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# TRANSCATHETER ARTERIAL CHEMOEMBOLIZATION OF HEPATOCELLULAR CARCINOMA ON LIVER CIRRHOSIS IN PATIENTS AWAITING LIVER TRANSPLANTATION

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OBJECTIVE. To evaluate the role of TACE as a method of neoadjuvant antitumor therapy of HCC before LT.

METHODS AND MATERIALS. From January 1998 to April 2020, we performed 245 OLTs in 229 patients, among them in 25 (10.2 %) for HCC associated with LC. We analyzed treatment results of 16 patients who received 49 TACE sessions as neoadjuvant therapy. 10 (62.5 %) patients fell under Milan criteria, 6 (37.5 %) – beyond them. According to the Child – Pugh score of LC, two (12.5 %) patients matched A stage, 12 (75 %) – B stage, two (12.5 %) – C stage. According to the BCLC (Barcelona Clinic Liver Cancer) staging system, 10 patients matched $A_1$–$A_4$ stage and 6 – B stage. Totally, we performed 49 TACE sessions, both classical with lipiodol and hemostatic sponge, and with drug-eluting beads from 1 to 7 (on average 3) times. In all cases Doxorubicin was used.

RESULTS. Technical success was 100 %. There were no complications. We performed RFA in three patients as an adjunct, in two patients – laparoscopic RFA-assisted atypical liver resection and in one patient – sequential resection and RFA. According to the m-Recist criteria, a complete response was observed in 6 (37.5 %), partial – in 7 (43.75 %), and stabilization – in 3 (18.75 %) patients. It was possible to achieve a tumor response to the treatment in 4 patients and return them to the Milan criteria. LT was performed in all 16 patients, among them – 14 (87.5 %) within the Milan criteria. The waiting periods for LT from the beginning of TACE were from 2 to 30 (on average 12.5) months. According to the histological studies, in 13 (81 %) patients, total and subtotal necrosis of HCC was revealed in excised organs.

CONCLUSION. The results of the performed study indicate that neoadjuvant TACE delays the growth of HCC masses and prolongs (up to 30 months) a safe waiting period for the donor liver.

**Keywords:** *hepatocellular carcinoma, liver cirrhosis, transcatheter arterial chemoembolization, neoadjuvant therapy, liver transplantation*

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**Introduction.** Hepatocellular carcinoma (HCC) in the structure of world disease and death rates is still in the sixth and second places with a tendency to increase [1–3]. In the Russian Federation, 40 % increase in the disease incidence has been noted over 10 years (from 2007 to 2017); HCC takes the nineteenth place among all newly diagnosed oncological diseases, and mortality from it is in the ninth place [4]. HCC is the most common virus – associated tumor: more than $^3/_4$ cases are diagnosed on the background of chronic viral hepatitis [5]. This significantly complicates the treatment, since both cancer and liver cirrhosis (LC) are competing life-threatening diseases. Early disease detection is complicated by the fact that on the background of nodular transformation of liver tissue, it is extremely difficult to identify a malignant tumor.

Possibilities of surgical removal of HCC are greatly limited on the background of LC: according to the world data, resectability does not exceed 10 % [6–8]. Damage of the density indices of the parenchyma and, as a consequence, hemodynamics inside the liver lead to low effectiveness of radiation therapy. None of the systemic chemotherapy regimens has been proven effective as well. Being the main methods in the treatment of most oncological diseases, radiation and chemotherapy inevitably lead to increased manifestations of liver failure on the background of LC. Inhibitors of protein kinase complexes remain the only drugs that have proven their

**Description of the study group**

| Age | CVH (+/–) | Child – Pugh | BCLC | MC before TACE (+/–) | TACE number | MC after TACE (+/–) | Waiting periods, months |
|---|---|---|---|---|---|---|---|
| 1. K., 28 | – | A | B | – | 4 | – | 7 |
| 2. B., 58 | + | B | B | – | 2 | + | 15 |
| 3. R., 45 | + | B | A | + | 1 | + | 2 |
| 4. Z., 54 | + | B | A | + | 3 | + | 6 |
| 5. E., 49 | + | C | B | – | 3 | + | 6 |
| 6. K., 52 | + | C | A | + | 7 | + | 26 |
| 7. K., 53 | + | B | B | – | 4 | + | 10 |
| 8. K., 43 | + | B | A | + | 1 | + | 12 |
| 9. K., 53 | + | B | A | + | 2 | + | 7 |
| 10. S., 61 | + | B | A | + | 2 | – | 5 |
| 11. T., 45 | + | A | A | + | 2 | + | 16 |
| 12. U., 48 | – | B | B | – | 2 | + | 12 |
| 13. Kh., 55 | + | B | B | – | 6 | + | 23 |
| 14. P., 52 | + | B | A | + | 6 | + | 15 |
| 15. S., 47 | + | B | A | + | 2 | + | 12 |
| 16. Sh., 64 | – | B | A | + | 2 | + | 30 |

Notes: CVH – chronic viral hepatitis; Child – Pugh – score of LC [15]; BCLC – Barcelona Clinic Liver Cancer classification [10]; TACE – transcatheter arterial chemoembolization; MC – Milan criteria [16].

relative effectiveness and are included in clinical guidelines [10, 11]. The above facts encouraged to develop minimally invasive treatment of HCC using interventional radiology methods, the main of which is transcatheter arterial chemoembolization (TACE). According to our data, TACE is a safe and effective palliative treatment technique in these patients [9].

Liver transplantation (LT) is the only curative treatment method that makes it possible to solve the problem of both diseases. However, taking into account the strict criteria, at the time of the initial detection of HCC, it is feasible in no more than 10–15 % of patients. It should be kept in mind that long-term results of LT are inversely proportional to the volume of tumor tissue. The average waiting time for a donor liver with a proven diagnosis varies from 9 to 15 months, and a two-time increase of the volume of HCC occurs within 2–4 months. Within a year, from 20 to 50 % of patients drop out of the waiting list due to the progression of the oncological disease [12–14]. Keeping the patient within the transplantation criteria is an important task.

The objective of this study – to evaluate the role of TACE as a method of neoadjuvant antitumor therapy of HCC before LT.

**Methods and materials.** From January 1998 to April 2020, we performed 245 OLTs in 229 patients, among them in 25 (10.2 %) for HCC associated with LC. 9 patients were diagnosed with HCC retrospectively during a detailed histologic study of the excised organs; all of them met the Milan criteria: no more than three foci, the maximum diameter of the detected nodes did not exceed 2 cm [16]. TACE was not performed in these patients.

The study group consisted of 16 patients who received 49 TACE sessions in various modifications as neoadjuvant therapy (*table*). For 10 (62.5 %) patients who fell under Milan criteria, the indication for TACE was to prevent tumor progression in order to save them on the waiting list (*fig. 1*). For 6 (37.5 %) patients, the TACE purpose was to reduce the biological activity of the tumor and/or decrease its volume in order to achieve the Milan criteria (*fig. 2*). In 13 patients, cirrhosis was formed on the background of chronic viral hepatitis (B, C and D), in two patients – due to autoimmune hepatitis; one patient had primary biliary cirrhosis. According to the Child–Pugh score of LC [15], two (12.5 %) patients matched A stage, 12 (75 %) – B stage, two (12.5 %) – C stage. At the beginning of neoadjuvant treatment according to the BCLC (Barcelona Clinic Liver Cancer) staging system, 10 patients matched $A_1$–$A_4$ stage and 6 patients – B stage [10].

TACE was performed according to the standard method described in detail in the previous works [9]. Taking into consideration significant manifestations of liver failure, we performed the maximum possible selective catheterization of the arteries supplying the foci, using 2.4–2.9 F microcatheters, when necessary (Progreat, «Terumo»; Neuro Renegate, «Boston»). As an embolizing agent, we used a doxorubicin chemo-oil suspension (10–50 mg) in super-liquid lipiodol, a finely fragmented hemostatic collagen sponge and drug-eluting beads (Hepasphere, «Biosphere Medical»; DC-Beads, Life Pearl – «Terumo»).

We evaluated the treatment results in 3–5 weeks by means of multispiral computed tomography (MSCT), magnetic resonance imaging (MRI) using m-Recist criteria [17] and the dynamics of the alpha-fetoprotein level (AFP). We performed TACE from 1 to 7 times (on average 3), repeated when the blood supply to the nodes was restored (contrast uptake according to MSCT or MRI) and/or in case of an increase in AFP concentration, in 1–8 (on average 3.7) months.

After TACE, upon reaching a partial response and reducing the size of a single tumor, we performed radio frequency ablation in three patients as an adjunct (RFA, observations 7, 8, 9), in two patients – laparoscopic (LS) RFA-assisted atypical liver resection (observations 14, 16), and in one patient with bilobar lesion – sequential resection and RFA (observation 2).

**Results.** Technical success was 100 %. There were no complications. According to the m-Recist criteria, a complete response was observed in 6 (37.5 %),

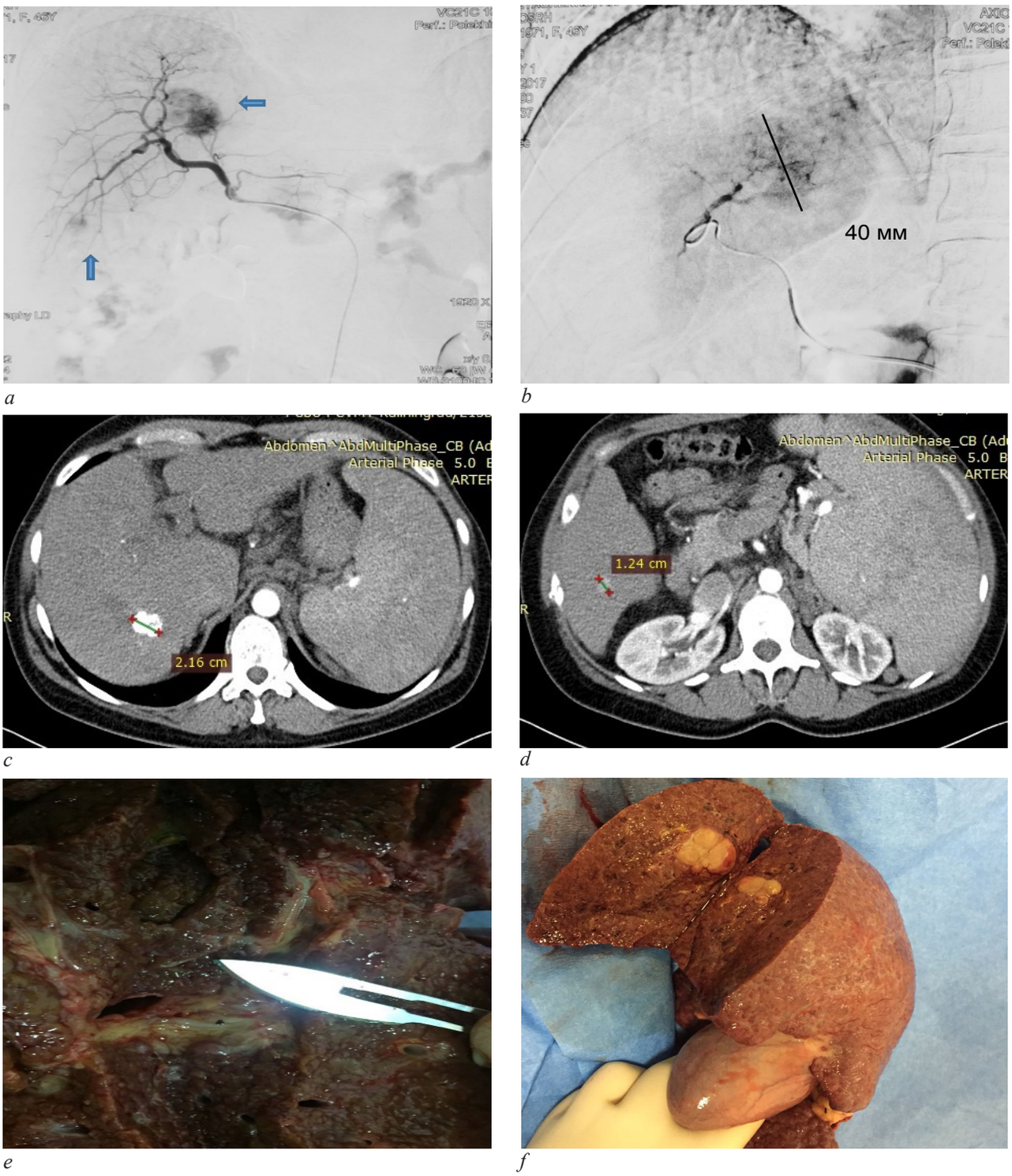


*Fig. 1. Neoadjuvant TACE of a patient with HCC within Milan criteria: superselective oil chemoembolization (observation 15): a – catheterization and angiography of the right hepatic artery: two hypervascular foci in the right lobe of the liver are visible (arrows); b – superselective catheterization and oil chemoembolization of the largest focus in S5; c, d – computed tomography 4 months after two TACEs: a focus in S5 is totally filled with chemoembolizate, does not accumulate the contrast agent, a section below the previous one – the tumor node in S6 up to 12 mm, without dynamics. Partial response (m-Recist); e, f – macroscopically retrieved specimen: total necrosis of the embolized focus with a central lysis zone, a vital HCC node in SVI*

partial – in 7 (43.75 %), and stabilization – in 3 (18.75 %) patients. By the time of LT, 14 patients matched BCLC $A_1$–$A_4$ stage, two patients – stage B. It was possible to achieve an objective tumor response to the treatment in 4 patients (observations 2, 5, 12, 13) and return them to the Milan criteria. Orthotopic LT was performed in all 16 patients, among them – 14 (87.5 %) within the Milan criteria. The waiting periods for LT from the beginning of TACE were from 2 to 30 (on average 12.5) months.

Currently, 9 patients are alive in the period from 4 to 156 (on average 60.2) months. Among them, tu-


*Fig. 2. Neoadjuvant TACE of a patient with HCC beyond Milan criteria: superselective oil chemoembolization; complete response (m-Recist); downstaging to MC (observation 5): a – computed tomography before TACE: HCC focus in the right lobe of the liver 62×50 mm; b – angiogram: super-selective TACE of the source feeding the HCC focus; c, d – arteriohepaticography and plain radiography: occlusion of tumor vessels after TACE, the HCC focus is totally filled with chemoembolizate; e – computed tomography 5 months after three TACEs: a tumor node is totally filled with chemoembolizate, without blood supply (complete response by m-Recist); f – macroscopically retrieved specimen: total necrosis of the HCC node*

mor progression occurred in two patients after 5 and 19 months (observations 4, 14). They both receive therapy with protein kinase inhibitors, in one of them, thoracoscopic resections of the right and left lungs and percutaneous RFA of the focus in the lung were successively performed (observation 4). The 1–3–5-year actuarial survival rates were 93–50–32 %, two patients lived for more than 10 years (observations 9, 12).

7 patients died in the period from 9 to 54 months: 5 - due to the HCC progression (transplant recurrence, metastatic lung lesions, dissemination), two – from concomitant disease: acute cerebrovascular accident,

cholangiogenic sepsis (observations 6, 7). The average life expectancy of the deceased was (28.0±3.0) months.

**Discussion.** LT is the only radical treatment for both HCC and LC; however, one cannot call it routine. When making a decision on the necessity for LT, specialists are always faced with the question of the risk of progression of HCC, especially taking into account immunosuppressive therapy. Indeed, there are enough patients without the concomitant oncological disease in the waiting list and, as a result, potentially with much better long-term results. This problem is the more acute, the higher the shortage of donor organs. The first selection criteria of patients with HCC on LC were defined in 1996, they were called Milan criteria [16]. According to them, LT is indicated when there is one pathological node no more than 5 cm, or no more than three foci up to 3 cm each. 4-year survival rates were 85 % [16].

These criteria are relevant to this day. However, due to the strict indications, and taking into account complications of early diagnosis of HCC, today, more than 20 transplantation criteria have been defined, expanded with respect to Milan [18]. In addition to the volume of tumor tissue, lately more and more attention has been paid to biologic markers that reflect the aggressiveness of the disease course. This is due to the fact that, being a virus-associated disease, HCC is more common in endemic countries, where the necessity for LT is higher. The purpose of the expanding of indications is to increase the number of patients who will be able to undergo radical surgery. In different countries, for ethical and geopolitical reasons, donor organ transplantation programs and the status of the waiting list differ. In this regard, there are many conflicting publications on the reasonability of neoadjuvant treatment before LT [19–21].

By now, at the same time, there are more than 10 classification systems and scores in the world that serve as guidelines on the choice of patient therapeutic approaches [22]. Apart from the volume of the tumor damage and LC, some of them take into account indices of biological activity of HCC. BCLC is the most widely used classification, reflecting the expected treatment results [10]. Since the first publication (2012), the classification provisions have caused hot discussion around the world, and in 2018, a number of changes was represented, which also affected LT. By volume of the tumor tissue, the BCLC classification dublicates the Milan criteria, but according to the new definition, the main indication for LT is LC.

In our clinic, TACE is used more widely in the treatment of HCC than recommended by BCLC. This fact has a historical aspect, because the interventional radiology department exists longer than the LT program in Russia itself. Thus, all patients who do not have absolute contraindications to endovascular treatment [9] receive TACE (at least two sessions). Then, depending on the stage of the LC, the damage volume and response to treatment (m-Recist), a joint decision is made of the possibilities of surgical treatment, including LT. Based on this, the main criterion for putting on the waiting list for LT is the response to the TACE. Further, in case of maintaining the signs of vital tumor tissue, patients continue to receive endovascular treatment, when necessary accompanied by RFA and laparoscopic liver resection. Evaluating our approach, we came to the conclusion that the closest classification system is the JSH Consensus-Based Clinical Practice Guidelines [23]. According to them, TACE is widely used in all cases, except for decompensated LC and extrahepatic extension of HCC. They reflect both combinations of methods of loco-regional treatment and down staging upon response to treatment. And the criteria for selecting patients for LT are best matched to UNOS-DS (United Network for Organ Sharing-down staging) [24].

According to our study, at the time of putting on the waiting list, 10 of 16 patients were within the Milan criteria; we managed to prevent the HCC progression in all of them and performed LT in these frames. By the time of LT, it was possible to achieve HCC down staging up to the Milan criteria in 4 patients who initially fell under the expanded criteria. LT was performed in two patients (12.5 %) with a pronounced response to treatment and beyond the Milan criteria, both had a relapse in the transplant in 2 and 7 months and then HCC dissemination. This experience caused more stringent selection of recipients in the future. Safe waiting periods for LT on average were 12.5 months (from 2 to 30 months). The longest waiting period was achieved with a combination of TACE, RFA, and LS-resection techniques. When following an approach to consider only those who responded to neoadjuvant treatment as a recipient, no one patient was dropped out of the waiting list due to HCC progression. Three patients were removed from the waiting list due to the complete response of HCC to treatment and improved liver function after antiviral therapy.

TACE was performed as much selectively as possible (into vessels supplying the tumor or segmental arteries) without affecting the «conditionally healthy» parenchyma. In this regard, we did not notice an obvious negative effect on liver function. There were no complications either. According to the histological studies of the excised organs, subtotal and total necrosis of HCC (in 81 %) was revealed in patients with a partial and complete response to the treatment.

**Conclusion.** The results of the study indicate that the neoadjuvant TACE delays the growth of HCC masses and prolongs (up to 30 months) a safe waiting period for the donor liver.

The safe waiting period for LT from the moment of diagnosis, according to various sources, is from 3 to 6 months. Compliance with these deadlines is possible in institutions where a great number of LT is performed. In our clinic, we cannot guarantee compliance with a

safe waiting period, and in these conditions, we believe that the neoadjuvant TACE before LT is justified.

**Conflict of interest**

The authors declare no conflict of interest.

**Compliance with ethical principles**

The authors confirm that they respect the rights of the people participated in the study, including obtaining informed consent when it is necessary, and the rules of treatment of animals when they are used in the study. Author Guidelines contains the detailed information.

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