EXPERIENCE EXCHANGE

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TREATMENT EXPERIENCE OF HEPATIC METASTASES FROM NEUROENDOCRINE TUMORS USING TRANSARTERIAL CHEMOEMBOLIZATION

The aim of this work was to evaluate the effectiveness of treatment for liver metastases from neuroendocrine tumors by the TACE method. We analyzed 7 clinical cases of gastrointestinal NETs with inoperable liver metastases in patients treated at Rostov Research Institute of Oncology in 2016-2018. We studied the symptoms in each clinical case and analyzed the results of computed tomography using RECIST 1.1 criteria before and after the transarterial chemoembolization procedure. According to the results of the analysis of computed tomography using the RECIST 1.1 criteria in dynamics with an interval of 3 and 6 months, the following was established: in 2 patients (28.6%) with a relative stabilization of the process 3 months after TACE, disease progression was observed after 6 months; 3 patients (42.9%) had a persistent partial response to therapy 3 and 6 months after TACE; in 1 patient (14.3%), stabilization was registered according to CT data 3 and 6 months after TACE. Moreover, out of 7 observations, only 1 case was fatal. In a small number of patients, we showed that TACE helped to normalize the general condition of patients, reduce the intensity of carcinoid syndrome, reduce the size of metastatic foci, causing a positive response (partial response or stabilization) in more than half of patients (57.2%).

Keywords: transarterial chemoembolization, neuroendocrine tumor, metastasis, RECIST 1.1 criteria.

Background. Neuroendocrine tumors (NETs) are a heterogeneous group of malignant human tumors originating from special cells of the APUD system (Amine Percursor Uptake and Decarboxylation) localized throughout the body [2]. About 66% of all NETs occur in the gastrointestinal tract, while 30% account for the bronchopulmonary system [1].

The annual incidence of NETs is 1.8 cases for women and 2.6 cases for men per 100,000 population [1, 3]. An increasing number of newly reported NETs have been registered over the past 30 years, largely due to the widespread use of immunohistochemical diagnostics and the advent of molecular genetic methods that greatly simplify the diagnosis [4].

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NETs often metastasize to the liver, which is the main factor that determines the quality of life of patients, and is usually associated with a poor prognosis. Despite the fact that a localized primary NET can be easily resected surgically, metastatic foci in the liver are most often inoperable and require a different approach to their treatment [5]. Unfortunately, all possible therapeutic methods are palliative ones and aimed only at improving the quality of life of such patients. These methods include somatostatin analogue therapy, targeted therapy, systemic chemotherapy, and various other locoregional techniques [2, 3, 9]. Thus, the 5-year survival rate for patients with surgically removed localized primary tumor is 60-90%, and only 25-40% for patients with secondary liver metastases [5, 7].

The prognosis of patients with NETs also depends on the tumor stage, the location of the primary tumor and its histological characteristics. The current World Health Organization (WHO) classification from 2010 distinguishes well-differentiated NETs with a proliferation index Ki67 <2% (G1), moderately differentiated NETs with a proliferation index Ki67 = 3-20% (G2), and poorly differentiated NETs with a proliferation index Ki67> 20 -100% (G3), respectively [8].

Most NETs are well-differentiated and non-functioning, without any hormonal activity and specific clinical picture [1, 6]. This, in turn, significantly complicates the early diagnosis of NET and is the reason for the presence of secondary liver metastases and, often, signs of local prevalence in 40-90% of patients already at the initial diagnosis [2, 6]. But since this histological form nevertheless has a favorable prognosis, it becomes quite feasible to use aggressive surgical treatment tactics even in the presence of distant liver metastases, which is usually not used for other malignant tumors. However, when more than 75% of the total liver volume is affected, radical resection is not feasible, so one of locoregional treatment methods - transarterial chemical embolization (TACE) - is recommended to use as a preoperative preparation or independently [2, 6, 8].

The purpose of the study was to assess the effectiveness of treatment for liver metastases from neuroendocrine tumors by the TACE method based on the analysis of 7 clinical cases.

Material and methods. We retrospectively analyzed 7 clinical cases of gastrointestinal NETs with inoperable liver metastases in patients treated at Rostov Research Institute of Oncology in 2016-2018. We studied the symptoms in each clinical case and analyzed the results of computed tomography using RECIST 1.1 criteria taking into account all types of treatment that patients received immediately before TACE (including therapy with somatostatin analogues). The patients included 6 women and 1 man aged between 34 and 68 years before the treatment. Primary tumors were in the rectum (n=1), pancreas (n=1), stomach (n=1), small intestine (n = 2), sacrum (n = 1); in one case, primary tumor focus was not detected. 4 patients (57.1%) had undergone prior surgical removal of the primary tumor (resection of the ileum, resection of the rectum, resection of the tail of the pancreas). Metastases were morphologically verified in 7 cases (100%) with needle biopsy and subsequent histological analysis. G1 – well-differentiated cancer (Ki67 <2%) was found in 28.6% of patients, G2 - moderately differentiated cancer (Ki67 = 3-20%) in 0%, G3 - low-differentiated cancer (Ki67 = 20-100%) in 71.4%, respectively. 85.7% of patients received TACE for the first time, and 14.3% of patients underwent several TACE courses for the entire treatment period. 71.43% of patients received polychemotherapy courses prior to TACE, 28.57% of patients did not (Table 1).

Table 1

Characteristics of patients before TACE

Criterium	Assessment (n=7)
Mean age	55 years
Gender	6/7 (85.7%) women. 1/7 (14.3%) men
Sizes (cm) of metastatic foci	From 4 to 11 cm
Prior removal of the primary tumor	4/7. 57.1%
Extrahepatic metastases	3/7. 42.9%
Tumor grade, Ki67, %	G1 (Ki67<2%) – 28.6% (2/7) G2 (Ki67=3-20%) – 0% (0/7) G3 (Ki67=20-100%) – 71.4% (3/7)
Clinical picture	General symptoms (weight loss. loss of appetite. weakness. abdominal pain) 7/7. 100% Symptoms associated with hormonal activity: carcinoid syndrome 5/7. 71.4%; insulinoma/ hypoglycemia 1/7. 14.3%; gastrinoma 1/7. 14.3%

The procedure of transarterial chemoembolization involves the following steps. The standard puncture of the right brachial artery is performed under aseptic X-ray conditions (angiographic 18 G needle), with the following Seldinger arterial catheterization (5F introducer 11 cm). CB1 catheter is sequentially inserted through the catheter guide .035” 150 cm into the right axillary and subclavian artery, brachiocephalic trunk, descending aorta. Catheter guide is removed, aortography is performed. Using P1 5F catheter with a hydrophilic guide .035” 180 cm, the right and then the left hepatic arteries are selectively sequentially catheterized. Using a microcatheter 2.6F 150cm on a .014 ”300cm micro-guide, segmental arteries supplying the tumor site are superselectively catheterized. An emulsion containing chemotherapeutic agents is prepared, and parenchymal chemoembolization of the liver is performed. Arterial embolization is performed with a Spongostan gelfoam slurry. During control angiography, a pronounced slowdown in contrast is determined by the segmental branches of the right hepatic artery supplying the tumor focus. The signs of nontarget embolization are detected. The catheter is inserted into the aorta. The tools are subsequently removed.

The hepatic artery is the best choice for selective chemoembolization because it supplies up to 95% of the liver tumor tissue [7]. Chemoembolization agents enter both the tumor and healthy liver tissue. Due to the muscle layer, the arterial bed of the unaffected parenchyma ensures the distribution and rapid elimination of the drug. Pathological tumor vessels do not have a muscle layer, which leads to the chemoembolization agent retention in the tumor [1, 3, 5].

Table 2

Comparative analysis of CT data and assessment of tumor response using RECIST 1.1 criteria

№	CT data before TACE	CT data 3 months after TACE	CT data 6 months after TACE and later	Assessment of results
1	A solitary lesion of 4x3.7 cm in S7 of the right lobe	A solitary lesion of 5x4.3 cm in S7 of the right lobe	A solitary lesion of 4.8x5.2 cm in S7 of the right lobe	Increase by 25% (stabilization)
2	Metastatic foci up to 6.2 cm in both lobes	Metastatic foci up to 5 cm in both lobes	Metastatic foci up to 3 cm in both lobes	Decrease by 50% (partial response)
3	CT image of multiple liver metastases. Coalesced metastatic foci up to 5 cm.	CT image of relative stabilization. процесса. Coalesced metastatic foci up to 4.5 cm.	CT image of multiple liver metastases with signs of progression. Coalesced metastatic foci up to 8 cm.	Increase by 60% (progression)
4	Coalesced metastatic foci up to 11 cm.	N/A	N/A	N/A
5	A solitary lesion of 6.7x7.0 cm in S8 of the right lobe	A solitary lesion of 5x5.2 cm in S8 of the right lobe	A solitary lesion of 4x4.3 cm in S8 of the right lobe	Decrease by 43% (partial response)
6	A metastatic focus 2.4x2 cm in S1 of the right lobe is closely adjacent to the inferior vena cava, deforming it. A metastatic focus 4.6x4 cm in S7	A metastatic focus 2.2x1.8 cm in S1 of the right lobe. A metastatic focus 3.2x3.5 cm in S7	A metastatic focus 1x1.2 cm in S1 of the right lobe. A metastatic focus 2.2x2 cm in S7	Decrease by 50% (partial response)
7	CT image of multiple liver metastases without changes in the number of metastases since December 19, 2017. An increase in the size of one of the lesions in the right lobe of the liver.	CT image of a relative stabilization. Multiple liver metastases without changes in the number of metastases. No increase in foci size.	Negative dynamics, the appearance of new small foci, an increase in the liver volume.	Progression

In our opinion, the indications for TACE in NETs were: inoperable liver metastases; sufficient functional reserves of the liver (bilirubin <70 μmol/l); hemoglobin >80 g/l; no extrahepatic tumor spread. Contraindications were: active systemic infection; ongoing bleeding; Child-Pugh C class; leukopenia (white blood cells <1000/ml); prothrombin time less than 40%; heart failure (left ventricular ejection fraction less than 50%); unmanageable sensitivity to the contrast; ECOG functional status >3; damage to more than 50% of the liver; extrahepatic metastases; tumor invasion into the inferior vena cava and the right atrium; ascites; severe thrombocytopenia; history of portocaval anastomosis; high total bilirubin> 60 μmol/l; LDH> 425 U/L; transaminases> 100 IU/L.

According to clinical recommendations, in the pre- and post-procedural period, patients received infusion therapy, octreotide (in case of pronounced hormonal activity), non-steroidal anti-inflammatory drugs, glucocorticoids (dexamethasone 4 mg, 2-3 times a day, per os, to manage postembolic syndrome and symptoms such as nausea, vomiting, fever, abdominal pain, decreased appetite), antibacterial drugs (a day before TACE to prevent complications such as liver abscess, cholangitis, sepsis), antifungal preparations.

Results and discussion. In all cases, we evaluated the response to therapy using CT data (Table 2) obtained 3-6 months after TACE, using RECIST 1.1 criteria (2009). 1 out of 7 patients died, 6 others report an objective improvement in their general condition. All 6 patients complain of periodic fatigue. 2 of them have severe abdominal pains with no relief after NSAIDs administration. Tumors were hormonally active in all 7 patients, in 5 of them there was a pronounced carcinoid syndrome (facial redness, stool up to 7-9 times a day, changes in blood pressure). After TACE, the intensity of carcinoid manifestations decreased (stool frequency up to 3-4 times a day). All 6 patients in the postoperative period receive polychemotherapy courses and therapy with somatostatin analogues.

Assessing the results of CT scans in dynamics with an interval of 3 and 6 months (Table 3), according to the RECIST 1.1 criteria, the following was established: in 2 patients (28.6%) with a relative stabilization 3 months after TACE, disease progression was observed after 6 months; in 3 patients (42.9%) - a persistent partial response to therapy 3 and 6 months after TACE; in 1 patient (14.3%) - stabilization based on CT data after 3 and 6 months after TACE.

Conclusions. In a small number of patients, we showed that TACE helped to normalize the general condition of patients, reduce the intensity of carcinoid syndrome, reduce the size of metastatic foci, causing a positive response (partial response or stabilization) in more than half of patients (57.2%). There was no clear correlation between the tumor stage, grade and the TACE effectiveness. Table 2 demonstrates the need for cyclic TACE every 2-3 months. Thus, the effectiveness of this technique, a clear tumor response, minimal toxicity, no damage to a healthy liver parenchyma, and minimal invasiveness make TACE a valuable “tool” in treatment of patients with NETs.

References

1. Кит О.И. Нейроэндокринные, клинические и морфологические аспекты рака желудка. Новочеркасск: Издательство «Лик», 2014: 187. [Kit OI. Neuroendocrine, clinical and morphological aspects of stomach cancer. Novocherkassk: Publ. “Lik”, 2014. 187 p. (In Russ.)].

2. Карнаухов Н.С., Новикова Е.А., Трифанов В.С. и др. Скрининг нейроэндокринного компонента в раке желудка. *Современные проблемы науки и образования*. 2016; 25(5): 45-49. [Karnauchov NS, Novikova EA, Trifanov VS. et al. Screening for the neuroendocrine component in stomach cancer. *Sovremennye problemy nauki i obrazovania*. 2016; 25(5): 45-49. (In Russ.)].

3. Eadens MJ, Grothey A. Curable metastatic colorectal cancer. *Curr. Oncol. Rep.* 2011; 13: 168–176.

4. Frankel TL, D’Angelica M.I. Hepatic resection for colorectal metastases. *J Surg. Oncol.* 2014; 109: 2–7.

5. Galizia M.S., Töre H.G., Chalian H. Evaluation of hepatocellular carcinoma size using two-dimensional and volumetric analysis: effect on liver transplantation eligibility. *Acad. Radiol.* 2011; 18: 1555-60.

6. Rahbari N, Mehrabi A, Mollberg N, et al. Hepatocellular carcinoma: current management and perspectives for the future. *Ann. Surg.* 2011; 253: 453–469.

7. Monsky WL, Garza AS, Kim I. Treatment planning and volumetric response assessment for Yttrium-90 radioembolization: semiautomated determination of liver volume and volume of tumor necrosis in patients with hepatic malignancy. *Cardiovasc. Intervent. Radiol.* 2011; 34: 306-18.

8. O'Dorisio TM, Anthony LB. A 25-year experience of gastroenteropancreatic neuroendocrine tumors and somatostatin (congeners) analogs: from symptom control to antineoplastic therapy. *Front. Horm. Res.* 2015; 44: 177- 92.

9. Trifanov VS, Novikova IA, Todorov SS. Clinical, pathological, and immunohistochemical features of pancreatic neuroendocrine tumors. *Journal of clinical oncology.* 2014; 15: 151-59.