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TRANSCATHETER ARTERIAL CHEMOEMBOLIZATION IN THE TREATMENT OF PATIENTS WITH HEPATOCELLULAR CARCINOMA ON ADVANCED LIVER CIRRHOSIS

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The OBJECTIVE was to evaluate the results of transcatheter arterial chemoembolization (TACE) in the treatment of patients with hepatocellular carcinoma (HCC) on advanced liver cirrhosis (LC) and intermediate stage (B) according to BCLC classification (Barcelona Clinic Liver Cancer classification).

METHODS AND MATERIALS. We evaluated results of TACE in 54 patients.

Of them, 12 (22 %) had stage A of cirrhosis and 42 (78 %) – stage B of cirrhosis according to the Child-Pugh score. Nine (17 %) patients matched stage A4 and 45 (83 %) – stage B according to BCLC classification. The TACEs was performed according to the conventional practice with using Lipiodol + gelfoam (n=40) and with a drug-eluting beads (n=14) from 1 to 16 (average 6) times. The Doxorubicin was used as a first-line therapy in all cases.

RESULTS. After TACE, two patients died of liver failure (3.7 %). According to the m-RECIST, complete response to treatment was observed in 9 (16.5 %), partial response – in 13 (24 %), stabilization – in 19 (35.5 %) and progression – in 13 (24 %) patients. At present, 22 (41 %) patients are alive for 1 to 51 (average 16.2) months. 32 patients (59 %) died between 2 to 62 months: 13 (24 %) – from HCC progression, 19 (35 %) – from liver failure. The 1– 2–3-year survival rate was 75–44–15 %; only one patient survived > 5 years. The median survival rate was (22.0±3.0) months, overall survival rate according to Kaplan – Meier was 26 months.

CONCLUSION. TACE is a relatively safe and effective treatment in patients with HCC on advanced LC and intermediate stage (B).

Keywords: *hepatocellular carcinoma (HCC), transcatheter arterial chemoembolization (TACE), intermediate stage, liver cirrhosis, Lipiodol, eluting beads*

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Introduction. Hepatocellular carcinoma (HCC) accounts for more than 85 % of all primary malignant hepatic tumors [1–3]. According to the WHO data, more than 800 000 new cases of HCC are recorded annually in the world (the 6th place in the structure of cancer morbidity) [4, 5]. The most common cause of HCC is liver cirrhosis (LC), which in most cases occurs due to chronic viral hepatitis [6–8]. The best survival rates are achieved with resection and liver transplantation, but they are feasible only in the early stages of the disease [9, 10]. TACE has been shown to be effective in treating inoperable HCC in the early stages and without LC [11, 12].

International staging systems TNM and AJCC-7 (2009), showing the stage of the tumor process, do not consider competitive disease of the LC, as well as the Child-Pugh score of LC does not take into account HCC [13, 14]. The most commonly used staging system, including both pathologies, is Barcelona Clinic of Liver Cancer, BCLC classification (*Fig. 1*). It also includes practical recommendations on the choice of approach and the expected results of treatment. According to the extent and prevalence of HCC, concomitant diseases, functional characteristics of the liver and patient status (ECOG), it has five stages (0 – very early, A – early, B – intermediate, C – advanced and D – terminal). Due to the pronounced heterogeneity, the early stage is additionally divided according to the functional characteristics of the liver into four subgroups (A_1–A_4). BCLC classification is widely used in Western countries [10, 15]. In Russian literature, there are only a few works that take into account this classification

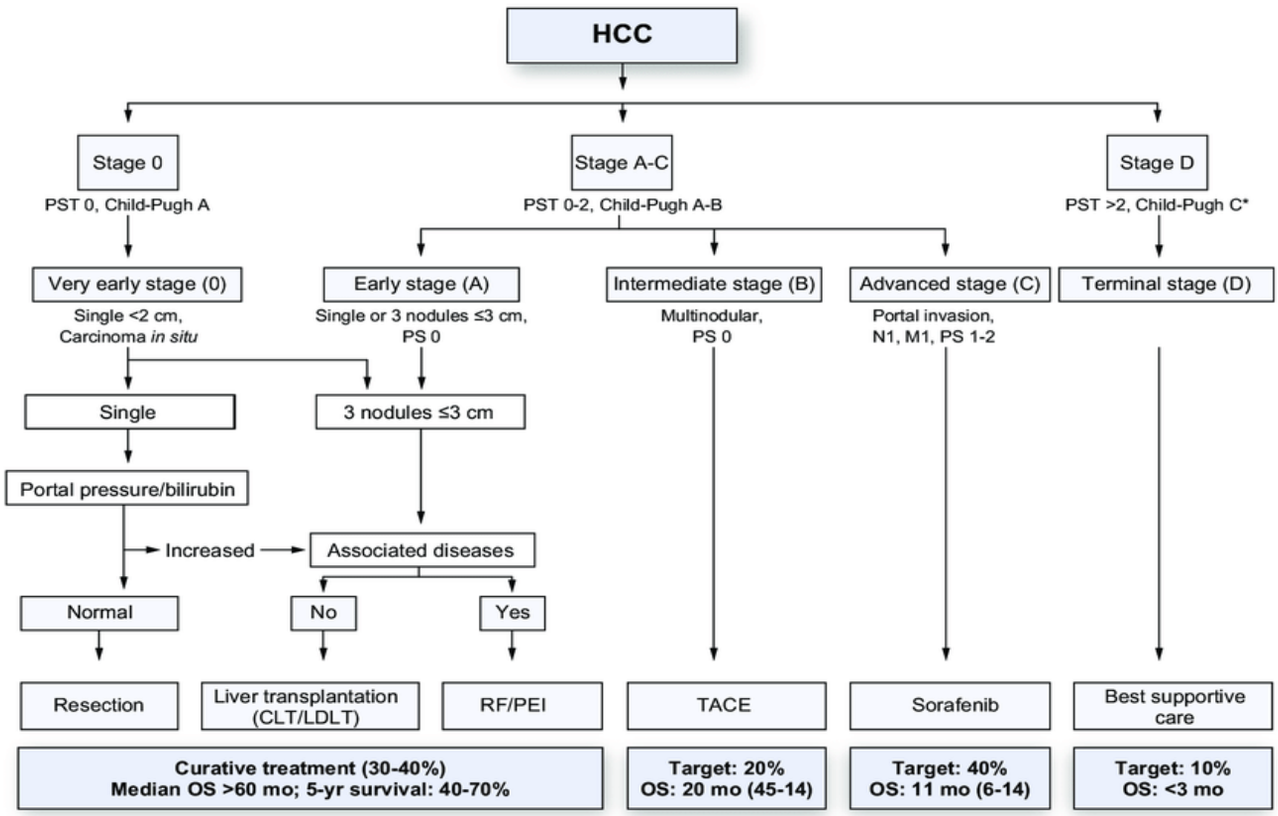


Fig. 1. Barcelona Clinic Liver Cancer classification (BCLC) and treatment strategies (modified from A. Forner et al., 2012 [3]): HCC – hepatocellular carcinoma; PS – patient status by ECOG scale; Child – Pugh – functional status of the severity of cirrhosis by Child – Pugh score; RF – radiofrequency; PEI – percutaneous ethanol injection; TACE – transcatheter arterial chemoembolization; OS – overall survival

and evaluate TACE as a part of independent therapy of the intermediate stage (BCLC-B) [16].

The objective of this study was to evaluate our results of TACE in patients with HCC on advanced LC and intermediate stage (A_4-B) according to BCLC classification.

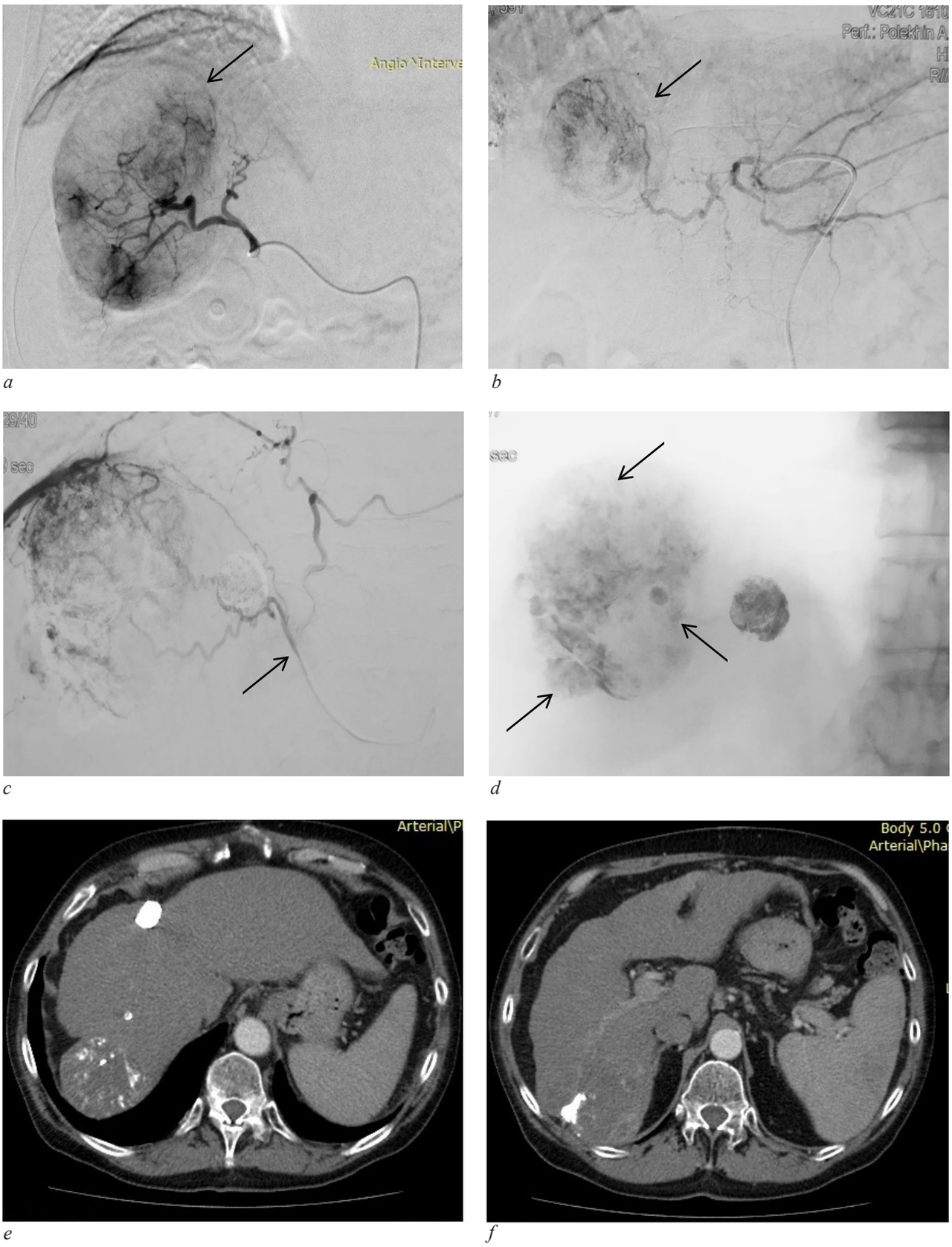
Methods and materials. Between 2009 and 2019, we performed 197 TACE sessions in 54 patients (37 men and 17 women aged 47 to 80 years) with HCC on LC. According to the Child–Pugh score of LC, 12 patients matched stage A (22 %) and 42 (78 %) – stage B. According to BCLC classification, 9 (17 %) patients matched stage A_4 and 45 (83 %) – stage B. Patients with stage A_4 had contraindications to surgical treatment or RFA represented by unfavorable tumor location (central location, intimate proximity of the great vessels) or ascites.

TACE was performed according to standard methods. Femoral artery puncture was performed according to Seldinger technique. Then, using Cobra or Hook 4–5 F catheters (1 F = 0.33 mm), the superior mesenteric artery and celiac trunk were catheterized and subtraction angiography was performed with 25–50 ml of Ultravist-370 or Omnipaque-360. Then we evaluated the arterial anatomy of the liver and blood flow in the portal vein: the direction (hepatopetal or hepatofugal) and the intensity of portal hypertension (gastroesophageal varicose veins, compensatory dilation of the umbilical vein). The presence of hepatofugal flow in the portal vein was regarded as an absolute contraindication to TACE. Then we performed selective catheterization of the common or proper hepatic artery for hepatic arteriography.

After evaluation of the extent and the blood supply to the tumor, the maximum possible superselective catheterization of HCC-feeding arteries was performed using, when necessary, 2.4–2.9 F microcatheters (Progreat; Terumo; Neyro Renegate; Boston). In case of multifocal lesion of one lobe, an oily suspension of Doxorubicin (10–50 mg) or Mitomycin C (5–10 mg) in 5–10 ml Lipiodol ultra-fluid was injected into the lobar artery. In case of bilobate lesions, two-stage successive TACE of the right and left hepatic artery was performed with an interval of 3 weeks (*Fig. 2*). Occlusion of the vessels supplying the tumor with small (1–2 mm) fragments of a hemostatic collagen sponge (n=40) was performed. A contraindication to the sponge use was considered the appearance of contrasting with an oily suspension of the segmental branches of the portal vein of the perinodular zone.

TACE with drug-eluting beads (DEB) was performed when <3 tumors with a diameter <6 cm and the possibility of selective catheterization of supplying vessels was present (*Fig. 3*). As a rule, 1–3 procedures of DEB-TACE was used as the first treatment (n=14). In case of progression, following treatment with Lipiodol-TACE was carried out. Non-selective TACE was not performed due to the high risk of cirrhotic altered liver depression. In all cases, DEB were eluted with 25–75 mg Doxorubicin, depending on the manufacturer recommendations (Hepasphere, Biosphere Medical; DC-Beads, Life Pearls, Terumo).

Evaluation of the treatment result and the decision on repeated TACEs was made by monitoring the level of alpha-fetoprotein (AFP), multispiral computed tomography (MSCT) and magnetic resonance imaging (MRI) 3–4 weeks after the procedure using m-RECIST [17]. TACE was performed 1 to 16 times and was repeated after 1–8 (average 3.8) months in case of progression. TACE techniques were partially changed depending on response, liver function and patient status. If necessary, medicamentous therapy was corrected. The treatment was discontinued in case of extrahepatic progression, as well as deterioration of the patient's physical status insusceptible to treatment.



a *b* *c* *d* *e* *f*

Fig. 2. Radiographs of patient with HCC: conventional TACE: a – superselective catheterization and chemoembolization of the branch right hepatic artery, which supplying a tumor in the right lobe of the liver (arrow); b – catheterization and chemoembolization of the replacement left hepatic artery, extending from the left gastric artery, supplying a tumor of the left lobe of the liver (arrow); c – catheterization and chemoembolization of the right lower diaphragmatic artery supplying the tumor of the right lobe of the liver (arrow); d –panoramic radiograph after TACE: enhanced accumulation of Lipiodol in tumor lesions in both liver lobes (arrows); e – computed tomography 6 months after three TACE: enhanced accumulation of Lipiodol in tumor nodes, partial response (m- RECIST); f – computed tomography, a partition below the previous one: zone of continued growth in the lower part of HCC of the right liver lobe

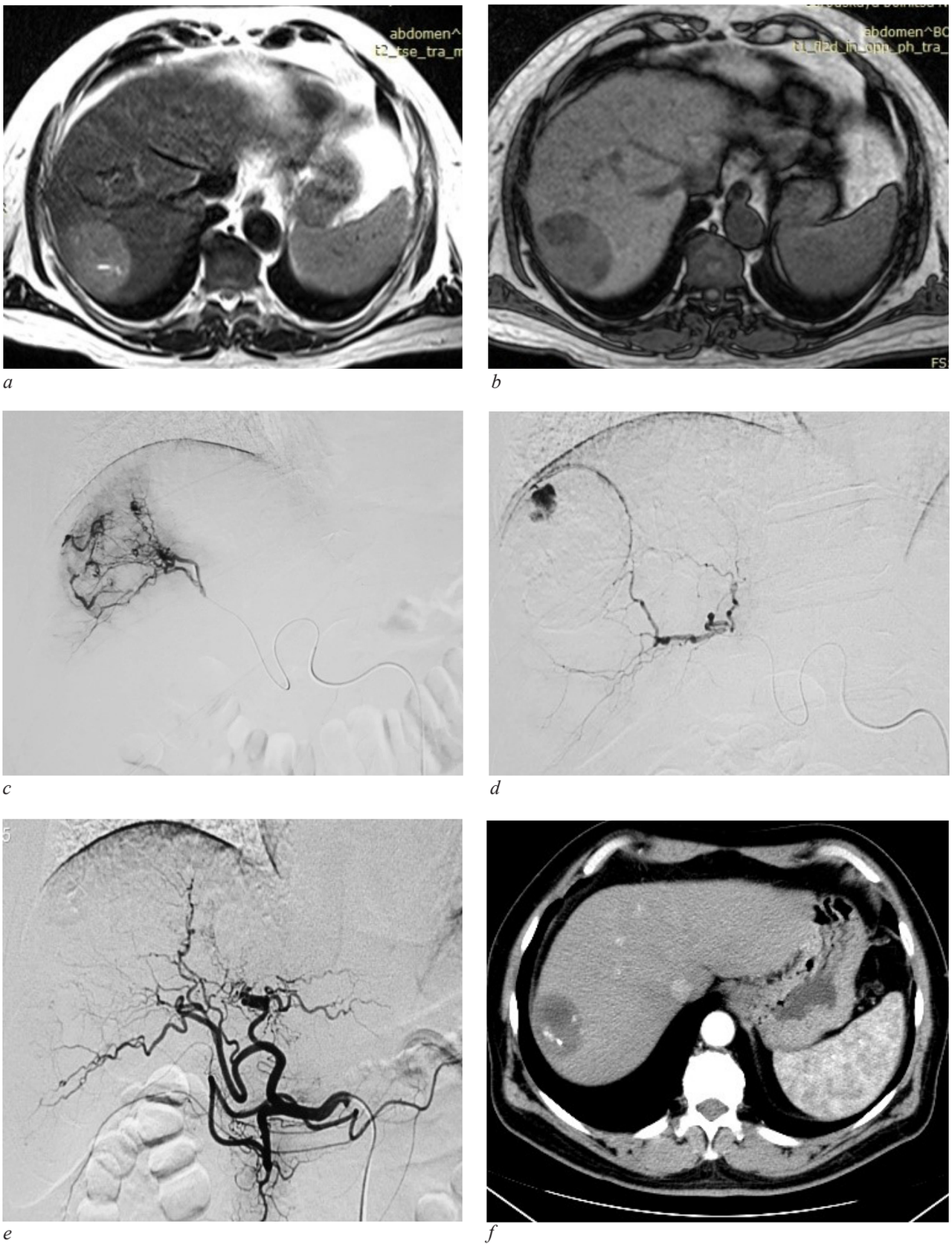


Fig. 3. Radiographs of patient with HCC: superselective DEB- TACE: a, b –magnetic resonance images before the DEB- TACE: HCC tumor in the right lobe of the liver; c, d – angiograms: superselective TACE of two sources of blood supply to the HCC using a microcatheter and doxorubicin-eluted beads (Life Pearl 200 µm Terumo); e – hepatic arteriography: occlusion of tumor vessels after DEB– TACE, the node of the HCC is not defined; f – computed tomography images 3 months after DEB- TACE: necrosis of the HCC node without signs of blood supply (complete response by m-RECIST)

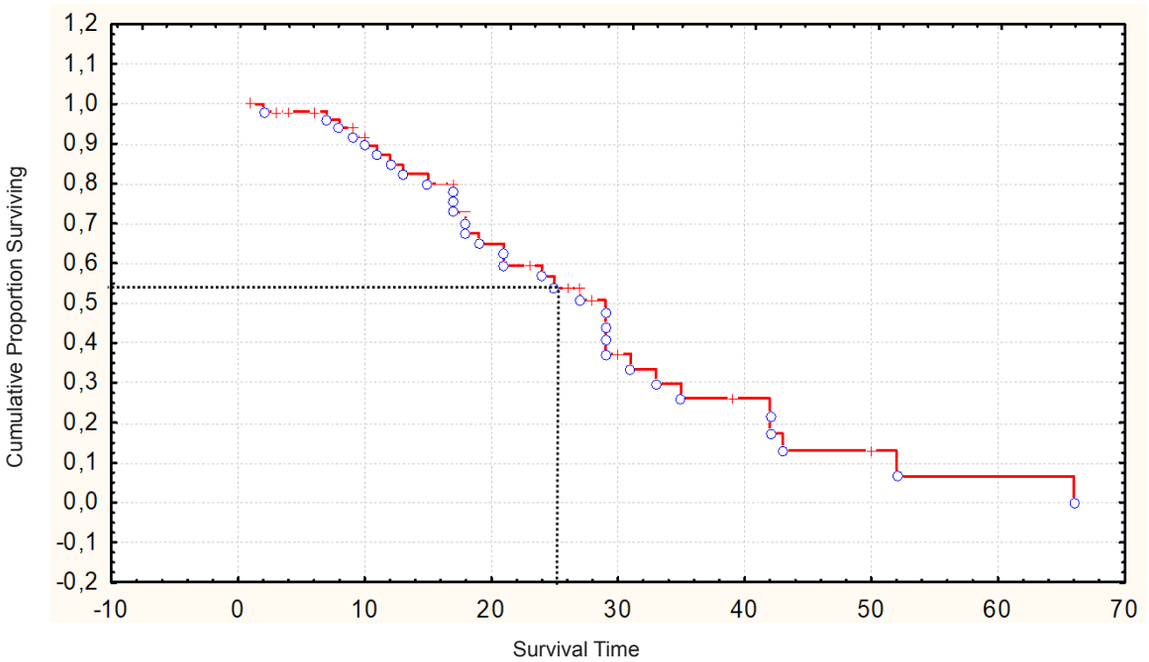


Fig. 4. Overall survival rate by the method of Kaplan – Meier: + – living; o – dead

Results. Postembolization syndrome including abdominal pain, nausea, fever was observed in 14 patients (26 %) and controlled by symptomatic therapy within 3–10 days. Complications included puncture-site pseudoaneurysm of the femoral artery (n=1), hepatic abscess (n=1), increase of the portal hypertension with gastrointestinal hemorrhage (n=2).

All complications have been resolved by surgery, minimally invasive puncture or endoscopy: excision of the aneurysm with prosthesis of the common femoral artery, percutaneous drainage of abscess, endoscopic ligation of gastric varices. Unfortunately, 2 other patients died from liver failure progression (depression of the liver function, hepatorenal syndrome, hyperbilirubinemia) despite intensive extracorporeal detoxication. Thus, occurrence of serious complications was 7.4 %, mortality rate – 3.7 %.

According to m-RECIST [17], complete response was observed in 9 (16.5 %), partial response – in 13 (24.0 %), stabilization – in 19 (35.5 %) and progression – in 13 (24.0 %) patients.

At present, 22 (41 %) patients are alive for 7 to 51 (average 16.2) months. 32 (59 %) patients died in the period from 2 to 66 months: 13 (24 %) due to HCC progression, 19 (35 %) – from LC (portal hypertension, gastrointestinal hemorrhage, hepatorenal syndrome). The 1–2–3-year survival rates were 75.0– 43.7–15.0 %; 1 patient lived for 5 years. The average life expectancy was (22.0±3.0) months, the median overall survival (OS) rate according to Kaplan – Meier was 26 months (*Fig. 4*).

Discussion. An increased frequency of viral hepatitis leads to an increase in the number of patients with HCC. In the Russian Federation, the incidence rate of HCC from 2005 to 2015 increased from 4.6 to 5.6 % [18]. All of our patients had chronic viral hepatitis.

The best treatment for HCC is surgery, but it is possible only in the early stages of the disease (BCLC 0-A3; overall survival >60 months). Unfortunately, according to official statistical reports, the number of resected cases does not exceed 10 %, because 58 % of newly detected HCCs are diagnosed in stages B–C according to BCLC classification [19]. In our opinion, the prognosis of patients in stage A_4 with three bilobate foci, even of a small size, and LC of Child – Pugh B class is even worse than that for stage B patients with solitary tumor >5 cm diameter and Child – Pugh A cirrhosis. Also for this group, the techniques of surgical treatment are far from always applicable. Due to this, we consider stage A_4 to be intermediate.

According to this classification (*Fig. 1*), TACE is considered the optimal treatment for the intermediate BCLC stage B: overall survival is 20 months. The techniques of TACE are very variable both in tactics (selective/non-selective) and in the choice of chemotherapeutic and embolization agents. There are many opinions regarding all these viewpoints, and each of them is supported by its own good results. Thus, according to some authors, a great efficiency of chemoembolization of non-resectable forms of HCR with Doxorubicin-eluted beads was shown [20, 21]. Others, however, believe that selective conventional oily TACE with Lipiodol is safer and increases OS compared with DEB [22]. In our opinion, the decision in choosing TACE strategy should be made by multidisciplinary team including interventional radiologist, surgeon and oncologist individually in each clinical case, and depends significantly on the results of

Barcelona Clinic Liver Cancer classification; addition of A-stage (BCLC-modified from Forner et al. [3])

BCLC Stage	ECOG	Tumor characteristic	Okuda Stage	Liver function
Stage A, early:				
A1	0	Single; <5 cm	I	No portal hypertension and normal bilirubin
A2	0	Single; <5 cm	I	Portal hypertension and normal bilirubin
A3	0	Single; <5 cm	I	Portal hypertension and increased bilirubin
A4	0	Three nodules; <3 cm	I–II	Child – Pugh A–B
Stage B, intermediate	0	Node >5 cm/ multinodular HCC	I– II	Child – Pugh A–B
Stage C, advanced	1–2	Macrovascular invasion/ extrahepatic spread	I– II	Child – Pugh A–B
Stage D, terminal	3–4	Any	III	Child– Pugh C

angiography obtained before embolization. According to our data, DEB-TACE helps to increase the frequency of the primary response rate compared to oily TACE and allows increasing the intervals between cycles from 3.8 to 7.4 months. This can improve the prognosis by reducing the total number of procedures, because the majority of deceased patients have died due to the progression of the liver cirrhosis (19 versus 13 from HCC). In this respect, our data coincide with the opinion of many authors that mortality from complications of liver cirrhosis prevails over mortality from progression of HCC [11, 15]. However, we cannot reliably estimate the increase in life expectancy, because in all cases, as it was mentioned above, the techniques were combined.

There are different, often conflicting opinions regarding the frequency of repeated courses and the completion of TACE in case of inefficiency or toxicity [11, 23]. The interval between TACE cycles depends on the chosen embolization tactic. If the liver function does not allow performing TACE of all pathological nodes, then, in our opinion, it is at first reasonable to embolize one liver lobe, or the most «dangerous» foci, i. e. located near the porta, the junction of the hepatic veins and extending beyond the organ. The reasonability of this approach is determined by the fact that even a minimal increase of such nodes of HCC can lead to serious complications: obstructive jaundice, increased portal hypertension, Budd-Chiari syndrome, intra-abdominal hemorrhage due to rupture. In these cases, the interval between cycles should be reduced to 7–21 days and regulated only by the status of the patient and liver function. In all other cases, repeated TACE should be performed after follow-up examinations, indicating progression according to m-RECIST. In case of insufficient treatment effectiveness, we changed cytostatic Doxorubicin with Mitomycin C. There were no accentuated systemic toxicities that required special treatment in any case. We relate this to a reduction in the dosage of the used cytostatic.

In our study, the median overall survival was 26 months. This even slightly exceeds 20 months according to EASL-EORTC data [10]. Compared to our previously published results [12, 24], survival rates improved from 6–9 to 22 months. We relate this to the introducing of new instrumental and embolization varieties, as well as a conceptual revision of the approach to this problem. An individual approach to each specific case allows developing an optimal treatment strategy for a complicated category of patients with interrelated, but differently life-threatening diseases, when all points are important.

CONCLUSION. Thus, TACE is a relatively safe and effective treatment in patients with intermediate stage of HCC on advanced LC.

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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