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Translation of the article

MESENCHYMAL TUMORS OF THE COLON AND RECTUM: DIAGNOSIS, TREATMENT, PROGNOSIS (case report and review)

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Mesenchymal tumors of the colon and rectum are extremely rare and do not have specific clinical manifestations, their diagnosis and staging cause certain difficulties.
Different types of mesenchymal tumors differ in prognosis and choice of the treatment. It explains the importance of differential diagnosis of these neoplasms among themselves and tumors-derivatives of other embryonic structures.
The article describes the clinical case of a rare mesenchymal tumor and management of the patient.

[Key words: mesenchymal tumor, gastrointestinal stromal tumor (GIST), leiomyoma, leiomyosarcoma]

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Epithelial tumors (adenoma and adenocarcinoma) are the most common tumors of the colon [1].

Mesenchymal colon tumors are detected much less frequently, with a frequency of 0.08% to 2% [2] and are represented by a heterogeneous group of neoplasms by histological structure, localization, degree of malignancy and prognosis.

Clinical diagnosis of mesenchymal tumors is quite difficult, since they do not have specific symptoms and may be asymptomatic in the early stages.

The main clinical manifestations are abdominal pain, intestinal bleeding, anemia, the presence of a volume formation in the abdominal cavity and intestinal obstruction.

Small polypoid mesenchymal tumors are often diagnosed accidentally during endoscopic examination.

Radiation diagnostic methods allow to diagnose the presence of a tumor and its prevalence, but the final verification of the histological type is possible only with morphological research.

Before the introduction of the immunohistochemical method into diagnostic practice and the description of gastrointestinal stromal tumor (GIST), leiomyoma and leiomyosarcoma were the most often diagnosed mesenchymal tumors of the gastrointestinal tract, especially in the colon and rectum, for which they are the most frequent, after the esophagus, tumor site.

Therefore, among mesenchymal tumors of the colon and rectum, of the most practical significance is the diagnosis of (GIST), which is believed to arise from interstitial Cajal cells, and tumors with smooth muscle differentiation (leiomyoma and leiomyosarcoma) due to different prognosis and treatment of these neoplasms.

Differential diagnosis of these tumors and assessment of prognostic factors are possible only with morphology including the determination of the immunophenotype and molecular genetics profile of the tumor.

Currently, the most common mesenchymal neoplasm of the gastrointestinal tract is a gastrointestinal stromal tumor, which occurs with a frequency of 0.1-0.3% [3,4].

The average incidence rate in the world is 1.0-1.5 cases per 100 thousand people per year. The incidence in men is 1.5 times higher than in women.

The mean age of patients is 63 years. In Russia, the

frequency of GIST is higher in women (57.5%) [5]. In 54-60% of cases, GIST is located in the stomach, in 30-35% of cases, GIST is detected in the jejunum, ileum and duodenum, in 10-20% of cases, a tumor of this structure is detected in the colon, most often in the rectum [6].

Most GISTs occur sporadically, 5-10% of cases are associated with various syndromes: Garney triad, Garney-Stratakis syndrome, family GIST syndrome, neurofibromatosis type 1.

About 85% of GISTs are associated with an activating mutation in oncogenes located on chromosome 4 (4q12) encoding type III tyrosine kinase receptors.

The most common (up to 75%) activating mutation in the KIT gene is located in 11 (66%) and 9 (9%) exons. A mutation in the PDGFRA gene occurs in 10% of GISTs (mainly with localization in the stomach), most often in 18 exons (8%), less often in 12 and 14 exons.

Patients with this mutation have a lower risk of metastasis, compared to patients with a tumor with a mutation in the KIT gene.

It is important to note that the mutation in exon 14 is associated with imatinib resistance [7-9]. Most GISTs with no mutation in the KIT and PDGFRA genes («wild» type) have alterations in SDH genes (5-10%), which in 60% of cases is due to an inactivating mutation (most often germinal), and in 40% of cases is associated with hypermethylation of the SDHC promoter (epimutation), leading to dysfunction and deficiency of succinate dehydrogenase (SDH-deficient GISTs).

Such tumors are most often found in young patients and children, as part of the Garney syndrome [10,11].

Externally (macroscopically), a gastrointestinal stromal tumor in most cases is represented by a solitary nodular formation with relatively clear borders (without a capsule), located intramurally, submucosally, or subserously.

Multifocal tumors are very rare and mainly as a manifestation of hereditary syndromes.

The size of the tumor node is very variable – from a few millimeters (the so-called micro-GIST) to large ones that can reach 30 cm in the largest dimension [12].

In large tumors, degenerative changes can be observed in the form of cystic cavities, foci of hemorrhage and necrosis.

Histologically, GIST most often (about 70%) have a fusiform cell structure, in 20-25% of cases – epithelial cell structure, in 10% of tumors there is a combination of fusiform and epithelial morphology.

GISTs are variable in the density of cell structures and the severity of the stroma, which can be hyalinized, with foci of calcification, myxomatosis.

The colon GIST is more characterized by a fusiform cell structure with the formation of palisade-like structures, which is most often (up to 90%) associated with KIT mutation.

Epithelioid cell morphology is more often observed in mutations in the PDGFRA gene, the wild type of GIST, and in SDH-deficient tumors.

The presence of nuclear and cellular polymorphism, a large number of mitoses is not typical of most GISTs, and their appearance may indicate the progression of the tumor and its dedifferentiation, or may be an outcome of neoadjuvant therapy with imatinib [13].

For the morphological diagnosis of GIST, it is necessary to conduct an immunohistochemical study with antibodies to KIT (CD117) and DOG1, which are the main diagnostic markers of this tumor.

In most GISTs, the diffuse expression of CD117 (membranous and cytoplasmic, perinuclear less) is defined. In a small part of cases, especially in the PDGFRA gene mutation, CD117(KIT) expression may be absent or weakly expressed.

In such cases, it is necessary to use the DOG1 marker, which is very sensitive and specific to GIST and is detected in 50% of CD117-negative tumors.

The majority of fusiformcell GISTs (75%) express CD34, and a small portion of GISTs can be determined by the expression of h-caldesmon, smooth muscle actinidesmin tumor cells.

In SDH-deficient tumors, the loss of expression of the SDHB protein is detected, which is specific for such tumors regardless of the presence of a mutation in the SDH gene [14,15].

In KIT (CD117) and/or DOG1 negative tumors, molecular genetic testing is recommended to determine the mutation status of the tumor, which is necessary for diagnosis, determining the risk of disease progression, and conducting adjuvant therapy [15-18].

The main prognostic factors for GIST, on the basis of which the risk of tumor progression and treatment tactics are determined, are mitotic activity (index), the size and site of the tumor.

The mitotic index is determined on an area of 5 mm^2 in 50 fields of view at high magnification of the microscope (×40). The threshold value is the number of mitoses equal to 5: if there are less than ⩽5 mitoses in the tumor, the mitotic index is considered as low, and if there are more than 5 mitoses – as high.

The size of the tumor (⩽2 cm; >2 cm–⩽5 cm; >5 cm–⩽10 cm; >10 cm) is the basis for tumor staging (category T) [3,6].

Depending on the site of primary tumor, GISTs are divided into two main prognostic groups: stomach/omentum tumors, which have a more favorable prognosis, and extra-gastric tumors, among which GIST of the small and large intestine have a high risk of progression.

With the progression of the tumor, most often metastases develop along the peritoneum and into the liver.

Depending on the site, morphological parameters and mutational status of the tumor, the clinical course of GIST can be assessed as benign, with an intermediate degree of malignancy, and malignant [6].

For clinical evaluation of tumor aggressiveness and adjuvant therapy with imatinib, a number of prognostic tables and schemes based on the main prognostic factors (site, size and mitotic index) are proposed, the optimal of which are the schemes proposed by Miettinen M. and Lasota J. (2006), Joensuu H. (2008) [6,18,19].

The standard treatment for local and locally advanced gastrointestinal stromal tumors of the colon and rectum is surgical removal [20].

In a localized process, surgery is the first and only stage of treatment when a patient has a low or very low risk of progression.

At the same time, it is possible to perform limited resections in compliance with oncological principles (preserving the integrity of the tumor and intact edges of the resection).

Lymphnode dissection is performed only if the presence of metastases in the lymph nodes is suspected.

In patients with locally advanced neoplasms, if radical intervention is not possible, neoadjuvant therapy with tyrosine kinase inhibitors is indicated in order to regress the tumor and make it possible to perform radical removal.

If the tumor is in the rectum, preoperative imatinib therapy is possible to reduce the size of the tumor and perform organ-preserving procedure.

Postoperative imatinib therapy is performed in patients with a high and intermediate risk of tumor progression for three years to increase overall and disease-free survival [6,21].

A colorectal GIST must first be differentiated from a tumor with smooth muscle differentiation – leiomyoma or leiomyosarcoma, which have a similar structure and site.

In the large intestine, leiomyoma most often develops from its own muscle plate of the mucosa (muscularis mucosae) and has an exophytic growth into the intestine lumen.

According to existing data, leiomyoma with localization in the rectum is very rare, and a small number of clinical observations are described in the literature.

So, He et al. [22] reported 160 cases of smooth muscle neoplasms of the gastrointestinal tract, while only 4 out of 160 (0.4%) patients had tumors localized in the rectum. Kusminsky et al. [23] over a twenty-year period described 79 cases of leiomyomas localized in the rectum, mainly at the age of 50-59 years.

Leiomyoma is most often found in the distal parts of the colon (sigmoid and rectum), the anal canal and mainly has an exophytic growth character.

Large tumors can grow intramurally, spreading not only into the lumen of the intestine, but also into the abdominal cavity or retroperitoneal space [23].

However, leiomyoma in the gastrointestinal tract does not tend to progress and transform into leiomyosarcoma.

Clinically, these are solid formations, rounded in shape, with fairly clear borders, without a capsule, tightly elastic consistency.

It should be noted that small leiomyomas, as well as GIST, are an accidental finding during screening colonoscopy, while large neoplasms can lead to the clinical manifestations – bleeding, violation of intestinal patency.

Histologically, colorectal leiomyoma most often has a fusiformcell structure with the formation of bundles, without nuclear polymorphism and mitosis, which, along with other morphological features, is a diagnostic criterion for diagnosing and differentiating leiomyoma from leiomyosarcoma and GIST.

When immunophenotyping, leiomyoma cells are diffusely positive for smooth muscle markers – desmin, smooth muscle actin (SMA), caldesmon, and calponin.

Leiomyosarcoma is a malignant variant of a tumor with smooth muscle differentiation.

This is an aggressive tumor with a high rate of local recurrence (40-80%) and metastatic disease (55-70%).

It should be noted that the true incidence of leiomyosarcoma before the year of 2000 cannot be determined reliably, since most GISTswere regarded as leiomyosarcoma.

After the year of 2000, 76 cases of this tumor were reported with the most often site in the small intestine (40%), colon and rectum (40% of cases) [15].

According to available data, leiomyosarcoma is 0.08% of cases among all colorectaltumors [24].

Leiomyosarcoma occurs in both the colon and rectum with the same incidence in males and females and usually develops at the age of over 50 years old [25].

As well as leiomyoma, it can grow intraluminally, or intramurally, and is represented by a solid nodular formation without clear borders and capsules, in which areas of ulceration, necrosis and cystic changes can be observed, which is not typical of leiomyoma.

The size of the tumor node can vary significantly, with the largest tumor size greater than 5 cm correlating with the prognosis.

Like other mesenchymal colorectal tumors, leiomyosarcomas can be asymptomatic for a long time and be detected accidentally (during screening colonoscopy) or give non-specific symptoms like abdominal pain, intestinal bleeding or obstruction.

Leiomyosarcoma is characterized by the appearance of distant hematogenous metastases in the liver and lungs, while metastases in regional lymph nodes rarely

develop.
Histologically, leiomyosarcoma of the gastrointestinal tract has a similar structure to leiomyosarcoma of other localities and has a more pronounced cellular and nuclear polymorphism than in leiomyomas, a large number of mitoses, the presence of necrosis and degenerative changes (areas of myxomatosis, hyalinosis, cystic transformation).
When immunophenotyping, tumor cells are positive to SMA, variably positive todesmin, calponin, and caldesmon.
As in leiomyomas, tumor cells are negative to KIT (CD117) and DOG1, which is the main diagnostic criterion for differentiating these tumors from GIST [25].
When morphological examination of the gastrointestinal leiomyosarcoma, as well as in other localities, it is necessary to determine the degree of malignancy of the tumor.
The most common system for evaluating the degree of malignancy (G) of sarcomas is the FNCLCC system developed by the French Federation Nationaledes Centers de Lutte Contrele Cancer [15,26], which uses a combination of tumor parameters such as differentiation, number of mitoses, and the presence of necrosis. It should be noted that this system is not applicable to GIST.
According to literature data, the following clinical and morphological factors correlate with a poor prognosis for gastrointestinal leiomyosarcoma: the size of more than 5 cm in diameter, the growth of the tumor outside the intestinal wall or its perforation, low differentiation of the tumor.
Such patients rarely pass the five-year mark; they usually die within the first year [27].
Surgical removal is the main treatment method for both leiomyoma and leiomyosarcoma.
Since leiomyoma is a benign tumor, radical organ-preserving treatment is possible with local removal of small exophytic tumors by endoscopic electro excision in the colon or transanal rectal excision.
Large leiomyomas are usually removed by transabdominal access, the criterion for which is performing R0-resection.
There is no data in the literature on large case series with leiomyomas.
Perhaps, the results of one of the largest series of patients with leiomyomas in Russia were published by Vorobiev G.I. et al. [28]. Over an 18-year period, 36 patients with rectal leiomyomas underwent various surgeries – endoscopic removal (for tumors up to 1.0 cm), local transanalremoval or using pararectal access (for tumors up to 5.0 cm), and abdominoperineal excision or intersphicteric resection of the rectum (for tumors larger than 10 cm).
It should be noted that the incidence of local recurrence was 25% (9/36 patients), and relapses were detected only in patients after local excision (transanal excision of the tumor), which maybe the main reason for this was the tumor fragmentation.
Treatment of leiomyosarcoma is only surgical, with the maximum possible volume of radical resection, due to the high risk of recurrence and the tumor progression.
Also, it is worth noting that there are no data in the literature on the results of treatment of patients with such rectal tumors and there are only singlepapers.
Radiotherapy, chemotherapy, or a combination of them are ineffective in the treatment of leiomyosarcoma [29].
As a clinical example of a rare gastrointestinal tumor, we would like to present the clinical case of a large leiomyosarcoma of the descending colon.
The patient S., aged 60 years old, was admitted to the Ryzhikh National Medical Research Center of Coloproctology in September 2019 with complaints of

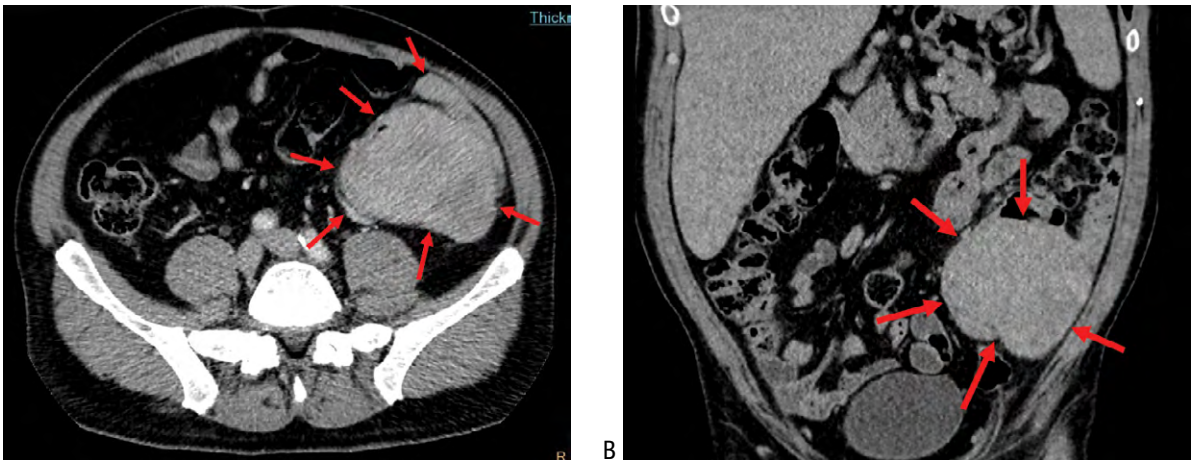

Figure 1. *Spiral computed tomography of the patient with a leiomyosarcoma of the descending colon. (A. coronary plane, B. axial plane)*

abdominal distension, periodic pulling pains in the left iliac region and palpable mass in this area. It is known that in June 2019, he began to notice a deterioration in his health because of the progression of the above-mentioned symptoms, which was the reason for consultation. During examination the patient's health status was satisfactory, the skin was of normal color, without pathological rashes.

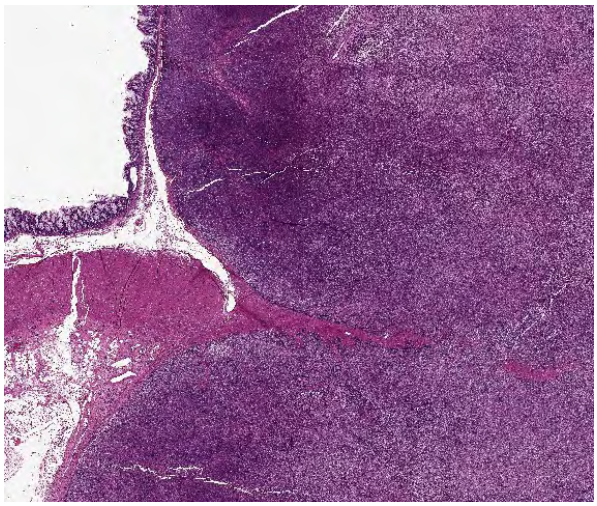

Figure 2. *Tumor of the colon (H&E, 4×)*

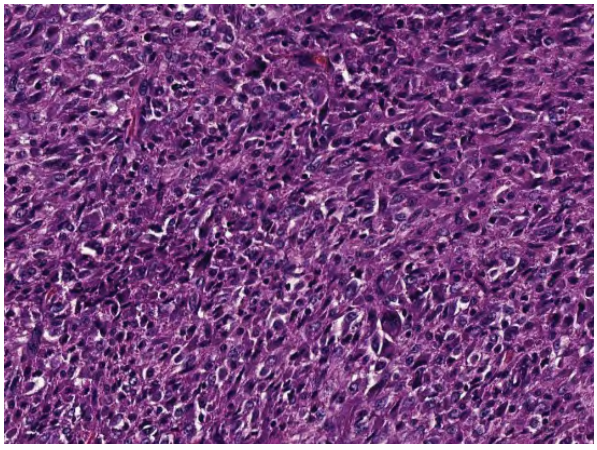

Figure 3. *Histologic features of tumor: cytologic and nuclear pleomorphism, high mitotic rate (H&E, 20×)*

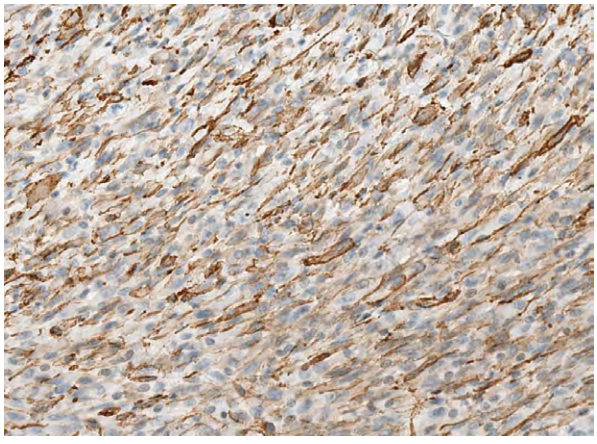

Figure 4. *The tumor cells are immunoreactive for SMA (immunostaining for SMA, 20×)*

The clinical examination of the respiratory, cardiovascular and genitourinary systems revealed no pathology. The lymph nodes available for palpation were not enlarged. During palpation of the abdomen, there were no peritoneal symptoms. At deep palpation in the left iliac region, a immobile painless tumor of 12×10 cm was detected.

During digital rectal examination of the rectum at the height of the finger, no pathological changes were detected.

A number of laboratory and instrumental tests were performed on the patient. The biochemical study of venous blood revealed no deviations from normal values.

According to the results of clinical blood analysis, anemia of a mild degree (hemoglobin level 102.0 g/l), a decrease in the number of red blood cells to 3.48×10^{12}/l, and the level of hematocrit – up to 32.0%. A leukimoid reaction of neutrophil type (leukocytosis – 23.69×10^{9}/l with a degenerative shift of the leukocyte formula to the right – segmentonuclear neutrophils 84.0%) was detected in combination with thrombocytosis up to 514.4×10^{9}/l and accelerated ESR up to 47 mm/h, which is one of the pathognomonic laboratory symptoms in leiomisarcoma [30].

There was no increase in the level of cancer markers (CEA 4.2 ng/ml, CA 19-9 3.1 U/ml).

During proctoscopy, the intestine was examined up to 20 cm. The rectal walls were smooth and elastic.

In the visualized areas, the vascular pattern was not changed, no mucosal defects or neoplasms were detected. During video colonoscopy, the device was held at the level of 50 cm from the edge of the anus (to the descending colon).

The further moving of the device was stopped due to the presence of the distal pole of the exophytic tumor at this level.

A tumor in the form of an invaginate, completely obturating the lumen, with a bumpy surface, in red color, at an instrumental palpation – of a dense consistency, with areas of necrosis and fibrin, expressed contact bleeding.

Peristalsis in the area of the tumor was not observed.

When pathomorphological examination of the material obtained from the biopsy of the tumor, detritus was detected. According to computer tomography (Fig. 1 A, B), there was a large tumor in the wall of the descending colon with a size of 10×9 cm, with an exophytic component, extending beyond the intestinal wall, of an inhomogeneous structure with the presence of calcinates with sizes from 0.3 to 0.7 cm, almost complete obstruction the intestine lumen.

The loops of the small intestine (located in the area of the left lateral canal), the peritoneum of the left lateral canal, and the Gerota's fascia were closely attached to the tumor, most likely with their involvement.
Enlarged paracolic lymph nodes were not visualized. There were no signs of metastasis in the liver or lungs.
Based on the complaints, history, objective status and results of instrumental examination methods, the patient was diagnosed with locally advanced cancer of the descending colon cT4bN0M0 involving the small intestine, peritoneum of the lateral canal and the Gerota's fascia, complicated by inflammation, partial bowel obstruction, secondary anemia of a mild degree.
Taking into account the data of the clinical and instrumental examinations, it was decided to perform the left hemicolectomy with the Gerot fascia resection *en bloc*.
The intraoperative revision revealed the intestine proximal to the tumor was filled with liquid intestinal contents. The tumor was detected in the descending intestine, in the largest dimension was 15 cm with pronounced perifocal inflammation and involving the adjacent tissues.
Para-aortic and apical lymph nodes of the inferior mesenteric artery were not detected.
Taking into account the tumor site, the signs of bowel obstruction – suprastenotic expansion of the right parts of the colon, expansion of the small intestine – the obstructive resection was performed in the volume of left hemicolectomy without anastomosis (Mikulicz's procedure).
During routine morphological study of the surgical specimen, the tumor node had the structure of mesenchymal tumor of fusiformcells forming multidirectional bundles mixed with areas of large histiocytic cells with marked polymorphism and nuclear atypia, presence of multinucleated cells, a large number of pathological mitotic figures (up to 35 per 50 fields of view at magnification ×40), foci of necrosis, a large number of vessels (Fig. 2,3).
When immunophenotyping in tumor cells, a diffuse positive reaction with SMA antibodies (in fusiform and part of histiocytic cells), focal staining of tumor cells with desmin antibodies was detected (Fig. 4).
The tumor was negative for CD117, DOG1, CD34 and S100, on the basis of which leiomyosarcoma (pleomorphic variant) of descending colon, high grade (Grade 3 according to FNCLCC classification), pT2bpN0cM0, was diagnosed.
The surgery was performed in the R0 resection. The postoperative period was uneventful. The patient was discharged on the 8th day in a satisfactory condition.
Additional molecular genetic testing was recommended to confirm the diagnosis.
Taking into account the degree of malignancy of the tumor and the high risk of progression, the patient underwent adjuvant chemotherapy with doxirubicin, in the amount of 6 courses.
The tolerability of chemotherapy is satisfactory.
Currently, the follow-up period is 8 months, and there are no signs of the disease recurrence.
Thus, there is a category of colorectal neoplasms that are extremely rare and have non-specific clinical manifestations, a difficult differential diagnosis, which makes choice of treatment hard.
Often patients with such tumors and their complications under a mask of colorectal cancer, diverticular disease or other inflammatory bowel diseases up on the operative theatre, where, often during intraoperative revision, the question of diagnosis remains open.
Intraoperative morphological examination of such tumors is not recommended.
The choice of the procedure should be based on the maximum possible radical removal of the tumor *en bloc* (without fragmentation).
The final diagnosis with the determination of the histological type and degree of malignancy of the tumor is possible only with a thorough morphological study with mandatory immunophenotyping.
In the differential diagnosis of mesenchymal colorectal tumors, primarily of fusiform cells, it is necessary to exclude GIST, since this is the only mesenchymal tumor that can be treated with targeted drugs, which is of fundamental importance for the choice of treatment and prognosis.
Morphological and additional molecular genetic studies currently play a key role in the diagnosis of mesenchymal tumors of the colon and rectum, determining the choice of postoperative treatment and prognosis, while radical surgical removal is the main method of treatment of this group of tumors.

THE PARTICIPATION OF THE AUTHORS:
Concept and design of the study: *Chernyshov S.V.*
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