

## ХИМИОЭМБОЛИЗАЦИЯ ПЕЧЕНОЧНОЙ АРТЕРИИ В ЛЕЧЕНИИ БОЛЬНЫХ МЕТАСТАТИЧЕСКИМ КОЛОРЕКТАЛЬНЫМ РАКОМ ПЕЧЕНИ

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**Цель.** Оценить эффективность химиоэмболизации печеночной артерии (ХЭПА) в лечении больных метастатическим колоректальным раком печени, а также определить оптимальный временной интервал при ее комбинации с другими методами лечения. **Материалы и методы.** В исследование включен анализ результатов лечения 30 больных с резектабельными метастазами колоректального рака печени. Первую группу составили 15 пациентов, кому резекционное вмешательство выполнено через 1 неделю после проведенной ХЭПА. Вторую группу составили 15 пациентов, кому резекционное вмешательство выполнено через 2 недели после проведенной ХЭПА с последующей оценкой морфологических изменений метастазов. **Результаты.** Лечебный патоморфоз зафиксирован у 25/30 больных. В первой группе лечебный патоморфоз наблюдался у 13/15 больных. У 11/13 больных зафиксирована 2 степень лечебного патоморфоза. У 2/13 больных – 1 степень. Во второй группе лечебный патоморфоз, наблюдался у 12/15 больных. У всех больных зафиксирована 2 степень лечебного патоморфоза. Не зафиксировано достоверных различий в степени лечебного патоморфоза на 7 и 14 день после регионарной химиотерапии ( $p=0,436$ ). **Заключение.** Химиоэмболизация печеночной артерии является эффективным методом лечения больных метастазами колоректального рака печени. При применении химиоэмболизации печеночной артерии в комбинации с другими хирургическими методами семидневный временной промежуток является оптимальным.

**Ключевые слова:** метастазы колоректального рака печени, регионарная химиотерапия, лечебный патоморфоз.

## TRANSARTERIAL CHEMOEMBOLISATION IN THE TREATMENT OF PATIENTS WITH METASTATIC COLORECTAL CANCER

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**Aim.** To assess effectiveness of chemoembolization of hepatic artery (CEHA) in treatment of patients with metastatic colorectal cancer, and also to determine the optimal interval in combination of CEHA with other treatment methods. **Materials and methods.** The study includes analy-



sis of the results of treatment of 30 patients with resectable metastases of colorectal cancer in the liver. The first group included 15 patients with resection made 1 week after CEHA. The second group consisted of 15 patients in whom resection operation was made 2 weeks after CENA with subsequent assessment of morphological changes in metastases. **Results.** Therapeutic pathomorphism was recorded in 25/30 patients. In the first group, therapeutic pathomorphism was observed in 13/15 patients. In 11/13 patients, the 2<sup>nd</sup> degree of therapeutic pathomorphism was recorded. In 2/13 patients – the 1<sup>st</sup> degree. In the second group, therapeutic pathomorphism was observed in 12/15 patients. In all patients the 2<sup>nd</sup> degree of therapeutic pathomorphism was recorded. No significant differences in the degree of therapeutic pathomorphism were recorded on the 7<sup>th</sup> and 14<sup>th</sup> day after regional chemotherapy ( $p=0.436$ ). **Conclusion.** Hepatic artery chemoembolization is an effective method of treating patients with metastases of colorectal cancer in the liver. In use of chemoembolization of hepatic artery in combination with other surgical methods, the seven-day time interval is optimal.

**Keywords:** *metastases of colorectal liver cancer, regional chemotherapy, therapeutic pathomorphosis.*

Liver is an organ which is most commonly damaged by metastatic tumor processes. In most cases the source for metastasis in the liver is colorectal cancer [1]. Colorectal cancer ranks fourth in the structure of oncological disease. In each third individual with colon cancer remote metastases are identified at the moment of making the diagnosis, first of all, in the liver (according to the international authors, in 20-50% of cases) [2]. Besides, up to 55% of patients who received potentially radical treatment of colon cancer, have risk of progress of the disease in the form of metastases. In 25% of observations, liver is the only organ damaged by metastases [3]. Speaking about prognosis, the only metastases that lead to the lethal outcome faster than damages to the liver, are metastases into the brain. [4,5]. According to different authors, survival rate in metastatic damages to the liver without treatment is less than 12 months. The only effective method of treatment of liver metastases giving satisfactory results, is surgical intervention. It provides 5-year survival rate in 20-58% of patients [6], but however, resectability of liver metastases is not more than 10-30% [7].

The most effective method of treating patients with non-operable colorectal liver metastases is radio frequency ablation (RFA) which provides 5-year survival in 17-51% of cases [8-10]. One of disadvantages of this

method is a high risk of local recurrences which reaches 25-50% with the size of lesion more than 3 cm and 16% with the size of lesion less than 3 cm. The main cause for a local recurrence is incomplete coagulation necrosis after ablation. The rate of complete necroses with the size of lesion more than 5 cm is less than 50% [11]. To increase the area of necrosis and reduce the risk of local recurrences a combination of RFA with chemoembolization of the hepatic artery (CEHA) is used [12,13]. In studies conducted on VX2 rabbits this combination was shown to reliably increase the concentration of heat shock proteins (HSP) ( $p<0.01$ ) in peritumorous tissues, in particular, of HSP70 protein, responsible for autocrine induction of chemokines by tumor cells (Fig. 1) [14].

HSP70 proteins obtained from tumor cells, function as cytokines which stimulate macrophages that produce anti-inflammatory cytokines and chemokines. Besides, HP70 can accompany antigens of damaged cells into T-cells, and induce in this way the anti-tumor immunity. Increase in the concentration of HSP70 in peritumorous tissues after application of RFA and CEHA combination also leads to a considerable increase in the concentration of T-cells in this zone [15].

The result of increased concentration of HSP70 and CD8+ T-cells was a reliably higher parameter of completeness of tumor necro-

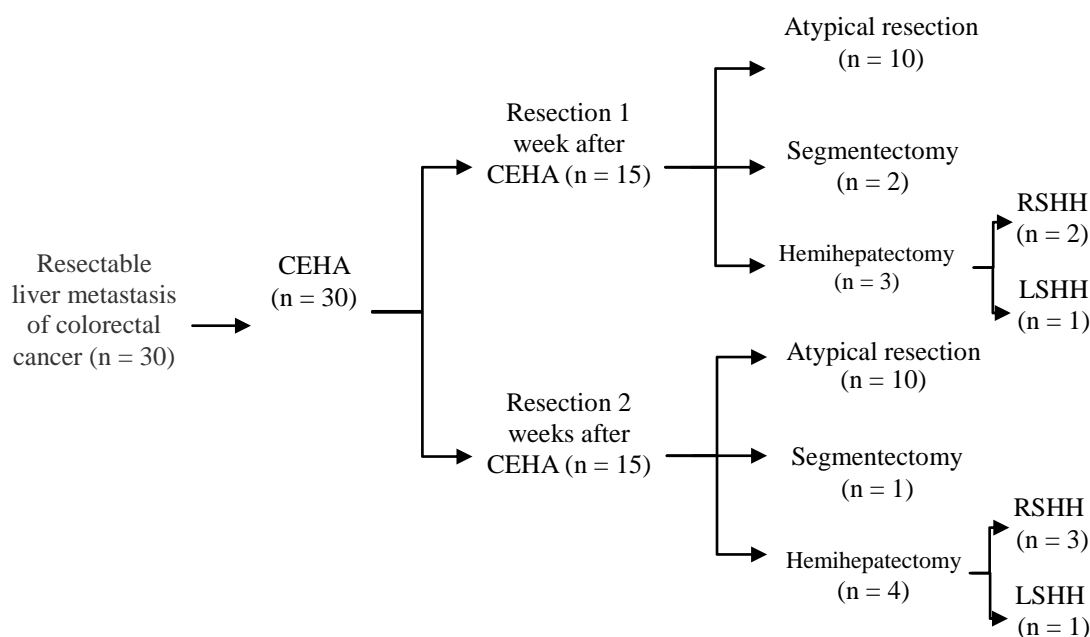


Fig. 1. Study protocol for determining the optimal time for the second stage of treatment

sis after application of a combination of RFA and CEHA [15]. A disadvantage of conducted studies was the fact that ablation was performed within one hour after embolization. Only ischemic effect of embolization was used because of the minimal time of action of chemoembolic agent on the tumor.

In the world literature the data have been published about use of a combination of RFA and CEHA only for treatment of patients with hepatocellular cancer (HCC) [12,13]. A disadvantage of these studies is different time intervals between stages of treatment (from several days to 3 weeks). At present the effectiveness of application of hepatic artery chemoembolization in treatment of patients with colorectal metastatic cancer is not determined. Besides, the treatment protocol of inoperable malignant neoplasms of the liver by a combination of RFA and CEHA is not yet standardized.

#### Materials and Methods

The basis of the prospective comparative randomized study included the analysis of the results of treatment of 30 patients with

the medium age of  $61.33 \pm 10.7$  years with resectable metastases of colorectal cancer in the liver who were under treatment in the department of surgery of liver and pancreas in the period from 2013 to 2014. Into the study the following patients were included: without severe concomitant pathology with resectable metachronous liver metastases of colorectal cancer; with the size of metastases from 3 to 5 cm; patients who did not receive systemic chemotherapy after liver metastases have been verified. To study therapeutic pathomorphism in different periods after regional chemotherapy the patients were divided into two groups. The first group included 15 patients with resection performed 1 week after CEHA with the subsequent histological examination and determination of the degree of therapeutic pathomorphism. The second group included patients with resection performed 2 weeks after CEHA with the subsequent histological examination according to the protocol, with determination of the degree of therapeutic pathomorphism (Fig. 1). A chemoembolic agent was a mixture consisting

of lipiodol 10 ml and mitomycin C 10 mg. The extent of therapeutic pathomorphism was evaluated according to Colorectal Cancer Structured Reporting Protocol (2nd Edition, 2012). Randomization of patients into groups was conducted by a method of «ballot box» (UD 2:1) at the stage of planning of regional chemotherapy.

A decision about resection operation was taken by the multidisciplinary oncoconcilium. Resection of the liver was conducted according to conventional standards and indications. In the first group the following interventions were conducted: atypical resection – 10; segmentectomy – 2; right-sided hemihepatectomy (RSHH) – 2; left-sided hemi-

hepatectomy (LSHH) – 1. In the second group the following operation were conducted: atypical resection – 10; segmentectomy – 1; right-sided hemihepatectomy (RSHH) – 3; left-sided hemihepatectomy (LSHH) – 1. In planning of resection of more than 3 segments of the liver, the volume of future liver remnant (FLR) was evaluated in all patients. In all patients the FLR was above the necessary values ( $>25\%$  in the absence of the liver pathology (hepatosis, cirrhosis),  $>35\%$  with existing pathology)). In all patients single-stage resections of liver were performed.

Further on systemic adjuvant therapy was conducted. Characteristics of the groups are given in Table 1.

Table 1

*Characteristics of patients with the definition of therapeutic pathomorphosis after regional chemotherapy*

Characteristics	1 group (n = 15)	2 group (n = 15)	p
Sex:			
male	7	8	0,775
female	8	7	
Age:			
<60 years	6	6	0,806
> 60 years	9	9	
Primary tumor:			
colon	12	7	0,126
rectum	3	8	
Primary tumor stage:			
Step 1-2	2	3	0,624
3 stage	13	12	
N-status of primary tumor:			
N+	2	3	0,775
N-	13	12	
The size of metastasis:			
3-4 cm	9	8	0,870
4-5 cm	6	7	
Level of REA:			
<60 ng / ml	12	12	0,653
> 60 ng / ml	3	3	
Localization of metastasis:			
central (S4,5,8)	8	7	0,486
peripheral	7	8	
Time to metastasis:			
<12 months	9	8	0,089
> 12 months	6	7	
ASA:			
Grade 1	9	6	0,367
Grade 2	6	9	

Description of the variables depended on their distribution. The kind of distribution was determined using Shapiro-Wilk test. If distribution of the variable approached the normal one (Gaussian distribution), for description of the quantitative data the mean value was used with the mean square deviation ( $M \pm s$ ), and in comparison of groups by this variable, parametric methods were used (Pearson correlation analysis, Student's t-test).

For analysis of the data by a variable, non-parametric Mann-Whitney criteria for independent groups were used. The obtained results were processed by Statistica program for Microsoft Windows, version 6.1, StatSoft Inc. (USA). Statistically significant level was taken  $p < 0.05$ .

### Results and Discussion

In all patients after CEHA, postembolization syndrome was observed. Pain syndrome was seen in 29 of 30 patients (herein-

after – 29/30) patients, hyperthermia – in 7/20, elevation in the level of transaminases – in 25/30 patients.

The average intensity of pain syndrome on the first day after CEHA determined by VAS test was  $41.37 \pm 15.17$  (0-75) mm. Administration of analgesics was required for 27/30 patients, in 26/27 patients pain syndrome was relieved by non-steroid anti-inflammatory drugs (NSAID), in 1/27 patient – by narcotic analgesics. On the second day after the procedure intensity of pain syndrome determined by VAS was  $19.97 \pm 9.65$  (0-43) mm. Administration of analgesics was required for 11/30 patients, pain syndrome in them was relieved by administration of NSAID. On the third day after the procedure some painful sensations were observed in 2/30 patients with the average intensity by VAS test  $3.31 \pm 6.75$  (0-21) mm. Administration of analgesics was not required (Fig. 2).

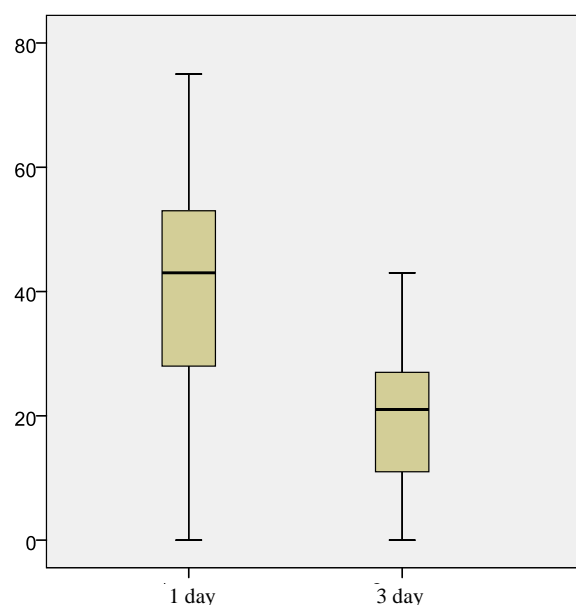


Fig. 2. Intensity of pain syndrome according to VAS for 1-3 days after regional chemotherapy

Hyperthermia  $\geq 38^\circ\text{C}$  on the 1<sup>st</sup> day after CEHA was in 1/30 patients,  $\geq 37^\circ\text{C}$  – in 6/30 patients. On the second day hyperthermia  $\geq 37^\circ\text{C}$  was in 3/30 patients, the temperature did not rise above  $38^\circ\text{C}$ . On the 3<sup>d</sup> day all patients had normothermia.

In all patients before CEHA the level of transaminases was within the norm. On the 1<sup>st</sup> day AsAT level increased in 24/30 patients, of AlAT – in 25/30 patients. On the 1<sup>st</sup> day the average level of AsAT was  $75.28 \pm 41.39$  (16-201) Un/L, of AlAT –  $59.78 \pm 36.47$  (22-207)

Un/L. On the 3<sup>d</sup> day elevation of AsAT was noted in 21/30 patients, of AlAT – in 19/30 patients. On the 3<sup>d</sup> day the average level of AsAT was  $40.78 \pm 25.5$  (20-138) Un/L, of AlAT –  $56.13 \pm 39.05$  (21-243) Un/L. On the 5<sup>th</sup> day after the procedure AsAT was in-

creased in 12/30 patients, AlAT – in 12/30 patients. On the 5<sup>th</sup> day the average level of AsAT was  $31.2 \pm 11.54$  (18-69) Un/L (Fig. 6), of AlAT –  $32.43 \pm 9.26$  (15-79) Un/L (Figs. 3 and 4). No complications and no lethality after CEHA were recorded.

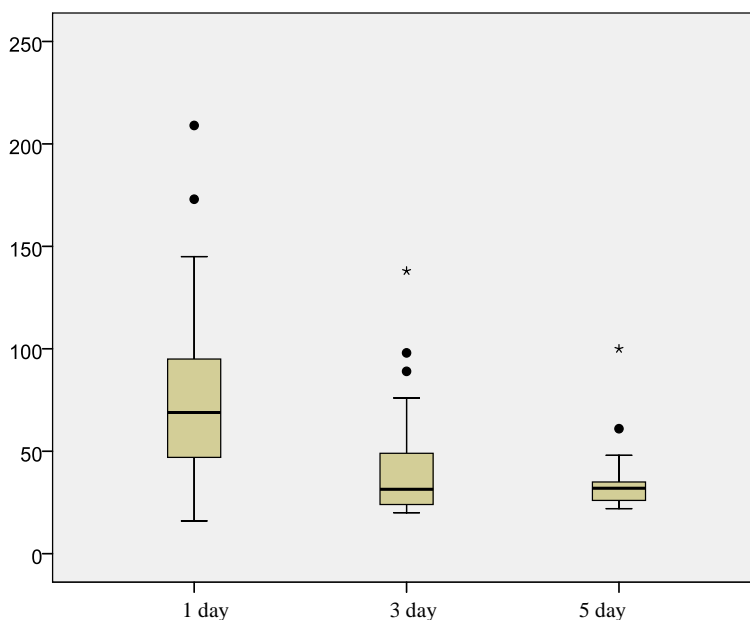


Fig. 3. AsAT level on the 1-5th day after CEHA

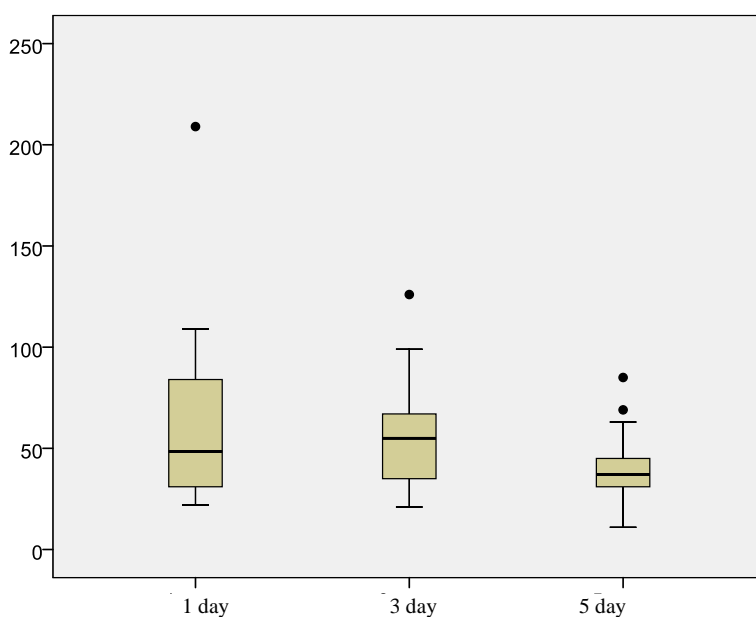


Fig. 4. AlAT level for 1-5 days after CEHA

The degree of therapeutic pathomorphism was traced in all patients included into the study.

In the first group where resection operation was conducted in 7 days after the regional chemotherapy, the therapeutic pathomorphism was observed in 13/15 patients. In 11/13 patients the 2<sup>nd</sup> degree of therapeutic pathomorphism was recorded that consisted in the existence of fibrosis fields and scarce inflammatory infiltration (Fig. 5) with the underlying preserved tumorous tissue.

In 2/15 patients no therapeutic pathomorphism was observed. In 2/13 patients the 1<sup>st</sup> degree of therapeutic pathomorphism was determined: in one patients in the form of fibrosis of separately located glands and calcified foci (Fig. 6), in the other patient – in the form of myxomatosis, diffuse inflammatory infiltration and necrotic foci.

In the second group where resection operation was conducted in 14 days after regional chemotherapy, the therapeutic pathomorphism was observed in 12/15 patients. In all these patients the 2<sup>nd</sup> degree of the therapeutic pathomorphism was identified. The 1<sup>st</sup> degree of therapeutic pathomorphism was not recorded. In 3/15 patients the therapeutic pathomorphism was absent.

The above described experimental data concerning combination of regional chemotherapy and radio frequency ablation showed better results with combined approach than with monotherapy (CEHA or RFA) [14,15]. In our opinion, a disadvantage of the conducted treatment was the fact that ablation was carried out within the first hour after embolization. Only ischemic effect was used, since the time of action of chemoembolization on the tumor was minimal. This can explain continued tumor growth (tumor growth rate –  $126.74 \pm 24.46\%$ ) after treatment and incomplete necrosis in a part of experimental rabbits (tumor necrotic rate –  $94.56 \pm 12.03\%$ ) (Fig. 3).

At the beginning of 2013 there was published a meta-analysis of 7 randomized controlled studies that compared effectiveness of use of combination of CEHA and RFA with use of only ablation type in treatment of patients with hepatocellular cancer (HCC). It showed that combination of CEHA and RFA in patients with lesions more than 3 cm reliably ( $p < 0.0001$ ) improved the results of 1,3,5-year survival rate. However, this combination did not improve the treatment results for patients with lesions less than 3 cm in size [16]. Besides, the above mentioned meta-analysis did not find statistically reliable increase in the number of complications with use of combination of CEHA and RFA which evidences safety of their combined use. A drawback of the given studies is different time intervals between stages of treatment. Most common is the method with ablation conducted in 1-2 weeks after CEHA [17]. This permits to effectively relieve postembolization syndrome and thus reduce the number of complications [18]. Some authors prefer to conduct ablation in 4 weeks [19]. In some studies both stages of treatment were conducted in one day [21].

In our research the therapeutic pathomorphism was recorded in the majority (25/30) of patients. At the same time no reliable difference between the degree of pathomorphism on the 7<sup>th</sup> and 14<sup>th</sup> day after CEHA was recorded ( $p = 0.436$ ).

Postembolization syndrome was recorded in all patients after regional chemotherapy, however, it was possible to manage it not later than on the 5<sup>th</sup>-7<sup>th</sup> day of postoperative period. Thus, on the 7<sup>th</sup> day not a single patient had contraindications for further interventions.

Thus, therapeutic pathomorphism develops after chemoembolization of hepatic artery and reaches maximum on the 7<sup>th</sup> day. Postembolization syndrome is effectively relieved in all patients on the 7<sup>th</sup> day after CEHA.

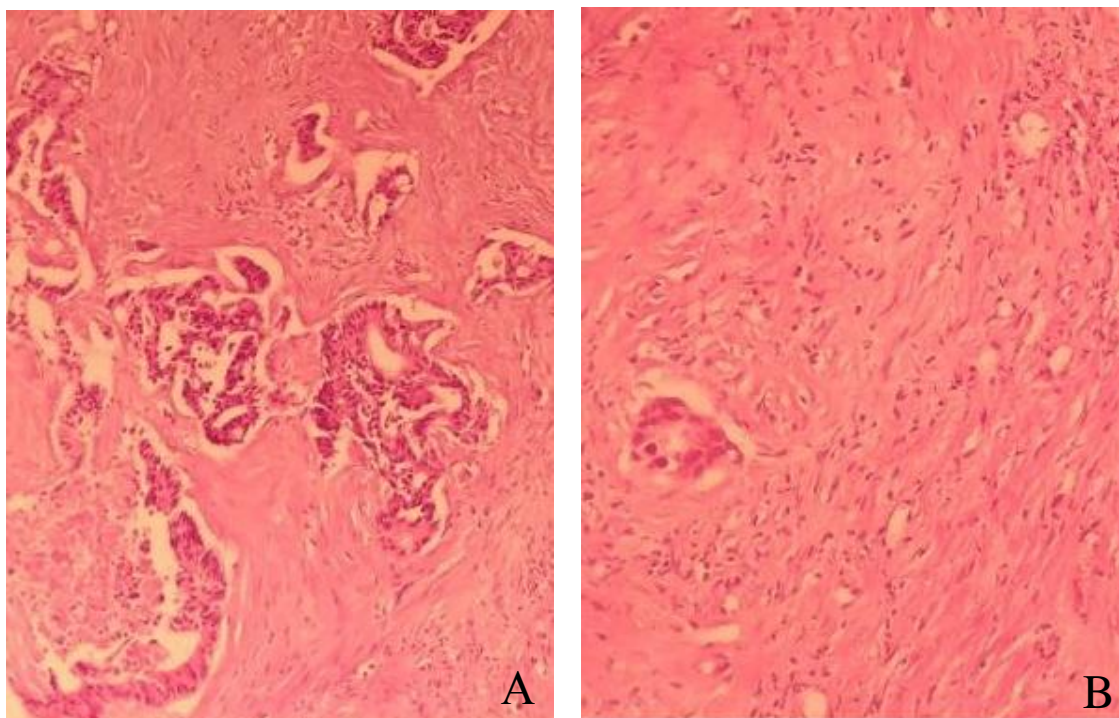


Fig. 5. Metastasis of adenocarcinoma of intestinal type with the presence of fields of fibrosis (A) and inflammatory infiltration (B). The second degree of therapeutic pathomorphosis (hematoxylin and eosin staining, x 400)

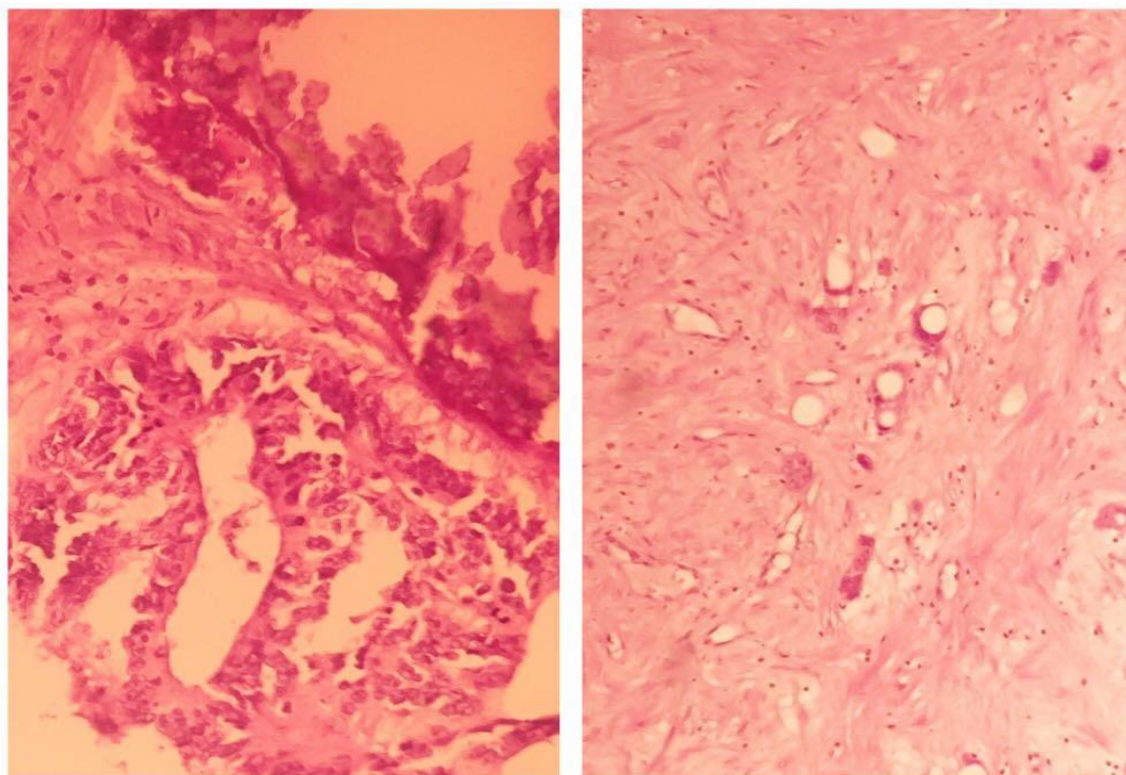


Fig. 6. Metastasis of adenocarcinoma of intestinal type. Moderate therapeutic pathomorphosis (grade 1). Fibrosis of separately lying glands and the appearance of calcifications. (hematoxylin and eosin staining, x 400)

### Conclusion

Chemoembolization of the hepatic artery is an effective method of treatment of patients with colorectal cancer with metastases into the liver. In combination of che-

moembolization of the hepatic artery with methods of local destruction in treatment of patients with inoperable metastatic cancer of the liver, the optimal interval is 7 days.

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