. *Removed specimen of appendix intussusceptions with Peutz-Jeghers polyps of patient B*

All variants lead to a violation of the function of the STK11 protein. Variant ex2-8 del, not previously described in international databases, leads to shortening (truncating mutation) and disruption of protein function, which causes clinical significance. The variant of the splicing site c.921-1G>A and the extended deletion of ex1 were previously described in patients with Peutz-Jeghers syndrome, colorectal cancer, pancreatic adenocarcinoma, gastrointestinal polyposis [12–15]. According to the information given in the literature, it is impossible to conduct a comparative analysis of the patient data, since each article highlights various aspects of PJS. For example, Resta N. et.al [12] described a patient with PJS, about whom it is known that she has no family history, there is no MN, and a variant c.921-1G>A was identified in the *STK11* gene. Bannon S.A. et.al [13] conducted a study of genes associated with pancreatic MN; among the identified variants there was an extended deletion of ex1 in the *STK11* gene in a patient with pancreatic adenocarcinoma; Ngeow J. et.al [15] revealed the same genetic variant in a patient with hamartomic polyps, while other clinical manifestations of PJS are not described in both papers.

When assessing the clinical and genetic features, the most severe disease was observed in a patient with an extended deletion of 2–8 exons, who had a large number of polyps and a history of surgeries. However, it is worth noting separately that in the described patient, melanocytic pigmentation has become less pronounced with age, unlike the patients with a point mutation and deletion of the first exon.

The risk of developing MN of various sites and the algorithm of dynamic control of carriers of germinal mutations in the *STK11* gene is presented in Table 2 [16–21]. Despite the fact that according to the literature, the carrier of truncating mutations correlates with a higher risk of cancer in comparison with the carriers of the missense variants in the patients described by us, MN was not observed. This may be due to the young age of the patients, the non-progressive disease, as well as their personalized approach, including check-up and removal of identified polyps, which probably reduced the risk of developing MN.

Table 2. *Cancer risk and National Comprehensive Cancer Network follow-up guidelines for Peutz-Jeghers syndrome*

MN Localization	Cumulative risk of developing MN during life, %	Age of screening initiation, years	Methods of dynamic control	Dynamic control intervals
Mammary gland	32–54	30	-Clinical examination of an oncologist-mammologist -Mammography and MRI of the mammary glands	– 1 time every 6 months – Every year
Stomach	29	8–10*, but no later than 18	EGDS	Every 2–3 years**
Small intestine	13	8–10*, but no later than 18	CT/MRI enterography or videocapsular endoscopy	Every 2–3 years**
Large intestine	39	8–10*, but no later than 18	Colonoscopy	Every 2–3 years**
Pancreas	11–36	30–35	-USAO or MRI/MRCPG	Every year
Cervix (malignant adenoma)	10	18–20	-Gynecological examination -Cytological examination with Papanicolaou staining	Every year
The uterus body	10	18–20	-Gynecological examination -Cytological examination with Papanicolaou staining	Every year
Ovaries (Tumor of the genital cord with annular tubules)	18–21	~8	-Gynecological examination -Cytological examination with Papanicolaou staining	Every year
Testicles (Tumor from Sertoli cells)	9	~10	Urological examination	Every year
Lungs	7–17	No specific recommendations		

*Note: * Possible earlier start of periodic examinations in the presence of clinical signs of lesion; **It is permissible to reduce the time intervals between examinations in the case of a larger number or size of polyps*
ABBREVIATIONS: MRI — magnetic resonance imaging, EGDS — esophagogastroduodenoscopy, CT — computed tomography, US — ultrasound examination, AO — abdominal organs, MRCPG — magnetic resonance cholangio-pancreatography.

According to the literature, point mutations in the *STK11* gene are most often detected. However, about 15%-20% of cases of PJS are associated with extended deletions/insertions [22,23]. Therefore, in the absence of a causative variant in the study by NGS sequencing, it is necessary to use an additional diagnostic method — MLPA. It is thanks to this method that we were able to confirm the diagnosis in two of the patients described in the paper.

To date, numerous studies have been aimed at studying the effect of the location of mutations on the protein structure and the severity of clinical manifestations [10,24] to establish a correlation between the severity of the course of PJS and the molecular variant in the *STK11* gene. Equally, efforts are being made to identify the dependence of the risk of developing MN on the type of mutation in the *STK11* gene [25,26]. Zhao Na et al. report about their functional analysis of the effect on the structure of the final product of variant C.921-2A>C, located at the same splicing site as the mutation in patient B.

This variant is considered as the cause of the disease in two patients aged 5 and 35 years old with a variable phenotype of PJS [27]. Orellana P. et al. as well as Shelygin Yu.A. et al. described mutations of the splicing site and deletion of the *STK11* gene, in which hyperpigmentation and polyposis of the stomach, small and large intestine were present in most patients, and the age of diagnosis ranged from 1 to 37 years [5,28].

CONCLUSION

Given the low prevalence of Peutz-Jeghers syndrome, it is necessary to create a unified register of patients carrying pathogenic variants in the *STK11* gene associated with PJS, which will allow identifying genotype-phenotypic correlations, as well as developing a personalized follow-up and treatment plan.

AUTHORS CONTRIBUTION

Concept and design of the study: *Natalya A. Bodunova, Alexey S. Tsukanov, Igor E. Khatkov, Vera V. Polyakova, Tatiana I. Yanova*
Collection and processing of materials: *Tatiana A. Savelyeva, Ivan A. Pavlov, Nikina G. Khodos, Ivan Yu. Nedoluzhko, Vera V. Polyakova, Tatiana I. Yanova*
Statistical processing: *Vera V. Polyakova, Tatiana I. Yanova*
Text writing: *Vera V. Polyakova, Tatiana I. Yanova*
Editing: *Alexey S. Tsukanov, Anastasia M. Danishevich, Vera V. Polyakova, Tatiana I. Yanova*

INFORMATION ABOUT THE AUTHORS (ORCID)

Tatiana I. Yanova — Clinical Geneticist of The Center for Personalized Medicine, ORCID: 0000-0001-5146-6925
Vera V. Polyakova — Gastroenterologist, Junior Researcher at the Center for Personalized Medicine, ORCID: 0000-0003-1782-2118
Igor E. Khatkov — Corresponding member of the Russian Academy of Sciences, Doctor of Medical Sciences, Professor, Director of the State Budgetary Healthcare Institution of Moscow «Moscow Clinical Scientific Practical center named after A. S. Loginov» of the Health department of Moscow, ORCID: 0000-0002-4088-8118
Alexey S. Tsukanov — MD, PhD Department of Laboratory Genetics Ryzhikh National Medical Research Center of Coloproctology, ORCID: 0000-0001-8571-7462
Nikina G. Khodos — surgeon, Department of High-Tech Surgery and Surgical Endoscopy, ORCID: 0000-0003-0611-3762
Ivan A. Pavlov — PhD, Endoscopist, Operative Endoscopy Department, ORCID:0000-0002-9680-4876
Ivan Yu. Nedoluzhko — PhD, Endoscopist, Surgeon of the Department of Operative Endoscopy, ORCID: 0000-0003-2647-4362
Anastasia M. Danishevich — geneticist, Center for Personalized Medicine, ORCID: 0000-0002-3573-8342
Tatiana A. Savelyeva — coloproctologist, 1st Surgical Department (General Coloproctology) Ryzhikh National Medical Research Center of Coloproctology, ORCID: 0000-0001-9934-3596
Natalya A. Bodunova — PhD in Medical Sciences, The Head of The Center for Personalized Medicine, ORCID: 0000-0002-3119-7673

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Reconstruction of the rectovaginal septum with a W-mesh for rectocele

Anton S. Lukianov[1], Oleg M. Biryukov[1], Elena P. Goncharova[1], Alexander Yu. Titov[1], Andrey A. Mudrov[1,2], Timur V. Nikishin[1], Ivan V. Kostarev[1,2]

[1]Ryzhikh National Medical Research Center of Coloproctology (Salyama Adilya str., 2, Moscow, 123423, Russia)

[2]Russian Medical Academy of Continuous Professional Education of the Ministry of Healthcare of Russia (Barrikadnaya str., 2/1-1, Moscow, 125993, Russia)

ABSTRACT *AIM: to assess of late results of original method of rectocele repair with non-absorbable polypropylene W-form mesh.*
PATIENTS AND METHODS: the pilot study included 37 patients which underwent surgery for rectocele repair using original technique of W-mesh. The late results were assessed in 21 (56.6%) of them ≥ 6 month after surgery. Before the surgery and 6 months after, patients underwent a clinical assessment of symptoms. Specialized questionnaires for assessment of constipation (Colonic evacuation disorder scale, PFDI-20, Cleveland Clinic Constipation Score) were used. Defecography and anorectal manometry were performed before and in 6-months after surgery for evaluation of pelvic floor disorders.
RESULTS: no obstructive defecation symptoms were revealed in 85.7% of patients 6 month after surgery. In ≥ 6 months after surgery all questionnaires showed decrease in scores by more than 2 times. Comparison of the results before and 6 months after the surgery showed significant differences for all questionnaires ($p < 0.0001$). According to defecography performed before and after the surgery a significant reduction ($p < 0.05$) of rectocele depth, time of rectal voiding (decreased by 1.5 times) and residual volume of contrast agent (decreased by 2.5 times) were revealed. There are no severe complications requiring re-operation were observed.
CONCLUSION: transvaginal mesh repair of symptomatic rectocele demonstrated good clinical results 6 months after surgery. Good results were revealed in 85,7% of patients confirmed by specialized questionnaires and defecography.

KEYWORDS: *rectocele, mesh implant, pelvic organ prolapse, plastic surgery of the rectovaginal septum, pelvic floor prolapse syndrome*

CONFLICT OF INTEREST: *The authors declare no conflict of interest.*

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ADDRESS FOR CORRESPONDENCE: *Lukianov A.S., Ryzhikh National Medical Research Centre for Coloproctology of the Ministry of Health of Russia, Salyama Adilya str., 2, Moscow, 123423, Russia; e-mail: lookmed@yandex.ru*

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INTRODUCTION

Rectocele is a protrusion of the rectal wall towards the vagina (anterior rectocele) or towards the anococceal ligament (posterior rectocele), the latter is much less common [1]. The rectocele incidence among women, according to various authors, ranges from 7.0% to 55.0%. However, clinical manifestations of the disease observed only in 25% of them [2–4]. Clinical manifestations of rectocele designated by a common name — obstructive defecation syndrome, which includes a number of symptoms: constipation, a feeling of incomplete emptying of the rectum, the need to use manual pressing on the back wall of the vagina or perineum to empty the rectum. Rectocele can also manifest itself as a feeling of a foreign body in the vagina and dyspareunia.

When rectocele with clinical manifestations is detected, conservative therapy is prescribed as the first stage, which includes measures aimed at improving bowel emptying, as well as strengthening the pelvic floor muscles [1,5]. In the absence of the effect of conservative therapy, the question of surgical treatment raised. There are various surgical methods for

rectocele, one of which is the installation of a mesh implant in the area of the rectovaginal septum. At the beginning of the XXI century, foreign variants of implantation systems, such as Prolift™ (Johnson & Johnson Company ©, USA) and Elevate™ (American Medical System, USA), became widespread. According to the results of many studies, these methods have demonstrated good clinical results of treatment, but their use in some cases is associated with the possibility of developing serious early and long-term postoperative complications. The causes of complications are most often associated with the surgical procedure itself, in which the 'wings' of the mesh implant are carried out and fixed to the structures of the pelvic floor using special conductors without direct visual control. These techniques use mesh implants made of non-absorbable material — polypropylene, which can also contribute to the development of complications. So, the study by Kasyan, G. et al. (2014) provides data on complications that occurred after the installation of the Prolift™ mesh implant within 3 months after the surgery. Because of this study, it was found that a total of 152 (22.5%) of 677 operated patients had complications [6]. Intraoperative and early postoperative complications were reported in 88 (13.0%) patients: in 15 (2.2%) cases intraoperative bleeding with a volume of more than 500 cm^3 developed; pelvic hematoma was observed in 37 (5.5%) patients; perineal hematomas — in 17 (2.5%) patients; injuries of the urinary system organs occurred in 14 (2.1%) patients; rectal lesion was noted in 5 (0.7%) cases. Complications associated with the installed mesh implant occurred in 64 (9.4%) cases. Among the frequent complications were erosion of the vaginal mucosa (32/677 [4.8%]), as well as dyspareunia with pain in the pelvic region in (16/677 [2.4%]) cases.

In the study by Vaiyapuri G.R. et al. (2011) are described long-term complications observed 1 year after the installation of the Prolift™ mesh. In this study, 209 patients were tracked 1 year after the surgery, of whom 24 (12.0%) patients had vaginal erosion, 12 (5.7%) patients had dyspareunia, and in 2 (1.0%) cases, patients noted the appearance of chronic pelvic pain [7]. In 2011, the U.S. Food and Drug Administration (FDA) published a warning about the dangers of using mesh due to possible complications; and therefore the use of these mesh implants has become limited in a number of countries [8].

In order to reduce the risk of complications during the installation of mesh, methods have begun to be developed, in which the implant to be installed, depending on the required size, is cut out intraoperatively; in addition, its installation takes place under the control of vision with fixation to sedentary structures of the pelvic floor. Also, in order to prevent complications, have been developed techniques that use biological collagen implants that have better biological compatibility with the patient's tissues than synthetic implants. At the FSBI RNMRC of Coloproctology in the period of between 2012 and 2015, a study was conducted on the use of synthetic (Ultrapro™ , Johnson & Johnson Company© , USA) and biological implants (Permacol™ , Sofradim© , France) to strengthen the rectovaginal septum during rectocele correction [9]. In both groups, plastic surgery of the rectovaginal septum by transvaginal access was used, consisting in the installation of a rhomboid implant cut out intraoperatively. After cutting out, the implant is placed on the anterior surface of the rectum with its subsequent fixation to the levator muscles, as well as with separate sutures to the place of attachment of the levator muscles to the descending branch of the pubic bone. When evaluating the treatment results 1 year after the surgery, according to defecography, it was found that in the group with the use of biological implants, the difference in the size of the protrusion of the anterior wall of the rectum before and after the surgery was insignificant ($p > 0.05$), in contrast to the group with synthetic implants ($p < 0.05$).

To date, the issue of developing a technique that allows to effectively eliminating rectocele with minimal risk of complications remains relevant. Thus, the method of treatment of rectocele — the rectovaginal septum plastywith a W-shaped mesh (patent No. 2675352 of 2018) was developed at the FSBI RNMRC of Coloproctology.

Since 2019, a prospective observational study has been launched to assess the effectiveness of this technique.

PATIENTS AND METHODS

For the period from 2018 to 2021, 37 patients were included in the study. In 6 months or more after the surgery, the results of the treatment were evaluated in 21 (56.8%) patients. In the remaining 16 (43.2%) patients, the time after the surgery did not reach 6 months.

The criteria for inclusion in the study are:

- Presence of rectocele of the 2nd-3rd degrees in patients (data from clinical examination and X-ray defecography).
- Clinical signs of obstructive bowel movement syndrome:
  - feeling of incomplete emptying of the rectum;
  - difficult defecation;
  - the need to use a manual assistance to empty the rectum.
- The presence of one or more radiological signs of rectal emptying disorder:
  - the direction vector of fecal masses is partially or completely directed towards the rectocele;
  - prolongation of the time of emptying the rectum;
  - increase in the residual volume of the rectal contents;
  - the absence of internal rectal invagination, in which the invaginate is displaced distal to the level of the rectocele and 'unlaces' it.

The average age of the patients was 54 ± 7.6 (32–65) years. The body mass index on average was25.86 ± 3.47 (21.4–35.5). Among the concomitant somatic pathology, hypertension prevailed, which observed in 8 (38.0%) patients. One (4.8%) patient had a history of hysterectomy. Assessing the nature of physical activities during life, 10 (47.6%) patients indicated the heavy nature of physical labor. 85.7% (18/21) of the patients had natural delivery. The history of the disease was 5 (0.7–19) years. According to the defecography, 19 patients had grade 3 rectocele (more than 4 cm), 2 patients had grade 2 rectocele (from 2 to 4 cm).

Before the surgery, the patients underwent a clinical check-up; instrumental diagnostics was performed, which included: high-resolution manometry, which allows to determine the type of functional defecation disorder, ultrasound with a rectal sensor, as well as defecography. In 6 and 12 months after the surgery, the following tests were performed: complex sphincterometry, which allows to identify indirect signs of defecation disorders during a straining test, ultrasound with a rectal sensor, defecography.

Before and after the surgery, questionnaires were used: the system of score evaluation of violations of colon evacuation function, developed at the FSBI RNMRC of Coloproctology of the Health Ministry of Russia; the register of pelvic floor disorders — Pelvic Floor Distress Inventory (PFDI-20); the Cleveland constipation Scale (Wexner Scale).

The system of score evaluation of violations of the colon evacuation function comprises 9 questions and allows to fully assessing the presence and nature of violations of the colon evacuation function.

This scale has a maximum of 22 points, which characterizes the worst function of emptying the rectum.

The PFDI-20 questionnaire comprises 20 questions and has a maximum of 300 points corresponding to the worst symptoms of pelvic organ prolapse.

The advantage of the questionnaire is that with the help of its application, it is possible to assess the symptoms of pelvic organ prolapse, since it includes questions on not only the violation of emptying of the rectum, but also questions on anal continence and violation of urination.

The Cleveland Constipation Scale includes 8 questions on the violation of emptying of the rectum and constipation. The scale has a maximum of 30 points, which characterizes unsatisfactory indicators. The advantage of this scale is that it includes questions that allow as per subjective complaints to conduct a clinically differential diagnosis between slow-transit and proctogenic constipation.

In addition, by interviewing the patients, a subjective assessment of the time of emptying of the rectum (in minutes) before and after the plastic surgery of the rectovaginal septum with a mesh implant was carried out. According to the time of rectal emptying, all the patients divided into 2 groups.

The first group included the patients with a rectal emptying time of up to 5 minutes; the second group included the patients with a rectal emptying time of more than 5 minutes.

Surgery Technique

Bowel cleansing for the surgery includes taking a laxative based on polyethylene glycol in a volume of 3–4 liters on the eve of the surgery.

The surgery was performed by transvaginal access. After a longitudinal incision of the vaginal mucosa (Fig. 1), the rectovaginal septum is split (Fig. 2), the rectum is mobilized from the right and left in an acute and blunt way to the level of the sacro-spinous ligaments.

In Figure 3, the intestine is shifted to the right and the area of the sacro-spinous ligaments is visualized, which are contoured in the form of whitish-colored strands, tightly elastic on palpation. With a vikril 2–0 thread, separate stitches are applied to the ligaments on each side, the ends of the threads, to which the wings of the mesh are subsequently fixed, are taken on holders.

After that, 3–4 corrugating sutures are applied to the anterior wall of the rectum with a 3–0 Vicryl thread. The measurement of the length of the rectum area on which the implant will be placed and the distance between the sutures applied to the sacro-spinous ligaments is performed. A W-shaped mesh implant is cut out and modeled according to the previously defined dimensions (Fig. 4). The study uses a lightweight partially absorbable Ultrapro™ mesh (Johnson & Johnson Company©, USA).

Then, through the 'wings' of the mesh, the sutures previously imposed on the sacro-spinous ligaments are carried out and the mesh is freely, without tension, straightened and lowered onto the rectal anterior wall. The proximal end of the mesh fits freely on the rectal surface; it is not fixed with special stitches (Fig. 5).

The distal edge of the mesh is fixed in the area of the lower corner of the wound to the muscular structures of the "perineal body", and then the vaginal mucosa is sutured with separate nodular sutures (Fig. 6).

The technique has several key features that distinguish it from the technique of installing the Prolift™ and Elevate™ mesh systems: firstly, the possibility of intraoperative cutting and modeling of a mesh implant of the required size, depending on the length of the rectocele; secondly, an important feature is the fixation of the "wings" of the implant to the non-displaced, strong structures of the pelvic floor under direct visual control,

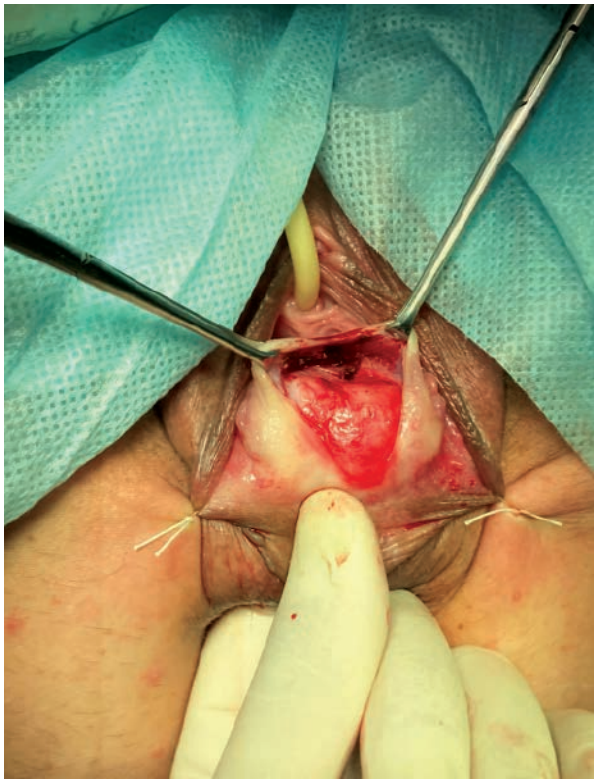

Figure 1. *Vaginal mucosa section. Patient T., 42 years old, diagnosis: 3rd grade rectocele*

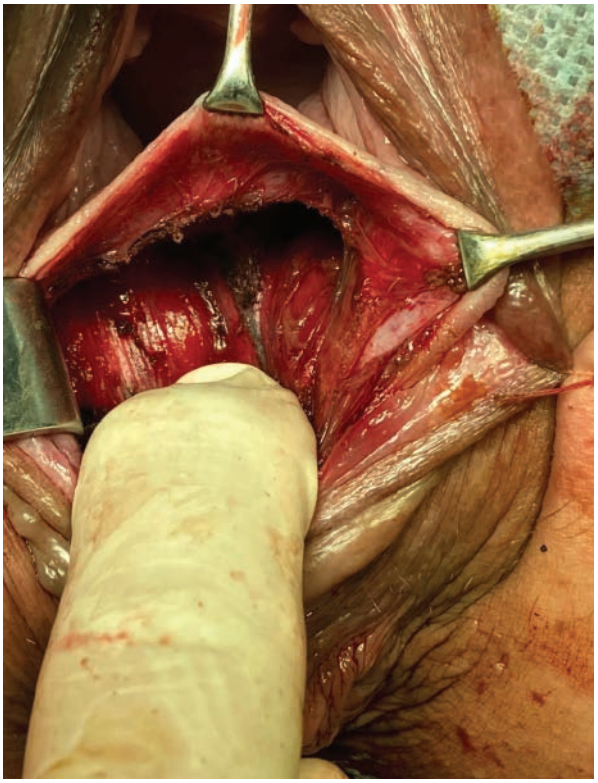

Figure 2. *Rectal anterior wall mobilization. Patient T., 42 years old, diagnosis: 3rd grade rectocele*

without the use of special conductors. This prevents the development of such serious intraoperative complications as perforation, bleeding. Also, the direct intraoperative cutting out of the mesh implant in size allows to avoid tension between the 'wings' of the mesh, which makes it possible to freely fix the implant, which allows to prevent the development of long-term complications in the form of dyspareunia, pain syndrome. Thirdly, the implant is fixed to the strong structures of the pelvic floor — sacro-spinous ligaments, which is the prevention of implant displacement in the long-term postoperative period. An important advantage is the use of a lightweight partially absorbable Ultrapro™ mesh, which can also be a prevention of complications in the near and long-term postoperative period.

In the postoperative period, daily sanitation of the suture line in the vagina is carried out with antiseptic solutions, the patients observe bed rest for 2–3 days. In order to prevent infectious complications, antimicrobial therapy is prescribed to the patients for 5 days — metronidazole at a dosage of 500 mg 3 times a day. The urinary catheter removed on the 3d day; in order to regulate the stool, volume-forming laxatives based on psyllium are prescribed. After the surgery, the patients are limited to sitting down for 2 weeks. The postoperative hospital stay was 8 (5–14) days. Subsequently, during a follow up after 2–3 weeks, the sutures in the vagina removed.

RESULTS

When assessing the severity of the obstructive bowel movement syndrome symptoms before and after the surgery, it was revealed that 16/21 (76.2%) patients used manual vaginal assistance before the surgery, and after the surgery only 1 (4.8%) patient presented the need for periodic manual assistance. Before the surgery, all (21) patients had difficulty emptying the rectum. After the surgery, only 3 (14.3%) patients had periodic difficulty with the defecation act.

Before and after the surgery, the patients estimated approximately and subjectively the time required for emptying the rectum. The data on the comparative evaluation of this parameter are given in Table 1.

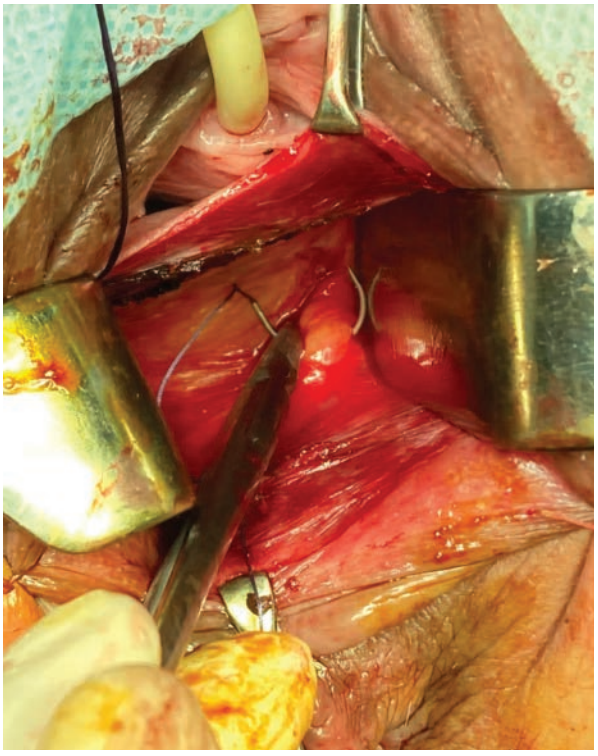

Figure 3. *Rectum right displacement. The sacrospinous ligaments saturation is performed. Patient T., 42 years old, diagnosis: 3rd grade rectocele*

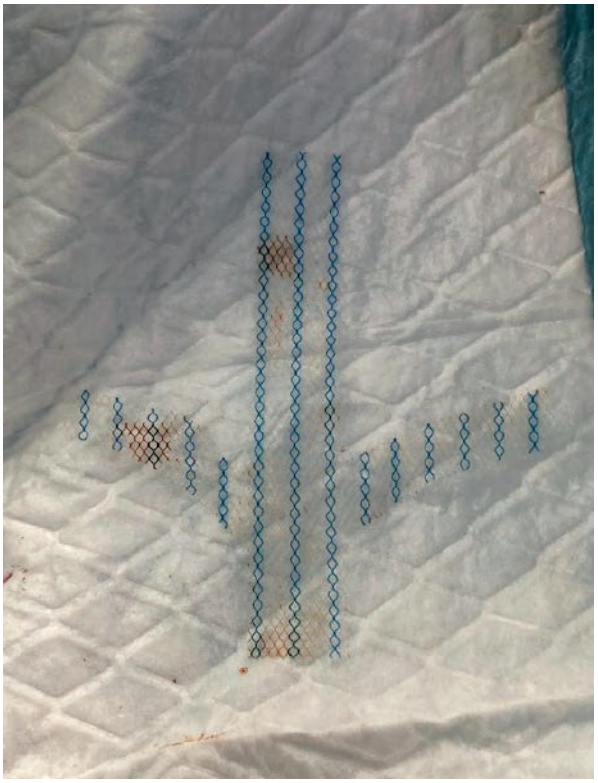

Figure 4. *Mesh implant's shape and size example. Patient T., 42 years old, diagnosis: 3rd grade rectocele*

When evaluating the data, it can be seen that in 14 (66.7%) patient before the surgery, the duration of rectal emptying exceeded 5 minutes, but after the surgery only in 2 (9.5%) patients the time required for emptying the rectum was more than 5 minutes; the differences are statistically significant ($p < 0.05$). Before the surgery the periodic need for enemas or microclysms was noted by 8 (38.1%) patients; after the surgery 2 (9.5%) patients periodically continued to use microclysms.

In the postoperative period, early and late complications were evaluated. It should be noted that there were no serious complications that required surgery.

Among the early complications, 4 (19.0%) hematomas were detected in the area of the postoperative wound. In all cases, the hematoma was emptied by revision of the wound between the sutures in the vagina, followed by sanitation of the area of its location. In one case, due to the abundant discharge of hemorrhagic discharge, it was necessary to install silicone drainage between the seams.

Among the late postoperative complications, it is possible to note the extrusion of the distal edge of the mesh in 1 (4.8%) case, which was detected during a control examination in 6 months after the surgery. This section of the mesh with a length of up to 1 cm was excised during the examination; subsequently the wound was epithelized. In 1 (4.8%) patient 1 month after the surgery, pain of a pulling nature appeared in the groin area, which persisted during evaluation in 6, 12 and 24 months after the surgery; however, this complication did not require any special therapeutic measures.

Before and after the surgery, special questionnaires were used, which allow a comprehensive, dynamic assessment of the symptoms of rectocele and other manifestations of pelvic floor prolapse syndrome.

According to the results of the survey, it was found that on all three scales, in 6 months or more after the surgery, there was a decrease in scores by more than 2 times, while a comparison of the score level before and 6 months or more after the surgery showed pronounced statistically significant differences ($p < 0.0001$).

Before and after the surgery, defecography was performed, in which the following main indicators were evaluated: the direction vector of the fecal masses, the depth of the rectocele, the time of evacuation of the rectal contents, the residual volume.

When assessing the direction vector of fecal masses according to the defecography data

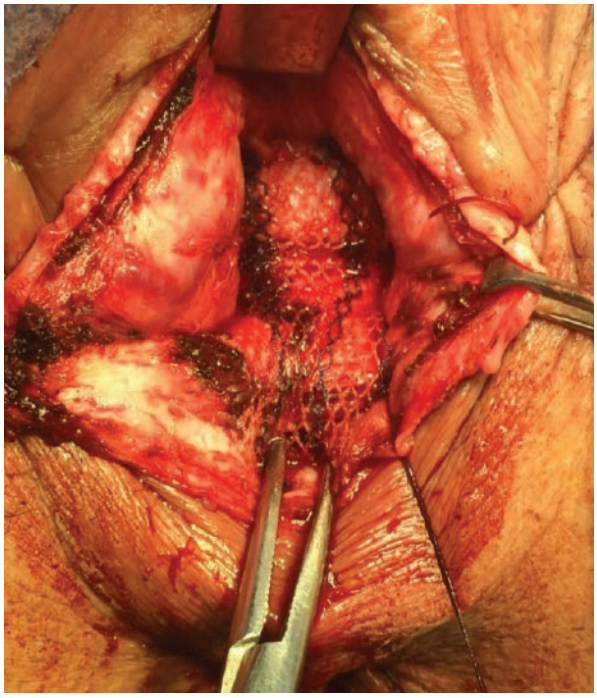

Figure 5. *The mesh implant is located in the rectum anterior wall. Patient T., 42 years old, diagnosis: 3rd grade rectocele*

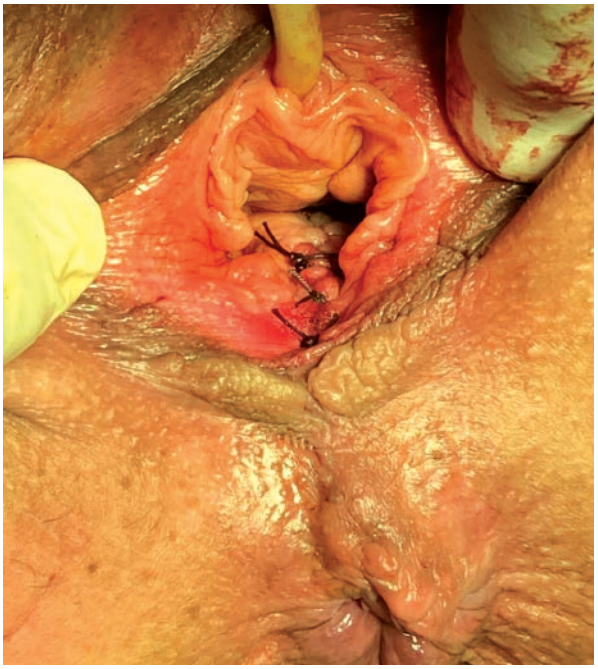

Figure 6. *Vaginal wound is sutured with separate sutures in the longitudinal direction. Patient T., 42 years old, diagnosis: 3rd grade rectocele*

Table 1. *Comparative evaluation of rectal emptying time before surgery and ≥ 6 months after surgery (N = 21)*

	Before surgery N (%)	6 months or more after surgery N (%)	p*
Time required for emptying the rectum (min.)	≤ 5 minutes: 7 (33.3%) > 5 minutes: 14 (66.7%)	≤ 5 minutes: 19 (90.5%) > 5 minutes:2 (9.5%)	< 0.05

*Note: * Fisher criterion*

Table 2. *Results obtained from patient questionnaires using rectal emptying dysfunction and constipation scores before surgery and ≥ 6 months after surgery (N = 21)*

Scale	Before surgery	6 months or more after surgery	p*
The system of point evaluation of violations of the evacuation function of the colon (NMRC of coloproctology named after A.N. Ryzhykh)	10 (6–16)	5 (1–8)	< 0.0001
PFDI-20**, Me (min-max)	101.1 (64.6–179.2)	48.9 (7.3–150)	< 0.0001
1) POPDI-6***	37.5 (8.3–66.7)	12.5 (0–54.2)	< 0.0001
2) CRAD-8****	34.4 (15.6–62.5)	15.6 (3.1–37.5)	< 0.0001
3) UDI-6*****	25 (8.3–79.2)	20.8 (0–83.3)	< 0.0001
Cleveland Constipation Scale (Wexner)	12 (5–19)	5 (1–9)	< 0.0001

*Note: * Wilcoxon criterion; ** Registry of pelvic floor disorders; *** Registry of disorders caused by pelvic organ prolapse; **** Registry of disorders of the lower gastrointestinal tract; *****Registry of urination disorders*

before the surgery, the vector was directed towards the rectocele in 11 (52.4%) patients, towards the anal canal as well as towards the anal canal and rectocele in 10 (47.6%) patients. After the surgery the fecal mass direction vector only towards the rectocele was not observed in any patient, while in all 21 (100%) patients the vector was directed into the anal canal or into the anal canal and rectocele; these differences are statistically significant ($p < 0.05$). When assessing such indicators of defecography before and after the surgery as rectocele depth, rectal contents evacuation time, and residual volume, a significant decrease in rectocele depth, rectal contents evacuation time (decreased by 1.5 times) and residual volume (decreased by 2.5 times) was revealed. It should be noted that all the results are statistically significant ($p < 0.02$ and $p < 0.0001$, respectively).

Prior to the surgery, all the patients underwent high-resolution manometry. As a result of this examination, 2 (9.5%) patients had functional defecation disorders in the form of dissenergy of the pelvic floor muscle function of the I type (puborectal loop spasm), and therefore they were prescribed physiotherapy in the form of BOS therapy. After a course of BOS therapy (9 sessions) during repeated examination, a manometric pattern of type III was revealed, indicating the dissynergic nature of defecation. Due to the persistence of the obstructive defecation symptoms, the patients underwent the surgery in the volume of plastic surgery of the rectovaginal septum with a W-shaped implant according to the above method. In 6 months or more after the surgery, all the patients underwent complex sphincterometry, according to the results of which during a straining test, no indirect signs of functional defecation disorders were detected in any observation, indicating an increase in pressure in the anal canal or the absence of its decrease by more than 20% of the value of the basal resting pressure.

Table 3. *Results of X-ray defecography in patients before surgery and ⩾ 6 months after surgery (N = 21)*

Defecography data	Before surgery	6 months or more after surgery	*p*
The vector of orientation of fecal masses	In rectocele: 11 (52.4%)	In rectocele: 0 (0%)	< 0.05*
	In the rectocele and anal canal: 3 (14.3%) + In the anal canal: 7 (33.3%)	In the rectocele and anal canal: 4 (19%) + In the anal canal: 17 (81%)	
Rectocele depth (cm)	5.2 (3.8–8.8)	0 (0–4)	< 0.02**
Evacuation time, seconds. (the norm is up to 19 seconds.)	30 (10–45)	20 (10–45)	< 0.0001**
Residual volume, % (the norm is up to 20%)	25 (20–50)	10 (10–30)	< 0.0001**

*Note: * Fisher criterion; ** Wilcoxon criterion*

DISCUSSION

Despite the fact that today a large number of surgeries have been proposed to correct the rectocele, the issue of choosing a surgery technique remains relevant. The most common method of rectocele correction is plastic surgery with local tissues (anterior levatoroplasty).

However, the high incidence of symptoms recurrence in the long term limits the use of this technique. Stapler transanal rectal resection allows to eliminate the excess of the rectal mucous membrane with simultaneous strengthening of the rectovaginal septum. However, this surgery is effective in case of unstrained and unexpressed rectal protrusion, as well as in combination of rectocele with small internal rectal invagination and internal hemorrhoids. Currently, rectocolposacropexy is an actively used method. So, according to Abdelnaby, M. et al. (2020), who performed a comparative analysis of the results of treatment of anterior rectocele using 2 methods — laparoscopic rectosacropexy and posterior colporaphy, it was found that the both methods showed satisfactory results (anatomical correction of the rectocele, improvement of the rectal evacuation function, improvement of the quality of life according to questionnaires). However, the rectosacropesia technique had statistically significant advantages in assessing the anatomical effect of the surgery, defecography data, as well as the results of a questionnaire using the Cleveland Scale Constipation (Wexner) ($p < 0.0001$) [10]. Nevertheless, the invasiveness of this technique limits its wide application for the isolated rectocele correction. Systems for the installation of mesh implants such as Prolift™ and Elevate™ have high efficiency in the long-term postoperative period.

However, currently their use in a number of countries is limited due to the high frequency of early and long-term postoperative complications associated with the implant installation technique and the material from which the mesh is made. The methodology developed at the FSBI RNMRC of Coloproctology of the Health Ministry of Russia takes into account the shortcomings of the technique of installing foreign versions of mesh implants (Prolift™ and Elevate™) and allowed to avoid serious complications during the surgery and in the postoperative period. For the evaluation period of the treatment results, which was 6 months or more after the surgery, this technique showed good effectiveness evaluated using specialized questionnaires, and demonstrated the absence of serious complications in the postoperative period. The technique can take its place among surgeries for the anterior rectocele correction.

CONCLUSION

The results of using the method of rectovaginal septum plasty with a W-shaped mesh implant in

patients with rectocele of the 2nd-3rddegrees demonstrated good clinical efficacy when evaluated in 6 months or more after the surgery, confirmed by the results of the survey using specialized questionnaires, as well as the results of defecography. The use of the technique is not accompanied by the development of serious complications that require surgery, both in the early and in the long-term postoperative period. Nevertheless, for a more detailed assessment of the effectiveness of this technique, it is necessary to evaluate the treatment results in the long-term follow-up period (12 months or more after the surgery) on more clinical material.

AUTHORS CONTRIBUTION

Concept and design of the study: *Ivan V. Kostarev, Anton S. Lukianov, Alexander Yu. Titov*
Collection and processing of the material: *Anton S. Lukianov, Ivan V. Kostarev, Oleg M. Biryukov, Elena P. Goncharova*
Statistical processing: *Anton S. Lukianov, Ivan V. Kostarev*
Writing of the text: *Anton S. Lukianov, Ivan V. Kostarev*
Editing: *Andrey A. Mudrov, Timur V. Nikishin*

INFORMATION ABOUT THE AUTHORS (ORCID)

Anton S. Lukianov — Postgraduate Student, Physician (coloproctology), Department of Minimally Invasive Proctology and Pelvic Surgery, Ryzhikh National Medical Research Centre for Coloproctology. ORCID: https://orcid.org/0000-0003-0627-382X
Oleg M. Biryukov — Cand. Sci. (Med.), Head of the Department of General and Reconstructive Coloproctology, Ryzhikh National Medical Research Centre for Coloproctology. ORCID: https://orcid.org/0000-0002-1081-1793
Elena P. Goncharova — radiologist of the Department of X-ray diagnostics, computer and magnetic resonancetomography, Ryzhikh National Medical Research Centre for Coloproctology. ORCID: https://orcid.org/0000-0001-6785-5191
Alexander Yu. Titov — Dr. Sci. (Med.), Head of the Department of General and Reconstructive Coloproctology, Ryzhikh National Medical Research Centre for Coloproctology. ORCID: https://orcid.org/0000-0002-1636-8075
Andrey A. Mudrov — Cand. Sci. (Med.), Researcher, Department of General and Reconstructive Coloproctology, Ryzhikh National Medical Research Centre for Coloproctology. Associate Professor at the Department of Coloproctology, Russian Medical Academy of Continuous Professional Education of the Ministry of Healthcare of Russia. ORCID: https://orcid.org/0000-0002-1207-5988
Timur V. Nikishin — resident National Medical Research Centre for Coloproctology. ORCID: https://orcid.org/0000-0001-6991-1716
Ivan V. Kostarev — Dr. Sci. (Med.), Head of the Department of Minimally Invasive Proctology and Pelvic Surgery, Ryzhikh National Medical Research Centre for Coloproctology. Associate Professor at the Department of Coloproctology, Russian Medical Academy of Continuous Professional Education of the Ministry of Healthcare of Russia. ORCID: https://orcid.org/0000-0002-1778-0571

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Neoadjuvant chemotherapy without radiation therapy for rectal cancer with negative prognosis

Alexey A. Nevolskikh[1,2], Violetta A. Avdeenko[2], Anna S. Belohvostova[1], Ruslan F. Zibirov[1,2], Yulia Yu. Mihaleva[1], Taras P. Pochuev[1], Tatiana P. Berezovskaya[1], Yana A. Daineko[1], Leonid O. Petrov[1], Sergey A. Ivanov[1,2,4], Andrey D. Kaprin[3,4]

[1]A. Tsyb Medical Radiological Research Centre — Branch of the National Medical Research Radiological Center of the Ministry of Health of the Russian Federation (Korolev st., 4, Obninsk, 249031, Russia)
[2]Obninsk Institute for Nuclear Power Engineering (Studgorodok st., 1, Obninsk, 249039, Russia)
[3]National Medical Research Radiological Centre of the Ministry of Health of the Russian Federation (Marshal Zhukov str., 10, Obninsk, 249031, Russia)
[4]Peoples' Friendship University of Russia, RUDN University (Miklukho-Maklaya str., 6, Moscow, 117198, Russia)

ABSTRACT *AIM: to assess the effectiveness of neo-CT in the FOLFOX6 regimen in patients with mid- and upper rectal cancer (RC) associated with poor prognosis.*
PATIENTS AND METHODS: fifty-two patients were included into study. All had neo-CT with subsequent surgical treatment between 2017 and 2021. Of them 94.2% had stage III and 5.8% had stage II. An extramural vascular invasion was detected by MRI in 33 (63.5%) patients. The distance between the tumor and the mesorectal fascia was ⩽ 2 mm in 17%. All patients had 4 cycles of neo-CT in FOLFOX6 regimen followed by surgery.
RESULTS: the compliance (⩾ 4 cycles of neo-CT) was 82.7% (n = 43). The overall toxicity rate was 35.6%. Sphincter-saving surgery was performed in 51 (98.1%) patients. Postoperative morbidity was 25.0%. Final pathology revealed stage III in 29 (55.8%) patients, stage 0 — stage II — in 22 (42.3%). In accordance with the degree of pathomorphosis (CAP, 2019), 12 (23.1%) patients showed a partial response. In one patient (1.9%) no signs of residual tumor were detected. Down staging of the T stage compared with MRI data before neo-CT was noted in 23 (44.2%) patients, N stage — in 29 (55.8%). With a mean follow-up of 31 (3-54) months, local recurrences were detected in 5 (9.6%) patients, and distant metastases in 4 (7.7%). The cumulative 3-year recurrence rate was 11.3 ± 4.8%. The three-year overall and recurrence-free survival rate was 88.2 ± 5.8% and 76.4 ± 7.4%, respectively.
CONCLUSION: the multimodal approach for RC with adverse prognostic factors using neo-CT in the FOLFOX6 regimen is well tolerated by patients, has a small toxicity and postoperative morbidity as well. It is necessary to develop new pathology criteria for tumor response to neo-CT.

KEYWORDS: *rectal cancer, neoadjuvant chemotherapy, chemoradiotherapy, pathomorphosis*

CONFLICT OF INTEREST: *the authors declare no conflict of interest*

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ADDRESS FOR CORRESPONDENCE: *Violetta A. Avdeenko, A. Tsyb Medical Radiological Research Centre — Branch of the National Medical Research Radiological Center of the Ministry of Health of the Russian Federation, Korolev st., 4, Obninsk, 249039, Russia; e-mail: avdeenko.vita@yandex.ru*

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INTRODUCTION

Rectal cancer (RC) is one of the most common tumors in the structure of oncological morbidity. Malignant rectal neoplasms affect 5.6% of the male population and 4.4% of the female population in Russia. At the same time, the proportion of RC detected in stage I–II is 51.4%, and another quarter (24.9%) accounts for tumor neoplasms detected in stage III [1].

Neoadjuvant radiation therapy (RT) or chemoradiotherapy (CRT) with further surgery is the standard approach for patients with locally advanced RC [2–4], as it allows to reduce the size of the tumor, which in turn decrease local recurrence rate and increase survival. However, RT and CRT are

accompanied by a significant number of radiation reactions and lesions, most often manifested by an increase in the incidence of genitourinary dysfunction, functional disorders after sphincter-preserving procedures, as well as an increased-postoperative morbidityrate [5,6]. It should also be noted that prolonged RT is associated with systemic chemotherapy up to 15–16 weeks [7], which can potentially negatively affect patients with a high risk of distant metastasis.

In connection with the above, approaches based on the inclusion of systemic therapy in the neoadjuvant treatment in the form of induction [8,9], consolidating [6,10], total neoadjuvant therapy [11,12], as well as only chemotherapy without radiation therapy as such, have become increasingly widespread in recent years. Carrying out neoadjuvant chemotherapy (NCT) instead of RT in RC makes it possible to avoid radiation reactions and lesion, as well as to start systemic treatment earlier, aimed not only at the primary tumor, but also at its possible micrometastases. At the same time, NCT is distinguished by better completion rates compared to adjuvant mode, and in a number of patients with postoperative morbidity and/or decompensation of concomitant diseases, adjuvant chemotherapy is in principle impossible [13–15].

The rate of complete answers, a surrogate indicator of the effectiveness of treatment, when performing NCT with oxaliplatin in combination with 5-fluoropyrimidines, varies widely from 0% to 17.8% [16–25]. In the vast majority of cases, these are data from non-randomized single-center studies. To date, there are results of only one phase III study of FOWARC, in which the results of NCT in FOLFOX6 mode were compared with standard CRT [26]. In patients in the FOLFOX6 group, the incidence of complete pathomorphological regressions was 6.5%, and in the CRT group — 14%. When comparing the recurrence-free and overall survival, as well as the incidence of local recurrences, no significant differences were found.

It should be noted that there are few completed studies in Russia on the use of NCT in the treatment of patients with RC [27,28]. Basically, speaking about this method, we are based on the data of foreign researchers. In this regard, the use of this method in the Russian population of patients is of interest from the point of view of effectiveness and tolerability. For this purpose, in the period from January 2017 to September 2021, the study of NCT effectiveness in FOLFOX6 mode in patients with cancer of the middle and upper RC with unfavorable prognosis.

PATIENTS AND METHODS

The study included 52 patients with rectal adenocarcinomas, who underwent neoadjuvant chemotherapy (NCT) followed by surgery between 2017 and September 2021 (Table 1).

To assess the prevalence of the tumor, we used magnetic resonance imaging (MRI), according to which we assessed the size of the neoplasm, the distance from the anal verge to the lower pole of the tumor, the depth of invasion, the presence of extramural vascular invasion (EVI), as well as the distance from the tumor to the potential lateral resection margins (LRM), represented by rectal fascia propria. The study included patients who, according to the results of the check-up, revealed one or more negative prognostic factors: the presence of EVI, affected regional lymph nodes (cN1-2) or involvement of LRM (distance to the mesorectal fascia ⩽ 2 mm) with the upper rectum.

The majority of patients had clinical stage III (IIIB — 59.6%, IIIC — 34.6%); 3 (5.8%) patients had clinical stage IIA. Clinical invasion of the tumor into adipose tissue without signs of lesion to adjacent organs was observed in 67.3% of patients (n = 35); invasion of the visceral peritoneum, spread to other organs and structures were detected in 32.7% (n = 17) of patients. The regional lymph nodes involvement was found in 94.2% of patients (n = 49) and was absent in 3 (5.8%) patients.

According to MRI, 33 (63.5%) patients were found to have EVI. The distance from the tumor to the mesorectal fascia ⩽ 2 mm was detected in 17 (32.7%) patients.

All the patients were scheduled to undergo neoadjuvant chemotherapy in FOLFOX6 mode (a two-hour infusion of oxaliplatin 85 mg/m^2 on the first day, then leucovorin 400 mg/m^2 for two hours, followed by a bolus injection of 400 mg/m^2 of 5-fluorouracil, and a 46-hour infusion of 2400 mg/m^2 of 5-fluorouracil) in an amount of 4 cycles. The

Table 1. *Clinical characteristics of patients (n = 52)*

Parameters	Data	%
Gender		
Males	21	40.4
Females	31	59.6
Median age, years	58 (42–71)	
Median body mass index, kg/m^2	29.2 (18–50)	
Distance from the anal verge to the lower pole of the tumor, cm	10.5 (4–15)	
< 6	1	1.9
6–10	26	50.0
11–15	22	42.3
> 15	3	5.8
Median tumor extent, cm	6 (1.3–13)	
MRI EVI		
Yes	33	63.5
No	19	36.5
MRI lateral resection margins		
Positive	17	32.7
Negative	35	67.3
Clinical stage (cTNM)		
II	3	5.8
IIIB	31	59.6
IIIC	18	34.6
Tumor invasion depth (cT)		
T3	35	67.3
T4a	10	19.2
T4b	7	13.5
Lymph nodes involvement (cN)		
N0	3	5.8
N1	22	42.3
N2	27	51.9
Tumor differentiation grade		
G1	21	40.4
G2	27	51.9
G3	4	7.7

Table 2. *Toxicities according to CTC AE scoring system (n = 45)*

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Total
Hematological					
Anemia	–	2 (4.4%)	–	–	2 (4.4%)
Neutropenia	–	3 (6.6%)	2 (4.4%)	1 (2.2%)	6 (13.3%)
Leukopenia	–	2 (4.4%)	–	–	2 (4.4%)
Thrombocytopenia	–	1 (2.2%)	–	–	1 (2.2%)
Non-hematological					
Hepatotoxicity	–	1 (2.2%)	–	–	1 (2.2%)
Nephrotoxicity	–	2 (4.4%)	–	–	2 (4.4%)
Weightloss	2 (4.4%)	–	–	–	2 (4.4%)
Intestinal obstruction	–	1 (2.2%)	–	1 (2.2%)	2 (4.4%)
Diarrhea	1 (2.2%)	–	–	–	1 (2.2%)
Nausea	1 (2.2%)	–	–	–	1 (2.2%)
Impaired glucose tolerance	–	1 (2.2%)	–	–	1 (2.2%)
Polyneuropathy	–	1 (2.2%)	–	–	1 (2.2%)
Pneumothorax	–	–	1 (2.2%)	–	1 (2.2%)
Total morbidity	**4 (8.9%)**	**14 (31.1%)**	**3 (6.6%)**	**2 (4.4%)**	**–**
Total patients with morbidity	**4 (8.9%)**	**11 (24.4%)**	**3 (6.6%)**	**2 (4.4%)**	**–**

toxicity assessment was carried out according to the criteria of the generally accepted CTC AE scale (version 5.0) [29].

In 3–4 weeks after the completion of chemotherapy, all the patients underwent a control MRI of the grade of tumor regression. The surgery was performed in 4–6 weeks after completion of the neoadjuvant treatment.

Biomedical packages Prism 3.1 and In Stat (Graph Pad Software, Inc., San Diego, USA) were used for statistical processing. The evidence level of the differences between the indicators was assessed using the Pearson χ^2-test. The differences were considered significant at $p < 0.05$. The survival rate of the patients was analyzed using the Kaplan-Meier test. A logarithmic rank test was used to compare the survival curves. The 3-year survival rate was assessed. When calculating the overall survival rate, the death of a patient was considered an 'event'. When calculating recurrence-free survival rate, the 'event' was considered a local recurrence, distant metastasis or death of the patient from any of the causes.

RESULTS

All the patients underwent NCT in 1–8 cycles (median — 4). In 6 cases, more than 4 cycles were used, which was associated with a good reaction to chemotherapy.

In two cases, there were deviations from the chemotherapy mode. The patients received neoadjuvant treatment in XELOX mode, one of the components of which is also oxaliplatin. In one patient, due to the inability to continue chemotherapy through central venous access, after the second course, FOLFOX6 mode was changed to XELOX.

Chemotherapy in full (≥ 4 cycles) was completed in 43 (82.7%) patients. In 9 (17.3%) patients, due to toxic reactions, a smaller number (1–3) of cycles of NCT were performed.

In total, toxic reactions or morbidity in the process of NCT were registered in 16 (35.6%) of 45 patients (Table 2).

In 7 cases, a reliable assessment of toxicity was not possible. Most often, in 31.1% of cases

Table 3. *Surgery results (n = 52)*

Parameter	Data	%
Operation time (median), minutes	225 (90–450)	
Median blood loss, ml	100 (10–2000)	
Median postoperative hospital stay, days	7 (4–42)	
Surgical access		
Laparoscopic	41	78.8%
Open	11	21.2%
Surgery type		
Anterior resection	48	92.3%
Hartmann's procedure	3	5.8%
APE	1	1.9%
Surgery volume		
Standard	36	69.2%
Multivisceral	16	30.8%
IMA ligature level		
High IMA ligation	27	51.9%
more distal than LCA	22	42.3%
no data	3	5.8%
Mobilization of the splenic bend		
performed	28	53.8%
did not perform	24	46.2%
Morbidityas per Clavien-Dindo classification		
Absent	39	75.0%
I grade	6	11.5%
II grade	4	7.7%
III grade	1	1.9%
IV grade	2	3.8%

Note: ARR — anterior rectal resection; APE — abdominal-perineal excision; IMA — inferior mesenteric artery; LCA — left colon artery; n.d. — no data

(*n* = 14), toxic reactions of the 2nd grade were detected. Grade 3–4 toxicity was observed in 5 (11.1%) patients and was most often represented by neutropenia. Morbidity unrelated to chemotherapy, but affecting the further continuation of the treatment, included intestinal obstruction in a patient with a tumor of the middle rectum, who underwent emergency surgery in the volume of transversostomy, as well as pneumothorax when placing a subclavian catheter before the 3rd cycle of NCT in another case.

According to the results of the control MRI after NCT, a decrease in the stage of the tumor process compared with the clinical one was noted in 15 (28.8%) patients. In these patients, there was a reduction in the extent of the tumor, a decrease in the depth of invasion, the appearance of fibrosis sites and reduction of diffusion restriction sites,

Table 4. *The relationship between clinical and pathological staging of the study patients (n = 52)*

Clinical category	Pathomorphological category								
	ypT0	**ypT1**	**ypT2**	**ypT3**	**ypT4a**	**ypT4b**	**ypN0**	**ypN1**	**ypN2**
cT3 (*n* = 35)	1	1	9	**21**	2	1			
cT4a (*n* = 10)				8	**1**	1			
cT4b (*n* = 7)				4	1	**2**			
cN0 (*n* = 3)							**2**		1
cN1 (*n* = 22)							9	**11**	2
cN2 (*n* = 27)							11	9	**7**
Total	1	1	9	33	4	4	22	20	10

as well as a decrease in the number of potentially affected lymph nodes. Progression of the disease was observed in 7 (13.5%) cases. In the remaining patients (*n* = 29; 55.8%), no changes were noted when comparing MRI before and after the treatment. With regard to the remaining factors of negative prognosis, it should be noted that EVI was established in 30 (57.7%) patients, and mesorectal fascia involvement (CRB ⩽ 2 mm) was noted in 15 (28.8%) patients.

All patients included in the study underwent surgery in 3–20 (median 5) weeks after the completion of NCT (Table 3).

In the overwhelming majority of cases (78.8%), laparoscopic approach was used. The operation time ranged from 90 to 450 minutes (median — 225). The mean blood loss was 100 ml (10–2,000). The mean postoperative hospital stay was 7 (4–42) days.

The surgery volume depended on the depth of the tumor invasion, the presence of affected lymph nodes, the growth of the tumor into the visceral peritoneum and surrounding organs, as well as the distance from the anal verge to the lower pole of the tumor. In 51 (98.1%) cases, procedures were sphincter-preserving: in 48 (92.3%) cases, anterior resections were performed, and in 3 (5.8%) patients — Hartmann's procedure due to intestinal obstruction.

Multivisceral procedures were performed in 16 (30.8%) patients, while resections of two or more organs were performed in 10 (19.2%) cases. Most often, hysterectomy was performed in 9 (17.3%) cases, resection of the small intestine in 5 (9.6%) cases, resection of the bladder in 4 (7.7%) cases; and in isolated cases, appendectomy, tubovariectomy, colorectal resection, seminal vesicles, ureter, cervix stump were removed. Also, two patients suspected of having distant metastases, according to the control check-up and intraoperative picture, underwent simultaneous procedures, including resection of the tenth segment of the right lung in one patient, the sixth and eighth segments of the liver in the second. In 83.3% of patients (40 out of 48), a preventive colostomy (90%) or ileostomy (10%) was done.

Postoperative morbidity developed in 13 (25.0%) patients: in most cases, grade I and II according to Clavien-Dindo classification. In 3 (5.8%) patients, morbidity required re-operations. No mortality occurred.

Pathomorphology of the removed specimens showed stage III was most often — in 29 (55.8%) patients, stage 0 — II were detected in 22 (42.3%) patients. In one case, in a patient with simultaneous resection of liver segments, according to histology confirmed the presence of distant metastases of stage IV.

The pathomorphosis was evaluated in accordance with the recommendations of the American Society of Pathomorphologists [CAP 2019]. In 3 (5.8%) cases, it was not possible. In 36 (69.2%) patients, grade 3 pathomorphosis was detected, which corresponded to the absence of a tumor reaction to the treatment. In 12 (23.1%) cases, a minimal tumor reaction (grade 2 pathomorphosis) was registered. In none of the cases was detected grade1 of pathomorphosis, the criteria of which is the predominance of fibrous changes over tumor. Only one (1.9%) patient with clinical stage III

after 4 cycles of NCT did not have a residual tumor during a pathomorphology, which allowed us to confirm a 0-gradepathomorphosis.

A decrease in the category of the extent of the tumor by pathomorphology compared with the data of MRI before NCT was noted in 38 (73.1%) patients. A decrease in category T was observed in 23 (44.2%) patients (Table 4), category N — in 29 (55.8%) patients. At the same time, complete regression of lymph nodes was found in 38.5% (20 patients), partial (from N2 to N1) — in 17.3% (9 patients).

Regression of the tumor extent to ypT0-T2 (stage 0-I) was found in 7 (13.5%) patients.

An increase in the category of the tumor extent compared with the data of MRI before NCT was noted in 6 (11.5%) patients: in 3 (5.8%) patients, an increase in category T was noted, in 3 (5.8%) — category N, a joint increase in categories T and N was not found. In 8 (15.4%) cases, stabilization of the tumor process was noted.

At the same time, in 2 (3.8%) cases, multidirectional changes were observed: during pathomorphology, an increase in the depth of tumor invasion with regression of lymph nodes was noted, which was not verified according to the MRI due to the limit of the diagnostic capability of the method.

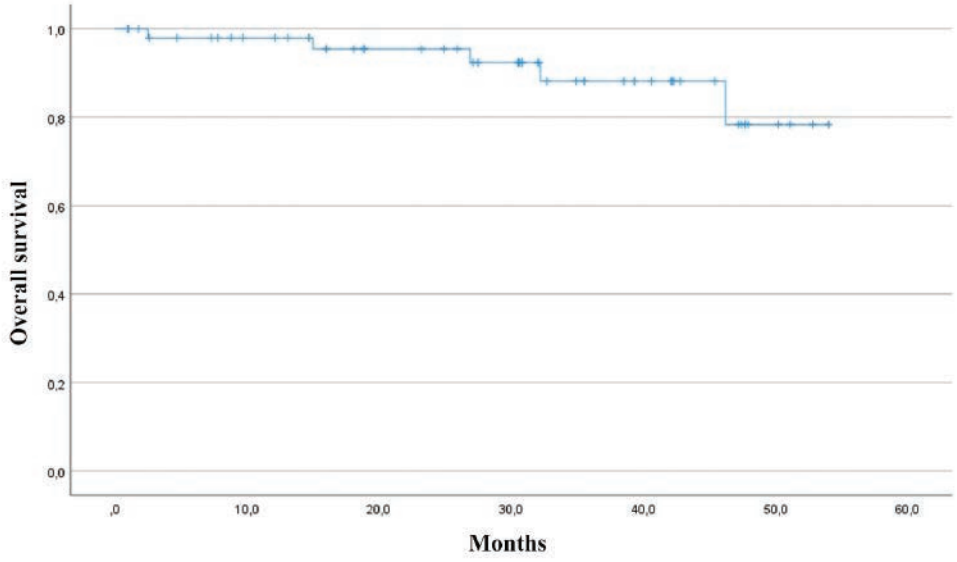

Figure 1. *Three-year overall survival*

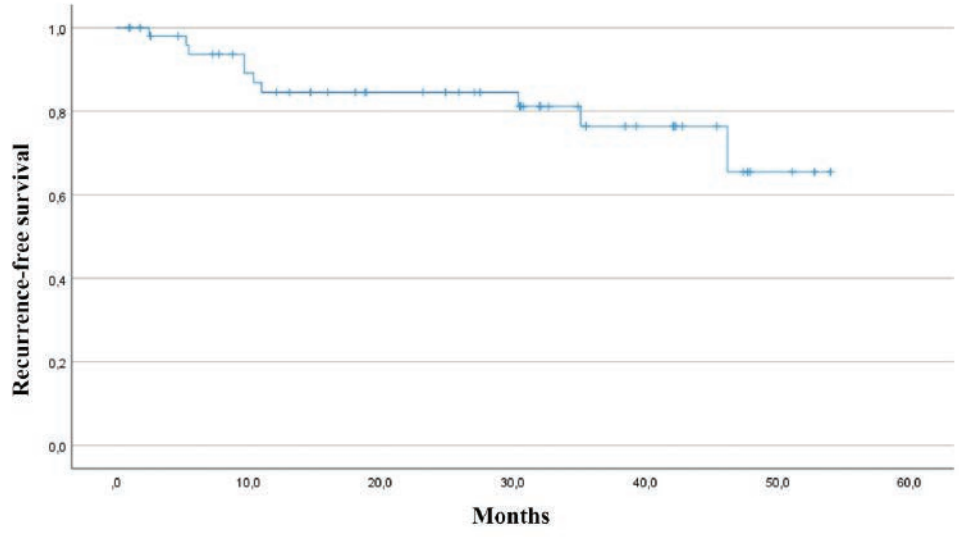

Figure 2. *Three-year recurrence-free survival*

Table 5. *Prospective clinical research on neoadjuvant two-component chemotherapy based on oxaliplatin drugs in patients with rectal cancer*

Author, year	N*	Clinical stage	Primary endpoint	Therapy modes	Number of cycles	Resectability	R0-resections	ypCR	LR	DM	CT	Survival
ALGizawy S.M. et al. 2015 [18]	45	II — 33% III — 67% (exceptT4b)	no data	FOLFOX6	6	100%	100%	17.8%	8.8%	17.7%	no data	3-year OS 80.8% 3-year RS 67.9%/
Ueki T. et al. 2016 [17]	29	II — 38% III — 62%	R0-resections	XELOX	3	100%	96.5%	10.3%	no data	no data	82.8%	no data
Kioke J. et al. 2017 [19]	52	II — 20.8% III — 79.2%	pCR, pPR	FOLFOX6	4–6	98%	91%	11.9%	no data	no data	59.6%	no data
Koizumi M. et al. 2018 [31]	30	II — 20% III — 80%	R0-resections	FOLFOX6	6	100%	100%	6.7%	6.7%	16.6%	no data	3-year OS 95.7% 3-year RS 77.5%
Nishimura J. et al. 2018 [21]	42 (45)	II — 57.1% III — 42.9%	2-year RS	CAPOX	4	91%	100%	7.3%	9.7%	31.7%	85.4%	2-year OS 92.7% 2-year RS 71.6%
Okuyama T. et al. 2018 [7]	27 (55)	II-III stage	3-year RS	SOX FOLFOX6 XELOX	2–9	100%	no data	3.7%	7.4%	7.4%	33%	4-year OS 96.3% 3-year RS 85.2%
Quezada-Diaz F. et al. 2018 [13]	12 (176)	II-III stage	no data	FOLFOX6 CAPOX FLOX	8 5 no data	100%	no data	25%	no data	no data	no data	no data
Cienfuegos J.A. et al. 2019 [32]	27	II — 29.6% III — 70.4%	R0-resections pCR, pPR, OS, RS	FOLFOX6	6–8	100%	100%	14.8%	3,7% 3.7%	11%	no data	5-year OS 85.0% 5-year RS 84.7%
Ichikawa N. et al. 2019 [23]	38 (41)	II — 21.1% III — 78.9%	The rate of postoperative morbidity	FOLFOX6	4	100%	100%	0%	no data	no data	no data	no data
Shiraishi T. et al. 2019 [39]	102	II — 51% III — 49%	no data	FOLFOX — 93% CAPOX — 7%	no data	100%	no data	no data	19.6%	20.6%	no data	5-year OS 87.0% 5-year RS 63.4%
Deng Y. et al. 2019 [26]	163 (495)	II — 27.9% III — 72.1%	3-year RS	FOLFOX6	4–6	93.3%	no data	6.5%	8.3%	no data	no data	3-year OS 90.7% 3-year RS 73.5%
Miwa K. et al. 2021[33]	110	FOLFOX6 II — 32% III — 68% SOX: II — 37.7% III — 62.3%	3-year RS	FOLFOX6 — 49% SOX — 51%	6	93.6%	96% 100%	10.4% 11.3%	no data	no data	79,2% 79.2% 83.0%	3-year OS 91.8% 3-year RS 73.4% 3-year OS 92.3% 3-year RS 69.4%
Our own data	52	II — 4% III — 96%	3-year RS	FOLFOX6 XELOX	4	100%	86.5%	2%	9.6%	7.7%	53.8%	3-year OS 88.2% 3-year RS 76.4%

*Note: * The number of patients who received NCT, figures in parentheses — the total number of patients in the study; pCR — complete pathomorphological reaction; pPR — partial pathomorphological reaction; LR — local recurrences; DM — distant metastases; OS — overall survival; RS — recurrence-free survival*

Special staining methods were not used to detect vascular invasion of the tumor. During routine pathomorphology, vascular invasion of the tumor was detected in 4 (7.7%) patients. Perineural invasion was detected in 9 (17.3%) cases. Involvement of LRM was detected in 6 (11.5%) cases.

Subsequently, 28 (53.8%) patients received adjuvant chemotherapy (chemoradiotherapy).

With a median follow-up of 31 (3–54) months, local recurrences were detected in 5 (9.6%) patients (median — 10 months; 5–11), distant metastases — in 4 (7.7%) patients (median — 35 months). 5 (9.6%) patients died: 3 — due to local recurrence of the disease, 1 — due to distant metastasis, 1 — due to another disease.

The overall 3-year survival rate (Fig. 1) was 88.2 ± 5.8%, the recurrence-free 3-year survival rate (Fig. 2) was 76.4 ± 7.4%. The cumulative 3-year rate of local recurrences was 11.3 ± 4.8%.

DISCUSSION

As a result of improving the surgical technique and methods of preoperative radiation (chemoradiotherapy) treatment of patients with RC, the rate of local recurrences has significantly decreased over the past 20–30 years [5]. Currently, one of the key issues in the treatment of patients with locally advanced RC and the presence of unfavorable prognosis (invasion depth ⩾ sT3c, the presence of affected lymph nodes, mrLRM + , EVI +) remains the prevention of distant metastases that occur during follow-up in about 1/3 of radically operated patients. The use of the standard treatment in the volume of preoperative CRT is associated with an increase in the interval between primary diagnosis and the beginning of systemic drug therapy, which this category of patients so much needs. Adjuvant chemotherapy, which is a standard method of preventing distant metastasis, is not possible in all patients who have received surgical treatment, and is characterized by a low completion rate [30]. At the same time, there are no reliable data that adjuvant chemotherapy in patients with locally advanced tumors who have received CRT contributes to an increase in recurrence-free survival. In this regard, more and more researchers are using NCT in patients with unfavorable prognostic factors instead of CRT [9,11,17,19,20,23].

Two-component oxaliplatin-containing modes are the most studied in the treatment of patients with non-metastatic RC (Table 5).

Despite the differences in the treatment modes used, the number of cycles, the primary endpoints of the studies, a small number of patients and the non-randomized nature of the studies, most authors note the good tolerability of NCT, the absence of influence on the incidence of postoperative morbidity and generally satisfactory results comparable to the effects of CRT. In most cases, the study included patients with resectable forms of stage II-III RC, while the percentage of patients with stage III varied widely (43–80%). However, some authors included patients with T4a and T4b disease categories [17,18,19,31,32,33]. It should be noted that in our study, the number of patients whose cT4 category of tumor was detected during MRI before the treatment was 32.7%, including 13.5% who had cT4b category.

In some studies, the assessment of toxic reactions and morbidity in patients during NCT was carried out. Among them is the study by Miwa et al. [33], according to which the overall rate of toxic reactions was higher in patients in the FOLFOX6 group and amounted to 34.2%. Of these, thrombocytopenia (18.9%) and neutropenia (13.2%) were the most common. It should be noted that in our study, morbidity was present in 35.6% of patients, among whom 11% had morbidity of the third grade or higher. The lower rate of toxic reactions can be explained by the smaller number of PCT cycles in our study — the median was 4 cycles (1–8).

As a rule, the completeness of NCT is higher compared to postoperative [30]. According to Miwa et al.'s studies [33], despite the high rate of toxic reactions, the completeness of NCT was 96%. Koizumi et al. provided similar data on the completion of chemotherapy in their study [31] — 93%. In our study, the completeness of ACT was slightly lower and amounted to 82.7%. It should be noted that the reasons for the incompleteness of the treatment in most cases were due not to the toxicity of chemotherapy as such, but to other factors (obstruction, pneumothorax, etc.), and it is difficult to draw any conclusions based on this indicator.

Postoperative morbidity in patients, who under went NCT, according to the literature, is 18.6% — 33.3% [13,17,31,33]. The results of our study are comparable with them, so the overall morbidity rate was 25%, of which morbidity of the III-IV grade according to the Clavien-Dindo classification were noted in 5.8%.

The incidence of R0 resections in the study was 86.5%, which is lower than in the data of other authors (91% -100%). It should be noted that in most cases, the involvement of LRM by pathomorphology was due to adjacent lymph nodes, in which the prognosis is better than when the resection margins are involved due to the primary tumor [34,35]. It should also be noted that most of these patients had high rectal tumors, in which CRT is associated with an increased risk of radiation lesion.

One of the main criteria for evaluating the effectiveness of NCT is the rate of complete pathomorphological reactions, which ranged widely from 0% in Ichikawa, N. et al.'s study [23], when using 4 cycles of chemotherapy in FOLFOX6 mode, up to 17.8% in the study by ALGizawy S.M. et al. [18], in which 6 cycles of NCT were used in the same mode. A common disadvantage of all studies on NCT is a small number of cases, the lack of uniform criteria for inclusion of patients, which does not allow us to draw any deep conclusions. If we rely on the data of studies with a total number of patients of 110 [33] and 165 [26], the authors obtained complete pathomorphological regressions in 10.4% and 6.5% of cases, respectively. In both studies, the most common FOLFOX6 chemotherapy mode was used (4–6 cycles).

It should be noted that in the study, a complete pathomorphological reaction was achieved only in 1.9% of cases, while 11.5% of patients showed an increase in the tumor category compared to clinical data, which in our opinion may be due to the insufficient effect of NCT in the amount of 4 cycles. Assessing the incidence of cases in which the tumor category increased after chemotherapy, it is also impossible to exclude such a factor as underestimating the extent of the tumor process, which may be due to the imperfection of the MRI method. However, according to Ichikawa, N. et al. [23], performing NCT in more than 4 cycles in patients who do not respond to the treatment can lead to tumor progression. Neoadjuvant chemotherapy in such patients seems to be a useless option, only increasing the interval between primary staging and surgery. Apparently, when planning more than 4 cycles of NCT in patients with prognostically unfavorable RC, it is necessary to conduct a control check-up every 4 cycles to exclude non-responding patients.

The incidence of local recurrences after NCT using oxaliplatin-containing modes (FOLFOX, XELOX, CAPOX) varies widely from 7.1% to 17.4%, and largely depends on the criteria for inclusion of patients in the study, but is generally comparable with the results of the treatment of patients receiving preoperative CRT. In the study, the cumulative 3-year rate of local recurrences with a median follow–up of 30.6 months was 11.3% (5 out of 52 patients), which from our point of view is a satisfactory indicator, taking into account the contingent of the patients (stage III — 94.2%, T4 — 32.7%). When discussing the possible advantages of standard methods of treatment in such patients, it should also be taken into account the fact that in most cases these were patients with upperrectal cancer, in which the benefits of radiation or CRT are not so obvious, and the risks of radiation lesion from normal tissues are quite high.

In many studies devoted to NCT, as the primary endpoint authors use such a criterion as recurrence-free survival, which is somehow associated with a decrease in distant metastasis rate. Thus, the 3-year recurrence-free survival rate according to a number of studies varied from 67.9% to 85.2%, while distant metastases rate also varied widely — 7.4–31.7%. In the research by Deng, Y. et al. [26], Miwa, K. et al. [33], including the largest number of patients with NCT, the 3-year recurrence-free survival rate was identical — 73.5% and 73.4%, respectively. In the study this indicator was 76.4%, and distant metastases rate was 7.7%. At the same time, it should be noted that the majority of patients had unfavorable factors of distant metastasis: 94.2% of patients had clinical stage III, 32.7% had tumor invasion into adjacent organs or visceral peritoneum. Such a good result in patients with an unfavorable prognosis may be due to both the good effect of NCT on micrometastases and insufficient follow-up periods of patients: median 30.6 (1–54) months.

Currently, we have data from only one randomized multicenter phase III study, in which the results of NCT in FOLFOX6 mode were compared with standard methods [26,36]. The study included patients with clinical stages II-III, randomized into three groups: radiation therapy in combination with chemotherapy in de Gramond mode (n = 158), radiation therapy in combination with chemotherapy in FOLFOX6 mode (n = 162), and only NCT in FOLFOX6 mode in the amount of 6 cycles (n = 163). The greatest number of toxic reactions was registered in the group where radiation therapy was used in combination with chemotherapy in the FOLFOX6 mode, the rate of toxic reactions of grade III-IV reached 16.5% for neutropenia and up to 14.5% for diarrhea. After the completion of the preoperative stage of the treatment, all the patients underwent surgery followed by adjuvant chemotherapy in FOLFOX6 mode (6 cycles). A complete pathomorphological reaction was achieved in 14% of the patients who received radiation therapy in combination with monochemotherapy in de Gramond mode, 27.5% of the patients after radiation therapy in combination with FOLFOX6 mode, and 6.5% of the patients who received only chemotherapy [36]. With a median follow-up of 45.2 months, the 3-year overall and recurrence-free survival rates were 91.3% and 72.9%, 89.1% and 77.2%, 90.7% and 73.5%, respectively [26]. There were no significant differences in the rate of local and distant recurrences (29.1%, 24.1%, and 28.2%). Within the framework of this study, functional disorders were assessed in the group of patients after sphincter-preserving procedures, in whom no disease progression was detected during follow-up. Incontinence of gas (p = 0.006), liquid ($p < 0.001$) and solid ($p < 0.001$) feces, as well as night incontinence (p = 0.001) were significantly more common in the patients who underwent CRT at the neoadjuvant stage. The number of patients with an average score on the Wexner scale of over 8 in the group of patients with NCT was 18% (16/89), in the group of patients after CRT with FOLFOX6 — 35.7% (25/70), and in the group of patients after CRT with chemotherapy in de Gramond mode — 41% (25/61); the differences are significant (p = 0.005).

It should be noted that the currently available pathomorphological methods for assessing the grade of tumor reaction are imperfect for patients after NCT. This is due to the peculiarities of the systemic effect of NCT on tumor and micrometastases. As a rule, in such patients, the decrease in category T compared to the initial one is less pronounced than category N. Patients who received NCT in comparison with patients who received chemoradiotherapy also have no pronounced fibrous tissue changes. So, in the study by Sakuyama N. et al. [37], when assessing the tumor reaction in the groups with NCT and CRT, a decrease in category T compared to the initial one was found in 25% and 47.7% of cases, respectively, and category N — in 59.1% and 20.5%, respectively ($p < 0.05$). Grade III fibrotic changes were observed in 6.8% and 59.1% of patients, respectively ($p < 0.05$). Thus, the traditional scales for assessing the tumor reaction (Mandard, Dworak, CAP, Rayn, Lavnikova, and others), based on determining the ratio of tumor and fibrous changes in the specimen, are ineffective in cases of NCT use.

Discussing further prospects for the use of NCT in the treatment of patients with prognostically unfavorable RC, it is necessary to consider such options as increasing the number of cycles of NCT, the use of three-component modes, as well as a combination of NCT and targeted therapy.

To date, there are data from one prospective phase II study by Zhang, J. et al. [38], in which the use of 4–6 cycles of NCT in the mFOLFOXIRI mode in 101 patients with locally advanced RC (stage III — 85% of patients, cT4b — 21%, mrtCRB + — 31%) allowed to achieve complete therapeutic pathomorphosis in 21% of patients, and tumor regression to stage 0-I in 47% of cases.

CONCLUSION

Thus, combined treatment using NCT in FOLFOX6 mode is satisfactorily tolerated by patients, is accompanied by a small number of toxic reactions and postoperative morbidity, and is a promising method of treating patients with prognostically unfavorable RC. The 3-year results of treatment of patients are comparable with the results of CRT followed by surgery.

According to the pathomorphological study, 73% of patients showed a decrease in the tumor

category compared to the MRI data before treatment, but this was not reflected in the extent of pathomorphosis, which requires further study, and in the future, the development of other more effective criteria for evaluating the tumor reaction to NCT.

AUTHORS CONTRIBUTION

Concept and design of the study: *Alexey A. Nevolskikh, Anna S. Belohvostova, Yulia Yu. Mihaleva, Taras P. Pochuev, Tatiana P. Berezovskaya, Yana A. Daineko, Leonid O. Petrov*

Collection and processing of the material: *Alexey A. Nevolskikh, Violetta A. Avdeenko, Ruslan F. Zibirov, Yulia Yu. Mihaleva, Taras P. Pochuev, Tatiana P. Berezovskaya, Yana A. Daineko, Leonid O. Petrov*

Statistical processing: *Violetta A. Avdeenko*

Writing of the text: *Alexey A. Nevolskikh, Violetta A. Avdeenko*

Editing: *Sergey A. Ivanov, Andrey D. Kaprin*

INFORMATION ABOUT THE AUTHORS (ORCID)

Alexey A. Nevolskikh — 0000-0001-5961-2958
Violetta A. Avdeenko — 0000-0002-2678-016X
Anna S. Belohvostova — 0000-0002-4709-1726
Ruslan F. Zibirov — 0000-0001-5252-0436
Yulia Yu. Mihaleva — 0000-0002-9449-2135
Taras P. Pochuev — 0000-0002-9243-6519
Tatiana P. Berezovskaya — 0000-0002-3549-4499
Yana A. Daineko — 0000-0002-4524-0839
Sergey A. Ivanov — 0000-0001-7689-6032
Andrey D. Kaprin — 0000-0001-8784-8415

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Endoscopic submucosal tunnel dissection for large benign colorectal neoplasms. Early results

Oleg M. Iugai, Viktor V. Veselov, Dmitriy A. Mtvralashvili, Alexey A. Likutov, Elmira U. Abdulzhalieva, Olga A. Mainovskaya, Stanislav V. Chernyshov, Oleg I. Sushkov

Ryzhikh National Medical Research Center of Coloproctology (Salyama Adilya str., 2, Moscow, 123423, Russia)

ABSTRACT *AIM: to evaluate the early results of endoscopic submucosal tunnel dissection (ESTD for large benign colon neoplasms.*

PATIENTS AND METHODS: a prospective non-randomized comparative study included 100 patients with large benign epithelial colon neoplasms (more than 3 cm in diameter). The main group included 50 patients who underwent endoscopic submucosal tunnel dissection. The control group included 50 patients who underwent traditional endoscopic submucosal dissection (ESD).

RESULTS: Four (4%) patients (1 in the main and 3 in the control group) were excluded from the study due to the conversion of endoscopic procedure. The incidence en bloc removal of neoplasms and the negative resection margins were significantly higher in the main group than in the control one — 98% and 87.2% (p = 0.04) and 89.8% and 70.2%, respectively (p = 0.01).

CONCLUSION: ESTD for large benign epithelial colon neoplasms shows better radicalness in comparison with endoscopic submucosal dissection.

KEYWORDS: *endoscopic submucosal dissection, benign colorectal neoplasms, tunnel method, ESTD, ESD*

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ADDRESS FOR CORRESPONDENCE: *Oleg M. Iugai, Ryzhikh National Medical Research Center of Coloproctology, Salyama Adilya str., 2, Moscow, 123423, Russia, e-mail: Oleg-ugai@mail.ru*

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INTRODUCTION

There are a large number of surgical techniques in the arsenal of an endoscopist that allow the effective and safe removal of benign colorectal neoplasms [1–4]. Nevertheless, such relatively simple and widely used methods as endoscopic mucosectomy, excision without prior lifting, and 'cold' loop excision can in some situations lead to fragmentation of the specimen, which makes it difficult to carry out its adequate morphological assessment and significantly increases the risk of local recurrence, especially when removing large neoplasms [4,5].

To remove the tumor *en bloc*, the method of endoscopic submucosal dissection (ESD) was developed. It was first used for the removal of neoplasms of the upper gastrointestinal tract (GT) [6], and is currently successfully used for the treatment of patients with colorectal tumors [7–9].

This method makes it possible to achieve negative resection margins when removing colorectal tumors in 90% of cases [8]. However, with large tumors > 30 mm, the incidence of R0 resection can decrease to 74% [10]. In all likelihood, this is due to technical difficulties in visualizing the submucosal layer in large tumors, which in some cases can lead to their non-radical removal [11].

In 2010, Inoue, H. et al. were the first to suggest the method of endoscopic submucosal tunnel dissection (ESTD) for performing oral endoscopic

Table 1. *Characteristics of patients in groups*

Indicator	ESTD (*n* = 50)	ESD (*n* = 50)	*p*
Age, years	62 (57;69)	63 (58;71)	0.3*
Gender			0.3**
Male	25 (50%)	20 (40%)	
Female	25 (50%)	30 (60%)	
Median size of the tumor, cm	4.7 (3,5;6)	4.5 (4;5)	0.2*
Tumor site in the large intestine			
Rectum	22 (44%)	7 (14%)	0.001**
Colon	28 (56%)	43 (86%)	

Note: p Mann-Whitney test; p** χ^2 Pearson test*

myotomy in a patient with achalasia of the cardia [12].

In the future ESTD was successfully used for the removal of neoplasms of the upper GT [17,18].

However, the introduction of this new endoscopic technique in colorectal surgery was slow. To date, the experience of using the tunnel submucosal dissection method for the removal of large colorectal tumors is reflected only in two publications [13,14]. Moreover, they were devoted exclusively to the ESTD use for the treatment of patients with large rectal tumors.

This fact prompted us to study the early results of ESTD for benign large colorectal tumors.

PATIENTS AND METHODS

A prospective non-randomized study, in the period between June 2019 and May 2021, included 100 patients with benign epithelial colorectal tumors, whose size was over 30 mm in the maximum measurement. The main group included 50 patients who underwent ESTD surgery. The control group (50 patients) was formed by random selection from a group of 132 patients with colorectal tumors larger than 30 mm using the resource *randomizer.org*. The classic ESD method was used to remove these neoplasms.

There were no statistically significant differences between the groups by gender and age (Table 1). The median size of neoplasms in the maximum measurement in the groups also did not differ statistically significantly. So, the median of this indicator in the ESTD group was 4.7 (3.5;6) cm, and in the ESD group — 4.5 (4;5) cm, respectively ($p = 0.2$).

When analyzing the incidence of tumor site, lesions in the main group were significantly more often located in the rectum than in the control group — in 22 (44%) and 7 (14%) cases ($p = 0.001$).

The assessment of the dimple pattern of the tumor surface in patients of the two groups was carried out using the Kudo, S. classification ($n = 93$) for adenomatous and the Kimura, T. classification ($n = 7$) for dentate neoplasms. The analysis showed that in 86 cases colorectal tumors were assessed as benign, which corresponds to IIIS, IIIL, IV and II-O types of pit pattern, whereas in 14 cases (7 in each group) endoscopic signs of malignancy without signs of deep invasion were detected, corresponding to type Vi according to the Kudo classification.

Evaluation of the vascular pattern according to Sano, Y., as well as the macroscopic type of tumor according to the Paris classification showed that the tumors in all the patients included in the study had no signs of invasion (Table 2).

Table 2. *Endoscopic characteristics of colorectal tumors in groups*

Indicator	ESTD (*n* = 50)	ESD (*n* = 50)	*p*
Classification by Kudo, S./Kimura, T.			
IIIL	6 (12%)	14 (28%)	0.2*
IIIs	7 (14%)	4 (8%)	
IV	27 (54%)	21 (42%)	
Vi	7 (14%)	7 (14%)	
IIO	3 (6%)	4 (8%)	
Classification by Sano, Y.			
II	40 (80%)	43 (86%)	0.4*
IIIa	10 (20%)	7 (14%)	
Paris Classification			
LST-G	36 (72%)	40 (80%)	0.6*
LST-NG	9 (18%)	7 (14%)	
LST-M	5 (10%)	3 (6%)	

Note: p — χ^2 Pearson*

There were no statistically significant differences between the groups by type of pit and vascular pattern (Table 2).

The dissection equipment in the two groups did not differ and included: Pentax EPC 7000/7010 video endoscopic processors, Pentax EC 34-I10L/EC 34-I10M operating colonoscopes, Pentax EG29-I10 gastroscope, Erbe operating unit 300D and the Olympus insufflator.

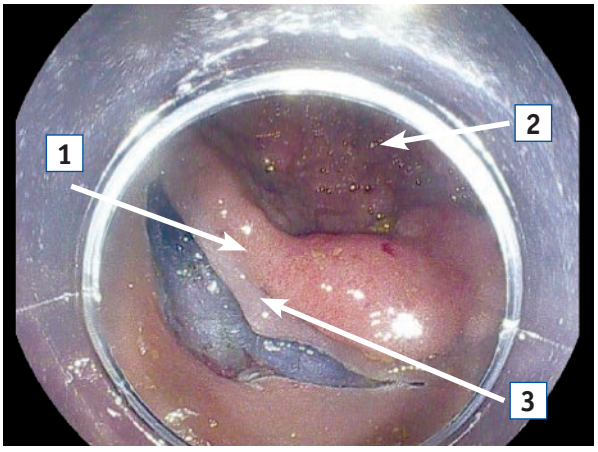


Figure 1. *Endophotography. ESTD of the sigmoid colon tumor. Patient Ch., aged 51. 1. Mucosal incision at the tumor distal edge. 2. Tumor of the sigmoid colon. 3. Submucosal layer of the intestinal wall.*

ESD Technique

After the final endoscopic evaluation of the tumor and the decision on the possibility of performing dissection according to the classical method in patients of the control group, an injection needle was used to inject a solution of a plasma-substituting agent stained with 0.4% indigocarmine solution under the tumor into the submucosal layer. The purpose of this procedure was to create a submucosal 'cushion' between the tumor and the muscular layer of the bowel wall in order to avoid the risk of its perforation.

When lifting reached more than 3–4 mm, a circular incision was made around the lesion > 5 mm, and then dissection was performed by dissecting the submucosal layer under the tumor in compliance with adequate resection margins. Large vessels were controlled using a coagulation grasper. After

removal of the tumor, the vessels in the defect were additionally coagulated with hemostatic forceps, and the resulting defect in the bowel wall, if necessary, was closed by endoscopic clips. The removed colorectal tumors was fixed on a plastic screen immediately after extraction, after which it was sent for pathomorphology.

ESTD Technique

When performing tunnel dissection in patients of the main group, the first stage was the injection of a plasma-substituting solution under the tumor into the submucosal layer, then an endoscopic knife was used to make an incision of the mucosa at the distal edge of the tumor with an indentation of more than 5 mm (Fig. 1). Then a tunnel was gradually formed by dissecting the submucosal layer under the tumor.

The tunnel was created in one of two ways (Fig. 2):

1) "Throughway", when it was created in the submucosal layer with an exit at the proximal edge of the tumor;
2) "Pocket way", in which the submucosal layer was dissected in stages, both in the proximal and lateral directions.

After the tunnel was created, a semilunar incision of the mucosa was performed first at the lateral, then at the medial edge of the tumor and its complete excision was completed within the submucosal layer.

Next, the intestinal wall defect was controlled, preventive endoscopic hemostasis was performed, and, if necessary, the wound defect of the bowel wall was closed.

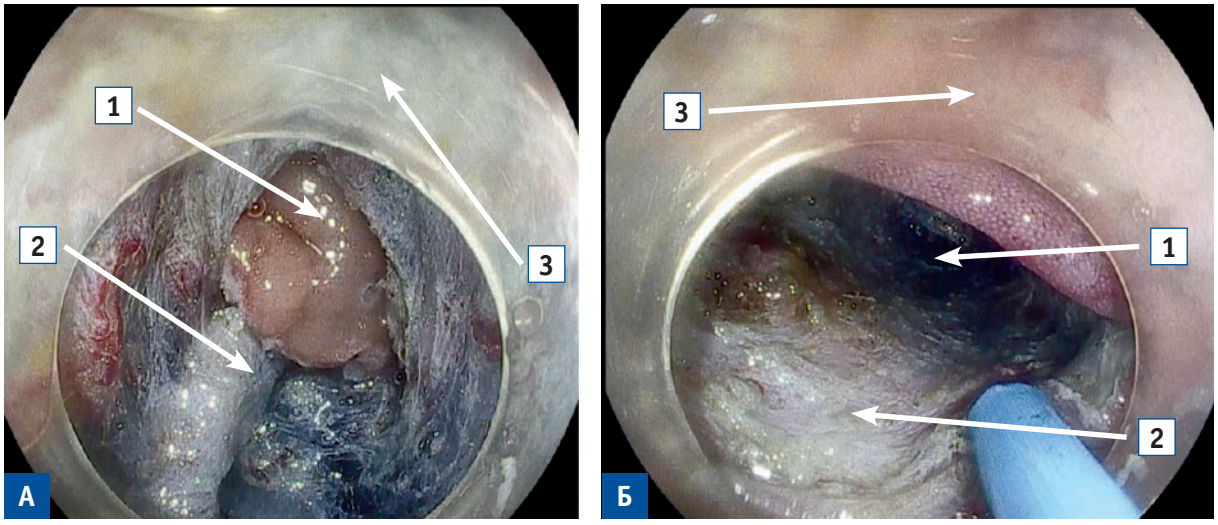
MATERIAL COLLECTION AND STATISTICAL ANALYSIS

The information about the patients was entered into a specially designed electronic database in the Excel program of Microsoft Office software for Windows. Statistical processing of the results was performed using the Statistica 13.3 program (Tibco, USA).

Verification of the correctness of the distribution of the data series was carried out using the Shapiro-Wilk test. In this study, the distribution of continuous indicators turned out to be nonparametric. Therefore, we evaluated their median values and quartiles, and used the Mann-Whitney test for comparison. Pearson's χ^2 test was used to analyze categorical data. The differences were considered statistically significant at $p < 0.05$.

RESULTS

The conversion of endoscopic surgery into laparoscopic bowel resection occurred in 1



Fugure 2. *Endophotography. ESTD of rectal tumor. The stage of endoscopic surgery is the formation of a "tunnel entry" in the submucosal layer. A. Submucosal tunnel. Patient B., aged 52 years old. 1. The end of the tunnel at the proximal edge of the tumor. 2. The muscular layer of the intestinal wall. 3. Rectal tumor (visualized behind the wall of the distal cap). Б. Tunnel in the "Pocket" form. Patient V., aged 71 years old. 1. "Pocket" created by dissecting the submucosal layer under the tumor. 2. The muscular layer of the intestinal wall. 3. Rectal tumor (visualized behind the wall of the distal cap).*

Table 3. *Characteristics of early results of dissections in groups*

Indicator	ESTD (N = 49)	ESD (N = 47)	*p*
Operation time, minutes	92 (70;150)	95 (50;120)	0.3*
Postoperative hospital stay, days	6 (5;6)	6 (5;7)	0.8*
Conversion rate N = 50/N = 50	1 (2%)	3 (6%)	0.3**
Postoperative morbidity rate N = 49/N = 48	9 (18.3%)	8 (16.7%)	0.8**
Bleeding	1 (2%)	0	
Perforation	0	1 (2.1%)	
Postcoagulation syndrome	8 (16.3%)	7 (14.6%)	
Median of endoscopic clipsused.	2 (1;3)	2 (2;3)	0.2*
Maximum size of the removed tumor	4.2 (3.5;5.6)	4 (3.4;4.7)	0.1*
En bloc resection rate	48 (98%)	41 (87.2%)	0.04**
Resection margins			
R0	44 (89.8%)	33 (70.2%)	0.01**
R1	4 (8.2%)	6 (12.8%)	0.4**
Rx	1 (2%)	8 (17%)	0,01** 0.01**
Histological structure of tumors			
Tubular adenoma	8 (16.3%)	9 (19.2%)	0.6**
Tubulo-villous adenoma	32 (65.3%)	29 (61.7%)	
Villous adenoma	4 (8.2%)	5 (10.6%)	
Adenocarcinoma	2 (4.1%)	0	
Dentatea denoma	3 (6.1%)	4 (8.5%)	

*P*Mann-Whitney Criterion; p** χ^2 Pearson*

(2.0%) of 50 patients of the main group and in 3 (6.0%) of 50 patients of the control group ($p = 0.3$).

At the same time, in 1 (2.0%) and 2 (4.0%) cases in ESTD and ESD accordingly, the conversion of endoscopic surgery occurred due to unsatisfactory lifting of the neoplasm during the surgery, which did not allow differentiating the layers of the bowel wall, as well as excluding malignancy of the tumor.

In another 1 (2.0%) patient of the control group, the cause of the conversion was perforation of the bowel wall during dissection of the submucosal layer, which gave rise to laparoscopically assisted anterior resection of the rectum with sigmorectal anastomosis. The postoperative period

was without unfavorable events. The patient was discharged from the hospital on the 9th day after laparoscopic surgery.

The patients with endoscopic surgery conversion were not included in the analysis of the early results of endoscopic procedures, which was eventually done in 49 and 47 patients of the main and control groups, respectively.

The analysis of the early results of surgeries in the groups showed that the median surgery time was shorter in the ESTD group, amounting to 92 (70;150) minutes, and in the ESD group this indicator was 95 (50;120) minutes ($p = 0.3$) (Table 3).

The analysis of hospital stay in patients after endoscopic procedures showed no difference between groups and was 6 (5;6) and 6 (5;7) days in the main and control groups, respectively ($p = 0.8$).

Complication rate after ESTD was 18.3% ($n = 9$), and in the ESD group — 16.7% ($n = 8$) ($p = 0.8$).

Postoperative complication developed in 1 (2.0%) patient of the main group and in none of the control one ($p = 0.3$). On the 2nd day after the surgery, intestinal bleeding was diagnosed. The patient urgently underwent a diagnostic colonoscopy. At the same time, bleeding from the wound surface was regarded as having taken place (type 2 according to the Clavien-Dindo classification). For preventive purposes, additional clipping of the postoperative defect was performed. The further course of the postoperative period was uneventful, the patient discharged on the 5th day after the surgery.

Postcoagulation syndrome (PS), manifested by pain during palpation of the abdomen in the surgery site, subfebrile hyperthermia, increased levels of C-reactive protein (CRP).It developed in 8 (16.3%) and 7 (14.6%) patients in the main and control groups, respectively. There were no statistically significant differences in the PS occurrence between groups ($p = 0.9$). In all cases, PS was successfully cured by antibiotics and nonsteroidal anti-inflammatory agents.

The analysis of the need to use endoscopic clips for ligation of submucosal vessels during endoscopic hemostasis and closure of wound defect of the intestinal wall showed that the mean value did not differ significantly between the groups — 2 (1;3) and 2 (2;3) clips in the group of tunnel and classical dissection, respectively ($p = 0.2$).

The analysis of the median sizes of the removed tumors did not reveal significant differences between the main group — 4.2 (3.5; 5.6) cm and the control one — 4 (3.4; 4.7) cm ($p = 0.1$).The incidence of removal of the specimen *en bloc* was significantly higher in the ESTD group — 48 (98.0%) cases, compared with the control group — 41 (87.2%) cases ($p = 0.04$). According to the pathomorphology, it was possible to achieve negative resection margins in 44 (89.8%) and 33 (70.2%) cases in the ESTD and ESD group, respectively ($p = 0.01$). At the same time, the incidence of cases when the resection margin could not be reliably estimated (Rx) during pathomorphological examination in the ESD group was significantly higher than in the ESTD group — 8 (17.0%) and 1 (2.0%) case, respectively ($p = 0.01$).

In 4 (8.2%) patients of the main group and 6 (12.8%) patients of the control group, the resection margin was less than 1 mm from the tumor edge, which, according to the available criteria, was estimated as R1. In all these patients, tumors were tubulo-villous and tubular adenomas with moderate and mild epithelial dysplasia. With a median follow-up of 7 (6;9) months, no endoscopic signs of tumor recurrence were detected in any case.

Pathomorphology of removed specimens in most patients, the histological structure of the tumor was represented by tubulo-villous adenoma — 32 (65.3%) cases in the ESTD group and 29 (61.7%) cases in the ESD group.

In 2 patients in the ESTD group, pathomorphology of the tumor revealed foci of moderately differentiated adenocarcinoma. It is worth noting that the resection margins in these 2 cases were evaluated as “R0”. Due to the inability to accurately determine the depth of invasion of the submucosal layer, the patients were offered to undergo colon resection. However, the patients refused radical treatment in favor of follow-up. It should be noted that during the control colonoscopy after 3, 6, and 12 months and computed tomography of the chest, abdominal cavity and pelvis after 6 and 12 months, there were no signs of local recurrence, distant metastases, or regional lymph nodes involvement. The patients remain under further follow-up.

DISCUSSION OF THE RESULTS

To date, the choice of the most rational method for patients with large benign colorectal tumors from the entire palette of endoscopic methods is a problem current interest in colorectal surgery [4,15].

In the present study, assessing the safety of the ESTD method, we did not obtain significant differences in the rate of postoperative morbidity in comparison with the group of classical submucosal dissection.

It turned out to be low and quite comparable with the data of other studies. So, in the study by Zou J. (2020), the rate of postoperative bleeding and perforations of the bowel wall in the ESTD and ESD groups was 2.4%, 1.7% ($p = 1$) and 3.6%, 1.7% ($p = 0.8$) cases, respectively [14]. The authors, whose point of view we share, concluded that the methods are comparable in safety.

Postoperative bleeding, which occurred in 1 (2.0%) patient in the ESTD group, did not require intensive therapy, blood transfusion, and intraabdominal surgery. Perforation of the bowel wall in the postoperative period was not observed in any patient. At the same time, intraoperative perforation of the wall of the distal third of the sigmoid colon during tumor removal occurred in the control group. Retrospectively, analyzing the causes of this situation, it is necessary to note the presence of pronounced submucosal fibrosis in this case, which, in turn, prevented choosing a more successful layer for dissection. Despite the absence of such a complication in the main group, in our opinion, the reason for its development is not due to the method, but to an error in choosing a method for removing the neoplasm, since pronounced fibrosis of the submucosal layer is considered by most authors as a relative contraindication to performing submucosal dissection.

The analysis of the surgery time in the ESTD and ESD groups in the study did not reveal significant differences between the two methods, which is consistent with the data of other authors [10,14,16].

It is worth emphasizing that the analysis of the results of macroscopic and microscopic control of removed specimens showed a greater radicality of the ESTD method, compared with the classical method of submucosal dissection. Thus, the incidence of *en bloc* removal of tumors was significantly higher in the tunnel dissection group, compared with the traditional one: 98% and 87% in the ESTD and ESD groups, respectively ($p = 0.04$). In addition, the rate of tumor-negative resection margins was 20% higher in the main group than in the control one. At the same time, the high incidence of cases with tumor fragmentation in the classical dissection group did not allow us to reliably assess the margins of resection of the specimen and the radicality of tumor removal (Rx).

CONCLUSION

Thus, the results of the study indicate that the use of the tunnel submucosal dissection method for the removal of large benign epithelial colorectal neoplasms makes it possible to obtain a higher-quality surgical specimen compared to the classical technique. At the same time, the incidence of *en bloc* removal of neoplasms and the achievement of negative resection margins, according to the pathomorphological study of the removed specimen, when using the tunnel dissection method is statistically significantly higher than with ESD. Considering the relatively recent introduction of the ESTD method into clinical practice for the removal of colorectal tumors, further studies aimed at studying the incidence of local recurrences, as well as the possibility of the method for the removal of malignant colorectal tumors, seems promising to us.

AUTHORS CONTRIBUTION

Concept and design of the study: *Oleg I. Sushkov, Viktor V. Veselov, Stanislav V. Chernyshov*

Collection and processing of the material: *Oleg M. Iugai, Dmitriy A. Mtvralashvili, Alexey A. Likutov, Olga A. Mainovskaya*

Collection and processing of materials: *Oleg M. Iugai, Elmira. U. Abdulzhalieva*

Text writing: *Oleg M. Iugai*

Editing: *Oleg I. Sushkov, Viktor V. Veselov*

INFORMATION ABOUT THE AUTHORS (ORCID)

Oleg M. Iugai — 0000-0003-4679-5497

Viktor V. Veselov — 0000-0001-9992-119X

Dmitriy A. Mtvralashvili — 0000-0003-3258-7881
Alexey A. Likutov — 0000-0001-5848-4050
Elmira U. Abdulzhalieva — 0000-0002-7750-603x
Olga A. Mainovskaya — 0000-0001-8189-3071
Stanislav V. Chernyshov — 0000-0002-6212-9454
Oleg I. Sushkov — 0000-0001-9780-7916

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Врожденная гипертрофия пигментного эпителия сетчатки у пациента с семейный аденоматозным полипозом толстой кишки (клинический случай)

Крячко А.А.[1,2], Чугузов К.Д.[1,2], Дурлештер В.М.[1,2], Карагодина П.А.[3]

[1]Федеральное государственное бюджетное образовательное учреждение высшего образования «Кубанский государственный медицинский университет» Министерства здравоохранения Российской Федерации (ул. им. Митрофана Седина, д. 4, г. Краснодар, 350063, Россия)
[2]Государственное бюджетное учреждение здравоохранения «Краевая клиническая больница № 2» Министерства здравоохранения Краснодарского края (ул. Красных Партизан, д. 6/2, г. Краснодар, 350012, Россия)
[3]Федеральное государственное автономное учреждение «Национальный медицинский исследовательский центр «Межотраслевой научно-технический комплекс" Краснодарский филиал (ул. Красных Партизан, д. 6, г. Краснодар, 350012, Россия)

РЕЗЮМЕ *Семейный аденоматозный полипоз толстой кишки — одно из самых трудно диагностируемых заболеваний во врачебной практике, на раннем этапе, множественные аденомы в толстой кишке клинически чаще всего никак не проявляются, а на более поздней стадии неизбежно трансформируются в колоректальный рак. Скудная клиническая симптоматика редко позволяет установить диагноз до появления малигнизации, поэтому спасательным кругом в диагностике данной патологии могут являться ее внекишечные проявления. Врожденная гипертрофия пигментного эпителия сетчатки — это доброкачественная опухоль, формирующаяся из пигментного эпителия сетчатки и может встречаться как в изолированной форме, так и у пациентов с семейным аденоматозным полипозом толстой кишки. К сожалению, в русскоязычной клинической литературе практически нет научных трудов, посвященной данной проблеме, и, соответственно, научные работы в этом направлении могут помочь врачу в ранней диагностике и своевременном лечении пациентов с полипозом толстой кишки.*
Клинический случай пациента П., 35 лет, который в плановом порядке поступил в хирургическое отделение с диагнозом семейный аденоматозный полипоз толстой кишки. Во время дообследования выявлены множественные опухолевидные поражения глаз по типу гипертрофии пигментного эпителия сетчатки. Из анамнеза выяснено, что в 2017 году пациент проходил плановый осмотр у офтальмолога, где раннее патологическое состояние было выявлено впервые, но на это клиническое проявление внимание врача не было обращено, и пациент в дальнейшем не было направлен на консультацию к колопроктологу с подозрением на семейный аденоматозный полипоз толстой кишки.

КЛЮЧЕВЫЕ СЛОВА: *полипоз толстой кишки, врожденная гипертрофия пигментного эпителия сетчатки, рак толстой кишки, мутация гена APC, MutYH*

КОНФЛИКТ ИНТЕРЕСОВ: *авторы заявили об отсутствии конфликта интересов*

ДЛЯ ЦИТИРОВАНИЯ: Крячко А.А., Чугузов К.Д., Дурлештер В.М., Карагодина П.А. Врожденная гипертрофия пигментного эпителия сетчатки у пациента с семейный аденоматозным полипозом толстой кишки (клинический случай). *Колопроктология.* 2022; т. 21, № 2, с. 114–120. https://doi.org/10.33878/2073-7556-2022-21-2-114-120

Congenital hypertrophy of the retinal pigment epithelium in the patients with familial adenomatous polyposis colon (case report)

Andrei A. Kryachko[1,2], Konstantin D. Chuguzov[1,2], Vladimir M. Durleshter[1,2], Polina A. Karagodina[3]

[1]Federal State Budgetary Educational Institution of Higher Education "Kuban State Medical University" of the Ministry of Health of the Russian Federation (Mitrofan Sedin St., 4, Krasnodar, 350063, Russia)
[2]State budgetary healthcare institution "Regional Clinical Hospital No. 2" of the Ministry of Health of the Krasnodar Territory (Krasnykh Partizan St., 6/2, Krasnodar, 350012, Russia)

[3]Federal State Autonomous Institution "National Medical Research Center" Intersectoral Scientific and Technical Complex" Krasnodar branch (Krasnyh Partizan st., 6, Krasnodar, 350012, Russia)

ABSTRACT *Familial adenomatous polyposis is one of the most difficult to diagnose diseases in medical practice, at an early stage, multiple colorectal adenomas are clinically most often not manifested in any way, and at a later stage they inevitably transform into colorectal cancer. Poor clinical manifestation rarely make it possible to establish a diagnosis before the onset of malignancy, so extraintestinal symptoms can be a lifeline in the diagnosis of this disease. Congenital retinal pigment epithelium hypertrophy is a benign tumor that develops from the retinal pigment epithelium and can occur both in an isolated form and in patients with familial adenomatous polyposis of the colon. Unfortunately, in the Russian-language clinical literature there are practically no scientific papers devoted to this problem.*

Clinical case of patient P., 35 years old, who was routinely admitted to the surgical unit with a diagnosis of familial adenomatous polyposis is presented. During the additional examination, multiple tumor-like lesions of the eyes were revealed according to the type of hypertrophy of the retinal pigment epithelium. From the anamnesis, it was found out that in 2017 the patient underwent a check-up by an ophthalmologist, where an early pathological condition was detected for the first time, but the doctor's attention was not paid to this clinical manifestation, and the patient was not subsequently referred for a consultation with a coloproctologist with suspicion of familial adenomatous polyposis.

KEYWORDS: *adenomatous polyposis colon, congenital hypertrophy of the retinal pigment epithelium, CHRPE, colon cancer, mutations of gene APC, MutYH*

CONFLICT OF INTEREST: *the authors declare no conflict of interest*

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АДРЕС ДЛЯ ПЕРЕПИСКИ: *Чугузов Константин Дмитриевич, ул. Заполярная, д. 35/10, кв. 11, Краснодар, 350012, Россия; тел.: +7 (953) 071-77-82; e-mail: fugazii1993@gmail.com*

ADDRESS FOR CORRESPONDENCE: *Chuguzov Konstantin Dmitrievich, Zapolyarnaya st., 35/10-11, Krasnodar, 350012, Russia; tel.: +7 (953) 071-77-82; e-mail: fugazii1993@gmail.com.*

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ВВЕДЕНИЕ

Врожденная гипертрофия пигментного эпителия сетчатки (ВГПЭТ) — это плоская доброкачественная опухоль на уровне пигментного эпителия сетчатки [1]. Как правило, данную патологию выявляют случайно, на плановом офтальмологическом осмотре или при других заболеваниях органов зрения. Также ВГПЭТ, по данным клинической литературы, встречается у 90% пациентов с семейным аденоматозным полипозом толстой кишки (САПТК), которое является облигатным предраком [2]. В связи с этим, есть необходимость проанализировать различия между типичной формой ВГПЭТ и вариантом, который встречается у пациентов с САПТК, для того, чтобы незамедлительно установить правильный диагноз и начать своевременное лечение.

Клинический случай

Пациент П., 35 лет, в 2017 году проходил плановый медицинский осмотр офтальмолога для получения врачебного заключения, требуемого с места работы. Жалоб на нарушения зрения пациент не предъявлял. Во время осмотра глазного дна врач-офтальмолог выявил округлые, гиперпигментированные поражения, размером 1–2 мм, расположенные в обоих глазах. В связи с отсутствием жалоб и доброкачественностью поражения, углубленного сбора анамнеза не проводилось. Спустя несколько лет, пациент стал периодически отмечать появление кровянистых выделений в стуле. После очередного эпизода кровотечения, пациент обратился на плановый осмотр колопроктолога в нашу клинику. После осмотра был установлен предварительный диагноз — хронический комбинированный геморрой 2 степени, неполная ремиссия. Для исключения патологии верхних отделов толстой кишки пациент направлен на фиброколоноскопию. Выполненное исследование показало, что во всех отделах толстой кишки, начиная от 18 см от анального канала, отмечаются полипы «сидячие» и на ножке, размерами от 0.4 до 3 см (Рис. 1). Биопсия из нескольких наиболее крупных полипов выявила доброкачественный характер без признаков озлокачествления (Рис. 2).

Для исключения глазной патологии, сочетанной с САПТК, пациент консультирован офтальмологом. При осмотре глазного дна левого глаза (Рис. 3) выявлено округлое, гиперпигментированное образование,

диаметром до 1 ДД, темного цвета, с неровными краями. В левом глазу множественные аналогичные поражения, находящиеся в разных квадрантах сетчатки (Рис. 4).

Также проведено генетическое исследование, несмотря на то, что САПТК и рак толстой кишки у своих близких родственников в анамнезе отрицает (у отца, матери, старшего брата) (Рис. 5). По данным генетического исследования имеется мутация гена *APC*: c.1370C>G (p.Ser457Ter). Мутации гена *MutYH* не выявлено.

Согласно полученным данным после дообследований и современных общемировых рекомендаций по лечению САПТК, пациенту было предложено плановое оперативное вмешательство по поводу полипоза толстого кишечника. Пациент в плановом порядке госпитализирован в колопроктологическое отделение для лечения. Учитывая молодой возраст и предпочтения пациента о нежелании жить с перманентной илеостомой, а также степень поражения толстой кишки (на протяжении 18 см прямой кишки отсутствует рост полипов), возможность сохранения моторной и эвакуаторной функции оставшейся части прямой кишки, было принято решение о выполнении оперативного вмешательства в объеме: колэктомия с резекцией прямой кишки и формированием илеоректального анастомоза на 17 см от анального канала. На удаленном макропрепарате злокачественного роста в полипах не обнаружено (Рис. 6). Спустя полгода после операции, на плановом эндоскопическом исследовании, рост полипов в зоне оставшейся прямой кишки не обнаружен. У пациента есть трехлетний сын, который находится под наблюдением у гастроэнтеролога и хирурга. Проведенное сыну молекулярно-генетическое исследование мутацию гена *APC* не выявило.

ОБСУЖДЕНИЕ

Семейный аденоматозный полипоз толстой кишки — это генетическое заболевание, передающееся по аутосомно-доминантному признаку. На слизистой оболочке толстой кишки развиваются множественные аденоматозные полипы от нескольких десятков до тысяч. Главная угроза САПТК проявляется в виде 100% трансформации аденом в колоректальный рак, чаще всего в четвертую декаду жизни, вследствие чего крайне важна своевременная диагностика и незамедлительное лечение [3]. Дополнительно ко всему, клиническая картина САПТК не изобилует симптомами, которые, особенно врачам в первичном звене и на плановых профилактических осмотрах, помогут заподозрить наличие заболевания и проинформировать пациента о необходимости дальнейшего лечения. Симптомы при САПТК начинают проявляться, когда количество и размер полипов увеличится, что может проявляться кишечными кровотечениями и даже анемией [4].

Характерной чертой САПТК являются внекишечные проявления, такие как: аномалии зубов, остеомы, десмоидные опухоли, а также сочетания САПТК с онкологией щитовидной железы, печени, желчных протоков и нервной системы [5].

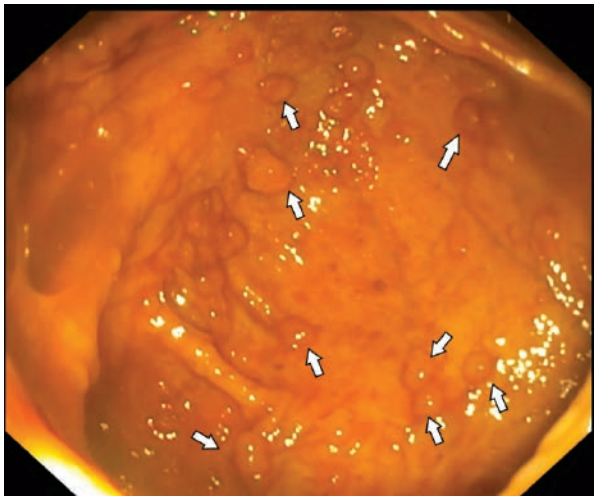

Рисунок 1. *Ректосигмоидный отдел толстой кишки на фиброколоноскопии. Стрелками частично указаны множественные полиповидные образования размерами от 0,3 см до 0,8 см*

Figure 1. *Rectosigmoid colon on fibrocolonoscopy. Arrows partially indicate multiple polypoid formations ranging in size from 0.3 cm to 0.8 cm*

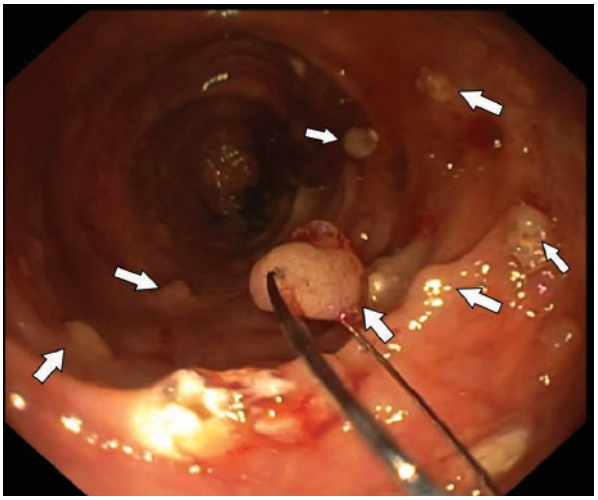

Рисунок 2. *Участок поперечноободочной кишки на фиброколоноскопии с диагностической биопсией. Стрелками частично указаны множественные полипы*

Figure 2. *A section of the transverse colon on fibrocolonoscopy with a diagnostic biopsy. Arrows partially indicate multiple polyps*

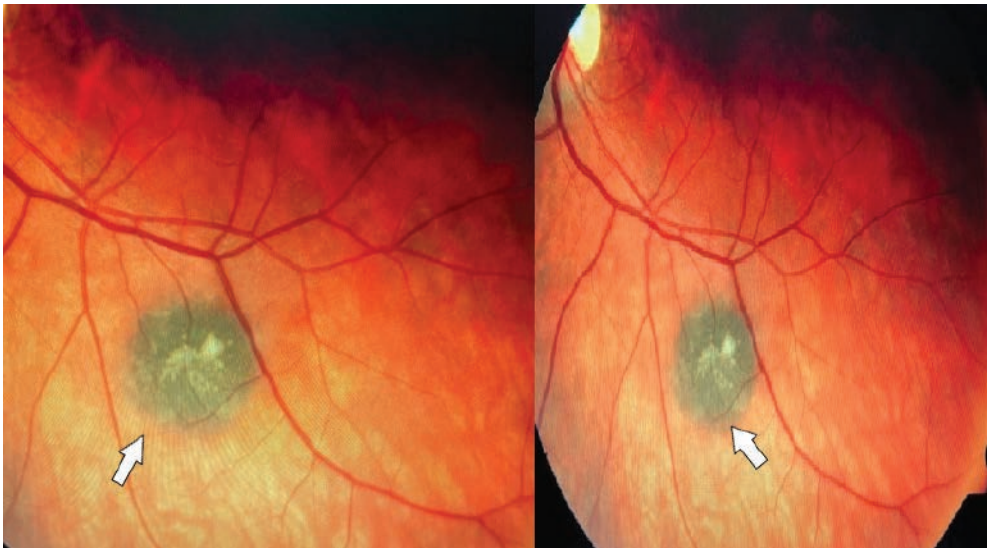

Рисунок 3. *Левый глаз. По ходу нижней височной аркады единичное, округлое, гиперпигментированное образование, диаметром около 1ДД с четкими границами*
Figure 3. *Left eye. Along the inferior temporal arcade, there is a single, round, hyperpigmented formation, about 1 DD in diameter with clear boundaries*

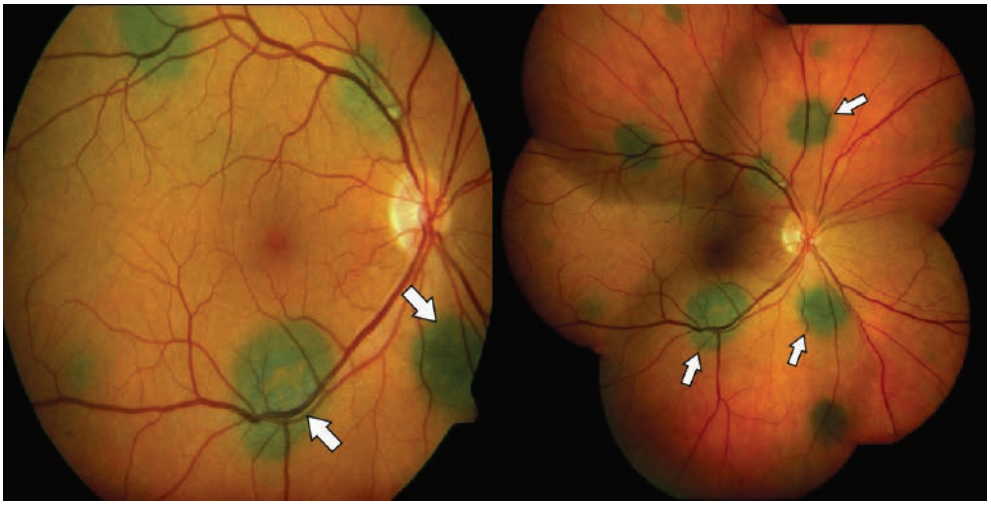

Рисунок 4. *Правый глаз. На глазном дне множественные гиперпигментированные образования, округлой формы с четкими границами, диаметром от 0,5 до 2ДД*
Figure 4. *Right eye. On the fundus there are multiple hyperpigmented formations, rounded in shape with clear boundaries, with a diameter of 0.5 to 2D*

Одним из часто встречающихся и самых ранних внекишечных проявлений САПТК считается синдром врожденной гипертрофии пигментного эпителия сетчатки [6]. Синдром ВГПЭС описывается как плоское, округлое или веретенообразное, темно-пигментированное поражение сетчатки, обычно в средней части глазного дна [7]. ВГПЭС, не связанный с САПТК, в основном расценивается как доброкачественное, стабильное поражение, которое у большинства пациентов может незначительно увеличиваться в размерах в течение жизни и не влиять на качество зрения [7,8]. Для ВГПЭС связанным с САПТК в клинической литературе есть ряд особенностей, которые могут натолкнуть врача на мысль, что у пациента возможен САПТК. Поражения, связанные с САПТК, почти всегда двусторонние, множественные, локализуются в нескольких квадрантах глазного дна, гороховидной, округлой или веретенообразной формы и неровными границами [8–10]. Наличие вышеуказанных особенностей может стать сигналом к прохождению эндоскопического исследования с целью исключения САПТК. В недавнем исследовании, которое опубликовали иранские врачи, рассматривали группу пациентов, состоящую из 23 человек с подтвержденным САПТК и 26 человек их родственников; у 10 человек поражение затрагивало только один глаз, а у 4 было

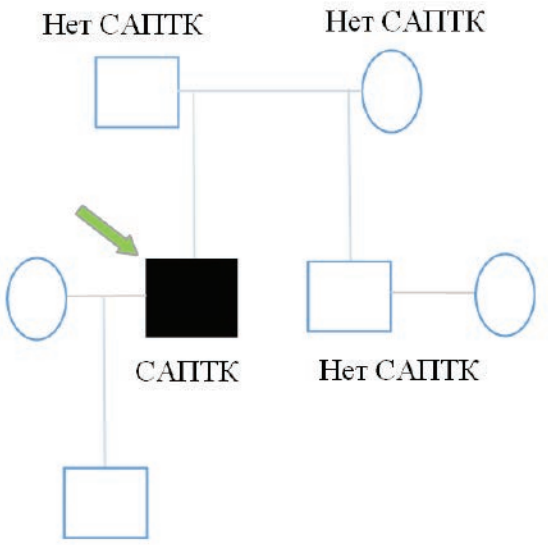

Рисунок 5. *Родословная пациента (указан стрелкой) с САПТК.*
Figure 5. *Family tree of patients (is indicated by the arrow) with FAP*

одиночным [11]. Как видим, синдром ВГПЭС у пациентов с САПТК не имеет каких-либо патогномоничных особенностей, поэтому всем пациентам с ВГПЭС, особенно с отягощенным семейным анамнезом по колоректальному раку необходимо проводить колоноскопию.

На современном этапе радикальное лечение САПТК только хирургическое. В арсенале хирургов имеется несколько видов профилактических операций: колпроктэтомия с выведением одноствольной колостомы на переднюю брюшную стенку, колэктомия с илеоректальным анастомозом, колпроктэктомия с илеоанальным анастомозом [4,12,13]. В зарубежной клинической литературе описаны результаты лечения при помощи нестероидных противовоспалительных препаратов, которые, в ряде случаев, приводят к уменьшению количества и размера полипов, но не препятствую озлокачествлению аденом [14]. В нашем случае, учитывая молодой возраст пациента, его негативного отношения иметь пожизненную стому и, что очень важно, интактность части прямой кишки относительно полипов, было принято решение о выполнении колэктомии с формированием илеоректального анастомоза. Гистологическое исследование удаленного препарата трансформацию аденом в рак не выявило. В дальнейшем пациент проходит два раза в год контрольные исследования (фиброколоноскопия), по результатам которых роста полипов в оставшейся части прямой кишки не отмечается.

По нашему мнению, синдром ВГПЭС является классическим примером, когда для успешного лечения заболевания необходимо тесное взаимодействие смежных специальностей. В описанном клиническом случае пациенту повезло, что за период от

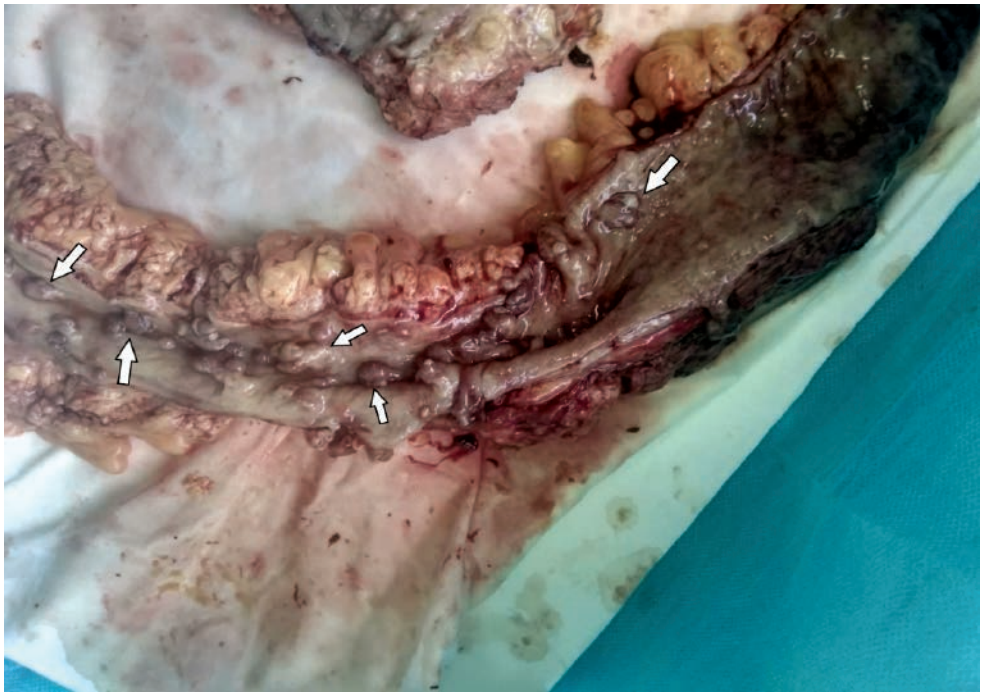

Рисунок 6. *Удаленный участок поперечно-ободочной кишки с переходом на левые отделы толстой кишки. На всем протяжении отмечаются мелкие полипы, диаметром от 0,5 см*
Figure 6. *Remote section of the transverse colon with a transition to the left sections of the colon. Small polyps are noted throughout, with a diameter of 0.5 cm.*

постановки диагноза ВГПЭС и оперативным лечением по поводу САПТК, не произошло озлокачествления полипов толстой кишки. Проведение исследований на ВГПЭС является очень простым, не требует инвазивных манипуляций, легко переносится пациентом и, по сравнению с генетическим исследованием или фиброколоноскопией, дешевле. Генетический скрининг при ВГПЭС, по-нашему мнению, также необходим, так как отрицательный семейный анамнез не гарантирует мутацию *de novo*, и когда на колоноскопии выявлено больше 10 полипов. При обнаружении ВГПЭС необходимо проверить на САПТК всех членов семьи, находящихся в зоне риска.

ЗАКЛЮЧЕНИЕ

Скрининг на ВГПЭС — доступный, простой в проведении и безопасный для пациентов метод исследования. Он может быть использован в качестве первой линии диагностики САПТК. В сочетании с дополнительными методами диагностики, исследование глазного дна на ВГПЭС имеет неоценимое значение для ранней диагностики пациентов с семейным полипозом толстой кишки.

УЧАСТИЕ АВТОРОВ

Концепция и дизайн исследования: *Крячко А.А., Чугузов К.Д., Дурлештер В.М.*

Сбор и обработка материала: *Чугузов К.Д., Карагодина П.А.*

Написание текста: *Чугузов К.Д., Крячко А.А., Карагодина П.А.*

Редактирование: *Крячко А.А., Дурлештер В.М., Чугузов К.Д.*

AUTHORS CONTRIBUTION

Concept and design of the study: *Andrei A. Kryachko, Konstantin D. Chuguzov, Vladimir M. Durleshter.*

Collection and processing of the material: *Konstantin D. Chuguzov, Polina A. Karagodina.*

Writing of the text: *Konstantin D. Chuguzov, Andrei A. Kryachko, Polina A. Karagodina.*

Editing: *Andrei A. Kryachko, Vladimir M. Durleshter, Konstantin D. Chuguzov.*

СВЕДЕНИЯ ОБ АВТОРАХ (ORCID)

Крячко Андрей Анатольевич — кандидат медицинских наук; ассистент кафедры хирургии № 3 ФПК и ППС федерального государственного бюджетного образовательного учреждения высшего образования «Кубанский медицинский университет» Министерства здравоохранения Российской Федерации; врач-хирург-колопроктолог хирургического отделения № 3 государственного бюджетного учреждения здравоохранения «Краевая клиническая больница № 2» Министерства здравоохранения Краснодарского края; https://orcid.org/0000-0001-6399-2340

Чугузов Константин Дмитриевич — аспирант кафедры хирургии № 3 ФПК и ППС федерального государственного бюджетного образовательного учреждения высшего образования «Кубанский медицинский университет» Министерства здравоохранения Российской Федерации, врач-хирург хирургического отделения № 3 государственного бюджетного учреждения здравоохранения «Краевая клиническая больница № 2» Министерства здравоохранения Краснодарского края; https://orcid.org/0000-0003-1192-5239

Дурлештер Владимир Моисеевич — доктор медицинских наук, профессор; заведующий кафедрой хирургии № 3 ФПК и ППС федерального государственного бюджетного образовательного учреждения высшего образования «Кубанский медицинский университет» Министерства здравоохранения Российской Федерации; заместитель главного врача по хирургии государственного бюджетного учреждения здравоохранения «Краевая клиническая больница № 2» Министерства здравоохранения Краснодарского края; https://orcid.org/0000-0003-2885-7674

Карагодина Полина Алексеевна — врач-офтальмолог краснодарского филиала федерального государственного автономного учреждения «Национальный медицинский исследовательский центр «Межотраслевой научно-технический комплекс»; https://orcid.org/0000-0002-9411-7052

INFORMATION ABOUT THE AUTHORS (ORCID)

Andrei A. Kryachko — 0000-0001-6399-2340

Konstantin D. Chuguzov — 0000-0003-1192-5239

Vladimir M. Durleshter — 0000-0003-2885-7674

Polina A. Karagodina — 0000-0002-9411-7052

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Комментарии редколлегии к статье

«Врожденная гипертрофия пигментного эпителия сетчатки у пациента с семейный аденоматозным полипозом толстой кишки (клинический случай)», авторы: Крячко А.А., Чугузов К.Д., Дурлештер В.М., Карагодина П.А.

Статья посвящена описанию клинического наблюдения за пациентом с семейным аденоматозом толстой кишки (САТК), у которого на доклинической стадии заболевания была выявлена врожденная гипертрофия пигментного эпителия сетчатки (ВГПЭС), однако связь между этими состояниями не была установлена вовремя. Из мировой литературы хорошо известно, что ВГПЭС впервые была описана в 80-е годы прошлого столетия как одно из наиболее ранних внекишечных проявлений САТК [1]. При этом было отмечено, что феномен ВГПЭС наблюдали почти у 90% пациентов-носителей мутации в гене *APC* в то время как частота выявления в общей популяции составляла 1,2–4,4% [2,3]. Таким образом в то время многие специалисты, в том числе и отечественные, рассматривали исследование глазного дна для выявления ВГПЭС как метод ранней диагностики заболевания среди близких родственников больных с САТК [4]. Однако результаты опубликованного недавно систематического обзора, основанного на анализе 28 клинических исследований, включивших данные о 4451 пациенте, свидетельствуют о 89% специфичности при чувствительности 79% метода выявления ВГПЭС в качестве индикатора наличия у пациента САТК. На основании этого авторы приходят к выводу о высокой вероятности ложноотрицательных результатов (наличие САТК у пациента при отсутствии ВГПЭС) [5]. Таким образом, в настоящее время с развитием медицинских технологий и успехов молекулярной генетики офтальмологический осмотр *может* быть использован в комплексной диагностике САТК, однако ведущими методами продолжают оставаться эндоскопическое исследование толстой кишки и молекулярно-генетическое исследование с определением наличия патогенной мутации в гене *APC*.

Одновременно с этим считаем крайне важным отметить, что хирургическая тактика лечения, выбранная у пациента из приведенного клинического наблюдения, не соответствует современным отечественным и зарубежным клиническим рекомендациям. Учитывая приведенные в статье данные, мы вправе констатировать наличие у него классической формы САТК (возраст манифестации, количество полипов, ранее описанная патогенная мутация в гене *APC*) [6]. Несмотря на указанные данные об отсутствии полипов в прямой кишке на момент диагностики, не вызывает сомнений тот факт, что в оставленных 17 см кишки заболевание будет прогрессировать с высоким риском развития рака, что в конечном итоге приведет к необходимости выполнения повторной операции по удалению оставленных отделов прямой кишки.

В заключение хотим обратить внимание на тот факт, что в современных условиях только сочетание своевременного выявления заболевания с адекватным лечением на основе принятых стандартов может являться залогом успешности ведения больных.

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Эффективность и безопасность лапароскопической вентральной ректопексии сетчатым имплантом (систематический обзор)

Хитарьян А.Г.[1,2], Головина А.А.[1,2], Ковалев С.А.[1,2], Бурцев С.С.[1]

[1]ФГБОУ ВО «Ростовский государственный медицинский университет», кафедра хирургических болезней №3 (пер. Нахичеванский, д. 29, г. Ростов-на-Дону, 344022, Россия)
[2]ЧУЗ «Клиническая больница «РЖД-Медицина» (ул. Варфоломеева, д. 92а, г. Ростов-на-Дону, 344011, Россия)

РЕЗЮМЕ *ЦЕЛЬ ИССЛЕДОВАНИЯ: изучение эффективности и безопасности метода лапароскопической вентральной ректопексии сетчатым имплантом в лечении пациентов с ректоцеле и выпадением прямой кишки.*
МАТЕРИАЛЫ И МЕТОДЫ: нами был проведен систематический обзор литературы по эффективности и безопасности лапароскопической вентральной ректопексии у пациентов с ректоцеле и/или выпадением прямой кишки. После составления поискового запроса в базах данных PubMed, MEDLINE, EMBASE, Scopus, Cochrane library, CENTRAL, ISI Web of Science и eLibrary было найдено 2716 публикаций. Из них по критериям включения в обзор было отобрано 34 работы с общим числом прооперированных пациентов — 2101 человек.
РЕЗУЛЬТАТЫ: период наблюдения за пациентами после проведения оперативного лечения варьировал от 12 до 74 месяцев (среднее — 30,1 мес.). В 20 из 34 исследований средний возраст пациентов был более 60 лет, и, в среднем, составил 62,1 год. Среднее время операции составило 122,3 мин. (от 85 до 200 минут). Среди проанализированных работ общее число осложнений составило 138 (6,5%) пациентов. Рецидив заболевания наблюдался в 4,1% случаев от общего числа включенных больных. Значительное улучшение симптомов обструктивной дефекации отмечено в 79,6% наблюдений.
ВЫВОДЫ: лапароскопическая вентральная ректопексия является эффективной методикой коррекции пролапса заднего компартмента тазового дна в отношении как анатомических, так и функциональных результатов, безопасной и имеет низкий риск возникновения осложнений. Однако требуется проведение дальнейших исследований по разработке показаний для применения данного вмешательства в качестве «операции выбора».

КЛЮЧЕВЫЕ СЛОВА: *лапароскопическая вентральная ректопексия, ректоцеле, выпадение прямой кишки, ректальная инвагинация, синдром обструктивной дефекации*

КОНФЛИКТ ИНТЕРЕСОВ: *авторы заявляют об отсутствии конфликта интересов*

ДЛЯ ЦИТИРОВАНИЯ: Хитарьян А.Г., Головина А.А., Ковалев С.А., Бурцев С.С. Эффективность и безопасность лапароскопической вентральной ректопексии сетчатым имплантом (систематический обзор). *Колопроктология*. 2022; т. 21, № 2, с. 122–131. https://doi.org/10.33878/2073-7556-2022-21-2-122-131

Efficiency and safety of laparoscopic ventral mesh rectopexy (a systematic review)

Alexander G. Khitaryan[1,2], Anastasia A. Golovina[1,2], Sergey A. Kovalev[1,2], Spartak S. Burtsev[1]

[1]FSBEI HE "Rostov State Medical University", Department of Surgical Diseases №3 (Nakhichevansky lane, 29, Rostov-on-Don, 344022, Russia)
[2]Private Healthcare Institution "Clinical Hospital" Russian Railways-Medicine"(Varfolomeeva street, 92a, Rostov-on-Don, 344011, Russia).

ABSTRACT *AIM: to assess the efficacy and safety of laparoscopic ventral mesh rectopexy in patients with rectocele and rectal prolapse.*
MATERIALS AND METHODS: a systematic review of the literature on the efficacy and safety of laparoscopic ventral mesh rectopexy in patients with rectocele and/or rectal prolapse. After compiling a search query, 2716 publications were found in the PubMed, MEDLINE, EMBASE, Scopus, Cochrane library, CENTRAL, ISI Web of Science and eLibrary databases. Twenty-four papers were selected according to the inclusion criteria for the review, with a total number of 2101 operated patients.

RESULTS: the follow up period after surgery ranged 30.1 (12-74) months. In 20 of 34 studies, the median age of patients was over 60 years, with a median of 62.1 years. The mean operative time was 122.3 minutes (85 to 200 minutes). Complications were revealed in 138 patients (6.5% observations), recurrence — in 4.1%. A significant improvement in the symptoms of obstructive defecation was noted in 79.6%.
CONCLUSION: laparoscopic ventral mesh rectopexy is an effective method for posterior pelvic floor compartment prolapse in terms of both anatomical and functional results. It is safe and has a low risk of complications. However, further research is required to develop indications for the use of this proctdure as a "gold standard".

KEYWORDS: *laparoscopic ventral mesh rectopexy, rectocele, rectal prolapse, rectal intussusception, obstructive defecation syndrome.*

CONFLICT OF INTEREST: *the authors declare no conflict of interest*

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АДРЕС ДЛЯ ПЕРЕПИСКИ: *Хитарьян А.Г., ФГБОУ ВО «РостГМУ», ул. Варфоломеева, д. 92а, Ростов-на-Дону, 344011, Россия; e-mail: khitaryan@gmail.com*
ADDRESS FOR CORRESPONDENCE: *Khitaryan A.G., Rostov State Medical University, Varfolomeeva st., 92a, Rostov-on-don, 344011, Russia; e-mail: khitaryan@gmail.com*

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ВВЕДЕНИЕ

За последние десятилетия было разработано значительное число новых методов лечения различных форм пролапса заднего компартмента тазового дна. Существующие на сегодняшний день методики можно условно разделить на две большие подгруппы: вмешательства, выполняемые с использованием тазового доступа (промежностные, трансвагинальные и трансректальные) и трансабдоминальные операции. Первые чаще применяются у пожилых и коморбидных пациентов, однако, они также имеют более высокий процент рецидивов [1,2]. Общее направление развития хирургии в сторону минимально-инвазивных вмешательств и максимально быстрой реабилитации, а также активного внедрения высокотехнологичных операций, в пельвиоперинеологии отразилось в нарастающем тренде увеличения доли лапароскопических и робот-ассистированных вмешательств при пролапсе тазовых органов. На рисунке 1 представлена динамика общих тенденций хирургического лечения пациентов с диагнозом «выпадение прямой кишки» и «тазовый пролапс» на основе анализа данных о ведении 481 051 больных в период с 2003 по 2017 гг. [3]. Из рисунка наглядно видно, что несмотря на рост числа выполняемых лапароскопических операций, процентное соотношение между числом промежностных, трансабдоминальных и комбинированных операций остается существенно большим в сторону промежностного доступа.

К сожалению, в настоящий момент строгих рекомендаций по выбору метода оперативного лечения той или иной формы тазового пролапса как в России, так и за рубежом, не существует [2,4].

Нарастающая популярность трансабдоминальных вмешательств обусловлена их высокой эффективностью и низким процентом осложнений. Одной из самых распространенных трансабдоминальных операций для коррекции ректоцеле, внутренней инвагинации и полнослойного выпадения прямой кишки на сегодняшний день является вентральная ректопексия с использованием сетчатого импланта. Данная методика была впервые предложена бельгийским хирургом D'Hoore в 2004 году в качестве техники, позволяющей выполнить коррекцию ректального пролапса без увеличения частоты обструктивной дефекации и обстипационного синдрома *de novo* за счет ограничения площади диссекции вдоль прямой кишки исключительно ее передней поверхностью и, как следствие, сохранения автономной иннервации стенок кишечника [5]. Суть ее заключается следующем: после установки троакаров, осмотра органов брюшной полости и малого таза сигмовидную кишку отводят инструментом влево и начинают рассечение париетальной брюшины по J-образной кривой линии от области мыса крестца до самой глубокой точки прямокишечно-маточного углубления. С осторожностью, чтобы не повредить правый мочеточник, гипогастральные нервы и подвздошные сосуды, в области мыса обнажают переднюю продольную связку позвоночника и формируют площадку для фиксации одного из концов сетчатого импланта. Затем выполняют диссекцию тканей в области Дугласова кармана до уровня мышц тазового дна с последующей установкой сетчатого импланта в форме ленты в ректовагинальном пространстве и фиксацией его противоположного конца к передней продольной связке крестца, как изображено на рисунке 2.

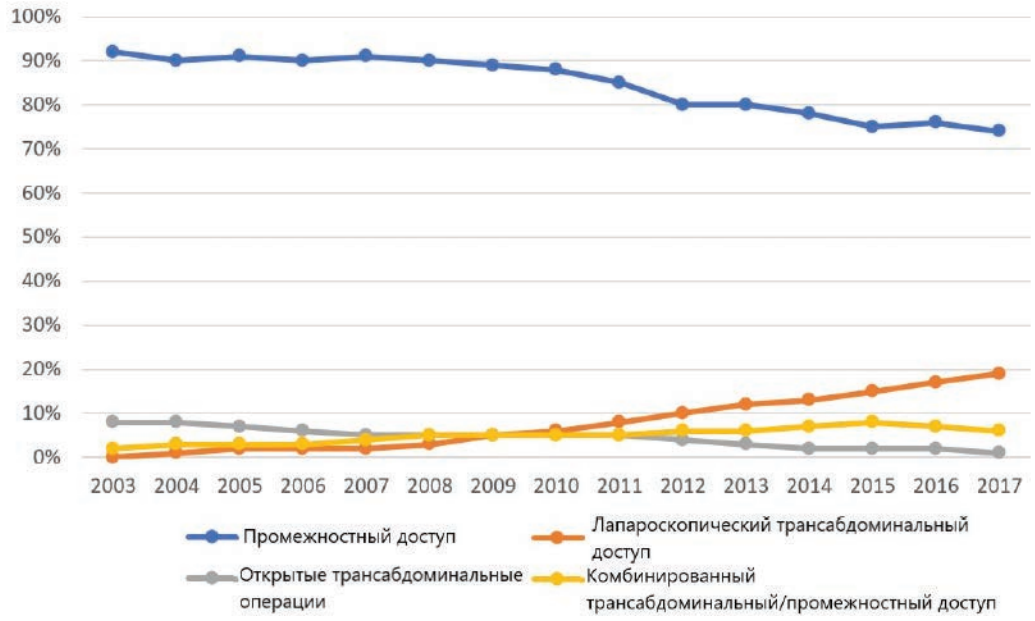

Рисунок 1. *Тренды в оперативном лечении заднего тазового пролапса [3]*
Figure 1. *Trends in surgical treatment of posterior pelvic prolapse [3]*

В последние годы лапароскопический и робот-ассистированный варианты исполнения данной методики набирают все большую популярность в качестве малотравматичного, безопасного и высокоэффективного способа коррекции различных форм пролапса заднего компартмента тазового дна (в т.ч. ректоцеле, внутренней инвагинации и полнослойного выпадения прямой кишки, энтероцеле) [6,7]. Однако имеющиеся в доступной зарубежной и отечественной литературе данные в основном ограничиваются исследованиями с небольшим числом включенных пациентов, что требует проведения обобщенного анализа для повышения уровня доказательности полученных сведений о безопасности и эффективности методики. Нерешенным также остается вопрос разработки критериев отбора пациентов для проведения данной процедуры, а имеющаяся на сегодняшний день практика основывается в большей степени на опыте конкретного хирурга и медицинского учреждения.

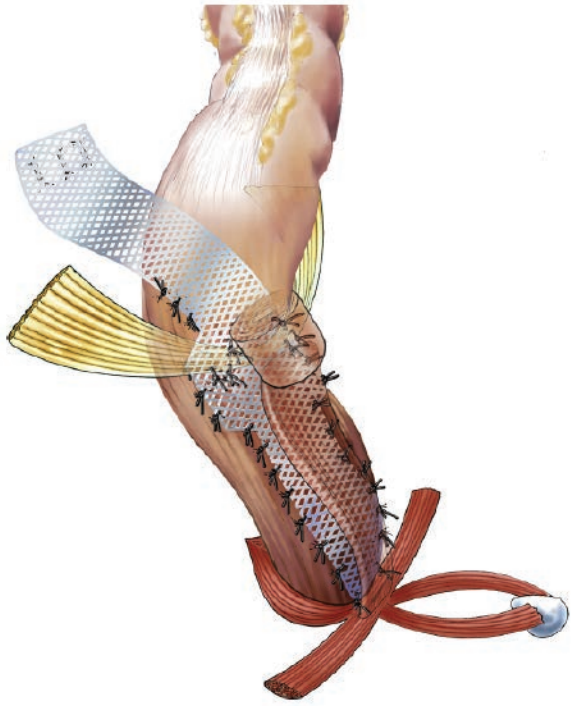

Рисунок 2. *Схематическое изображение расположения импланта при лапароскопической вентральной ректопексии сетчатым имплантом*
Figure 2. *Schematic representation of the implant location during laparoscopic ventral rectopexy with a mesh implant*

ЦЕЛЬ ИССЛЕДОВАНИЯ

Целью настоящего исследования было изучение эффективности и безопасности метода лапароскопической вентральной ректопексии сетчатым имплантом в лечении пациентов с ректоцеле и выпадением прямой кишки.

МАТЕРИАЛЫ И МЕТОДЫ

Нами был проведен анализ доступной литературы по эффективности и безопасности лапароскопической вентральной ректопексии у пациентов

с ректоцеле и/или выпадением прямой кишки (Табл. 1). Поиск публикаций проводился по электронным базам данных PubMed, MEDLINE, EMBASE, Scopus, Cochrane library, CENTRAL, ISI Web of Science и eLibrary по ключевым словам “rectopexy”, “ventral rectopexy”, “laparoscopic rectopexy”, “ventral mesh rectopexy”, “anterior rectopexy”, “rectocele”, “external rectal prolapse”, “total rectal prolapse”, “full-thickness rectal prolapse”, “obstructed defecation” and “fecal incontinence” в сочетании с медицинскими предметными рубриками (MeSH terms) “robotics”, “laparoscopy”, “rectocele”, “rectal prolapse”, “constipation”, “fecal incontinence”, и “rectopexy”. Для расширения поиска использовали также функцию «связанные публикации» и просматривали список использованной литературы всех статей на предмет соответствующих ссылок.

Критериями отбора публикаций были определены следующие параметры:

– полнотекстовые статьи, содержащие результаты проспективных рандомизированных клинических исследований, обсервационных когортных исследований, исследований случай-контроль;
– публикации на английском или русском языках или с доступной развернутой аннотацией на английском языке;
– исследования, в которых лапароскопическая вентральная ректопексия выполнялась как минимум 10 пациентам;
– срок наблюдения 12 месяцев и более;
– за период с января 2000 года по апрель 2020 гг.

Из анализа данных были исключены клинические случаи и короткие сообщения, редакционные комментарии и письма, не полнотекстовые статьи, обзоры литературы и метаанализы, а также исследования с периодом наблюдения за пациентами менее 12 месяцев. Дополнительно были исключены исследования, в которых не указана методология проведения работы, недостаточно определенно описана техника оперативного вмешательства, демографические характеристики пациентов и результаты лечения.

Полученные по результатам поиска статьи затем были проанализированы на предмет дублирования исследуемых групп в разных публикациях одних и тех же авторов и на предмет наличия описания хотя бы одной из следующих конечных точек: анатомические и функциональные результаты вмешательства, частота рецидивов, продолжительность операции, осложнения, период наблюдения. Полнотекстовые версии всех публикаций были изучены одним из авторов под руководством и супервизией главного автора (А.Г.Х.) на предмет соответствия критериям включения в настоящий обзор и оценки качества рассматриваемой работы.

После составления поискового запроса в электронных базах данных было найдено 2716 публикаций. Из них при скрининге заголовков, аннотаций и полнотекстовых форматов статей по критериям включения в обзор было отобрано 34 работы (Рис. 3).

Настоящий обзор представлен в соответствии с рекомендациями группы PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [8].

Все полученные данные были собраны и структурированы в одну базу данных при помощи программы MS Excel 12 (производитель Microsoft, США). Описательный и сравнительный статистический анализ осуществляли при помощи пакетов прикладных программ SPSS Statistic 26.0 (производитель IBM, США) и Statistica 10.0 (производитель StatSoft, США). Для описания категориальных (номинальных) данных использовали абсолютные (количество) и относительные (проценты) данные, а для их сравнения применяли критерий χ^2 Пирсона. При сравнительном анализе статистически значимыми различия между группами считали, когда уровень значимости p был менее 0,05 ($p < 0,05$).

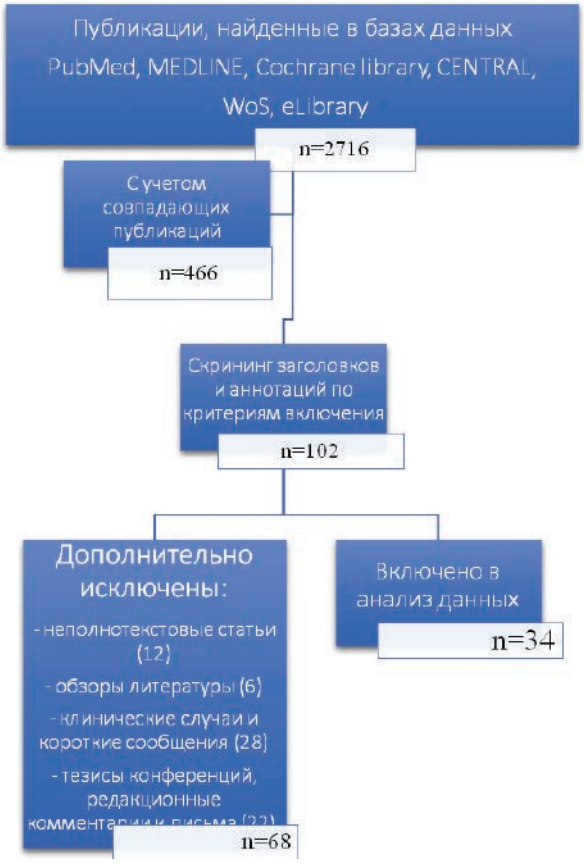

Рисунок 3. *Схема поиска и отбора публикаций для включения в обзор*

Figure 3. *Scheme of search and selection of publications for inclusion in the review*

Таблица 1. *Характеристика включенных в обзор исследований вентральной ректопексии у пациентов с ректоцеле и/или выпадением прямой кишки*
Table 1. *Characteristics of the studies of ventral rectopexy included in the review in patients with rectocele and/or rectal prolapse*

Исследование, авторы	Год	Страна	Тип исследования	Число пациентов, абс.	Период наблюдения, мес. (медиана)
Albayati et al. [9]	2017	Австралия	Ретроспективное	51	22
Benoist et al. [10]	2001	Великобритания	Ретроспективное	14	24
Bjerke et al. [11]	2014	Дания	Ретроспективное	40	18
Boons et al. [12]	2010	Великобритания	Проспективное	65	19
Brunner et al. [13]	2018	Германия	Проспективное	13	29
Byrne et al. [14]	2008	Австралия	Проспективное	126	60
Chandra et al. [15]	2016	Индия	Ретроспективное	15	34
Collinson et al. [16]	2010	Великобритания	Проспективное	75	12
Consten et al. [17]	2015	Многоцентровое	Ретроспективное	242	40
D'Hoore et al. [18]	2006	Бельгия	Проспективное	109	–
Emile et al. [7]	2017	Египет	РКИ	25	18
Faucheron et al. [19]	2012	Франция	Проспективное	175	74
Franceschilli et al. [20]	2015	Италия	Проспективное	98	20
FormijneJonkers et al. [21]	2014	Многоцентровое	Ретроспективное	40	42
Fu and Stevenson [22]	2017	Австралия	Ретроспективное	113	47
Gleditsch et al. [23]	2018	Норвегия	Ретроспективное	22	29
Gosselink et al. [24]	2015	Великобритания	Проспективное	91	12
Hidaka et al. [25]	2019	Многоцентровое	РКИ	34	72
Lechaux et al. [26]	2005	Франция	Ретроспективное	35	36
Luglio et al. [27]	2017	Италия	РКИ	20	12
Lundby et al. [28]	2016	Дания	РКИ	38	12
Madbouly et al. [29]	2017	Египет	Ретроспективное	41	46
Maggiori et al. [30]	2013	Франция	Проспективное	20	42
Mantoo et al. [31]	2013	Франция	Проспективное	23	16
Mehmood et al. [32]	2014	Великобритания	Проспективное	34	12
Ogilvie et al. [33]	2014	США	Проспективное	33	16
Owais et al. [34]	2014	Великобритания	Проспективное	18	42
Portier et al. [35]	2011	Франция	Проспективное	40	22
Randall et al. [36]	2014	Великобритания	Проспективное	190	29
Rautio et al. [37]	2016	Финляндия	Ретроспективное	52	56
Tsunoda et al. [38]	2016	Япония	Проспективное	44	26
Tsunoda et al. [39]	2019	Япония	Ретроспективное	58	49
Wahed et al. [40]	2012	Великобритания	Проспективное	27	12
Wijffels et al. [41]	2011	Великобритания	Ретроспективное	80	23

РЕЗУЛЬТАТЫ

Из полученных источников была отобрана следующая информация:
- тип исследования, страна, год;
- период наблюдения за пациентами;
- предоперационные характеристики пациентов, включая их число, пол, возраст, выраженность клинических симптомов по различным шкалам, предшествующие операции на прямой кишке и органах малого таза;
- технические детали операции, включая продолжительность, частоту конверсий, тип и размеры сетчатых имплантов, способы фиксации, число интраоперационных осложнений;
- число, вид и степень тяжести послеоперационных осложнений;
- частота рецидивов, анатомические и функциональные результаты.

Обобщенные данные отобранных исследований по лапароскопической вентральной ректопексии представлены в таблице 1.

В настоящий обзор были включены данные 34 работ, опубликованных в период с 2000 по 2020 гг. Среди них 26 исследований было проведено в странах Европы, 3 — в Австралии, по 2 — в Египте и Японии, и по 1 — в США и Индии. Семнадцать исследований являлись проспективными, 13 — ретроспективными, 4 — РКИ (рандомизированными клиническими исследованиями).

Общее число пациентов составило 2101 человек, среди которых женщин было 1745 человек, мужчин — 207, а для 149 человек пол указан не был. Соотношение полов между мужчинами и женщинами — 1:9. Период

Таблица 2. *Предоперационные характеристики пациентов*
Table 2. *Preoperative characteristics of patients*

Исследование, авторы	Число пациентов, абс.	Возраст пациентов, лет (медиана)	Пол — доля женщин, %	Предшествующие операции по поводу пролапса, *n* (%)
Albayati et al. [9]	51	57	100	4 (8)
Benoist et al. [10]	14	76	100	3 (21)
Bjerke et al. [11]	40	83	100	14 (30,4)
Boons et al. [12]	65	72	92	0
Brunner et al. [13]	13	65	94	2 (1,7)
Byrne et al. [14]	126	56	–	–
Chandra et al. [15]	15	50	60	2 (13,3)
Collinson e tal. [16]	75	58	92	–
Consten et al. [17]	242	56	95	–
D'Hoore et al. [18]	109	46	92	18 (20)
Emile et al. [7]	25	40	62	0
Faucheron et al. [19]	175	58	90	6 (3,4)
Franceschilli et al. [20]	98	63	100	–
FormijneJonkers et al. [21]	40	67	90	–
Fu and Stevenson [22]	113	65	100	38 (33,6)
Gleditsch et al. [23]	22	72	83	10 (7,7)
Gosselink et al. [24]	91	63	93	–
Hidaka et al. [25]	34	57	91	–
Lechaux et al. [26]	35	53	92	0
Luglio et al. [27]	20	68	100	–
Lundby et al. [28]	38	60	92	–
Madbouly et al. [29]	41	55	81	–
Maggiori et al. [30]	20	64	85	–
Mantoo et al. [31]	23	62	–	74 (51)
Mehmood et al. [32]	34	59	94	19 (55,9)
Ogilvie et al. [33]	33	72	100	–
Owais et al. [34]	18	35	0	41 (60)
Portier et al. [35]	40	61	100	40 (100)
Randall et al. [36]	190	69	87	46 (24,2)
Rautio et al. [37]	52	46	0	4 (7,7)
Tsunoda et al. [38]	44	76	100	–
Tsunoda et al. [39]	58	80	90	–
Wahed et al. [40]	27	62	93	4 (6,8)
Wijffels et al. [41]	80	84	98	33 (42,1)

наблюдения за пациентами после проведения оперативного лечения в данных работах варьировал от 12 до 74 месяцев (среднее — 30,1 мес.). В 20 из 34 исследований средний возраст пациентов был более 60 лет, и, в среднем, составил 62,1 год. Медиана ИМТ составила 25 кг/м^3 (22–29 кг/м^3). Медиана продолжительности симптомов у пациентов на момент проведения хирургического лечения была 60 месяцев (от 15,6 до 120 месяцев). 358 пациентов из 20 включенных исследований были ранее оперированы по поводу пролапса заднего компартмента тазового дна. В 14 работах доля пациентов, имевших предшествующие вмешательства по поводу пролапса тазовых органов, а также другие операции в аноректальной области, не сообщается.

Предоперационных характеристики пациентов, включенных в исследования и рассматриваемые в рамках настоящего обзора, представлены таблице 2.

Среди проанализированных работ общее число осложнений составило 138 (6,5%) пациентов. Наиболее частыми отмечены различные осложнения со стороны мочевыводящей системы: инфекция НМВП встречалась в 29 (2,4%) наблюдениях, острая задержка мочеиспускания — у 7 (0,3%) пациентов, а также наблюдались единичные случаи повреждения мочеточников и мочевого пузыря. Mesh-ассоциированные осложнения в изученных работах встречались в 0,7% случаев. Частота всех осложнений более подробно представлена в таблице 3.

В стандартизованной технике выполнения лапароскопической вентральной ректопексии среди включенных исследований наблюдалась определённая неоднородность в отношении типа используемого сетчатого имплантата (Табл. 4), а также его формы и способа фиксации. В большинстве рассмотренных работ для фиксации применяли одну полосу

синтетической полипропиленовой или полиэстеровой сетки, за исключением двух исследований, в которых имплантат состоял из 2 полос. Длина используемой сетки также варьировала от 15 до 20 см. Различался и способ фиксации краниального конца к передней продольной связке: в половине работ использовали герниостеплер (Protack), в остальных — либо шов, либо эндогерниостеплер.

Среднее время операции составило 122,3 мин. (от 85 до 200 минут). Состав хирургической бригады и опыт оперирующего хирурга освещен лишь в нескольких исследованиях. Частота конверсий в совокупности составила 1,8% наблюдений.

Рецидив заболевания наблюдался у 4,1% от общего числа включенных больных. Значительное улучшение симптомов обструктивной дефекации наблюдалось в 79,6% наблюдений. Однако для оценки степени выраженности синдрома обструктивной дефекации и анального недержания в рассматриваемых исследованиях использованы различные методики: шкалы Векснера и Cleveland Clinic, St. Mark's incontinence score, Римские критерии 2 пересмотра, ВАШ и отдельные сообщения о необходимости ношения гигиенических прокладок. Данный факт существенно затрудняет объективный анализ описываемых функциональных улучшений в послеоперационном периоде. Неосвещенным также остается и динамика функционального состояния органов малого таза с течением времени в различные периоды после проведенного оперативного лечения.

По данным литературы, лапароскопическая вентральная ректопексия является высокоэффективной процедурой для анатомической коррекции заднего тазового пролапса, имеет низкий риск осложнений и короткий реабилитационной период [8–24]. В ходе вмешательства от хирурга требуется проведение прецизионной дифференциации и диссекции тканей и четкое обнаружение анатомических ориентиров — гипогастральных нервов, правого мочеточника, правых общей и внутренней подвздошной артерии, срединных сакральных артерии и вены, продольной связки крестца, а также точные манипуляции в ограниченном пространстве малого таза.

Таблица 3. *Частота возникновения различных послеоперационных осложнений при выполнении лапароскопической вентральной ректопексии*

Table 3. *Frequency of occurrence of various postoperative complications during laparoscopic ventral rectopexy*

Инфекция мочевыводящих путей	**29 (2,4)**
Троакарная грыжа	14 (0,7)
Парез кишечника	12 (1)
Гематома	11 (0,8)
Боль	8 (0,5)
Острая задержка мочеиспускания	7 (0,3)
Гнойные осложнения п/о ран	5 (0,4)
Перфорация кишечника	3 (0,2)
Пневмония	3 (0,2)
Подкожная эмфизема	3 (0,2)
Недержание мочи	3 (0,2)
Повреждение мочеточника	2 (0,1)
Кишечная непроходимость	2 (0,2)
Инфекция неуточненная	2 (0,2)
Ателектаз легкого	1 (0,1)
Повреждение мочевого пузыря	1 (0,1)
Каловый завал	1 (0,1)
Гиперволемия	1 (0,1)
Поясничный спондилодисцит	1 (0,1)
Инфаркт миокарда	1 (0,1)
Кровотечение неуточненное	1 (0,1)
Тазовый абсцесс	1 (0,1)
Неуточненные осложнения	25 (1,2)
Всего	**138 (6,5)**

ВЫВОДЫ

Лапароскопическая вентральная ректопексия является на сегодняшний день широкого распространенным видом оперативного вмешательства в коррекции пролапса заднего компартмента тазового дна. Методика является эффективной в отношении как анатомических, так и функциональных результатов, безопасной и имеет низкий риск возникновения осложнений. Однако требуется проведение дальнейших исследований по разработке показаний для применения данного вмешательства в качестве «операции выбора».

УЧАСТИЕ АВТОРОВ

Концепция и дизайн исследования: *Хитарьян А.Г., Головина А.А.*

Сбор и обработка материала: *Головина А.А., Ковалев С.А., Бурцев С.С.*

Статистическая обработка: *Головина А.А., Бурцев С.С.*

Написание текста: *Хитарьян А.Г., Головина А.А.*

Редактирование: *Хитарьян А.Г., Головина А. А.*

AUTHORS CONTRIBUTION

Concept and design of the study: *Alexander G. Khitaryan, Anastasia A. Golovina*

Collection and processing of material: *Anastasia A. Golovina, Sergey A. Kovalev, Spartak S. Burtsev*

Statistical processing: *Anastasia A. Golovina, Spartak S. Burtsev*

Text writing: *Alexander G. Khitaryan, Anastasia A. Golovina*

Editing: *Alexander G. Khitaryan, Anastasia A. Golovina*

Таблица 4. *Сводная таблица результатов лапароскопической вентральной ректопексии*
Table 4. *Summary table of laparoscopic ventral rectopexy results*

Исследование, авторы	Осложнения абс. (%)	Время операции, мин.	Тип используемого сетчатого импланта	Улучшение обструктивной дефекации (%)	Улучшение анального держания (%)	Рецидив абс. (%)
Albayati et al. [9]	7 (13,7)	176	Биологический	11 (33,3)	6 (13,3)	3 (5,8)
Benoist et al. [10]	2 (14)	113,5	Не указано	–	9 (64)	0 (0)
Bjerke et al. [11]	7 (15,2)	135	Синтетический (Vypro)	33,3	–	2 (4,3)
Boons et al. [12]	11 (16,9)	140	Синтетический (полипропилен)	71,8	85,1	1 (1,5)
Brunner et al. [13]	17 (14)	–	Биологический	86,7	95	6 (5)
Byrne et al. [14]	3 (3,78)	–	Синтетический	39		5 (4)
Chandra et al. [15]	4 (26,6)	200	Синтетический (полипропилен)	84,6	92,6	0
Collinson et al. [16]	3 (4)	–	Синтетический	53	71	4 (5)
Consten et al. [17]	65 (26,8)	–	Синтетический (полипропилен, Марлекс, Hi-TECH)	61	63,3	13 (5,4)
D'Hoore et al. [18]	8 (7)	–	Синтетический	–	–	4 (3,7)
Emile et al. [7]	5 (20)	114	Синтетический (полипропилен)	100	75	2 (8)
Faucheron et al. [19]	7 (4)	–	Синтетический	–	–	2 (1,1)
Franceschilli et al. [20]	16 (16)	–	Биологический	92	95	14 (14,3)
Formijne Jonkers et al. [21]	4 (10)	–	Синтетический (полипропилен или Hi-TECH)	59,1	72,7	0
Fu and Stevenson [22]	7 (6,2)	85	Синтетический или биологический (Пермакол, Biodesign)	–	–	16 (14,1)
Gleditsch et al. [23]	13 (14)	–	Биологический или синтетический	–	–	3 (14)
Gosselink et al. [24]	3 (7,3)	–	Синтетический (полипропилен)	–	48,8	1 (2,4)
Hidaka et al. [25]	0	–	Не указано	–	–	3 (9)
Lechaux et al. [26]	4 (8)	193	Синтетический	74	64	1 (3)
Luglio et al. [27]	0	–	Не указано	100	97,6	0
Lundby et al. [28]	2 (5,2)	125	Синтетический (полипропилен)	–	–	0
Madbouly et al. [29]	7 (17,1)	122.3	Не указано	59,3	66,7	1 (2,4)
Maggiori et al. [30]	2 (7)	–	Синтетический	–	–	0 (0)
Mantoo et al. [31]	6 (13)	190	Синтетический	–	–	2 (9)
Mehmood et al. [32]	6 (17,6)	115	Биологический	–	–	0
Ogilvie et al. [33]	0	190	Синтетический	19	7	5 (15)
Owais et al. [34]	11 (6,2)	–	Преимущественно синтетический	45	24	0 (0)
Portier et al. [35]	3 (7,5)	–	Синтетический	–	–	1 (3)
Randall et al. [36]	18 (9,3)	–	Синтетический (полипропилен или полиэстер)	–	92,6	1 (0,5)
Rautio et al. [37]	9 (17,3)	114	Преимущественно синтетический (полипропилен, полиэстер или биологический)	–	–	9 (17,3)
Tsunoda et al. [38]	4 (11)	–	Синтетический	59	19	1 (2)
Tsunoda et al. [39]	6 (13)	–	Синтетический	12	7	15 (34)
Wahed et al. [40]	3 (4,6)	–	Биологический	–	–	1 (4)
Wijffels et al. [41]	13 (16,2)	–	Синтетический (полипропилен или полиэстер)	–	–	2 (2,5)

СВЕДЕНИЯ ОБ АВТОРАХ (ORCID)

Хитарьян А.Г. — д.м.н., проф., зав.кафедрой хирургических болезней № 3 ФГБОУ ВО «РостГМУ»; заведующий хирургическим отделением ЧУЗ «Клиническая больница «РЖД-Медицина»; г. Ростов-на-Дону; ORCID 0000-0002-2108-2362

Головина А.А. — врач-хирург ЧУЗ «Клиническая больница «РЖД-Медицина», аспирант кафедры хирургических болезней № 3 ФГБОУ ВО «РостГМУ», г. Ростов-на-Дону; ORCID 0000-0001-5647-1192

Ковалев С.А. — к.м.н., доцент кафедры хирургических болезней №3 ФГБОУ ВО «РостГМУ»; врач-хирург ЧУЗ «Клиническая больница «РЖД-Медицина», г. Ростов-на-Дону; ORCID 0000-0001-7697-3384

Бурцев С.С. — ординатор кафедры хирургических болезней №3 ФГБОУ ВО «РостГМУ», г. Ростов-на-Дону; ORCID 0000-0002-4549-0643

INFORMATION ABOUT THE AUTHORS (ORCID)

Alexander G. Khitaryan — 0000-0002-2108-2362

Anastasia A. Golovina — 0000-0001-5647-1192

Sergey A. Kovalev — 0000-0001-7697-3384

Spartak S. Burtsev — 0000-0002-4549-0643

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Памяти Владимира Борисовича Александрова (01.02.1931 – 16.04.2022)

16 апреля 2022 года на 92 году жизни ушел из жизни Владимир Борисович Александров.

Владимир Борисович родился 1 февраля 1931 года в городе Пятигорске. В 1954 году окончил педиатрический факультет 2-го Московского государственного медицинского института и начал свою трудовую деятельность участковым педиатром в больнице села Куровское. Вскоре был назначен заведующим отделом здравоохранения Куровского района. В дальнейшем работал хирургом одной из районных больниц Московской области.

В 1965 году В.Б. Александров по решению профессора А.Н. Рыжих был зачислен в штат научно-исследовательской лаборатории по проктологии с клиникой Министерства здравоохранения РСФСР (в настоящее время ФГБУ «Национальный медицинский исследовательский центр колопроктологии имени А.Н. Рыжих» Минздрава России). В 1969 году им защищена кандидатская диссертация: «Осложнения и ближайшие исходы комбинированных брюшно-промежностных экстирпаций прямой кишки по поводу рака».

В.Б. Александров являлся пионером в использовании сшивающих аппаратов в хирургии прямой кишки. В его докторской диссертации «Передняя резекция прямой кишки при раке», защищенной в 1971 г., впервые описано сочетание однорядного скобочного шва аппаратом КЦ-28 и цианакрилатного клея.

После смерти профессора А.Н. Рыжих Владимир Борисович Александров с 1970 по 1972 гг. являлся директором научно- исследовательской лаборатории по проктологии с клиникой Министерства здравоохранения РСФСР.

В 1972–1978 гг. В.Б. Александров работал заведующим отделением, а в дальнейшем зам. главного врача по хирургии центральной республиканской больницы Министерства здравоохранения РСФСР.

С 1978 по 2012 гг. В.Б. Александров являлся главный врачом городской клинической больницы № 24 Департамента здравоохранения города Москвы. Будучи убежденным сторонником сфинктерсохраняющих операций, В.Б. Александров разрабатывал и внедрял в повседневную практику низкую переднюю резекцию прямой кишки, активно пропагандировал возможность хирургического удаления метастазов колоректального рака в печени. Одним из первых в России освоил выполнение лапароскопических хирургических операций при заболеваниях толстой кишки.

В 1986 году В.Б. Александров был назначен главным внештатным специалистом-колопроктологом ДЗМ. В 1993 г. на базе ГКБ № 24 ДЗМ им была создана служба реабилитации стомированных больных.

За годы работы В.Б. Александров создал свою школу колоректальной хирургии, воспитал сплоченный коллектив высококвалифицированных хирургов-колопроктологов. Результаты его научной и практической деятельности отражены в более чем 300 публикациях.

За плодотворный труд Владимир Борисович был награжден правительственными наградами: орден Трудового Красного знамени (1986), медаль «За трудовую доблесть» (1970), медаль

«Ветеран труда» (1987). За разработку новых методов лечения Александров В.Б. награждён Золотой и Бронзовой медалями ВДНХ (1970, 1971). В 2008 г. ему было присвоено звание «Заслуженный врач Российской Федерации».

Редколлегия журнала «Колопроктология», коллектив Городской клинической больницы № 24 ДЗМ, члены правления Ассоциации колопроктологов России, ученики Владимира Борисовича и хирургическое сообщество глубоко скорбят о кончине профессора Александрова и выражают искренние соболезнования родным и близким.

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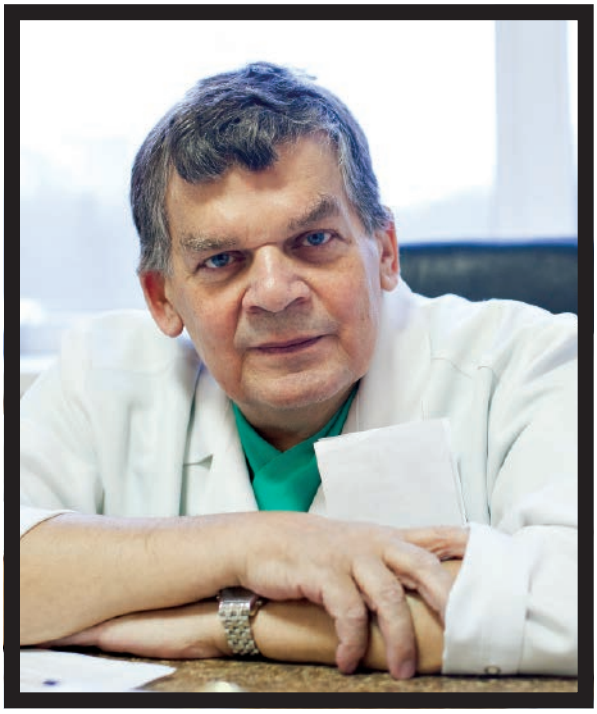
Васильев Сергей Васильевич (24.06.1951 – 12.05.2022)



12 мая 2022 года скоропостижно скончался один из лидеров и основателей Ассоциации колопроктологов России, в течение последних тридцати лет во многом определившим развитие нашей специальности.

Утрата эта тяжела и невосполнима.

Сергей Васильевич родился 24 июня 1951 г. в городе Опочка Псковской области. В 1974 году он окончил 1-й Ленинградский медицинский институт им. акад. И.П. Павлова, в 1984 году — аспирантуру в том же институте, где Сергей Васильевич начал работу, посвященную хирургической реабилитации пациентов с кишечными стомами, определившую его жизнь в профессии.

В 1984 году им была защищена кандидатская диссертация на тему «Восстановление кишечной непрерывности после операций, завершённых наложением колостомы», а в 1993 году — докторская диссертация «Первичное восстановление кишечной непрерывности при осложненных формах рака ободочной и прямой кишок».

С 1984 года С.В. Васильев работал в Первом Санкт-Петербургском государственном медицинском университете имени академика И.П. Павлова (ранее 1-й Ленинградский медицинский институт): ассистентом (1984–1991 гг.), доцентом (1991–1993 гг.), заведующим кафедрой хирургических болезней стоматологического факультета и профессором (1993–2022 гг.).

С 1991 года С.В. Васильев — главный колопроктолог Санкт-Петербурга, с 1999 г. — руководитель Санкт-Петербургского городского центра колопроктологии, в 2016-2022 гг. — главный врач СПб ГБУЗ «Городская больница №9» (Городской центр колопроктологии). Сергей Васильевич также был членом экспертного совета Минздрава России по специальности «Колопроктология», членом правления Ассоциации колопроктологов России и входил в редакционный совет нашего журнала.

Под руководством и при консультации С.В. Васильева подготовлены 2 докторские и 11 кандидатских диссертаций. Сергей Васильевич — автор более 350 научных трудов, опубликованных в отечественной и зарубежной печати, в том числе монографий: «Опухоли толстой кишки» (2004), «Новые аспекты аллопластики грыж брюшной стенки полипропиленовыми сетчатыми протезами» (2008).

Профессиональная деятельность профессора С.В. Васильева была отмечена рядом правительственных наград: медалью «К 300-летию Санкт-Петербурга» (2004 г.), «Отличник здравоохранения» (2009 г.), званием «Заслуженный врач России» (2012 г.).

Члены Правления Ассоциации колопроктологов России, члены редакционных коллегии и журнала «Колопроктологии», сотрудники НМИЦ колопроктологии имени А.Н. Рыжих выражают глубокие соболезнования родным, близким, ученикам Сергея Васильевича Васильева и Первому Санкт-Петербургскому государственному медицинскому университету имени академика И.П. Павлова

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УНИКАЛЬНЫЙ МЕХАНИЗМ ДЕЙСТВИЯ КЛАССА ИНГИБИТОРОВ ИЛ-12/23, ОБУСЛОВЛЕННЫЙ БЛОКИРОВАНИЕМ КЛЮЧЕВЫХ РЕГУЛЯТОРНЫХ ЦИТОКИНОВ, ОБЕСПЕЧИВАЕТ ЭФФЕКТИВНОСТЬ СИСТЕМНОГО И БЕЗОПАСНОСТЬ СЕЛЕКТИВНОГО БИОЛОГИЧЕСКОГО ПРЕПАРАТА[1].

- **Быстрое наступление эффекта:** уменьшение боли в животе и частоты дефекаций уже на 1-й неделе терапии при болезни Крона[2] и уменьшение частоты дефекаций и крови в стуле уже на 2-й неделе терапии при язвенном колите[3]
- **Долгосрочная эффективность:** 3 из 4 пациентов сохраняют ремиссию в течение не менее 3 лет при болезни Крона[4] и в течение не менее 2 лет при язвенном колите[5]
- **Благоприятный профиль безопасности:** профиль переносимости устекинумаба в отношении риска возникновения инфекций, в том числе туберкулёза, и малигнизации сопоставим с плацебо и препаратами селективного механизма действия[6]
- **Сочетание эффективности и безопасности:** самая высокая выживаемость терапии по сравнению с другими ГИБП при болезни Крона в любой линии — более 70% пациентов за 2 года наблюдения остаются на терапии[7]

1. Brand S. Gut. 2009; 58: 1152–67, Neurath M.F. Nat. Med. 2007; 13: 26–8, Benson, et al. mAbs 2011; 3: 535–45.
2. Sandborn W.J., et al. 2017 WCOG poster abstract P2145.
3. Sands B.E., et al. Early Improvement After Intravenous Ustekinumab Induction in Patients With Ulcerative Colitis. Results from the UNIFI Induction Trial: 689. The American Journal of Gastroenterology. October 2019; 114: S404.
4. Hanauer S., et al. IM-UNITI: 3 Year Efficacy, Safety and Immunogenicity of Ustekinumab Treatment of Crohn's disease. Journal of Crohn's and Colitis. January 2020; 14 (1): 23–32.
5. Sands B.E., et al. Efficacy of Ustekinumab for ulcerative colitis in biologic non-failure, and biologic failure populations through 2 years: UNIFI Long-term extension. TU188.
6. Click B., Regueiro M. Managing Risks with Biologics. Inflammatory Bowel Disease. 2019; 1: 1–11.
7. Ko Y., et al. Presentation at ECCO 2020; P361.

КРАТКАЯ ИНСТРУКЦИЯ ПО МЕДИЦИНСКОМУ ПРИМЕНЕНИЮ ПРЕПАРАТА СТЕЛАРА, ЛП-005728

Перед применением ознакомьтесь с полной версией инструкции.

Торговое наименование препарата – Стелара (устекинумаб), концентрат для приготовления раствора для инфузий. **Показания к применению. Болезнь Крона.** Препарат Стелара в лекарственной форме концентрат для приготовления раствора для инфузий предназначен для терапии взрослых пациентов с болезнью Крона умеренной и тяжёлой степени. Препарат Стелара в лекарственной форме концентрат для приготовления раствора для инфузий предназначен для: *индукции клинического ответа, индукции клинической ремиссии, достижения бесстероидной ремиссии, индукции эндоскопической ремиссии, улучшения связанного со здоровьем качества жизни.* У взрослых пациентов с активной болезнью Крона умеренной и тяжёлой степени, у которых: *прогрессирование заболевания продолжалось на фоне терапии иммуномодуляторами или кортикостероидами, или была выявлена непереносимость этих препаратов, или наблюдалась зависимость от кортикостероидов, или прогрессирование заболевания продолжалось на фоне терапии одним или несколькими ингибиторами ФНО, или была выявлена непереносимость одного или нескольких ингибиторов ФНО.* **Язвенный колит.** Лечение взрослых пациентов с активным язвенным колитом умеренной и тяжёлой степени с неадекватным ответом, утратой ответа или непереносимостью стандартной или биологической терапии, или имеющих медицинские противопоказания к проведению такой терапии. **Противопоказания.** Клинически значимая повышенная чувствительность к устекинумабу или любому вспомогательному веществу препарата; клинически значимая активная инфекция (например, активный туберкулёз); детский возраст до 18 лет. **Способ применения и дозы.** ***Болезнь Крона и язвенный колит. Дозы.*** Пациентам с болезнью Крона или язвенным колитом рекомендовано однократное, инициирующее терапию внутривенное введение препарата Стелара в дозе, рассчитанной на основании массы тела (Таблица 1). Через 8 недель после введения инициирующей дозы препарат Стелара вводится подкожно в дозе 90 мг (первое подкожное введение). Для подкожного введения используется препарат Стелара в лекарственной форме раствор для подкожного введения. Информация о последующих подкожных введениях препарата указана в инструкции по медицинскому применению препарата Стелара, раствор для подкожного введения. ***Способ применения.*** Препарат Стелара, концентрат для приготовления раствора для инфузий, 130 мг, предназначен только для внутривенного инфузионного введения. Внутривенное инфузионное введение препарата Стелара должно проводиться только квалифицированными медицинскими работниками.

ТАБЛИЦА 1: ИНИЦИИРУЮЩАЯ ДОЗА ПРЕПАРАТА СТЕЛАРА (ВНУТРИВЕННОЕ ВВЕДЕНИЕ)[a]

Масса тела пациента на момент введения препарата	Доза	Количество флаконов препарата Стелара, концентрат для приготовления раствора для инфузий, 130 мг
≤ 55 кг	260 мг	2
> 55 кг – ≤ 85 кг	390 мг	3
> 85 кг	520 мг	4

[a] Рекомендованная доза (около 6 мг/кг).

ТАБЛИЦА 2: ОБЗОР ПОБОЧНЫХ ДЕЙСТВИЙ, ЗАРЕГИСТРИРОВАННЫХ В КЛИНИЧЕСКИХ ИССЛЕДОВАНИЯХ

Побочное действие	
Инфекции и инвазии	Инфекции верхних дыхательных путей, назофарингит, синусит, воспаление подкожной жировой клетчатки, одонтогенные инфекции, опоясывающий лишай, вирусные инфекции верхних дыхательных путей, вульвовагинальные грибковые инфекции
Нарушения со стороны психики	Депрессия
Нарушения со стороны нервной системы	Головокружение, головная боль
Нарушения со стороны дыхательной системы, органов грудной клетки и средостения	Орофарингеальная боль, заложенность носа
Нарушения со стороны ЖКТ	Диарея, тошнота, рвота
Нарушения со стороны кожи и подкожной клетчатки	Зуд, акне
Нарушения со стороны опорно-двигательного аппарата и соединительной ткани	Боль в спине, миалгия, артралгия
Общие нарушения и реакции в месте введения препарата	Усталость, эритема в месте введения, боль в месте введения, реакции в месте введения (в том числе, кровотечение, гематома, уплотнение, припухлость и зуд), астения

ТАБЛИЦА 3: ПОСТРЕГИСТРАЦИОННЫЕ СООБЩЕНИЯ

Опыт пострегистрационного применения.

Нарушения со стороны иммунной системы	Реакции гиперчувствительности (в том числе сыпь, крапивница), серьёзные реакции гиперчувствительности (в том числе анафилаксия и ангионевротический отёк)
Инфекции и инвазии	Инфекции нижних отделов дыхательных путей
Нарушения со стороны дыхательной системы, органов грудной клетки и средостения	Аллергический альвеолит, эозинофильная пневмония
Нарушения со стороны кожи и подкожной клетчатки	Пустулёзный псориаз, эритродермический псориаз, лейкоцитокластический васкулит

Особые указания. ***Инфекции.*** Препарат Стелара является селективным иммунодепрессантом и потенциально может увеличивать риск возникновения инфекций и реактивации латентных инфекций. В ходе клинических исследований у пациентов, получавших препарат Стелара, наблюдались случаи возникновения серьёзных бактериальных и вирусных инфекций. Препарат Стелара не следует применять у пациентов с клинически значимой активной инфекцией. Следует с осторожностью применять препарат Стелара у пациентов с хронической инфекцией или рецидивирующей инфекцией в анамнезе. ***Злокачественные новообразования.*** Препарат Стелара является селективным иммунодепрессантом. Препараты-иммунодепрессанты могут способствовать увеличению риска развития злокачественных новообразований. У некоторых пациентов, получавших препарат Стелара в рамках клинических исследований, наблюдалось развитие кожных и некожных злокачественных новообразований. Следует проявлять осторожность при назначении препарата Стелара пациентам со злокачественными новообразованиями в анамнезе, а также при рассмотрении возможности продолжения терапии препаратом Стелара у пациентов с диагностированными злокачественными новообразованиями. ***Реакции гиперчувствительности.*** В ходе пострегистрационного наблюдения были зарегистрированы серьёзные реакции гиперчувствительности, включая анафилаксию и ангионевротический отёк. ***Вакцинация.*** Не рекомендуется применять живые вирусные или живые бактериальные вакцины одновременно с препаратом Стелара. ***Иммуносупрессия.*** В исследованиях у пациентов с болезнью Крона и язвенным колитом совместное применение препарата Стелара с иммуномодуляторами (6-меркаптопурином, азатиоприном, метотрексатом) или с кортикостероидами не влияло на безопасность и эффективность препарата Стелара. ***Иммунотерапия.*** Безопасность и эффективность применения препарата Стелара у пациентов, прошедших иммунотерапию аллергических заболеваний, не установлена.

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Состав*. Очищенная микронизированная флавоноидная фракция 500 мг: диосмин 450 мг, флавоноиды в пересчете на гесперидин 50 мг. Очищенная микронизированная флавоноидная фракция 1000 мг: диосмин 900 мг, флавоноиды в пересчете на гесперидин 100 мг. **Показания к применению*.** Терапия симптомов хронических заболеваний вен (устранение и облегчение симптомов). Терапия симптомов венозно-лимфатической недостаточности: боль, судороги нижних конечностей, ощущение тяжести и распирания в ногах, усталость ног. Терапия проявлений венозно-лимфатической недостаточности: отеки нижних конечностей, трофические изменения кожи и подкожной клетчатки, венозные трофические язвы. Симптоматическая терапия острого и хронического геморроя. **Способ применения и дозы*.** Венозно-лимфатическая недостаточность — 1000 мг в сутки. Острый геморрой — до 3000 мг в сутки. Хронический геморрой — 1000 мг в сутки. **Противопоказания*.** Повышенная чувствительность к активным компонентам или к вспомогательным веществам, входящим в состав препарата. Беременность и период грудного вскармливания (опыт применения ограничен или отсутствует). Детский возраст до 18 лет (опыт применения отсутствует). Дополнительно для Детралекс® суспензия 1000 мг: непереносимость фруктозы. **Особые указания*.** Назначение препарата не заменяет специфического лечения заболеваний прямой кишки и анального канала. Если симптомы геморроя сохраняются после рекомендуемого курса лечения, следует пройти осмотр у проктолога, который подберет дальнейшую терапию. **Взаимодействие с другими лекарственными средствами*. Беременность*/Период грудного вскармливания*.** Предпочтительно не применять препарат. **Влияние на способность управлять транспортными средствами, механизмами*. Побочное действие*.** *Часто:* диарея, диспепсия, тошнота, рвота. *Нечасто:* колит. *Редко:* головокружение, головная боль, общее недомогание, кожная сыпь, кожный зуд, крапивница. *Неуточненной частоты:* боль в животе, изолированный отек лица, губ, век. *В исключительных случаях* — ангионевротический отек. **Передозировка*. Фармакологические свойства*.** Детралекс® обладает венотонизирующим и ангиопротективным свойствами. Препарат уменьшает растяжимость вен и венозный застой, снижает проницаемость капилляров и повышает их резистентность. **Форма выпуска*. Номер регистрационного удостоверения:** ЛП-003635, ЛП-004247, П N011469/01.

** Для получения полной информации, пожалуйста, обратитесь к инструкции по медицинскому применению лекарственного препарата или получите консультацию специалиста.*

Детрагель®: краткая информация по безопасности

Состав*. Гепарин натрия 100,0 МЕ, эссенциальные фосфолипиды 10,0 мг, эсцин 10,0 мг. **Показания к применению*.** Терапия симптомов хронических заболеваний вен. Варикозная болезнь с симптоматикой в виде боли, отеков, ощущения тяжести и усталости в ногах, ночных судорог икроножных мышц и с признаками в виде телеангиэктазий (сосудистые звездочки и сеточки) и варикозных вен. Поверхностный флебит, тромбофлебит. Гематомы при травмах, включая спортивные растяжения и ушибы. Послеоперационные гематомы без нарушения целостности кожных покровов. **Способ применения и дозы*.** Наружно. Гель наносят тонким слоем на проблемный участок кожи и равномерно распределяют легкими массирующими движениями: 2—3 раза в сутки ежедневно до исчезновения симптомов. Продолжительность лечения — не более 15 дней. Возможность проведения более длительного курса лечения определяется врачом. **Противопоказания*.** Гиперчувствительность к компонентам препарата, геморрагический диатез (в т.ч. тромбоцитопеническая пурпура), гемофилия, нарушение целостности кожных покровов в месте нанесения препарата (открытые раны, язвенно-некротические поражения), ожоги, экзема, кожные инфекции. Противопоказан к применению на слизистых. Возраст до 18 лет. **Особые указания*.** Нанесение геля на слизистые оболочки противопоказано. Избегать попадания в глаза. При развитии аллергических реакций немедленно прекратить применение препарата и обратиться к врачу. **Взаимодействие с другими лекарственными средствами*.** Нельзя наносить на кожу одновременно с другими лекарственными препаратами для наружного применения. **Беременность* и период кормления грудью*.** До настоящего времени не было сообщений о нежелательных эффектах в отношении матери и плода при применении препарата беременными женщинами. Применение во время беременности и в период лактации возможно только в тех случаях, когда ожидаемая польза терапии для матери превышает потенциальный риск для плода, поэтому перед применением препарата следует проконсультироваться с врачом. **Влияние на способность управлять автомобилем и выполнять работы, требующие высокой скорости психических и физических реакций*.** Исследований по изучению влияния препарата на способность водить автомобиль и управлять механизмами не проводилось. **Побочное действие*.** *Очень редко:* контактный дерматит, крапивница, кожная сыпь, кожный зуд, бронхоспазм. При местном применении эсцина сообщалось о единичных случаях развития острых анафилактических реакций. **Передозировка*. Фармакологические свойства*.** Комбинированный препарат, оказывает местное антикоагулянтное, противовоспалительное, венотонизирующее и антиагрегантное действие, снижает проницаемость вен, улучшает микроциркуляцию. **Форма выпуска*.** Гель для наружного применения. **Номер регистрационного удостоверения:** ЛП-001044.

** Для получения полной информации, пожалуйста, обратитесь к инструкции по медицинскому применению лекарственного препарата.*

Материал предназначен для специалистов

АО «Сервье»: 125196, г. Москва, ул. Лесная, д. 7, этаж 7/8/9. Телефон: +7 (495) 937-0700, факс: +7 (495) 937-0701

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