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TRANSCATHETER HEPATIC ARTERIAL CHEMOEMBOLIZATION IN CIRRHOTIC PATIENTS WITH HEPATOCELLULAR CARCINOMA BEFORE LIVER TRANSPLANTATION: THE PROGNOSTIC VALUE OF ALPHA-FETOPROTEIN CONCENTRATIONS

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Objective: to study liver transplantation (LT) outcomes in cirrhotic patients with hepatocellular carcinoma (HCC), who underwent transcatheter hepatic arterial chemoembolization (THACE). **Materials and methods.** From January 1998 to April 2020, we performed 245 orthotopic liver transplantation (OLTs) in 229 patients of which 25 (10.2%) had HCC in cirrhosis. In 9 (36%) patients, LT was performed without neoadjuvant therapy (Group 1). Group 2 consisted of 16 (66%) patients who underwent 49 THACE cycles before LT. 10 (62.5%) patients fell within the Milan criteria, while 6 (37.5%) were outside. According to the BCLC (Barcelona Clinic Liver Cancer) classification, 10 patients had A_1–A_4 stage, while 6 were in B stage. In 11 (68.5%) of 16 patients, increased serum alpha-fetoprotein (AFP) concentrations from 20 to 2463 (on average 493.8) ng/mL was revealed before treatment. In performing THACE, both the classical method (with lipiodol and hemostatic sponge) and the method with drug-eluting beads were performed 1 to 7 (on average 3) times. Doxorubicin was used in all cases. **Results.** Group 2 recorded a 100% technical success. There were no complications. We performed radiofrequency ablation (RFA) in three patients as an adjunct. In two patients, we performed laparoscopic RFA-assisted atypical liver resection, and in one – sequential resection and RFA. Under the m-Recist criteria, complete response was observed in 6 (37.5%), partial response in 7 (43.75%), and stabilization in 3 (18.75%) patients. Change in AFP concentrations were as follows: in 5 out of 11 patients with increased concentrations, we were able to reduce their AFP concentrations to the reference values, their long-term outcomes are comparable to those of Group 1. Four patients showed a 13–84% decrease; a directly proportional relationship between the degree of AFP decrease and the time to tumor progression was revealed. In 2 patients, there were 42% and 320% increase in AFP concentrations, the time to tumor progression was 3 and 1 month, both did not live up to 12 months. Among 9 (56%) of the living 16 patients, a maximum of 156 months and a minimum of 4 months (60.2 average) have elapsed since the surgery. Two of these nine have tumor progression (Cases 4 and 14). Seven (44%) patients died within 9 to 54 months. The 1, 3, 5-year actuarial survival rates were 93, 50, 32%, two patients lived more than 10 years. The average life expectancy was 28.0 ± 3.0 months. **Conclusion.** Serum AFP concentration is an important prognostic factor influencing the long-term outcomes of LT. Good biological response to THACE can be a positive predictor; LT outcomes in these patients are comparable to those in patients who meet the Milan criteria. A decrease in AFP concentrations by less than 50% after neoadjuvant THACE is an unfavorable factor, and its increase is extremely adverse.

Keywords: hepatocellular carcinoma, cirrhosis, hepatic arterial chemoembolization, neoadjuvant therapy, liver transplantation, alpha-fetoprotein.

INTRODUCTION

Liver transplantation (LT) is the only radical treatment for hepatocellular cancer (HCC) associated with liver cirrhosis (LC). However, in reaching a compromise between transplantation criteria and treatment guidelines for HCC, LT remains far from a routine operation and is feasible only in 10–15% of patients [1]. According to reports, over 55% of patients drop out of the waiting list within a year due to HCC progression [2, 3]. According to official statistical reports over the past 10 years, the peak incidence of HCC in the Russian Federation has not yet been passed [4–6]. Existing antiviral drugs against chronic hepatitis C virus (HCV) can significantly affect HCC statistics, as is the case in Western countries, but such drugs cannot yet be said to be widely available [7, 8].

Over 20 years have passed since the first transplant criteria was formulated. Being the basis and guarantor of

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achieving the best survival rates (4-year survival rate is 83%), the Milan criteria are quite strict [9]. And during this time, various countries have come up with alternative LT guidelines for HCC against the background of LC. In addition to the number and size of foci, recent guidelines take into account biological tumor markers, the degree of differentiation, and tumor response to treatment. Presently, more than 20 extended LT criteria have been formulated. All of them are aimed at increasing the number of operations, with achievement of acceptable long-term outcomes, which directly depend on HCC progression in this group of patients [10, 11]. In order to keep the patient on the LT waiting list, methods of local anticancer treatment are increasingly being used, which, in addition to curbing the tumor process, can reduce the HCC stage, creating more favorable conditions for LT [12, 13]. The most commonly used is transcatheter hepatic arterial chemoembolization (THACE).

Objective of the study: to investigate our own LT outcomes in HCC patients on the background of LC, who underwent THACE.

MATERIALS AND METHODS

From 1998 to 2020, 229 patients underwent 245 orthotopic LTs with a graft from a deceased donor, of which 25 for HCC against the background of LC. In 22 patients, cirrhosis formed due to chronic hepatitis (B, C and D) virus, in two patients due to autoimmune hepatitis; one patient had primary biliary cirrhosis. Two patients (8%) were Child-Pugh class A, 18 (72%) were Child-Pugh class B, while 5 (20%) were Child-Pugh class C [14].

HCC diagnosis in 9 (36%) patients was established only by histological examination of the removed organs, and no THACE was performed in them. All of them retrospectively fell under the Milan criteria: maximum nodule diameter did not exceed 2 cm, no more than three foci in each organ, and stage "0" according to the BCLC classification (Barcelona Clinic Liver Cancer classification) [15]. These patients constituted Group 1.

In 16 (64%) patients of Group 2, 49 THACE cycles in various modifications were performed as neoadjuvant therapy (Table).

Of these, for 10 patients who met the Milan criteria, the goal of THACE was to prevent tumor progression in order to keep them on the waiting list. In 6 patients, THACE goal was to reduce the tumor volume to the Milan criteria and decrease its biological activity. At the start of treatment, 10 (62.5%) patients were BCLC A_1–A_4, while 6 (37.5%) patients were BCLC B [15]. Elevated serum alpha-fetoprotein (AFP) level from 20 to 2463 (mean 493.8) ng/mL was detected in 11 (68.5%) of 16 patients before treatment.

THACE was performed according to the standard technique using 10–50 mg of doxorubicin mixed with 5–10 mL of super-liquid Lipiodol, finely chopped hemostatic sponge, or doxorubicin-saturable spheres (Hepasphere, Biosphere Medical; DC Beads, Life Pearls, Terumo). Given the presence of severe manifestations of liver failure in patients, only superselective THACE was used, if necessary using 2.4–2.9 F microcatheters (Progreat, Terumo; Neuro Renegate, Boston).

Table

Group 2 characteristics

No./age	AFP before THACE	AFP after THACE	BCLC	MC after THACE (+/–)	Waiting time (months)	Time to tumor progression (months)	Outcome (month)	
							Alive	Died
1. K., 28	N	N	B	–	7	12		26
2. B., 58	N	N	B	+	15	–	62	–
3. R., 45	20	N	A	+	2	–	77	–
4. Z., 54	1300	1122 (<14%)	A	+	6	19	76	–
5. E., 49	183	30 (<84%)	B	+	6	24	–	36
6. K., 52	346	111 (<68%)	A	+	26	–	–	54
7. K.A., 53	113	N	B	+	10	–	–	19
8. K.B., 43	N	N	A	+	12	12	–	33
9 K., 53	59	N	A	+	7	–	138	–
10. S., 61	30	51 (>42%)	A	–	5	3	–	9
11. T., 45	2463	8666 (>320%)	A	+	16	1	–	20
12. U., 48	N	N	B	+	12	–	168	–
13. N., 55	31	N	B	+	23	–	62	–
14. P., 52	343	300 (<13%)	A	+	15	2	21	–
15. S., 47	N	N	A	+	12	–	30	–
16. Sh., 64	544	N	A	+	30	–	34	–

Note. BCLC – Barcelona Clinic Liver Cancer classification [14]; THACE – transcatheter hepatic arterial chemoembolization; MC – Milan Criteria [8]; AFP – alpha-fetoprotein.

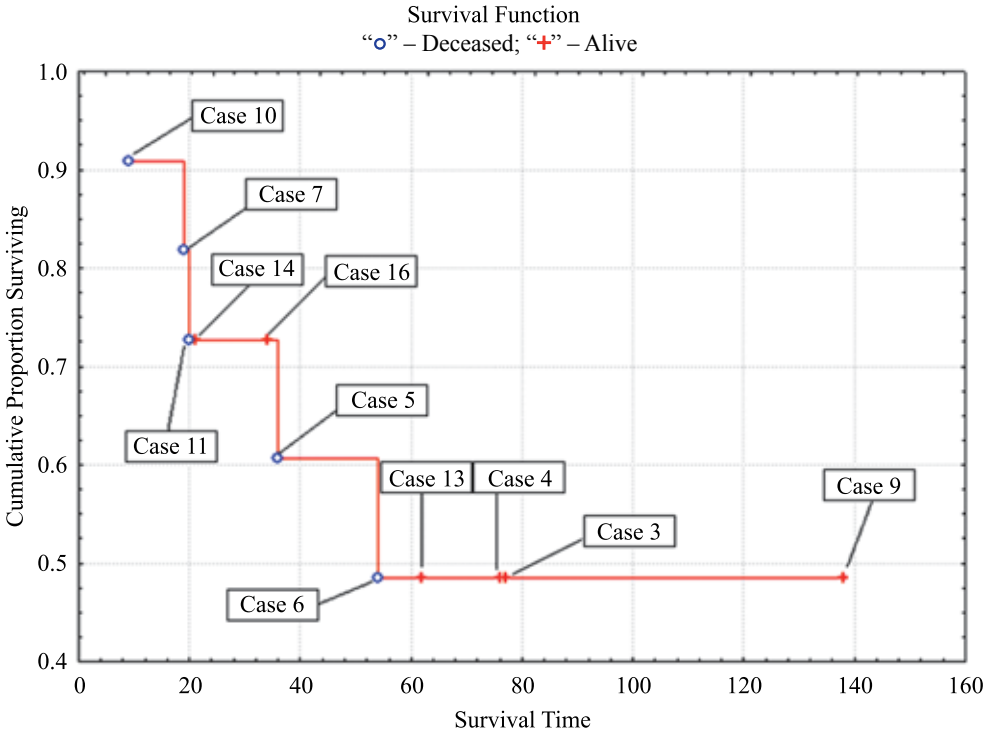

Fig. Calculation (by the Kaplan–Meier method) of survival in patients with increased AFP concentrations: "+" – alive; "o" – deceased

Treatment outcomes were assessed at week 3–5 based on data from multispiral computed tomography (MSCT) or magnetic resonance imaging (MRI) using the mRECIST criteria; AFP concentration dynamics were evaluated [16]. THACE was performed 1 to 7 times, and was repeated only with proven progression at worth 1–8 (mean 3.7).

After THACE, when partial response was achieved and tumor size decreased, radiofrequency ablation (RFA) was performed as an adjunct in three patients (Cases 7, 8, and 9), laparoscopic (LS) RFA-assisted atypical liver resection in two patients (Cases 14 and 16), successive resection and RFA in one patient with bilobar lesion (Case 2).

RESULTS

To date, 7 (78%) of 9 patients in Group 1 are alive at month 24 to 134 (mean 69.8), all without signs of HCC progression. The 1-3-5-year actuarial survival rates were 78–45–44%, with one patient alive for over 10 years. Two died within 1 (sepsis) and 7 months (HCC recurrence and graft rejection).

In Group 2, THACE's technical success was 100%. There were no complications. According to the mRECIST criteria, a complete response was observed in 6, partial in 7, stabilization in 3 patients. By the time of LT, 14 patients were BCLC A_1–A_4, 2 were BCLC B (Cases 1 and 10). In 4 out of 6 patients, we managed to achieve tumor response to treatment and return them to the Milan criteria (Cases 2, 5, 12 and 13). AFP dynamics was as follows: 5 of 11 patients with elevated levels were able to achieve reference values, 4 had a 13–84% decrease, 2 had 42% and 320% increases (Table).

At present, 9 (56%) of 16 patients are alive at month 4 to 156 (mean 60.2), of whom 2 had tumor progression (Cases 4, 14). Seven (44%) patients died between month 9 to 54: 5 due to HCC progression that occurred at month 1–24 (mean 11) (relapse in the graft, metastatic lung disease, dissemination), two from intercurrent disease (acute cerebral circulation disorder, cholangiogenic sepsis). The 1-3-5-year actuarial survival rates were 93–50–32%, two patients survived for more than 10 years. Average life expectancy was 28.0 ± 3.0 months.

In 5 out of 11 patients who managed to achieve reduction in AFP levels to reference values (according to mRECIST), complete response to treatment and total tumor necrosis based on histological studies were observed. In Cases 7 and 13, the patients were outside the Milan criteria before treatment. Currently, 4 out of 5 (Cases 16, 13, 3 and 9) are alive at month 34, 62, 77, and 138, with no signs of HCC progression. One patient (Case 7) died at month 19 from a cause unrelated to tumor progression. These results are comparable to those of Group 1.

Patients with decreased AFP levels according to mRECIST recorded a partial response. In Cases 5 and 6, AFP decreased by 84 and 68%, while in Case 6 there was no HCC progression, and in Case 5 it occurred after 24 months. Both patients died at month 36 and 54. The patient with a smaller decrease in AFP and from intercurrent disease lived for the longest period (Case 6). In

Cases 4 and 14, AFP decreased by 14% and 13%, the time to progression was 19 and 2 months, respectively.

Two patients with stable HCC showed a 42% and 320% increase in AFP, the time to progression was 3 and 1 month, both did not survive for 12 months.

DISCUSSION

The "stumbling block" in the formation of a waiting list for HCC patients with LC is the frequent inconsistency of stages of the tumor process and liver cirrhosis. So, if the reference Milan criteria are met, LT is indicated in the presence of one or three tumor nodes no larger than 3 cm in size. At the same time, following another rule, LT is indicated for subcompensated LC. Indeed, recently, with the development of surgical technologies, there is increasing evidence of sparing liver resections, and various methods of interventional radiology, which quite safely and effectively allow to control the tumor process even at late stages [17, 18]. So, the main indication for LT remains LC with irreversible liver dysfunction.

Let us imagine a common situation: a patient with single HCC up to 3 cm in diameter and Child-Pugh class B cirrhosis. According to the main choice of treatment tactics, BCLC classification, LT is indicated for him. Two months have passed since the moment of being placed on the waiting list, the focus has increased to 4 cm, and the AFP level has risen from 80 to 380 ng/mL. Is it worth doing nothing in such a situation? In our opinion, if nothing is done, then after another two months, only treatment with protein kinase inhibitors will be possible according to BCLC. Given the impossibility of guaranteeing even an approximate LT timeframe, we believe that all such patients should be treated with antitumor therapy. We consider THACE to be the most accessible and safest [19].

Over half of the available LT criteria take into account biological tumor markers, the most accessible of which is determination of AFP concentration. The criticality of its value, according to different authors, varies from 20 to 1000 ng/mL [10, 11]. According to the EASL and RUSSCO guidelines, a combination of clinical, radiological and laboratory data (LIRADS 2 or more + LC + tenfold increase in AFP concentration) is sufficient to diagnose HCC [15, 20, 21] without biopsy, associated with a high risk of bleeding after liver puncture against the background of hypocoagulation. Accordingly, evaluation of tumor differentiation degree is often performed only after LT. Both AFP and morphological picture, along with the number and size of tumor nodules, became the basis for formulation of prognostic scales of LT outcomes in HCC [11].

In our study, in Group 2, 11 (68.5%) of 16 patients had elevated AFP levels. After THACE, 5 out of 11 patients managed to achieve AFP reduction to reference values (Cases 3, 7, 9, 13, 16). As a result, such indicators as time to progression and survival in these patients were comparable to those of Group 1. In another 4 patients, THACE was able to achieve decreased AFP concentrations. In Cases 5 and 6, the decrease in AFP was 84% and 68%; HCC progression occurred only in Case 5 at month 24. In Cases 4 and 14, AFP decreased by 14% and 13%; the time to progression was 19 and 2 months, respectively. In two patients with an increase in AFP concentration (Cases 10, 11), time to progression was very short: 3 and 1 month, despite the fact that LT was performed in Case 11 according to the Milan criteria.

So, the dynamics of serum AFP levels was an important prognostic factor influencing long-term LT outcomes. A good biological response to THACE can serve as a positive prognosis factor; LT outcomes in these patients are comparable to those in patients who meet the Milan criteria. A less-than-50% decrease in AFP levels after neoadjuvant THACE was an unfavorable factor, and its increase was extremely unfavorable.

The authors declare no conflict of interest.

REFERENCES

1. *Gautier SV, Moysyuk YG, Poptsov VN et al*. Long-term outcomes of deceaded donor liver transplantation. *Russian Journal of Transplantology and Artificial Organs*. 2014; 16 (3): 45–53. (In Russ.).
2. *Salvalaggio PR, Felga G, Axelrod DA et al*. List and liver transplant survival according to waiting time in patients with hepatocellular carcinoma. *American J Transplant*. 2015; 15 (3): 668–677.
3. *Benmassaoud A, Tsochatzis EA*. Loco-regional treatments on the liver transplant waiting list: unmasking hepatocellular carcinoma (HCC) biology. *Hepatobiliary Surg Nutr*. 2018; 7 (3): 199–201.
4. *Bray F, Ferlay J, Soerjomataram I et al*. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018; 68 (6): 394–424.
5. *Balakhnin PV, Shachinov EG, Shmelev AS*. The role of surgical technologies in the treatment of virus-associated tumors on the example of hepatocellular carcinoma. *Practical oncology*. 2018; 19 (4): 348–377. (In Russ.).
6. *Kaprin AD, Starinskij VV, Petrova GV*. Zlokachestvennye obrazovanija v Rossii v 2017 godu (zabolevaemost' i smertnost'). M.: RIIS FIAN, 2018. 250. (In Russ.).
7. *Crespo G, Trota N, Londono M-C et al*. The afficacy of direct anti-HCV drugs improves early post-liver transplant survival and induces significant changes in waiting list composition. *Journal of Hepatology*. 2018; 69 (1): 11–17.
8. EASL recommendation on treatment of hepatitis C 2018. *Journal of Hepatology*. 2018; 69 (2): 461–511.
9. *Mazzaferro V, Regalia E, Doci R et al.* Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med*. 1996. (334): 693–699.
10. *Schielke A, Meurisse N, Lamproye A et al*. Selection criteria for liver transplantation in patients with hepa-

tocellular carcinoma. Eastern and western experiences, and perspectives for the future. *Acta Gastroenterol Belg*. 2019; 82 (2): 314–318.
11. *Maltseva AP, Syutkin VE, Kolyshev IYu et al*. Transplantation in oncology: the future of a multidisciplinary approach. *Transplantologiya. The Russian Journal of Transplantation*. 2019; 11 (3): 218–233. (In Russ.).
12. *Pompili M, Francica G, Romana Ponziani F et al*. Bridging and downstaging treatments for hepatocellular carcinoma in patients on the waiting list for liver transplantation. *World J Gastroenterol*. 2013; 19 (43): 7515–7530.
13. *Kulik L, Heimbach JK, Zaiem F et al*. Therapies for patients with hepatocellular carcinoma awaiting liver transplantation: A systematic review and meta-analysis. *Hepatology*. 2018. 67 (1): 381–400.
14. *Child CG, Turcotte JG*. Surgery and portal hypertension. *The liver and portal hypertension*. Philadelphia: W.B. Saunders Co., 1964: 50.
15. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol*. 2018; 69 (1): 182–236.
16. *Lencioni R, Llovet JM*. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis*. 2010; (30): 52–60.
17. *Patjutko JuI, Kudashkin NE*. Hirurgicheskoe lechenie bol'nyh gepatocelljuljarnym rakom BCLC B. *Malignant Tumor*. 2016; 4, specvypusk 1: 46–47.
18. *Bhandare MS, Patkar S, Shetty N et al*. Liver Resection for HCC Outside the BCLC Criteria. *Langenbecks Arch Surg*. 2018; 403 (1): 37–44.
19. *Polekhin A.S., Tarazov PG, Polikarpov AA, Granov DA*. Transcatheter arterial chemoembolization in the treatment of patients with hepatocellular carcinoma on advanced liver cirrhosis. *Grekov's Bulletin of Surgery*. 2019; 178 (6): 29–35.
20. *Breder VV, Balahnin PV, Virshke ER et al*. Prakticheskie rekomendacii po lekarstvennomu lecheniyu gepatocellyulyarnogo raka. *Zlokachestvennye opuholi: Prakticheskie rekomendacii RUSSCO*. 2019; 9 (2): 420–438. (In Russ.).
21. American College of Radiology. Quality and safety resources: Liver Imaging – Reporting and Data System. Available at: http://www.acr.org/QualityB Safety/Resources/LIRADS. Accessed April 22, 2012.

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