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TRANSARTERIAL CHEMOEMBOLIZATION IN THE INTERMEDIATE STAGE OF HEPATOCELLULAR CARCINOMA: SURVIVAL ANALYSIS

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Abstract

Hepatocellular carcinoma is the most common primary tumor pathology of the liver (> 85%), an aggressive course with an unfavorable prognosis. Objective: to elucidate the survival of various categories of patients with hepatocellular carcinoma in stage B hepatocellular carcinoma after transarterial chemoembolization.

The study was conducted on the basis of the JSC "National Scientific Center of Surgery" named after A.N. Syzganov in the period 2013-2018. When analyzing survival, patients were divided into the following categories: gender, age, degree of liver function damage according to Child-Pugh scale, the presence of viral hepatitis B and C, and the level of alpha-fetoprotein.

The average age of the patients was 60.4 years. The follow-up period was 2-64 months. The average length of stay of the patients studied in the hospital was 7.2 days. In patients older than 60 and 70 years, the 3-years and 5-years survival rates were 0%, the 1-year survival rate of the subjects studied in the group over 70 years of age was 14.3%. The one-year survival after transarterial chemoembolization in the total cohort left 42%, 2-years - 15% and 3-years - 5%, respectively. The survival rate among patients with cirrhosis of stage B on the Chile-Pugh scale was significantly lower than that of stage A patients (82% vs 56% for 6 months and 50% vs 31% for a year, respectively). In the group, a substantial increase of alpha-fetoprotein (>1000 IU/ml), the Kaplan-Meier survival curve showed a survival rate of 0% 18 months after the first transarterial chemoembolization.

Transarterial chemoembolization showed good results in the group among women, and the life expectancy was higher in the middle-age group (50-59 years). Adult age, a high degree of liver dysfunction, as well as high alpha-fetoprotein values are additional factors that dramatically reduce the life expectancy of patients after transarterial chemoembolization with hepatocellular carcinoma hepatocellular carcinoma in stage B.

Keywords: *chemoembolization, hepatocellular carcinoma.*

Introduction

Hepatocellular carcinoma (HCC) is the most common primary tumor pathology of the liver (>85%), an aggressive course with an unfavorable prognosis - 5 years of survival does not exceed 15% [*Siegel R. et al., 2014*]. Among the causes of cancer mortality in the world, HCR ranks 2nd - about 746,000 patients died in 2012 [*Bray F et al., 2008; Ferlay J et al., 2014*].

According to various sources, in patients with hepatocellular cancer, the diagnosis of concomitant cirrhosis varies from 30 to 80% [*Oh J-K et al., 2012*]. In the etiology of HCC, the leading theory is the theory of viral carcinogenesis, which is a complex and multi-step process. The risk groups for HCC are patients with cirrhosis of any etiology, chronic viral hepatitis, alcoholic and nonalcoholic steatohepatitis, hemochromatosis [*Aliev M et al., 1997*].

Currently, the generally accepted and widespread classification of HCC is the Barcelona Clinical Liver Classification (BCLC, Barcelona Clinic Liver Cancer), which takes into account the prevalence of the tumor process, the functional state of the liver, the objective state of the patient and the intended effectiveness of the treatment. People with hepatocellular carcinoma in the intermediate (B by BCLC) stage have large, multiple cancer nodules, without severe liver failure and macrovascular invasion [*Roccarina D et al., 2017*].

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Transarterial chemoembolization (TACE) is considered to be the best treatment method for patients with HCC in the intermediate stage [*Poon RT et al., 2007; Varela M et al., 2007*]. The procedure consists of inserting a mixture of chemotherapeutic and embolizing agents through the catheter into the hepatic artery. The purpose of TACE is to deliver a high dose of the chemotherapeutic agent directly to the tumor, to increase the contact time between the tumor cells and the agent, while minimizing the systemic effect of the chemotherapeutic agent.

For untreated HCC in stage B the expected median of agents is 16 months [*Llovet J, Bruix J, 2003; Lencioni R, 2012*] or 49% by 2 years [*Llovet J, Bruix J, 2003*]. According to a meta-analysis of clinical studies, chemoembolization increases survival in this group of patients up to 19-210 months [*Llovet J, Bruix J, 2003*]. However, here, inside the intermediate stage, there is a significant heterogeneity of the median of overall survival - from 36-45 months [*Takayasu K. et al., 2006; Burrel M. et al., 2012*] with a good immediate effect of TACE, up to 11 months with no further treatment (placebo group from the study SHARP for BCLC B patients [*Llovet J et al., 2008*].

Thus, the use of TACE in the treatment of patients with HCC intermediate stage, requires further study [*Sagatov IY, Medeubekov USh., 2019*]. This article analyzes the survival of patients after chemoembolization with this pathology.

Objectives: to elucidate the survival of various categories of patients with hepatocellular carcinoma in stage B (BCLC) after transarterial chemoembolization.

MATERIAL AND METHODS

The study was conducted on the basis of the JSC "National Scientific Center of Surgery named after A.N. Syzganov" in the period 2013-2018. All subjects underwent blood sampling for routine laboratory tests; alpha-fetoprotein (AFP) level; the presence of hepatitis B, C; ultrasound examination of the liver and CT. When analyzing survival, patients were divided into the following categories: gender, age, degree of liver function damage according to Child-Pugh, the presence of viral hepatitis B and C, and the level of AFP. It is worth noting that the study did not analyze the survival of patients depending on the number and size of HCC nodes, invasion of tumor in the hepatic or portal vein, as well as the number and combination of chemotherapeutic agents during TACE.

Statistical calculations were performed using Excel, SPSS Statistics by estimating the survival rate using the Kaplan-Meier method.

RESULTS

The total number of patients with HCC was 148 patients, among them 58 patients had an intermediate stage in BCLC. Patients who subsequently underwent open surgery after arterial chemoembolization were excluded from the study. The average age of the patients was 60.4 years. The follow-up period was 2-64 months. The average length of stay of the patients studied in the hospital was 7.2 days. Overall patients data of survival are listed in table 1.

The study revealed the following statistically significant differences: the influence of old age (>60 years old) is directly proportional to the decrease in survival, so in patients over 60 and 70 years old, 3 years and 5 years survival rate was 0%, moreover, the 1-year survival rate of the studied people in the group over 70 years old amounted to 14.3%.

TABLE 1.

Distribution of background factors

Categories of patients	Survival (%)			
	Less than 1 year	1 year	3 years	5 years
Gender				
Male (n=28)	71.4	10.7	7.1	3.6
Female (n=22)	50	36.3	13.6	0
Age				
30-39 y (n=2)	50	50	50	0
40-49 y (n=2)	50	50	0	0
50-59 y (n=29)	65.5	37.9	34.4	3.4
60-69 y (n=10)	100	100	0	0
70-79 y (n=7)	85.7	14.3	0	0
Degree of liver damage				
Child-Pugh A (n=34)	73.5	14.7	11.8	3
Child-Pugh B (n=16)	37.5	31.2	6.3	0
HBV and HCV				
HBV + (n=18)	72.2	22.2	16.6	5.5
HCV + (n=16)	53.3	46.6	0	0
Both positive (n=2)	50	50	0	0
Both negative (n=14)	57.1	35.7	14.2	0

NOTES: HBV - hepatitis B virus; HCV - hepatitis C virus.

In the general cohort, men prevailed over women, 28 by 22, respectively; however, when assessing survival in this category, it was noted that women are more adapted than men. So, if the annual survival after TACE in men was about 10%, this indicator in women reached up to 37% over the same period.

It is interesting to note that only 36 patients had positive test results for viral hepatitis. Along with this, patients with positive hepatitis C showed 0% survival 18 months after TACE.

In our case, the procedure of transarterial chemoembolization was carried out with the use of Doxorubicin in dosages of 50 and 100 *mg* in combination with Lipiodol or embolizing microspheres of different diameters. In many cases, TACE was conducted with an intercourse interval of 1.5-2 months. Thus, only 50 patients underwent 103 TACE interventions in isolation, of which 15 patients underwent 2 courses of TACE, 8 patients - 3 courses, 3 patients - 4 courses, 2 patients - 5 courses and in 1 case 6 courses, respectively.

The study period of survival was 2-64 months, the overall survival of the entire cohort of patients correlated with world literature data (Fig. 1).

One-year survival after TACE in the total cohort left 42%, 2-years- 15% and 3-years - 5%, respectively. It is worth noting that the patient's comorbid background, as well as complications such as portal vein thrombosis, were not considered here.

In the distribution of groups according to the degree of liver tissue damage, we used the Child-Pugh standard scale (Fig. 2).

Taking into account the impaired liver function, a comparative analysis of patient survival showed the following changes: there were statistically significant differences of 6 month and one year survival, so the percentage of survival among patients in stage B on the Chile-Pugh scale was significantly low in patients with stage A (82% vs. 56% within 6 months and 50% vs. 31% during the one year, respectively). Moreover, one patient from the group with a violation of the liver function of stage A according to Child-Pugh lived up to 5 years.

The average AFP value was 399 *IU/ml* (12.7-60500 *IU/ml*), while the median rate was 63.8 *IU/ml* (Fig. 3). 34 patients were tested to determine the level of AFP in the blood, according to these data, the subjects were divided into 3 groups: group 1 - patients with normal values or with a slight increase of AFP (0-99 *IU/ml*), group 2d - 100-999 *IU/ml* and 3th group with a marked increase >1000 *IU/ml*.

In this category, patients with statistically significant differences were found in the group with a pronounced increase in AFP (>1000 *IU/ml)*, the Kaplan-Meier survival curve shows a survival rate of 0% after 18 months since the first TACE. Thus, it can be assumed that the level of AFP, in particular, a pronounced increase in its value correlates with a low survival rate.

We would like to note that in this study, the number and size of nodes, the presence of concom-

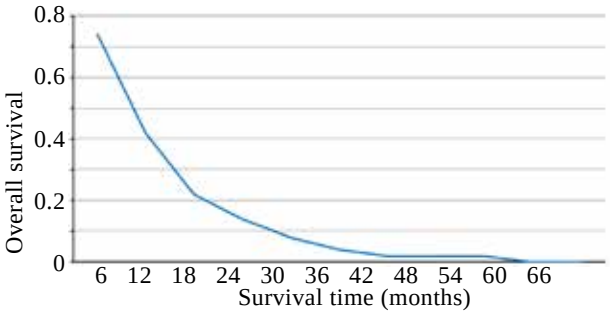

Figure 1. *Overall survival in total cohort (n=50)*

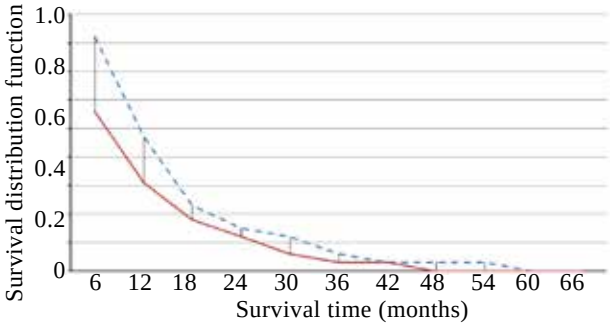

Figure 2. *Distribution by degree of liver function damage Drifting line - Child-Pugh A (n=34), Solid line - Child-Pugh B (n=16)*

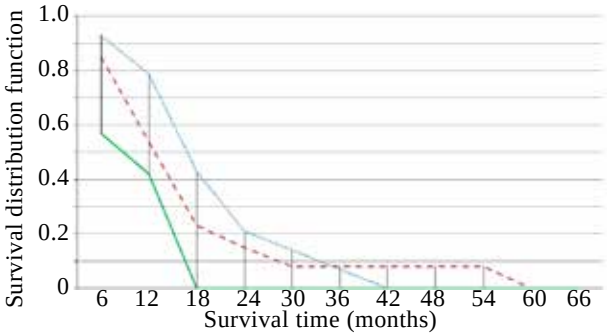

Figure 3. *Distribution by degree of alpha-fetoprotein (IU/ml) Dotted line - 0-99 (n=14), Drifting line - 100-999 (n=13) , solid line - >1000 (n=7),*

itant pathology and the cause of death of the patient were not taken into account, which requires additional observation.

CONCLUSION

Summarizing the above results, we concluded that, despite the small number of patients studied, TACE showed good results in the group among women, as well as life expectancy was higher in the group of middle age (50-59 years).

Elderly and senile age, a high degree of liver dysfunction, as well as high AFP values are additional factors that dramatically reduce the life expectancy of patients after TACE with HCC in stage B-BCLC.

Active discussions continue between surgeons, interventionists, therapists regarding the priority treatment options for intermediate stage HCC. Undoubtedly, only as a result of constant productive dialogue within a multidisciplinary group can the effectiveness of medical care be increased.

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