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EXPERIENCE OF LIVER TRANSPLANTATION IN CASE OF HEPATOCELLULAR CARCINOMA

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Abstract

Hepatocellular carcinoma is the most common type of malignant liver tumor. The article presents the experience of liver transplantation at the National Scientific Center of Surgery named after A.N. Syzganov in patients with hepatocellular carcinoma.

Present study aimed to analyze the results of liver transplantation in patients diagnosed with hepatocellular carcinoma, as well as to determine the effectiveness of liver transplantation in this pathology.

A retrospective and prospective study for the period from 2011 to 2017 includes 100 patients with chronic liver disease who underwent liver transplantation on the basis of the department of hepatobiliary surgery and liver transplantation. From this, 86 cases of liver transplantation were carried out from a live donor, while 14 patients performed liver transplantation from a post-mortem donor. In 7 cases, patients were diagnosed with hepatocellular carcinoma, in 3 cases the morphological verification of the diagnosis of hepatocellular carcinoma was determined after transplantation.

The mean value of alpha fetoprotein was 657.05 (2.35-3465) ng/ml, from which it was higher than normal only in 3 patients, and in 4 patients it was in normal limits. Hepatitis B virus + hepatitis D virus is diagnosed in 3 cases, positive hepatitis C virus is detected in 3 recipients, whereas in 1 case – hepatitis B virus. The average tumor size was 3.01 (1.0-5.5) cm. Transarterial chemoembolization was performed in two patients before the operation. In 2 cases, taking into account the high alpha fetoprotein values ≥ 1000 and 3465 ng/ml, a bypass system was used in performing hepatectomy. The histological material after transplantation corresponded to hepatocellular carcinoma, with predominance of the trabecular type of hepatocellular carcinoma. The lethal outcome was in one case due to a vascular complication in the early postoperative period.

Despite the small number of patients, the results obtained by us testify to the high efficiency of liver transplantation in patients with hepatocellular carcinoma.

Keywords: *liver transplantation, hepatocellular carcinoma, liver cirrhosis*

Introduction

The incidence of cancer is increasing worldwide. Each year there are 10.9 million new cases of cancer and 6.7 million cancer-related deaths. The most commonly diagnosed cancers are lung, breast and colorectal cancle, while the most common causes of cancer death are lung, stomach, and liver cancer [*Bruix J et al., 2001; National Cancer Institute, 2010*].

Hepatocellular carcinoma (HCC) is the primary malignant tumor from hepatocytes. Annually, more than 600.000 people die from HCC all over the world [*Ferenci P et al., 2010*].

Hepatocellular carcinoma is the sixth most fre-

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quent malignant tumor in the world; the fifth in frequency in men and the eighth in women. It is the third most frequent cause of death from cancer, after lung and stomach cancer. Hepatocellular carcinoma is the most frequent malignant growth in parts of Africa and Asia [*Sangiovanni A et al., 2006*].

Cirrhosis is an important risk factor for HCC, and may be caused by chronic viral hepatitis, alcohol, inherited metabolic diseases such as hemochromatosis or alpha-1-antitrypsin deficiency and non-alcoholic fatty liver disease. All etiologic forms of cirrhosis may be complicated by tumor formation, but the risk is higher in patients with hepatitis infection. Overall, one-third of cirrhotic patients will develop HCC during their lifetime [*El-Serag H et al., 2001*]. Obesity, diabetes and fatty liver disease have come to be recognized as a cause of HCC [*Marrero J et al., 2005; Trichopoulos D et al., 2011*], although the mechanisms by which these overlapping conditions contribute to cancer development remain elusive. Cirrhosis due to non-alcoholic steatohepatitis may give rise to HCC but it appears that these factors may also be additive to chronic viral hepatitis [*Marcellin P et al., 2008*]. Epidemiologic evidence of a link between cigarette smoking and the occurrence of HCC was traditionally conflicting [*Nurgaziyev K et al., 2014*], but recent evidence support that smoking is a clear co-factor [*EASL-EORTC Clinical Practice Guidelines, 2012*]. Heavy smokers have a higher risk than non-smokers. In the general population, the incidence of HCC is increased among patients with HIV infection compared to controls, and HIV appears to be an additive co-factor, exacerbating the risk of HCC in patients with chronic viral hepatitis [*Choti M, 2009*].

In Kazakhstan, the detectability of liver cancer is low – 15 ranked. In the structure of mortality, liver cancer ranks the 8th. The specific gravity of the I-II stages in the diagnosis is 8.7%, the lowest among all cancers. Five-year survival rate is in 31.8% – the lowest among all malignant neoplasms [*Sotiropoulos G et al., 2009*].

Hepatocellular carcinoma develops in patients with hepatitis and liver cirrhosis associated with hepatitis B, C, D viruses, non-alcoholic fatty disease, autoimmune and cholestatic diseases, hemochromatosis, Wilson-Konovalov's disease, alpha 1-antitrypsin deficiency [*Salgia R et al., 2014*].

Primary prevention of HCC can be achieved with universal vaccination against hepatitis B virus infection [*Study Group, 2009*]. Vaccination against hepatitis B is recommended to all newborns and high risk groups, following the recommendations of the World Health Organization [*WHO, 2009*]. Since perinatal or early postnatal transmission is an important cause of chronic hepatitis B virus infections globally, the first dose of hepatitis B vaccine should be given as soon as possible after birth, even in low-endemicity countries (those with prevalence of HBsAg carriers <2%). Vaccination is also recommended in age-specific cohorts (young adolescents) and people with risk factors for acquiring hepatitis B virus infection (i.e. health workers, travelers to areas where hepatitis B virus infection is prevalent, injecting drug users, and people with multiple sex partners).

Two randomized controlled trials have been published on HCC surveillance. In one population-based study cluster randomization (randomizing entire villages) was performed comparing surveillance (ultrasound and alpha fetoprotein measurements every 6 months) versus no surveillance in a population of Chinese patients with chronic hepatitis B infection, regardless of the presence of cirrhosis [*Zhang B et al., 2004*]. Despite suboptimal adherence to the surveillance program (55%), HCC-related mortality was reduced by 37% in the surveillance arm as a result of increased applicability of resection in detected cases. The other alpha fetoprotein-based surveillance study carried out in Qidong (China) in high-risk individuals (males, HBsAg+) did not identify differences in overall survival [*Chen J et al., 2003*].

Nowadays, liver transplantation in case of HCC is a surgical treatment with a long-term effect in patients with HCC and with cirrhosis, because it offers the possibility of treating a tumor and underlying liver disease. The issue of liver transplantation, in the treatment of HCC, for a long time remained controversial [*EASL-EORTC Clinical Practice Guidelines, 2012*]. In the case of a long waiting time by the recipient of the donor (more than 6 months), resection, local ablation or transarterial chemoembolization is recommended to minimize the risk of tumor progression and offer a "bridge" for transplantation.

The study was aimed to analyze the results of liver transplantation in patients diagnosed with

Table 1.

Features of recipients

Recipient	LDLT (n=86)	DDLT (n=14)
Age	40.7 (0.5-61)	37 (21-52)
Sex (M/F)	33/53	3/11
Body mass index	22.1 (15.5-28.4)	22 (16-26.3)
Model for end-stage liver disease score	16.7 (9-32)	15 (12-31)
Child Pugh score	11.01 (7-15)	8.8 (7.5-8.12)
Standard liver volium (*ml*)	1084 (961-1184)	1278.1 (1103-1497)
Hepatocellular carcinoma	6	1

HCC, as well as to determine the effectiveness of liver transplantation in this pathology.

Material and methods

A retrospective and prospective study for the period from 2011 to 2017 includes 100 patients with different etiologies who underwent liver transplantation on the basis of the Department of Hepatobiliary Surgery and Liver Transplantation of the National Scientific Center for Surgery named after A.N. Syzganov. From these, 86 cases of liver transplantation were performed from a living donor liver transplant, while 14 patients (deceased donor liver transplantation) (Table 1) performed liver transplantation from a postmortem donor. In 7 cases patients (average age was 54 (51-55), 4 male, 3 female) were diagnosed with HCC, in 3 cases the morphological verification of the diagnosis of HCC were determined after transplantation (Table 2**).**

Laboratory tests were conducted for all patients: alpha-fetoprotein (Electro-chemiluminescence immunoassay, in-vitro quantitative determination of α1-fetoprotein in Human serum and plasma, Cobas e411, Roche, Germany), total bilirubin (Cobas c 501 module, Diazo dye-based assay, Roche, Germany), alanine aminotransferase and aspartate aminotransferase (Cobas c 501 module, Test ALTL, test ID 0-495 and Test ASTL, test ID 0-494 acc. to IFCC without pyridoxal phosphate activation, Roche, Germany); as was instrumental investigation: computer tomography (Aquilion/CXL 6, model name: TSX-101A, Toshiba, Japan), immunological assay for hepatitis B virus and hepatitis C virus (Immunoassay in vitro qualitative detection of total antibodies to hepatitis C virus in human serum or plasma and hepatitis B core antigen, Antibody to hepatitis C virus and Antibodies to hepatitis B core antigen, Cobas e411, Roche, Germany) and biochemical and histological analysis of liver tissue or tumor specimen before or after intervention treatment according to international criteria.

Clinical and laboratory studies. All of the tested ones underwent the following clinical and laboratory studies: alpha-fetoprotein, total bilirubin, alanine aminotransferase, aspartate aminotransferase, total protein, primary tumor volume and primary tumor inflammation, hepatitis B virus, hepatitis C virus, hepatitis D virus.

Instrumental investigations. The main instrumental method of investigation was computed tomography with contrasting organs of the abdominal cavity. Endomedeoeducations were conducted to exclude the concomitant pathology or onco-process of the organs of the gastrointestinal tract.

Morphological studies: Pieces of tissue were

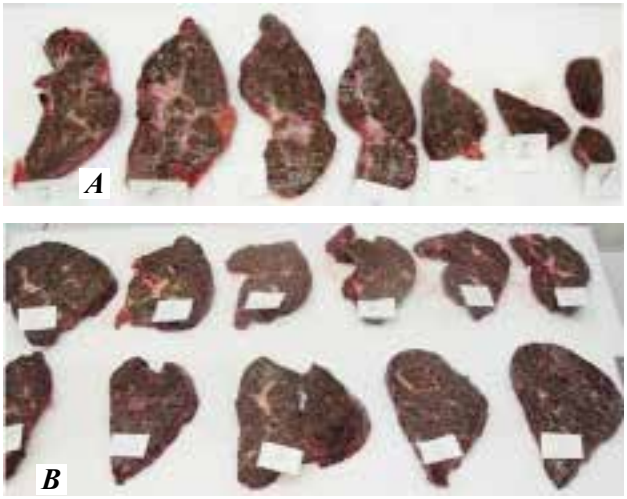

Figure. 1. *Histological material of the left (**A**) and right lobe (**B**) of the liver.*

Table 2.

The laboratory data of recipients with HCC

	Hepatitis	Tumor-node metastasis	Stres (*cm*)	AFP (*ng/ml*)	Bilirubin (μmol/ml)	Totaiprotein (*g/l*)	ALT (*U/l*)	AST (*U/l*)	PT (%)
1.	HCV	pT3pN0pM0 G2	5.5	12.41	50	66	34	73	62
2.	HBV+HDV	pT2pN0M0 G2	1.6	13.32	32	56	23.4	52	88
3.	HBV	pT1pN0pM0 G2	1.6	99.76	46	59	32	71	58
4.	HCV	pT1pN0pM0 G2	3.7	1000	30	63.4	95	103	55
5.	HBV+HDV	pT2pN0M0 G2	2.0	2.33	55	59	79	87	44
6.	HBV+HDV	pT3pN0pM0 G2	5.0	3465	29	68.3	18.6	43	124
7.	HCV	pT1pN0M0 G2	2.2	8.9	101.8	67.3	40	59	63

Note: Tumor-node metastasis; AFP - alpha fetoprotein; ALT - Alanin transferaza; AST - Aspartat transferaza; PT - Prothrombin time

cut out on a board for cutting biological material (Fig. 1 a, b). Pieces were fixed in a 10% solution of neutral formalin. From the preparations, the pieces with the most altered macrostructure were cut out, taking into account the recommendations of the College of American Pathologists protocols in compliance with generally accepted standards.

The study protocol was approved by our Institutional Local Research Ethics Committee (26/06/2016), and the study protocol was developed by conforming with the ethical standards of the Declaration of Helsinki (Br. Med. J. 1964; p.177). All participants in the study submitted informed consent.

All analyses were conducted with SPSS software version 18.0 and MedCalc. A Z-statistic, Chisquared ($\chi 2$), with a relative p-value of <0.05 was used to determine significance. Continuous data are presented as mean standard deviation or median and categorical data are presented as frequency in percentages.

Results

Results of clinical and laboratory studies. Based on our results, the average alpha-fetoprotein value was 657.05 (2.35 to 3465) *ng/ml*, while in 4 patients its level remained within the normal range, and the remaining 3 had a multiple increase in the mean value. Also in subjects with the help of enzyme immunoassay the positive result of hepatitis B virus + hepatitis D virus was revealed in 3 cases, positive hepatitis C virus was diagnosed in 3 recipients, whereas in 1 case only hepatitis B virus was detected. The average value of total bilirubin in the patients was 49.1 μmol/*ml*, while the total protein was 62.7 *g/l*. Table 2 presents the detailed characteristics of each recipient.

Results of instrumental investigation. Diagnosis – hepatocellular carcinoma is established by means of multiphase computer or magnetic resonance imaging. According to the studies, the protocol of multiphase computer tomography with bolus injection of contrast medium should include 4 standard scanning phases (native, late arterial, portal and delayed phases), the amount of CV is introduced according to the concentration of the drug used per *kg* of body weight [*Tanabe M et al., 2016*]. The quality of the research depends on the correct interpretation of the data.

In the department of Radiodiagnostics, JSC "National Scientific Center of Surgery" after A.N. Syzganov a CT scan was performed at the 64th MSCT of Toshiba (Japan) with bolus contrasting to 7 patients with hepatocellular carcinoma of the viral etiology.

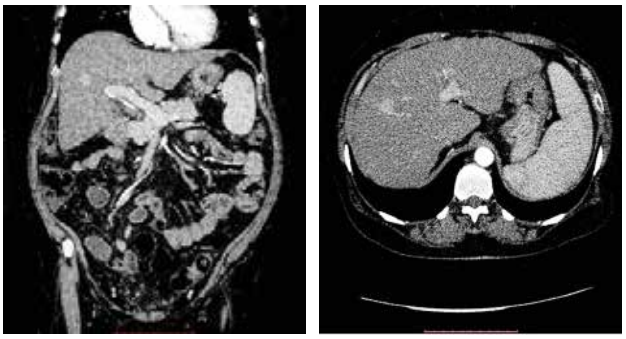

Figure 2. *The patient (female) K., 1966. In the SVIII projection of the liver, the presence of formations (2) is noted, intensively, nonuniformly accumulating the contrast substance in the arteriovenous phase, d 1.6 cm and 0.9 cm, density +34 - +36 units.*

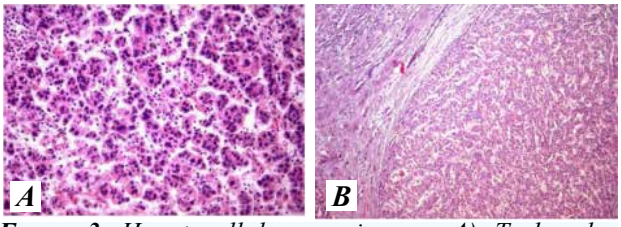

Figure 3. *Hepatocellular carcinoma:* ***A)*** *Trabecular variant. Stained with hematoxylin and eosin, enlargement 100/200;* ***B)*** *A compact variant. Stained with hematoxylin and eosin, enlargement 400*

The average size was 3.08 (1.0-5.5) *cm* (Fig. 2). Below is a description of the CT scans of the recipient with HCC. Concomitant pathology: Ascites. Varicose veins of the n/3 esophagus, around the stomach. Adenopathy of para-aortic lymph nodes. Cholelithiasis. Involuntary changes in the uterus and appendages.

Morphological studies. Based on the results of morphological studies, a slice of 6 patients showed a trabecular variant of HCC, whereas in 1 case a compact variant (Fig. 3 A, B).

The tactics of surgical treatment were determined according to the Milan criteria. In our center, all patients with HCC diagnosis had a related transplantation of an intravital liver donor, of which, in 4 cases, the right lobe and 3 patients were transplanted to the left lobe of the liver, respectively. Transarterial chemoembolization was performed in two patients before the operation. In 2 cases, taking into account the high alpha fetoprotein values ≥1000 and 3465 *ng/ml*, a bypass system was used in performing hepatectomy. From the concomitant pathologies, a cytomegalovirus infection was detected in 1 case, as well as a positive human IgG and IgM herpes virus was diagnosed in 1 recipient. In 1 case there was a fatal outcome of a patient with HCC after liver transplantation in connection with vascular complications. Nowadays, the remaining 6 recipients are alive, moreover, after liver transplantation, tumor recurrence was not observed in these patients. During the post-transplant period, all patients undergo a quarterly clinical and instrumental examination.

Discussion

According to clinical and laboratory studies, there is a weak correlation between alpha fetoprotein levels and the presence of a diagnosis of HCC, but a limited number of patients with this diagnosis do not allow predict only from the results of clinical trials. At the stage of radiation diagnosis, knowledge of the structural features of these neoplasms can facilitate their correct interpretation during the study.

It is shown that the life expectancy of patients inversely correlates with the size of the nuclei of tumor cells [*Sears R et al., 1998*]. The relationship between the increase in the size of the cell nuclei and the degree of differentiation of the hepatic carcinoma is noted: the degree of malignancy of the tumor increases with an increase in the nuclear area [*Pollice L, Zito F, 1989*].

Analysis of life expectancy after liver transplantation indicates a high effectiveness of this intervention in most terminal liver diseases [*Khubutia* M *et al., 2010*]. According to some data, the 5-year survival after liver transplantation in patients with various diseases varies from 58% to 71%, which indicates the high effectiveness of this method of surgical treatment, however, the results of life-span in recipients diagnosed with HCC after transplantation are not presented [*Rahbari N et al., 2011*].

Conclusion

Accurate histomorphological diagnosis of HCC after surgical treatment has a valuable prognostic significance. Precision thorough examination of the entire liver tissue, histological examination for the detection of formations in the postoperative period, predicts the frequency of detection and relapse of the tumor and improves the long-term survival results.

Despite the fact that the information we provide is limited in connection with a small number of patients, our observations indicate a high efficiency of liver transplantation in patients with HCC.

It should be noted that the majority of recipients directly diagnosed with HCC, were operated in 2016-2017, respectively, to carry out an analysis of life expectancy in these patients is not possible Identification of molecular genetic prognostic factors and risk factors for more careful planning of the optimal treatment method is a promising direction for further study of this pathology.

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