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Diagnosis and Therapy of Patients with Colorectal Cancer Metastases, Endovascular Approach

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

According to current data, in Europe and North America, primary colon carcinoma diseases are detected with a frequency of 60-75 cases per 100 thousand population. In Russia over the past 10 years, there are up to 40-46 thousand cases annually. Active surgical tactics in the treatment of patients with colorectal cancer metastases in the liver can increase the overall survival time. The study showed that with the use of chemotherapy, the life expectancy of patients increases. Various options for complex treatment of patients with colorectal cancer metastases in the liver, especially with the use of endovascular and radiofrequency interventions, are relatively safe and effective, provided they are carried out in specialized oncological and coloproctological hospitals.

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1. INTRODUCTION

"Colon carcinoma" or "colon cancer" is a common name for a wide range of malignant neoplasms, which are one of the most formidable pathologies of the gastrointestinal tract. This is a malignant neoplasm that consists of epithelial tissue, affecting the blind, colon and / or rectum, including the anal part. According to statistics, in developed and developing countries of the planet, there is an expansive increase in newly detected cases of colon cancer compared to malignant tumors of any other area of the body (except lung and breast cancer). In the Russian Federation, colon carcinoma occupies one of the top positions.

Among the male population with malignant neoplasms, colon carcinoma is in third place after lung and stomach cancer, and in women, respectively, after breast and skin cancer. Over the past 50 years, the number of primary diseases of colon carcinoma has increased almost 8 times. Over 10 years, the number of patients has increased by 24% and reached more than 45 thousand per year [1].

An alarming fact is the high mortality rate within a year after diagnosis. This is due to the fact that during the initial treatment of patients to the doctor, more than 65% of patients with colon cancer have advanced forms of cancer (3-4 stages). More than 50% of patients have rectal cancer. Moreover, in this scenario, less than half of sick people undergo surgical treatment.

According to current data, in Europe and North America, primary colon carcinoma diseases are detected with a frequency of 60-75 per 100 thousand population, and in Russia over the past 10 years (2010-2020), there are up to 40-46 thousand cases annually. At the same time, neoplasms are more often localized in the colon than in the rectum in a ratio of 2:1, in developing countries - 1:1 [2, 3]. Moreover, in this scenario, less than half of sick people undergo surgical treatment.

It follows from this that recently the problem of colorectal cancer has become one of the most urgent medical and social problems that require the closest attention of doctors and scientists.

Colorectal cancer can start in the colon or rectum. Colorectal cancer most often begins with a polyp, a non-cancerous growth. If the polyp is not treated or removed, it can degenerate into a malignant tumor.

There are several forms of polyps:

Adenomatous polyps. They can be detected by colonoscopy. They are a precancerous form.

Hyperplastic polyps can also develop in the colon and rectum. They are not considered precancerous. Polyps are easiest to detect during colonoscopy because they usually rise above the surface of the colon. About 10% of colon polyps are flat, they are difficult to detect by colonoscopy if a dye is not used to isolate them. These flat polyps have a high risk of developing cancers.

Most cases of intestinal cancer are a type of tumor called adenocarcinoma. It is a malignancy of the cells lining the inner surface of the colon and rectum. Other types of oncoprocess, which are much less common, but can still occur, include neuroendocrine tumor of the gastrointestinal tract, gastrointestinal stromal tumor, small cell carcinoma and lymphoma.

1.1 Grouping of Cancer by Stages

Stage 0: also called carcinoma in situ. Tumor cells are found only in the mucous membrane or the inner lining of the intestine.

Stage I: The oncoprocess has sprouted through the mucous membrane and penetrated into the muscular layer of the intestine. He did not capture nearby organs or lymph nodes (T1 or T2, N0, M0).

Stage IIA: the neoplasm has grown through the wall of the colon or rectum, but has not spread to adjacent organs and lymph nodes (T3, N0, M0).

Stage IIB: The oncoprocess passed through the muscle layers to the visceral peritoneum. It has not spread to nearby lymph nodes or anywhere else (T4a, N0, M0).

Stage IIC: the formation has sprouted through all the layers of the intestine, penetrating into neighboring organs. It has not spread to the lymph nodes or anywhere else (T4b, N0, M0).

Stage IIIA: the cancer has grown through several layers of the intestine. He moved to 1-3 lymph nodes or tumor nodes in the intestinal tissues. Did not switch to other organs (T1 or T2, N1 or N1c, M0 or T1, N2a, M0).

Stage IIIB: the cancer has grown through the layers of the intestine or into the surrounding organs. Also in 1-3 lymph nodes or in the tumor node of the intestine. It does not capture neighboring organs (T3 or T4a, N1 or N1c, M0; T2 or T3, N2a, M0; or T1 or T2, N2b, M0).

Stage IIIC: Oncology has spread to 4 (or more) lymph nodes, but not to distant organs and systems (T4a, N2a, M0; T3 or T4a, N2b, M0; or T4b, N1 or N2, M0).

Stage IVA: the neoplasm has moved to 1 distant organ (any T, any N, M1a).

Stage IVB: Oncology has captured 2 or more organs (any T, any N, M1b).

IVC stage: the process has moved to the peritoneum. It can also capture other areas or organs (any T, any N, M1c).

1.2 Risk Factors for Colon Carcinoma

Colon carcinoma is usually a degeneration of adenomatous benign polyps [4]. Despite the fact that the genetic background significantly increases the risk of developing this cancer, most cases are unpredictable, not familial. Approximately 85-97% of sporadic cases versus 10-25% of cases with hereditary etiology. Among all other types of cancer in humans, colon cancer has the greatest association with familial morbidity. Although the genetics of colon carcinoma is unclear, recent scientific work shows great importance in the development of the disease [5].

So, according to Tomislav Dragovich, a genetic mutation in the APC gene is the cause of familial glandular polyposis, in which the patient has an almost complete probability of developing colon cancer by the age of 40-42 years. Hereditary colon cancer without polyposis is also associated with a greater risk of colon cancer in people under the age of 55. Unlike familial adenomatous polyposis in Lynch syndrome, the proximal colon is more likely to suffer. Patients with this syndrome are at risk of spreading metastases to the ovaries and the uterine body at a fairly young age. This syndrome is caused by replication errors in the genes hMLH1, hMSH2, hMSH6, hPMS1, hPMS2 and possibly in those that are not yet known [6 – 9].

Other predisposing factors are inflammatory diseases (ulcerative colitis, hereditary Crohn's disease). The risk of developing carcinoma increases with the duration of these pathologies. The incidence of colorectal cancer begins to increase approximately 8-10 years after the onset of inflammatory bowel disease and increases to 15-20% after 30 years. The main risk factors are the duration of the course, the prevalence of the lesion, young age and the presence of complications.

There are factors that increase the risk of developing carcinoma. It has been found that people who eat food that is poor in fiber, but at the same time with a high content of animal protein, fat and refined carbohydrates are more predisposed to this problem. Obesity (especially morbid) increases the risk of colorectal cancer by 1.5 times, and to a greater extent in men. Alcohol abuse and tobacco smoking are also among the risk factors [10 – 13].

1.3 Diagnosis of Colorectal Cancer

In addition to a full-scale clinical examination, laboratory and instrumental methods are used in the diagnosis of colon carcinoma [4]. An early diagnosis can be established only with random rectoromanoscopy in 2% of cases in asymptomatic patients. Timely diagnosis is complicated by a long period of hidden or masked flow [14]. The most accessible and sufficiently informative screening methods for the diagnosis of carcinoma are tests for occult blood in the feces of the patient [15 – 17].

The so-called "Hemoccult-test Greegor Veber" method is based on determining the peroxidase activity of hemoglobin in fecal matter by placing a sample with a special resin. There is an indication of the activity of the enzyme, which allows you to detect traces of neoplasm. Stool samples are examined for several days while following a diet, as well as iron and ascorbic acid preparations. Sensitivity of the method 53-82% [17 – 21].

An immunochemical test for hidden blood in faeces is carried out with disposed antibodies to

the human Hb (hemagglutination method). Unlike the hemocultest, the immunochemical test does not react to the presence of non-human peroxidase contained in vegetables and fruits, and therefore does not require diet, which simplifies the study. There is also a hemoporphyrin test, which is based on the fluorescence reaction of decarboxylated porphyrins; - determination of the rate of cell proliferation by studying some nuclear proteins (Ki-67, PCNA, DNA polymerases). PCNA proliferation indices (proliferating cell nuclear antigen) and Ki-67 can serve as criteria for the prediction of CRC, as indicated by PCNA overexpression [22-24]. There are still a sufficient number of tests, but these are probably some of the most common.

As for the tools. In the diagnostic search for rectal cancer carcinoma, the following methods are used:

1. Flexible and rigid rectoromanoscopy, allowing to detect a tumor in the distal colon. Thus, it is possible to establish its localization, extent, growth pattern and make a targeted biopsy [25];
2. Colonofibroscopy is an alternative option for diagnostic screening. It is performed once with a time interval of 5-7 years, combined with a targeted biopsy (sensitivity is almost 100%). This is an expensive method that requires special preparation of the body. Complications are possible, especially in patients older than 60 years (bleeding – 0.3%, perforation – 0.1%). A biopsy causes great trauma to the tumor [26-30]. Virtual colonoscopy involves computed tomography with the analysis of a transformed image resembling that obtained by an optical colonoscope [31];
3. Transabdominal and endoscopic ultrasonography – detect volumetric neoplasms in the abdominal cavity, foci of metastasis in the liver and lymph nodes, the spread of cancer to surrounding organs (non-invasive method);
4. Computed tomography – allows to clarify the degree of tumor invasion and the presence of liver metastases [31];
5. Irrigoscopy and irrigography – retain their diagnostic value, because they allow to determine the localization and extent of the lesion, tumor decay, germination into neighboring organs and tissues, fistulas, abscesses, intestinal obstruction and perforations. During the procedure, double contrast and multi-projection X-ray examination are used [17].

1.4 Endovascular Approach in Complex Therapy of Patients with Metastases of Colon Carcinoma

The life expectancy of patients with colon carcinoma with metastases to the liver or other vital organs without the use of chemotherapy does not exceed six months or a year. Only a small group of patients are able to undergo radical surgical intervention, consisting in the elimination of the primary tumor and liver resection [32-35]. Resection in operable patients makes it possible to achieve 5-year survival, however, the complication rate is up to 45%, and postoperative mortality is 4-7% [33, 36].

According to the data of modern literature, radiofrequency ablation of liver metastases makes it possible to achieve five-year survival in almost half of all cases [32, 37 - 39]. The most promising direction in the treatment of patients with metastases of colon carcinoma in the liver is an integrated approach, including the combined sequential use of neoadjuvant endovascular local chemoembolization of metastases through hepatic arteries, radiofrequency ablations and liver resections, modern systemic adjuvant chemotherapy.

According to a large scientific research project of Adam et al. (2004), the results of therapy of 39 patients with metastases of colon carcinoma in the liver were presented [37]. Simultaneous simultaneous operations on the colon and liver were performed in 28 patients. In 11 patients with metachronous metastases, X-ray endovascular interventions were used in the course of therapeutic treatment. Endovascular chemoembolization of metastases with 5-fluorouracil on lipiodole was performed in 5 patients. Complex treatment: preoperative chemoembolization in combination with radiofrequency ablation or liver resection was performed in 6 patients. A preliminary assessment of long-term results indicates a tendency to improve survival rates after various options for complex treatment of patients with colorectal cancer metastases to the liver, especially with the combined use of X-ray endovascular and radiofrequency interventions.

The aim of the study was to evaluate the effectiveness of various methods of therapy of

patients with colorectal cancer metastases in the liver, based on the research of Adam et al. (2004).

2. MATERIALS AND METHODS

In the center of coloproctology in the city of Krasnoyarsk for the period from 2004 to 2008, 39 patients aged 45-65 (55±9.5) years with metastases of colorectal cancer in the liver were treated.

27 (69.2%) patients received complex treatment in various variants. The criteria for exclusion from the protocol of complex treatment were: cardiovascular and hepatic-renal insufficiency, distant extrahepatic metastases, pronounced ascites, liver damage over 2/3 of the volume, locally widespread metastatic process beyond the liver (patient data is provided in Table 1).

The study included the following categories of patients:

The first group included 7 patients with multiple bilobar liver damage with a diameter of metastases from 1.5 to 2.0 cm, in an amount from 3 to 7. They underwent sclerotherapy in combination with electrothermodestruction of metastases synchronously with colon surgery.

The second group consisted of 5 patients with a lesion of one lobe of the liver with solitary metastases, with a diameter of foci from 4.0 to 7.0 cm. In this group, traditional liver resections were performed synchronously with colon surgery.

The third group included 5 patients with multiple bilobar lesions, with a diameter of foci from 2.0 to 4.0 cm, in an amount from 7 to 10, when the liver lesion exceeded 2/3 of its volume (according to CT or MRI). These patients underwent endovascular chemoembolization of the hepatic artery. Embolization was performed on the side of the prevailing lesion. Subsequently, patients received adjuvant systemic chemotherapy - xeloda (2500 mg / m2, 4-6 courses).

The fourth group was represented by 9 patients with multiple bilobar lesions, with a diameter of foci from 2.0 to 3.0 cm, in an amount from 5 to 8. In these patients, radiofrequency ablation of metastases was performed synchronously with colon surgery. Subsequently, they received adjuvant systemic chemotherapy - xeloda (2500 mg / m2, 4-6 courses).

Table 1. Summary of patient data

Group number	Number of patients, people	Features of patients	Complex of therapeutic measures
1	**7**	Multiple bilobar liver lesions, metastasis diameter 1.5-2.0 cm, quantity - 37 pcs.	Sclerotherapy, electrothermodestruction of metastases, colon surgery
2	**5**	Lesion of one lobe of the liver by solitary metastases, diameter 4.0-7.0 cm	Colon surgery, traditional liver resection
3	**5**	Multiple bilobar lesions, the diameter of the foci 2.0-4.0 cm, the number of 7-10 pcs., liver damage exceeded 2/3 of its volume	Endovascular chemoembolization of the hepatic artery, adjuvant systemic chemotherapy with xeloda
4	**9**	Multiple bilobar lesions, with a diameter of 2.0-3.0 cm foci, the number of 5-8 pcs.	Radiofrequency ablation of metastases, colon surgery, adjuvant systemic chemotherapy with xeloda
5	**7**	Lesion of one lobe of the liver by solitary metastases, the diameter of the foci is 4.0-7.0 cm	Radiofrequency fried resection, colon surgery, adjuvant systemic chemotherapy with xeloda
6	**6**	**Independently developed method of treatment**	Neoadjuvant chemoembolization of the hepatic artery, radiofrequency ablation of metastases or radiofrequency resection of the liver, adjuvant systemic chemotherapy in XELOX mode.

The fifth group consisted of 7 patients with a lesion of one lobe of the liver with solitary metastases, with a diameter of foci from 4.0 to 7.0 cm. In this group, radiofrequency liver resection was performed synchronously with colon surgery. Subsequently, all these patients received adjuvant systemic chemotherapy with xeloda (2500 mg/m2, 4-6 courses).

The sixth group included in the study protocol is currently represented by 6 patients who used a treatment complex developed by them, consisting of a sequential combination of methods: neoadjuvant chemoembolization of the hepatic artery, radiofrequency ablation of metastases or radiofrequency resection of the liver.. Neoadjuvant endovascular chemoembolization of the hepatic artery includes: Stage 1 - proximal catheterization of the right or left hepatic artery from the transfemoral Seldinger access; 2 - chemoembolization of the hepatic artery with 5-fluorouracil (1000 mg) on lipiodole or PVA 500; 3 - occlusion of the blood flow with Gianturco spirals or a hemostatic sponge.

1 month after chemoembolization of the hepatic artery, these patients underwent liver surgery: three had radiofrequency ablation of metastases with multiple bilobar lesions, foci diameter from 2.0 to 4.0 cm, in an amount from 7 to 10. Three patients with a lesion of one lobe of the liver with solitary metastases, with a diameter of foci from 4.0 to 7.0 cm – radiofrequency liver resection. All patients in this group received this adjuvant systemic chemotherapy in XELOX mode.

3. RESULTS AND DISCUSSION

Active surgical tactics in the treatment of patients with colorectal cancer metastases in the liver allowed to increase the overall survival time. More than a year lived in more than 90% of cases, and 24 months - 79.5%. The overall three-year survival rate was almost 55%. In the group of patients with chemotherapy, it was 60%.

Thus, various options for complex treatment of patients with colorectal cancer metastases in the liver, especially with the use of endovascular and radiofrequency interventions, are relatively safe and effective, provided they are carried out in specialized oncological and coloproctological hospitals. Neoadjuvant endovascular chemoembolization of the hepatic artery increases the effectiveness of complex treatment of colorectal cancer metastases in the liver, contributes to an increase in the ablasticity of operations. However, the question of the combined use of endovascular chemoembolization of hepatic arteries and radiofrequency interventions on the liver requires further study.

4. CONCLUSION

Active surgical tactics in the treatment of patients with colorectal cancer metastases in the liver can increase the overall survival time. Various options for complex treatment of patients with colorectal cancer metastases in the liver, especially with the use of endovascular and radiofrequency interventions, are relatively safe and effective, provided they are carried out in specialized oncological and coloproctological hospitals. The effectiveness of various methods of therapy of patients with colorectal cancer metastases in the liver was evaluated, based on the research of Adam et al. (2004). A preliminary assessment of long-term results indicates a tendency to improve survival rates after various options for complex treatment of patients with colorectal cancer metastases to the liver, especially with the combined use of X-ray endovascular and radiofrequency interventions.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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