# MULTIDISCIPLINARY APPROACH TO TREATMENT OF A PATIENT WITH UNRESECTABLE METASTATIC LIVER LESION SPAWNED BY HER2+ GASTRIC ADENOCARCINOMA GIVING

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In 85% of patients worldwide, gastric cancer (GC) metastasizes from the very beginning or within three years. In 30–50% of cases, metastases, both synchronous and metachronous, grow into liver. Multifocal liver metastases translate into an unfavorable prognosis: the median survival period is 10–15 months, with less than 10% of the patients surviving past three years. In such cases, the palliative treatment option is systemic chemotherapy. Combined with immunotherapy, transarterial chemoembolization (TACE), a relatively new method of local treatment of metastatic foci, offer new options of combating liver metastases. This work presents a clinical case of application of this combination coupled with chemotherapy to treat a patient with unresectable liver metastases spawned by HER2+ gastric adenocarcinoma. From the day of diagnosis, the patient's life expectancy was 42 months.

**Keywords:** gastric cancer, liver metastases of gastric cancer, transarterial chemoembolization, immunotherapy, chemotherapy

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**Compliance with ethical standards:** the patient has signed a voluntary informed consent to publication of anonymized medical information.

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# МУЛЬТИДИСЦИПЛИНАРНЫЙ ПОДХОД К ЛЕЧЕНИЮ ПАЦИЕНТА С НЕРЕЗЕКТАБЕЛЬНЫМ МЕТАСТАТИЧЕСКИМ ПОРАЖЕНИЕМ ПЕЧЕНИ HER2+ АДЕНОКАРЦИНОМОЙ ЖЕЛУДКА

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У 85% больных во всем мире сразу или в течение трех лет рак желудка (РЖ) переходит в метастатическую форму. Печень является органом метастазирования РЖ с частотой 30–50%, включая как синхронные, так и метахронные метастазы. При наличии мультифокальных метастазов печени прогноз для пациентов весьма неблагоприятен: медиана выживаемости составляет около 10–15 месяцев, а трехлетняя выживаемость — менее 10%, и паллиативным вариантом лечения в таких случаях является системная химиотерапия. Внедрение относительно молодого локального метода воздействия на метастатические очаги — трансартериальной химиоэмболизации (ТАХЭ) в комбинации с иммунотерапией открыло новые возможности лечения метастазов в печень. Представлен клинический случай использования методики ТАХЭ в комбинации с иммунотерапией, а также химиотерапией у пациента при нерезектабельном метастатическом поражении печени HER2+ аденокарциномой желудка с продолжительностью жизни 42 месяца с момента установления диагноза.

**Ключевые слова:** рак желудка, метастазы рака желудка в печень, трансартериальная химиоэмболизация, иммунотерапия, химиотерапия

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In the worldwide cancer rating, gastric cancer (GC) is on the 5th place in terms of morbidity, and 3rd in terms of mortality [1]. Over 700 thousand people die from GC every year throughout the world, since in most cases this disease is diagnosed at late stages, when the neoplasm has already spawned metastases [2, 3]. In the Russian Federation (RF), the incidence of GC is slightly lower: in 2019, it was on the 7th place of the oncological morbidity rating (5.7% of all cancer cases). However, in terms of mortality, GC in RF is a more common cause of death than worldwide: it holds the 2nd place in the respective rating, being the reason of 9.8% of deaths from malignant neoplasms. In RF, the share of late stage diagnoses is noticeably high. In 2019, GC was the third type of cancer most often diagnosed untimely, i.e., when it had already progressed to stage IV, and 45.8% of first-time GC patients died within a year from the day of diagnosis [2, 4]. Approximately similar number of patients have the tumor growing after treatment. As a result, in 85% of GC patients the disease turns metastatic immediately or within three years, which translates into an unfavorable prognosis [5].

Most often, GC spawns metastases into liver: it happens in 30–50% of cases, counting both synchronous and metachronous metastases. At the time of diagnosis, 35% of patients have signs of remote metastases, and in 4–14% the tumor metastasizes into liver; 25–30% have metachronous metastases after therapeutic gastrectomy, and 80% of them appear within the first two years after surgery. Patients with metachronous GC metastasizing into liver survive for 11 months on average, and less than 20% of them survive past the 5-year mark. Excision of primary tumors and liver metastases can increase the five-year survival rate to 23.8% [6].

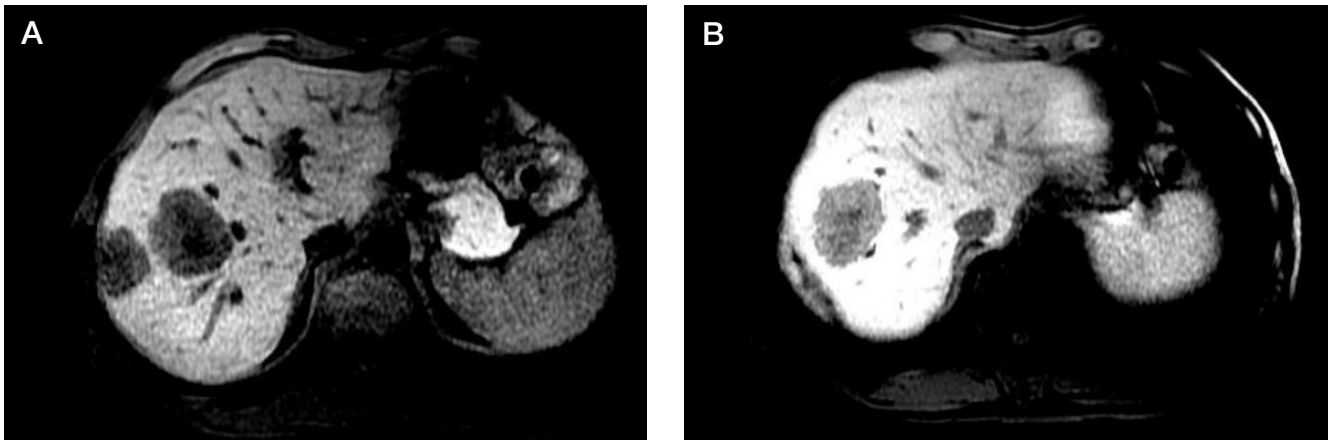


**Fig. 1. A, B.** MRI scan, abdominal cavity, 07.12.2019

Multifocal liver metastases translate into an unfavorable prognosis: the median survival period is 10–15 months, with less than 10% of the patients surviving past three years. In such cases, the palliative treatment option is systemic chemotherapy.

Combined with immunotherapy, transarterial chemoembolization (TACE), a method of local treatment of metastatic foci, offer new options of combating liver metastases. This method allows solving several tasks at once: achieving the optimal concentration of antitumor drugs directly in the tumor node and optimization of the neoplasm's exposure thereto; inducing ischemic necrosis of tumor tissue through impairment of vascularization; reducing systemic toxicity of cytostatic drugs by keeping their concentration in the systemic bloodstream low [5, 9–11]. There are studies that have demonstrated the effectiveness of TACE in GC patients with liver metastases, but they are few. One of the retrospective studies cites mean survival rate (MSR) of such patients after first TACE with mitomycin only at 6 months and 25.5 months, respectively, MSR after first TACE with mitomycin and gemcitabine — at 8.1 and 11.4 months, respectively, and MSR after TACE with mitomycin in combination with gemcitabine and cisplatin — at 15.3 and 30.5 months, respectively [2, 12–14].

About 10–15% of GC cases are associated with activation of HER2 (human epidermal growth factor receptor 2). It is the overexpression of HER2 that indicates an aggressive course of the disease and promises unfavorable prognosis: various studies report a correlation between amplification of the HER2 gene (HER2+ status) and low overall survival rates of GC patients. This fact necessitates introduction of more effective antitumor drugs into clinical practice. The most promising among the recent malignant neoplasm treatment methods is the immune checkpoint therapy (ICT), which proved highly effective against many types of tumors, including GC [15].

In this clinical observation, we assess the efficacy of a multidisciplinary approach to treatment of an HER2+ GC spawning unresectable metastases into liver: TACE with fluorouracil combined with immunotherapy and platinum-based drugs.

## Clinical case description

Patient K., born in 1967, self-referred to the clinic of Rostov State Medical University in July 2019, complaints — unmotivated weight loss, heaviness in the right hypochondrium. He considers himself ill since July 2018, when a checkup at a local clinic revealed GC; after the diagnosis, on 16.07.2018, he underwent gastrectomy and plastic reconstruction at the Stavropol Regional Clinical Oncology Dispensary.

Computed tomography of the abdominal cavity organs on 01.07.2019 revealed two metastatic foci in the right lobe of liver. Samples of the metastases were taken (needle core biopsy) on 20.07.2019, their histological analysis yielded the conclusion: glandular carcinoma. The diagnosis read: C78.7 secondary metastatic liver lesion; gastric cancer, pT3N1M0, st. IIIB, condition after gastrectomy on 16.07.2018, cl. gr. 2.

On 24.07.2019, the central venous port was implanted. Then the patient received 7 courses of chemotherapy, Ramucirumab with FOLFIRI: irinotecan 180 mg/m$^2$ + calcium folinate 400 mg + fluorouracil 400 mg/m$^2$ as bolus + fluorouracil 2400 mg/m$^2$ intravenously, 48-hour infusion + ramucirumab 8 mg/kg on the 1st and 15th days every 28 days.

Control examination of 22.10.2019 revealed the level of CEA at 21.50 ng/ml (reference values: 0–5.0) and CA at 19–9 — 44.56 units/ml (reference values: 0 × 37.0). During the courses of systemic chemotherapy, the patient assessed his condition as moderately severe, complaining of vomiting, diarrhea, dizziness, fatigue.

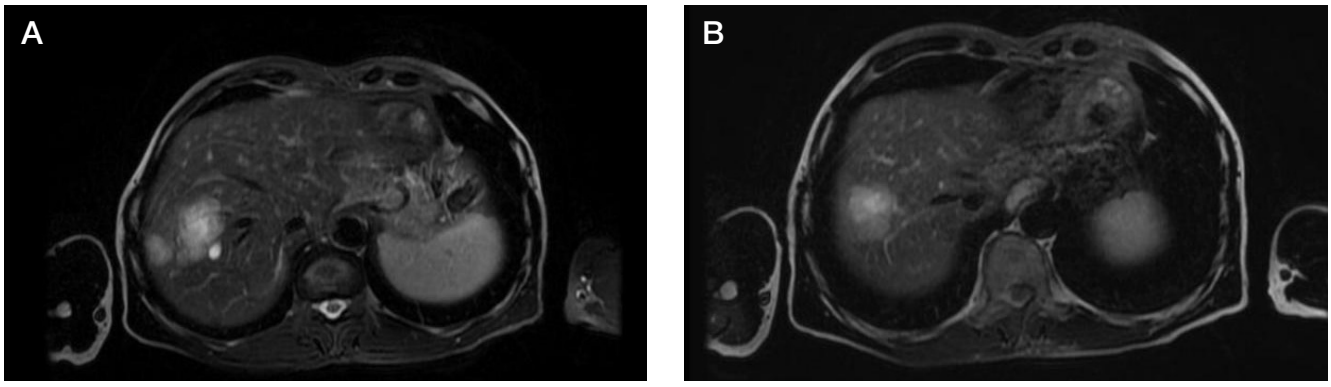


**Fig. 2. A, B.** MRI scan, abdominal cavity, 18.02.2020

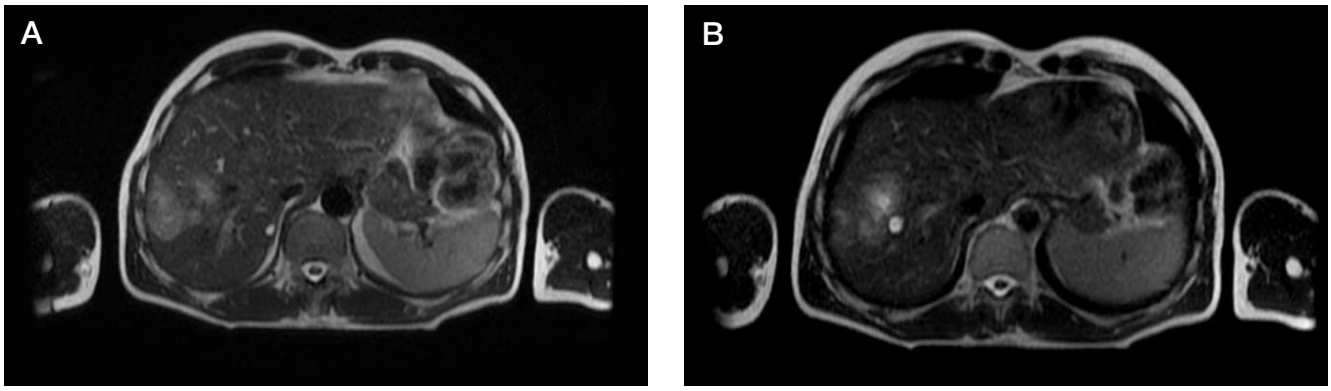


**Fig. 3. A, B.** MRI scan, abdominal cavity, 15.07.2020

Results of MRI of the abdominal cavity organs of 07.12.2019: locus measuring up to 45 × 48 mm in the right lobe of liver, S7–S8; locus measuring 31 × 37 mm in S7, on the lateral surface; locus measuring 8 × 10 mm in the posteromedial surface of S8; fuzzy 7-mm locus in the capsule of lower surface of S6; no data indicates recurrence or carcinomatosis of peritoneum (Fig. 1A, B). The patient considered his condition to be satisfactory. Factoring in the volume of damage to the liver, prevalence and negative dynamics, on 19.12.2019 the patient underwent another TACE with oxaliplatin 100 mg and fluorouracil 1000 mg.

The postoperative supportive pharmacotherapy course prescribed comprised:

– for analgesia — diclofenac 75 mg 2 times, IM, for 5 days;

– drotaverine hydrochloride 40 mg, 2 times a day, IM, for 5 days;

– octreotide 300 mcg, 2 times a day, SC, for 7 days;

– to prevent thromboembolic complications — enoxaparin sodium 0.4 mg, SC, once a day for 7 days;

– infusion therapy — glucose 5% 500 ml + insulin 6 units, once a day, IV, for 3 days; NaCl 0.9% 500 ml + 40 mg omeprazole, twice a day, IV, for 3 days.

– additionally, as prescribed by the vascular surgeon — thioctic acid 600 mg + NaCl 0.9%, 100 ml once a day, IV, for 5 days; deproteinized calf blood derivate 10 ml + NaCl 0.9%, 100 ml once a day, IV, for 5 days; meldonium 10 ml + NaCl 0.9%, 100 ml once a day, IV, for 5 days; sulodexide 2 ml once a day, IM, for 5 days.

When discharged, the patient assessed his condition as satisfactory, despite the volume of metastatic foci; his body temperature was slightly elevated during the first 2 days after the TACE.

Report of the IHC examination of 19.01.2020: the liver biopsy material contains adenocarcinoma metastases with extensive foci of necrosis and focal lymphoid infiltration. Given the clinical data, the likely situation is a gastric adenocarcinoma metastasizing into liver. Conclusion: $HER2^+$ gastric adenocarcinoma spawning metastases to liver.

Afterwards, the patient received chemotherapy courses in his local clinic. Control examination revealed positive dynamics: MRI of the abdominal cavity of 18.02.2020 had shown that liver was enlarged, the bilobed size was 188 × × 16 mm, parenchyma unevenly diffusely changed by signal; the MRI picture was that of a metastatic lesion, in the right lobe the focus measured up to 34 × 54 mm (previously 45 × 48 mm) in S7–S8, with the S7 focus, lateral surface, measuring 28 × 29 mm (previously 31 × 37 mm), and the S8 focus, posteromedial surface, measuring up to 5 × 10 mm (previously 8 × 10 mm), while the focus in the capsule of the lower surface of S6 could not be detected at all (previously 7 mm) (Fig. 2A, B).

On 19.02.2020, as planned, the patient consulted with a chemotherapist. Conclusion: as supportive therapy, the patient may receive a course of paclitaxel 175 mg/$m^2$ on day 1 + trastuzumab 6 mg/kg, loading dose 8 mg/kg, on day 1, cycling for 21 day. The patient underwent 3 courses of such chemotherapy.

Results of MRI of the abdominal cavity, 30.04.2020: growing single (2) metastases in the liver's right lobe, neoplasms tend to merge (negative dynamics), contours of the liver are smooth; the vertical size of the right lobe is 18.2 cm, left lobe is 5.1 cm, liver cysts S7, S6 measuring up to 9 × 12 mm. In S8, S7 — tumor nodes of measuring 39 × 60 and 27 × 44 mm (previously 35 × 54 and 28 × 29 mm), merging into a conglomerate.

With the extent of damage to the liver, prevalence and negative dynamics of the process, complaints of heaviness in the right hypochondrium accounted for, and given the satisfactory condition of the patient, it was decided to keep liver TACE in the treatment plan.

The patient was prescribed 5-day preoperative cardio and hepatotropic preparatory course: thioctic acid 600 mg + NaCl 0.9% 100 ml, IV, once a day, for 5 days; meldonium 5 ml + glucose 250 ml, IV, once a day, ademetionine 400 mg + glucose 250 ml, IV, once a day.

On 05.05.2020, the patient underwent TACE: lipiodol 10 ml + fluorouracil 1000 mg + 100 ml oxaliplatin. HydroPearl spheres (800 nm) were used for arterial embolization. The patient was prescribed post-surgery supportive pharmacotherapy.

From May to July 2020, the patient received 2 courses of immunotherapy at his local clinic: nivolumab 210 mg IV, once every 2 weeks. Results of MRI scanning, 15.07.2020: in S8, S7 — tumor nodes, measuring 49 × 57 and 41 × 61 mm (previously 39 × 60 and 27 × 44 mm), merging into a single conglomerate (Figure 3A, B), which indicates progression.

With the extent of damage to the liver, prevalence and negative dynamics of the process accounted for, the patient underwent liver TACE with lipiodol 10 ml + cisplatin 100 mg on 07.08.2020. Post-surgery, he received supportive pharmacotherapy.

Then, the patient underwent a course of chemotherapy (paclitaxel 175 mg/$m^2$ on day 1 + trastuzumab 6 mg/kg, loading dose 8 mg/kg) on day 1; cycle 21 days) combined with a course of immunotherapy (nivolumab 210 mg infused IV once every 2 weeks in the local clinic). During the courses, the patient noted the following side effects: itching around knees, skin redness, intermittent diarrhea and nausea.

Results of MRI of the abdominal cavity, 13.11.2020: a lesion measuring 54 × 78 × 52 mm found in the liver's S7, which indicated progression.

On 16.11.2020, the patient underwent parenchymal chemoembolization of the arteries supplying the foci (lipiodol

10 ml + fluorouracil 1000 mg) and arterial chemoembolization with 800 nm HydroPearl spheres (2 ml — 1 syringe) + 100 mg cisplatin. The patient was prescribed post-surgery supportive pharmacotherapy.

Afterwards, the patient received immunotherapy: nivolumab 210 mg, IV, once every 2 weeks. Control examination of 18.12.2020 revealed stabilization of the metastatic focus. MRI scanning results, abdominal cavity, 18.12.2020: tumor nodes measuring 49 × 57 and 41 × 52 mm in S8, S7, merging into a single conglomerate.

On 12.01.2021, the patient underwent TACE: EmboSphere microspheres (500–700 nm) + fluorouracil 1000 mg + cisplatin 100 mg. Post-surgery, he received supportive pharmacotherapy.

Results of MRI of abdominal cavity, 04.03.2021: solid formations measuring 98 × 61 × 70 mm (previously 49 × 57 mm) and 28 × 32 × 17 mm (previously not found) in S7; a cystic component therein measuring 16 × 11 × 14 cm, a solid formation 22 × 13 mm (previously not found) on the anterior diaphragmatic surface of the liver. Results of radiography of thoracic organs, 14.03.2021: no pathological changes detected in the lungs.

On 16.03.2021, the patient underwent TACE: HydroPearl microspheres (500–700 nm) + fluorouracil 1000 mg + cisplatin 100 mg. The patient was prescribed post-surgery supportive pharmacotherapy.

On 08.07.2021, the patient was admitted to the hospital for repeated TACE. Four courses of immunotherapy were conducted. Results of MRI of abdominal cavity, 05.07.2021: solid formations measuring 89 × 54 × 72 mm (previously 98 × 61 × 70 mm) and 24 × 29 × 14 mm (previously 28 × 32 × × 17 mm) in S7; a cystic component therein measuring 11 × 9 × × 12 cm, a solid formation 17 × 11 mm (previously 22 × 13 mm) on the anterior diaphragmatic surface of the liver.

With the extent of damage to the liver, prevalence and negative dynamics of the process accounted for, the patient underwent liver TACE with lipiodol 20 ml + fluorouracil 1000 mg + oxaliplati cisplatin 100 mg on 09.07.2021. Arterial embolization was done with hemostatic sponge suspension. Post-surgery, he received supportive pharmacotherapy.

To date, the patient is in a satisfactory condition, leads an active lifestyle and takes courses of systemic chemotherapy under the FOLFIRI regimen, despite a slight shrinking of metastatic foci in the liver.

**Clinical case discussion**

Surgical intervention against liver metastases spawned by HER2+ GC, which involved TACE with microspheres, allowed blocking arterial inflow to the tumor and enabled gradual release of the chemotherapy drug in the metastasis area, its cytostatic action selective, which translated into minimization of systemic side effects.

In turn, ICT inhibition is an important recent achievement in the field of antitumor therapy. Used against some malignant neoplasms, it shows encouraging results and significantly improves the prognosis for patients. Inhibition as part of ICT is advisable in late-stage GC cases, since GC is often resistant to chemotherapy. One of the inhibitors used in ICT is pembrolizumab, which was approved by the FDA in 2017 based on the results of KEYNOTE-059 study as the 3rd line therapy for metastatic GC/CEC with PD-L1 expression [8]. GC patients are also involved in a large number of clinical studies investigating other therapy regimens that rely on ICT inhibitors. Their combinations with targeted drugs and chemotherapy are among the most promising regimens [15].

## CONCLUSION

New composite methods of treatment that combine TACE, molecular targeted therapy (trastuzumab in the described case) and inhibition in ICT are based on individual characteristics of the tumor, its HER2+ status in particular. The intratumor activity of gastric is pronounced, and its primary tumor and metastases are heterogeneous; thus intracancerous heterogeneity in the expression of HER2+ may signal of decreased effectiveness of treatment. Determination of biomarkers or gene signatures that can be translated into clinically significant prognostic indicators of response to TACE is an important subject requiring investigation.

The multidisciplinary approach involving TACE, immuno- and chemotherapy in a patient with unresectable metastatic liver lesions spawned by HER2+ GC allowed controlling the course of the disease for 42 months, which is virtually 4 times longer than the median survival period in such cases. This is a solid confirmation of efficacy of the composite therapy this patient has received.

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