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ORIGINAL ARTICLE

Main aspects of personalized approach to the treatment of patients with chemotherapy resistant metastatic colorectal cancer

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ABSTRACT

Purpose of the study. To improve the results of treatment of patients with unresectable metastases of colorectal cancer in the liver that are not controlled by systemic chemotherapy.

Materials and methods. The study includes clinical data on the treatment of 76 patients with metachronous metastases of colorectal cancer in the liver that are not controlled by systemic chemotherapy. Patients underwent removal of the primary tumor according to urgent indications at the first stage of complex treatment, followed by systemic chemotherapy in an adjuvant mode. After 24.5 ± 0.2 months, patients were diagnosed with metastatic liver damage, and therefore systemic chemotherapy was initiated. After changing two lines of drug therapy with a registered progression of the oncological process, liver metastases were recognized as uncontrolled by systemic chemotherapy. After that patients were included in the given study and divided into two groups. The study group included 40 patients who underwent regional chemotherapy. The control group included 36 patients who continued systemic chemotherapy with subsequent line changes. The effectiveness was evaluated according to the RECIST 1.1 and mRECIST scales, as well as the overall one-year, two- and three-year survival rates.

Results. The median overall survival of patients in the control and study groups was 30.0 ± 0.8 and 41.5 ± 0.5 months, respectively, $p < 0.05$. The total one-year, two- and three-year survival of patients in the control and study groups was 94.4 %, 69.4 %, 33.3 % and 100 %, 82.5 %, 57.5 %, respectively, $p < 0.05$. The median life expectancy of deceased patients in the control and study groups was 22.5 ± 0.4 and 27.0 ± 0.4 months.

Conclusions. As a result of a comparative analysis of the detection of adverse events and complications of the treatment, patients of the study group underwent treatment much easier than patients of the control group – in patients in the group of systemic chemotherapy, moderate and severe complications were detected in 44.4 % of cases, in the study group – in 2.5 % of cases. According to the results of a clinical study, regional chemotherapy is an effective method of treating patients with colon cancer metastases in the liver that are not controlled by systemic chemotherapy and is associated with a statistically significant increase in overall survival ($p < 0.05$). For a more detailed study of the benefits of regional chemotherapy in this category of patients, further prospective clinical studies are necessary.

Keywords: colorectal cancer, liver metastases, hepatic artery chemoembolization, chemotherapy resistant metastases

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Compliance with ethical standards: the study was carried out in compliance with the ethical principles set forth in the Declaration of the World Medical Association of Helsinki, 1964, ed. 2013. The study was approved by the Committee on Biomedical Ethics at the 4Russian Scientific Center of Radiology and Surgical Technologies named after Academician A. M. Granov (extract from the minutes of the meeting No. 01-04/2024 dated 04/04/2024). Informed consents were received from all participants of the study

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ОРИГИНАЛЬНАЯ СТАТЬЯ

Роль регионарной химиотерапии в лечении больных с метахронными метастазами колоректального рака в печени, не контролируемыми системной химиотерапией

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РЕЗЮМЕ

Цель исследования. Улучшить результаты лечения больных с нерезектабельными метастазами колоректального рака в печени, не контролируемыми системной химиотерапией.

Пациенты и методы. В настоящее исследование включены клинические данные о лечении 76 пациентов с метахронными метастазами колоректального рака в печени, не контролируемыми системной химиотерапией. На первом этапе комплексного лечения пациентам проведено удаление первичной опухоли по срочным показаниям с последующим проведением системной химиотерапии в адъювантном режиме. Через 24,5 ± 0,2 месяцев у пациентов диагностировано метастатическое поражение печени, в связи с чем начата системная химиотерапия. После смены двух линий лекарственной терапии с зарегистрированной прогрессией онкологического процесса, метастазы в печени были признаны не контролируемыми системной химиотерапией, после чего больные были включены в настоящее исследование и разделены на две группы. В исследуемую группу включены 40 пациентов, которым проводилась регионарная химиотерапия. В контрольную группы включены 36 пациентов, которым продолжена системная химиотерапия с последующей сменой линий. Оценка эффективности проводилась согласно шкалам RECIST 1.1 и mRECIST, а также оценивалась общая годичная, двух- и трехлетняя выживаемость.

Результаты. Медиана общей выживаемости больных контрольной и исследуемой групп составила 30,0 ± 0,8 и 41,5 ± 0,5 месяцев соответственно, $p < 0,05$. Общая годичная, двух- и трехлетняя выживаемость больных контрольной и исследуемой групп составила 94,4, 69,4, 33,3 и 100, 82,5, 57,5 % соответственно, $p < 0,05$. Медиана продолжительности жизни умерших больных контрольной и исследуемой группы составила 22,5 ± 0,4 и 27,0 ± 0,4 месяцев.

Заключение. В результате сравнительного анализа выявления нежелательных явлений и осложнений проводимого лечения выяснили, что больные исследуемой группы перенесли лечение значительно легче, нежели больные контрольной группы – у больных в группе системной химиотерапии осложнения средней и тяжелой степени выявлены в 44,4 % случаях, в исследуемой группе – в 2,5 % случаях. По результатам проведенного клинического исследования, регионарная химиотерапия является эффективным методом лечения больных с метастазами рака толстой кишки в печени, не контролируемыми системной химиотерапией и ассоциирована со статистически значимым увеличением общей выживаемости ($p < 0,05$). Для более детального изучения преимуществ регионарной химиотерапии в данной категории больных необходимо дальнейшее проведение проспективных клинических исследований.

Ключевые слова: колоректальный рак, метастазы в печень, химиоэмболизация печеночной артерии, химиорезистентные метастазы

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Соблюдение этических стандартов: в работе соблюдались этические принципы, предъявляемые Хельсинкской декларацией Всемирной медицинской ассоциации (World Medical Association Declaration of Helsinki, 1964, ред. 2013). Исследование одобрено Комитетом по биомедицинской этике при ФГБУ «Российский научный центр радиологии и хирургических технологий им. акад. А. М. Гранова» Министерства здравоохранения Российской Федерации (выписка из протокола заседания № 01-04/2024 от 04.04.2024 г.). Информированное согласие получено от всех участников исследования

Финансирование: финансирование данной работы не проводилось

Конфликт интересов: все авторы заявляют об отсутствии явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи

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INTRODUCTION

Currently, colon cancer occupies one of the leading positions among all oncological diseases [1–3]. One of the main causes of death in patients with malignant tumors of the colon is the prevalence of the oncological process, which in 20–60 % of patients manifests itself in the form of metastatic liver damage [4–6]. Without special antitumor treatment of patients with metastatic liver damage, life expectancy does not exceed one year [3].

The progressive development of oncology led to a deep understanding of the biology of colon tumors and determined the need for immunohistochemical and molecular genetic studies, which made it possible to apply a personalized therapeutic approach [7, 8]. However, systemic chemotherapy (SCT) remains the main method of treating patients with advanced forms of colorectal cancer (CRC) today [9–11].

There is an extensive group of patients with bilobar metastatic liver damage who need to stop CT due to the development of chemoresistance or adverse events [12, 13]. The question of possible treatment options for these patients remains open today.

The study purpose was to improve the results of treatment of patients with unresectable metastases of colorectal cancer in the liver that are not controlled by systemic chemotherapy

PATIENTS AND METHODS

The study included 76 patients aged 40 to 81 years with a morphologically confirmed diagnosis of colon cancer. The average age was 63.6 ± 8.7 years. The primary tumor is represented by adenocarcinoma of various degrees of malignancy – in 23 (30.3 %) cases, highly differentiated adenocarcinoma (G1) was diagnosed, in 48 (63.1 %) cases and in 5 (6.6 %) cases, moderate (G2) and low-differentiated (G3) adenocarcinoma, respectively.

All patients at the first stage of complex treatment underwent surgical treatment for urgent indications due to the development of intestinal obstruction (88.2 %) and the threat of massive bleeding (11,8 %), aimed at removing the primary tumor of the colon. Right-sided hemicolectomy was performed in 25 (32.9 %) cases, sigmoid colon resection was performed in 17 (22.4 %) cases, anterior rectal resection was performed in 19 (25.0 %) cases, left-sided hemicolectomy was performed in 6 (7.9 %) cases and transverse colon resection was performed in 9 (11.8 %) cases. After the surgical intervention, a histological examination of the surgical material was performed, followed by the determination of the final stage according to the TNM classification (8th edition).

Stage T1 was detected in 11 (14.5 %) cases, stage T2 was diagnosed in 29 (38.2 %) cases, stages T3 and T4 were detected in 27 (35.5 %) and 9 (11.8 %) cases, respectively. When assessing regional metastasis, stage N0 was established in 32 (42.1) cases, N1 in 29 (38.2 %) cases, and N2 in 15 (19.7 %) cases (Table 1). No distant metastasis was detected in any patient.

As can be seen from Table 1, stage I was diagnosed in 19 (25 %) patients, stage II was diagnosed in 11 (14.5 %) patients, and stage III in 46 (60.5 %) patients (Fig. 1).

In all cases, patients underwent radical resection of the primary tumor R0.

It was mandatory for all patients to undergo a molecular genetic study determining mutations in the KRAS, NRAS, and BRAF genes. KRAS mutations were detected in 19 (25.0 %) patients. Wild types of KRAS and NRAS were diagnosed in 57 (75.0 %) patients. Given the unfavorable prognosis and the need for more aggressive treatment of patients with mutations in the BRAF gene, the latter were not included in this study.

In 51 (67.1 %) cases, patients underwent systemic chemotherapy in adjuvant mode – in 48 (63.1 %)

Table 1. Distribution of patients according to T and N categories

Category	N0	N1	N2
T1	8 (10.5 %)	3 (3.9 %)	0
T2	11 (14.5 %)	13 (17.1 %)	5 (6.6 %)
T3	9 (11.8 %)	11 (14.5 %)	7 (9.2 %)
T4	2 (2.6 %)	4 (5.3 %)	3 (3.9 %)

cases in patients with the spread of the pT1–4N+ tumor process and in 3 (3.9 %) cases in patients with pT3N0M0 who had negative prognosis factors (high degree of malignancy of the primary tumor, perineural and lymphovascular invasion). In 39 (51.3 %) cases, patients underwent drug therapy in the XELOX mode, in 37 (48.7 %) cases the FOLFOX mode was used. On average, each patient underwent 6.4 ± 1.4 courses of CT (Fig. 2).

As can be seen from Figure 2, in two cases, systemic chemotherapy is limited to one and two courses. The treatment of patients was interrupted due to the development of adverse events. In one case, on the 7th day after the first course of drug therapy in XELOX mode, a myocardial infarction was diagnosed. In the second case, after the second course of CT in FOLFOX mode, an acute stomach ulcer was detected.

All patients whose clinical data are included in this study underwent regular follow-up examinations according to clinical recommendations. The median before the progression of the tumor process was 24.5 ± 0.2 months. All patients were diagnosed with bilobar metastatic liver disease. On average, 5.1 ± 1.4 metastatic foci were diagnosed in each patient. The average sum of the diameters in the largest measurement of liver formations in each patient was 49.9 ± 12.7 mm (Fig. 3).

After the liver formations were detected, according to computed tomography with intravenous contrast, a percutaneous transhepatic trepan biopsy was performed under ultrasound guidance. In all cases, the morphological picture of metastatic foci corresponded to the primary tumor.

After receiving histological confirmation of secondary liver foci, a collegial discussion of further therapeutic tactics was conducted with the participation of an oncologist, surgeon, chemotherapist, radiologist. As a result, patients were prescribed chemotherapy in the following regimens: modified FOLFOX6 – in 22 (28.9 %) cases, XELOX – in 14 (18.4 %) cases, FOLFIRI – in 24 (31.6 %) cases, XELIRI – in 11 (14.5 %) cases, capecitabine in monotherapy in 5 (6.6 %) cases. Chemotherapy courses were conducted against the background of biotherapy. Taking into account the data of the molecular genetic study, bevacizumab was prescribed to patients in 19 (25.0 %) cases, and erbitux was prescribed in 57 (75.0 %) cases. The effectiveness of the drug treatment was evaluated after the fourth course.

When performing a control examination after the fourth course of PCT, 66 (86.8 %) patients showed progression of the tumor process, in 10 (13.2 %) cases, adverse events were detected, and therefore chemotherapeutic treatment was interrupted. In patients with the progression of the tumor process, an increase in targeted foci was diagnosed in 46 (60.5 %) cases, the appearance of new foci was registered in 17 (22.4 %) cases, and in 28 (36.8 %) cases, an increase in blood cancer markers (CA 19–9,

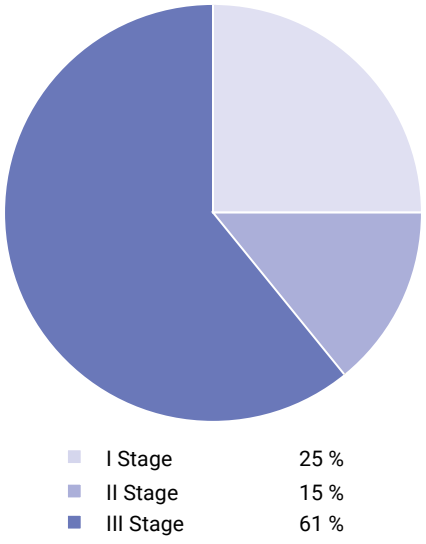

Fig. 1. Distribution of patients by tumor process stages according to TNM classification

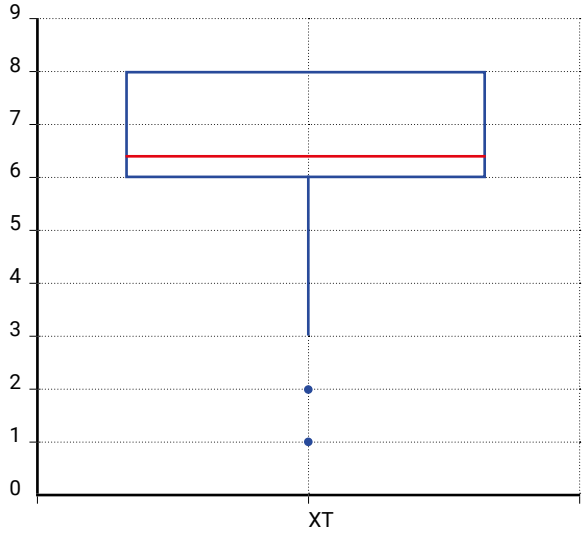

Fig. 2. Distribution of patients by the number of SCT courses performed

cancer-embryonic antigen, alpha-fetoprotein) was revealed in comparison with the baseline level. The patients underwent a change of the chemotherapy line. FOLFIRI CT was prescribed in 26 (34.2 %) cases, FOLFOXIRI in 27 (35.5 %) cases, irinotecan monotherapy was performed in 12 (15.8 %) cases, and XELIRI in 11 (14.5 %) cases. After the control examination, further progression of the tumor process was revealed in 59 (77.6 %) patients, in 17 (22.4 %) cases, adverse events were diagnosed. Given the ineffectiveness of two lines of systemic chemotherapy, metastatic foci are recognized as chemo resistant. Considering the chemo resistant nature of metastatic liver damage, a molecular genetic study of biopsies of liver foci was performed. As a result, 5 (6.6 %) patients showed heterogeneity of metastatic foci in comparison with the primary tumor, which consisted in the detection of the mutant KRAS gene in the wild type of KRAS primary tumor. In this regard, the patients underwent correction of biotherapy.

In patients with a pronounced degree of toxic manifestations of drug therapy, metastatic foci are recognized as uncontrolled by systemic chemotherapy. All the patients presented above are included in this study and divided into two groups.

The first study group included 40 patients with chemo resistant liver metastases, including 17 patients with moderate and severe toxicity on the background of CT. The second, control group included 36 patients with chemo resistant liver metastases.

Patients of the study group underwent regional chemotherapy of secondary foci of the liver, i. e. the hepatic artery chemoembolization (HACE) using Biosphere microspheres 50–100 μm. Irinotecan was used as a cytostatic agent in the first line of RCT, with the ineffectiveness of the latter, doxorubicin was used as a line 2 drug.

HACE was performed in the following mode for all patients – the first two cycles were performed at intervals of 3 weeks, then 1 month after the second cycle, a control computed tomography was performed to assess the effectiveness of the treatment and then decide whether it was advisable to continue the RCT cycles when stabilization/response was obtained or a cytostatic change was detected with the progression of the tumor process (Fig. 4).

Patients in the control group underwent a change of systemic chemotherapy lines. The effectiveness of treatment was evaluated after the fourth course of SCT. The following regimens were used as 3 SCT lines: FOLFIRI, XELIRI, irinotecan in monotherapy, capecitabine in monotherapy. Irinotecan in monorode, capecitabine in monorode and FOLFOXIRI were used as the 4th line of SCT.

The obtained results of the study in both groups were subjected to a comparative analysis. The effectiveness of treatment in the study group was assessed using the response evaluation criteria in solid tumors (RECIST 1.1, 2009) and modified RECIST (mRECIST) scales, in the control group – on the RECIST 1. 1 scale.

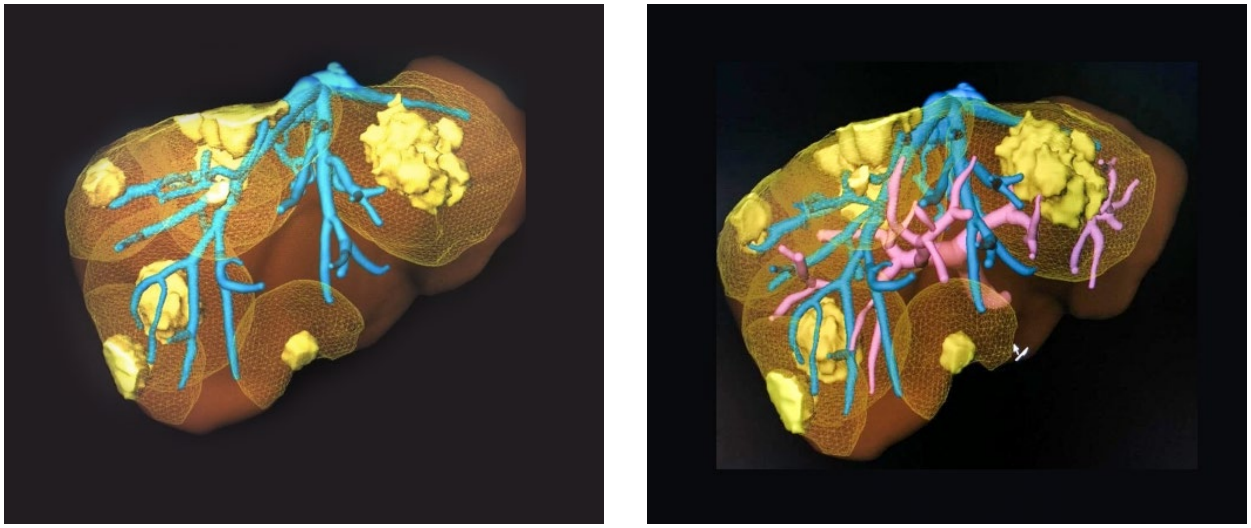

Fig. 3. 3D reconstruction of the liver in patients with CRC metastatic lesions

When simultaneous progression on the RECIST 1.1 scale and stabilization or response on the recist scale were detected, that is, with local extrahepatic metastasis was diagnosed in the response, patients continued to undergo HACE against the background of resumption of systemic chemotherapy.

STUDY RESULTS

A year after the start of RCT in patients of the study group, a partial response on the RECIST 1.1 scale was detected in 8 (20.0 %) patients, stabilization of the tumor process in the liver in patients was diagnosed in 18 (45.0 %) patients, progression of the metastatic process was detected in 8 (20.0 %) patients. In 6 (15.0 %) cases, the appearance of a new metastatic lesion in the liver was registered, despite the local response of the observed foci, and therefore the result was regarded as progression according to the RECIST 1.1 scale and stabilization according to the mRECIST scale. There were no deaths within 12 months after the HACE.

In the control group, one year after inclusion in the present study, stabilization was noted in 16 (44.4 %) patients after CT on the RECIST 1.1 scale, and 20 (56.6 %) patients were diagnosed with progression of the tumor process, including extrahepatic metastasis.

It is worth noting that 5 (13.9 %) patients included in the control group with heterogeneous mutational KRAS status of primary and metastatic tumors showed stabilization of the tumor process against the background of a change in targeted therapy.

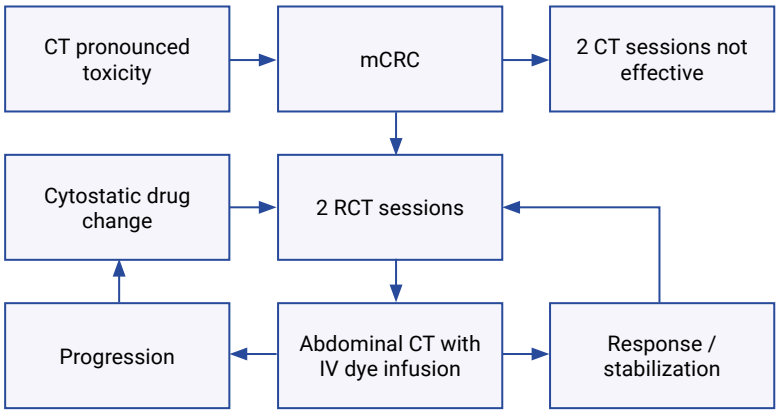

Fig. 4. Algorithm of regional chemotherapy in patients of the research group

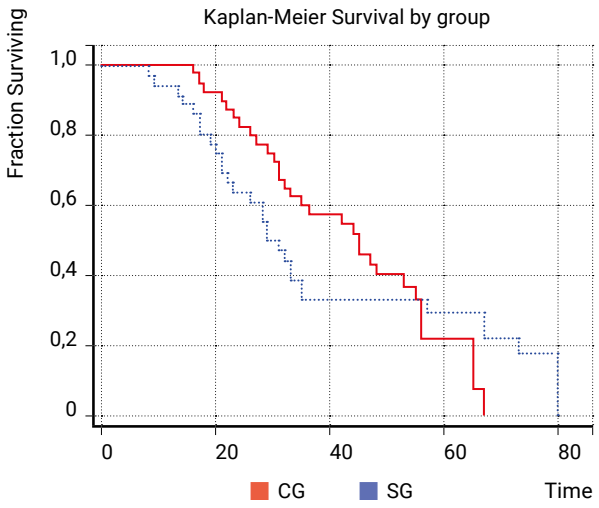

Fig. 5. Overall survival of patients in the study group (SG) and the control group (CG)

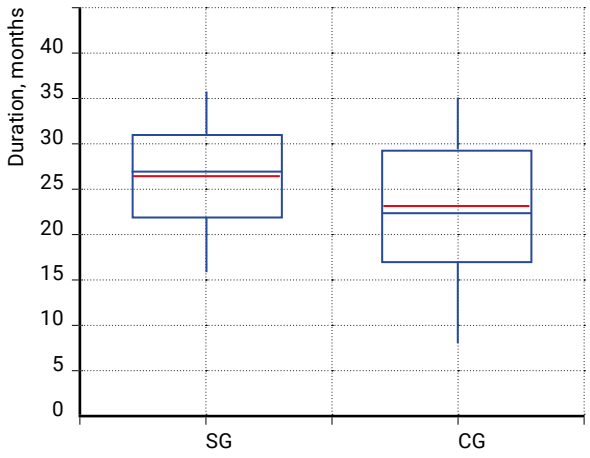

Fig. 6. Life expectancy of deceased patients of the study group (SG) and the control group (CG)

The median overall survival of patients in the control and study groups was 30.0 ± 0.8 and 41.5 ± 0.5 months, respectively, $p < 0.05$ (Fig. 5).

The total one-year, two- and three-year survival of patients in the control and study groups was 94.4 %, 69.4 %, 33.3 % and 100 %, 82.5 %, 57.5 %, respectively, $p < 0.05$.

The median life expectancy of deceased patients in the control and study groups was 22.5 ± 0.4 and 27.0 ± 0.4 months (Fig. 6).

The indicators of cancer markers were monitored: in the case of HACE, there was a decrease in the indicators of cancer markers in 57.5 % of cases, and an increase in their level was noted in 42.5 % of cases.

In the case of CT, 72.2 % of the subjects had an increase in cancer markers and only 27.8 % had stabilization. There were no pronounced phenomena of systemic toxicity, liver and kidney failure after HACE: 6 (15.0 %) patients had a change in Child-Pugh scores (an increase of maximum 1 point from the initial 3–5 points). Postembolization hepatotoxicity (increased activity of gamma-glutamyltraspeptidase (GGTP), alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT)) was noted in 9 (22.5 %) patients.

In the control group, toxic reactions and complications of varying severity were detected after systemic chemotherapy. Hepatotoxicity was detected in 22 (61.1 %) patients, 8 (22.2 %) of whom had a deterioration in the functional state of the liver according to the Child-Pugh scale. Neurotoxicity was detected in 10 (27.8 %) cases, which manifested itself in the form of the development of peripheral polyneuropathy. The development of acute cardiovascular insufficiency against the background of systemic chemotherapy was detected in one patient (2.8 %), this complication led to a fatal outcome.

In the study group, an assessment and analysis of the developed complications were also carried out. All patients had a manifestation of postembolization syndrome (PES), which manifested itself as a moderate intensity pain syndrome and hyperthermia up to 37.4 °C for three days after HACE was performed. The pain syndrome was completely stopped by a single intramuscular injection with NSAID drugs. One patient treated by us had a case of extrahepatic embolizate injection into the cystic artery. In this regard, the patient was treated conservatively with a positive effect. No surgical intervention was required.

DISCUSSION

A common form of colorectal cancer is one of the leading causes of death among patients with malignant tumors worldwide. The main organ of CRC metastasis is the liver [14].

Currently, methods of a personalized therapeutic approach have been developed and introduced into clinical practice, developed based on an understanding of carcinogenesis and tumor biology. According to clinical recommendations, surgical intervention is the main method of choosing treatment for patients with metastatic colorectal liver cancer. However, liver resection is possible in no more than 30 % of cases due to the prevalence of the tumor process, technical features or the burdened comorbid status of patients. Therefore, chemotherapy remains the main method of treatment for patients of the presented cohort [15].

Systemic chemotherapy is associated with a high risk of toxicity and chemoresistance, which requires discontinuation of drug treatment in the first case or a change of the SCT session in the second case. Thus, the treatment of colon cancer patients with chemoresistant or uncontrolled chemotherapy liver metastases is an urgent topic of discussion [15–17].

In the presented clinical study, a comparative analysis was carried out between treatment with systemic and regional chemotherapy in patients with multiple unresectable chemoresistant liver metastases. Before inclusion in the present study, patients underwent at least two lines of CT. As a result of the conducted clinical study, HACE showed high effectiveness – in 26 (65.0 %) cases, a result was achieved according to the RECIST 1.1 scale and in 32 (80.0 %) cases according to the mRECIST scale, compared with 16 (44.4 %) cases of positive results in patients of the control group. It is worth noting that the evaluation of the results of regional chemotherapy separately on the RECIST 1.1 scale or on the mRECIST scale does not reliably reflect the effectiveness of the treatment. Thus, the appearance of new extrahepatic metastases (progression according to the RECIST 1.1 scale) does not correlate with the ineffectiveness of HACE due to the limited local effect of the latter, which may be accompanied by a response according to the mRECIST scale, which was recorded in 6 cases in patients of the study group. In this regard, the presented patients need to undergo both

systemic chemotherapy and influence extrahepatic foci and continue regional chemotherapy.

As a result of a comparative analysis of the detection of adverse events and complications of the treatment, patients of the study group underwent treatment much easier than patients of the control group – in patients in the group of systemic chemotherapy, moderate and severe complications were detected in 44.4 % of cases, in the study group – in 2.5 % of cases.

CONCLUSION

Thanks to a personalized approach, which includes an assessment of the prevalence of the tumor process, the degree of malignancy of the primary tumor, the results of histological and molecular genetic research methods, as well as the severity of adverse events of chemotoxicity and individual reactions, it is possible to develop an individual treatment plan that will increase the overall and relapse-free survival of patients with uncontrolled systemic chemotherapy metastases of colorectal cancer in the liver. According to the results of a clinical study, regional chemotherapy is an effective method of treating patients with chemo resistant metastases of colon cancer in the liver and is associated with a statistically significant increase in the overall survival of patients compared with systemic chemotherapy ($p < 0.05$). For a more detailed study of the benefits of regional chemotherapy in this category of patients, it is necessary to further conduct prospective clinical studies.

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