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HEPATOCELLULAR CARCINOMA: DIAGNOSTIC CRITERIA AND SURGICAL TREATMENT

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Abstract

Hepatocellular carcinoma is the most frequent type of liver malignancy. ***Purpose:*** *To assess the prognostic value of morphological and immunological characteristics of hepatocellular carcinoma.* ***Material and methods:*** *Cross-sectional analysis of the prospective study was performed at the JSC National Scientific Center of Surgery, named after A. Syzganov, among 45 patients with HCC (19, 42.2%) and chronic liver disease (26, 44.4%). The average age of the patients was 44.6 ± 2.9 years. The patients with hepatocellular carcinoma underwent surgical liver resection and radiofrequency ablation, and transarterial chemoembolization, before living-donor liver transplantation.* ***Results:*** *A positive antibody titer for hepatitis B virus and hepatitis C virus as well as a double positive titer for hepatitis B virus and hepatitis C virus. Patients with elevated levels of alfa-fetoprotein, alanine aminotransferase, and total bilirubin were detected. Morphological signs of hepatocellular carcinoma with a predominance of a trabecular hepatocellular carcinoma type rather than a solid type of tumor were found. Living-donor liver transplantation was performed on five (26.3%) patients with hepatocellular carcinoma according to the Barcelona clinic liver cancer stage (0–1) and cirrhosis (Child–Pugh A or A-B) after transarterial chemoembolization procedures. Liver resection was performed on five (26.3%) patients with hepatocellular carcinoma. One-year survival rate was 89.5% in patients with hepatocellular carcinoma. Survival of less than 1 year was observed in 2 (10.5%) cases after repeated transarterial chemoembolization among patients with hepatocellular carcinoma. Conclusions: The diagnosis and determination of the tactics of surgical treatment of hepatocellular carcinoma should be studied, taking into account the expanded laboratory characteristics of cancer.*

Keywords: *hepatocellular carcinoma, cirrhosis, liver resection, transarterial chemoembolization*

Introduction

According to GLOBOCAN 2012, hepatocellular carcinoma (HCC) is one of the most common types of cancer, afflicting 7.93 per 100,000 of the population, of them 12.18 men and 5.25 women in Kazakhstan. Mortality from hepatocellular carcinoma is 7.57 per 100,000 of the population, of them 12.02 men and 4.87 women [*GLOBOCAN 2012*]. In Asia and Africa, the incidence of hepatocellular carcinoma, recording the greatest prevalence of hepatitis infection, is 120 per 100,000 [*Parkin DM, et al. 2005*].

Those with a combination of risk factors, chronic hepatitis B virus (HBV), and cirrhosis have a 100-fold increased risk of HCC. Approximately 5% to 30% with hepatitis C virus (HCV) will have chronic liver disease, and 30% of them will have cirrhosis and hepatocellular carcinoma [*Jin-Kyoung Oh, et al. 2012; Chen CJ, et al. 2006*]. A combination of alcohol abuse and chronic hepatitis C virus doubles the risk of hepatocellular carcinoma compared to hepatitis C virus infection alone. Fifty- to 60-year-old patients had the highest incidence. The age of liver cancer is 40 years old in Africa and 50 years old in Asia, significantly younger than worldwide [*Chen CJ, et al. 2006; Masao Omata, et al. 2017*].

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In Kazakhstan, for a long time, diagnostic and treatment issues have remained relevant to liver tumors [*Aliev, MA, et al. 1997*] due to the complexity of early diagnosis, chemotherapy's lack of effectiveness, cirrhosis's underlying primary disease, and the complexity of choosing treatment tactics with invasive methods [*Ting-Shuo H, et al. 2013*].

The purpose of this study is to assess the prognostic value of morphological and immunological characteristics of hepatocellular carcinoma.

Materials and methods:

This study uses cross-section analysis of prospective study among patients with hepatocellular carcinoma and chronic liver disease who have been treated in the Department of Hepatopancreatic Surgery from 2015 to 2017. Forty-five patients were treated; 19 (42.2%) had hepatocellular carcinoma, and 26 (57.8%) had other chronic liver disease. The patients included 25 (55.6%) women and 20 (44.4%) men. The average age of the patients was 44.6 ± 2.9 years. Nineteen patients had hepatocellular carcinoma at ages ranging from 34 to 70 years (58.1 ± 2.8), of them 63.2% men and 36.8% women. Patients with chronic liver disease gender characteristics numbered 30.8% male and 69.2% female (Table 1).

Laboratory tests were conducted for all patients: alfa-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: ultrasound (Philips iU22 Ultrasound Systems), computer tomography (Aquilion / CXL 6, model name: TSX-101A), immunological assay for HBV and HCV (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. Data were collected prospectively in the Institutional hepatocellular carcinoma Registry.

The tactics of surgical treatment (liver transplantation, resection, ablation and transarterial chemoembolization (TACE)) depends of morphological criteria HCC with or without liver cirrhosis and was determined according to the Barcelona clinic liver cancer (BCLC) staging of hepatocellular carcinoma and with apply Milan criteria.

In our center, interventions by transarterial chemoembolization conducts with the installation of a microcatheter *(Embocath 2.7 Fr)* on the coronary conductor *(Pilot 0.14–165 cm)* by introduction of the HepaSphere 50–100 μM and 2 ml *(50 mg)* of doxorubicin.

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. All participants in the study submitted informed consent.

All analyses were conducted with SPSS software version 18.0 and MedCalc. A Z-statistic, Chi-squared *(χ2)*, with a relative P-value of <0.05 was used to determine significance. Continuous data are presented as mean standard deviation or median,

Table 1.

The main features

	Hepatocellular carcinoma		Chronic liver disease		95% CI	Chi-squared
	n	%	n	%		
Patients (no)	19	42.2	26	57.8	16.4; 43.1	1.1
Age (yeas)	58,1±2,8		47.2± 3.2		9.2; 12.7	11.8*
Women (no)	7	36.8	18	69.2	15.6; 67.8	2.1
Men (no)	12	63.2	8	30.8	17.9; 67.9	1.9

*Statistical significance p≤0.05

and categorical data are presented as frequency in percentages. Comparisons of patients' characteristics and outcomes were conducted in the two groups of patients, those with hepatocellular carcinoma and those with chronic liver disease.

Results

The main group included twelve (63.1%) patients with hepatocellular carcinoma and liver cirrhosis, and seven (36.9%) patients with hepatocellular carcinoma without liver cirrhosis, whereas the control group included eleven (42.3%) with liver fibrosis, seven (26.9%) with primary biliary cirrhosis, three (11.6%) with autoimmune hepatitis and also five (19.2%) patients with cirrhosis for another causes.

Enzyme-linked immunosorbent assay detected antibodies with titer positive to HBV in 7 (36.8%) patients and HCV in 6 (31.6%) patients, of whom 1 (5.3%) patient had positive results for both HBV and HCV. Four patients with chronic liver disease showed antibodies with titer positive for HBV (15.4%), and four patients tested positive for HCV (15.4%) (Table 2).

The average mean of alfa-fetoprotein consisted is 22,2 ± 10,3 *U/ml*, under n=15, of whom only 7 (36.8%) patients had increased alfa-fetoprotein levels (41.1 ± 17.7 *U/ml*) of the patients with hepatocellular carcinoma. The alfa-fetoprotein values were statistically much higher than in the control group; the alfa-fetoprotein was within the norm of 3.9 ± 3.3 *units/ml*, in 24 patients, the difference in value of alfa-fetoprotein, (z = 8.7, 95% CI:14.4 to 23.1, P value ≤0.05).

The mean values of alanine aminotransferase were 90.34 ± 13.14 *U/ml*, and aspartate aminotransferase values were 89.0 ± 11.9 *U/ml* in 19 patients, 12 (63.2%) patients had higher alanine aminotransferase levels (106.8 ± 13.9 *U/ml*) than the norm. Values of alanine aminotransferase and aspartate aminotransferase in patients with hepatocellular carcinoma were 77.3 ± 70.4 *U/ml* and 98.1 ± 79.6 *U/ml*, respectively, which are not statistically different.

The average value of total bilirubin was 23.17 ± 5.1 μmol/l in 19 patients with hepatocellular carcinoma, of them eight (42.1%) had a bilirubin level of 47.0 ± 12.4 μmol/l. Patients with chronic liver disease had a much higher level of total bilirubin, at 59.8 ± 10.4 μmol/l, which was statistically meaningful in patients with chronic liver disease (z = 8.7, 95% CI: 14.4 to 23.1), P value ≤0.05.

Ultrasound detected signs of ascites in eight (42.1%) patients hepatocellular carcinoma and cirrhosis, and tumor size more than 5.5 × 5.5 cm (>50% parenchyma) in six (31.6%) patients before intervention.

Morphological data was characterized for hepatocellular carcinoma signs, with a predominance of 18 (94.7%) trabecular HCC type over one (5.3%) solid tumor type. Stromal germinating, tumor cell invasion in portal vessels, and the presence of dysplastic lesions were noted. Degree of malignancy according to the Edmondson-Steiner system was defined in four (21.1%) patients as Grade I; eight (42.1%) patients as Grade II; five (26.3%) patients as Grade III; and two (10.5%) patients as Grade IV.

Table 2.

Clinical characteristics

	Hepatocellular carcinoma		Chronic liver disease .		95% CI	Significance level
	n	%	n	%		
HBV	7	36.8	4	15.4	44.3; 64.7	0.5
HCV	6	31.6	4	15.4	48.6; 63.6	0.3
HBV + HCV	1	5.3	-	-	-	-
AFP (*U/ml*)	22.2±10.3		3.9±3.3		14,4; 23,1	8.7*
Bilirubin (*μmol/l*)	23.0±5.1		59.8±10.4		14.4; 23.1	8.7*
ALT (*U/ml*)	90.3±3.1		77.3±70.4		47.7; 21.7	0.7
AST (*U/ml*)	89.0±11.9		98.1±79.6		29,4; 45,0	0.4
Total protein (*g/l*)	71.4±1.4		65.0±10.0		1.7; 11.1	2.7*

*****Statistical significance p≤0.05

Surgical treatment

Twelve (63.2%) patients had clinical signs of hepatocellular carcinoma and cirrhosis (alfa-fetoprotein: 5.21 ± 1.7 *U/ml*, alanine aminotransferase: 46.5 ± 26.7 *U/ml*, and total bilirubin 17.8±4.5 *μkmol/l*, histomorphology showed hepatocellular carcinoma involving the right lobe of the liver, with extensive necrotic areas of solid structure and areas of fibrosis; F I, HAI 5 points; pT3a, p Nx1 p Mo Ro G3) TACE was performed. (Figure 1, archived liver resection). Two (10.5%) patients, who underwent right-side laparotomy by Chernii, had a cholecystectomy with right lateral sector resection and drainage of the pelvic cavity and right sub-diaphragmatic space. One (5.3%) patient had a cholecystectomy right-side laparotomy by Fedorov's, method, atypical liver resection of V-VI Sq. In addition, with subsequent drainage of the abdominal cavity, the radiofrequency ablation VIII Sg intraoperative procedures were implemented.

One patient (5.3%) had cirrhosis by Child–Pugh score but had clinical signs of hepatocellular carcinoma (alfa-fetoprotein: 7.3 *u/ml*, alanine aminotransferase: 34.0 *u/ml*, and total bilirubin 20.0 *μkmol/l*, Ultrasound detected liver's diffuse fibrotic change by type of cirrhosis, with a space-occupying lesion in the left lobe of the liver). The strategy of surgical treatment was to perform a laparotomy of the left lobe resection of the liver, followed by drainage of the abdominal cavity. Histomorphology data had shown the left lobe of the liver with hepatocellular carcinoma with necrosis in extensive areas, massive hemorrhage, and vascular infestation (Edmonson-Steiner Grade 2); Fibrosis degree F 1–6 points (cirrhosis).

One patient (5.3%) had clinical signs of hepatocellular carcinoma (alfa-fetoprotein: 172.6 *u/ml*, alanine aminotransferase: 98.0 *u/ml* and total bilirubin 85.0 *μkmol/l* and magnetic resonance imaging showed hepatocellular carcinoma in the left lobe of the liver). Upper-median laparotomy and left-sided hemihepatectomy with drainage of the sub-hepatic space were performed. Histomorphology corresponded to moderately differentiated intrahepatic cholangiocarcinoma with abundant area of disintegration and invasion of G2 vessels (Stage 2).

Living-donor liver transplantation was performed on five (26.3%) patients with hepatocellular carcinoma according to the BCLC stage (0–1) and cirrhosis (Child–Pugh A or A-B) after transarterial chemoembolization procedures.

Transarterial chemoembolization was performed repeatedly at intervals of 4 to 6 months five times for one (5.3%) patient; twice for four (21.1%) patients; three times for two (10.5%) patients; and one time for 10 (52.6%) patients (Figure 2).

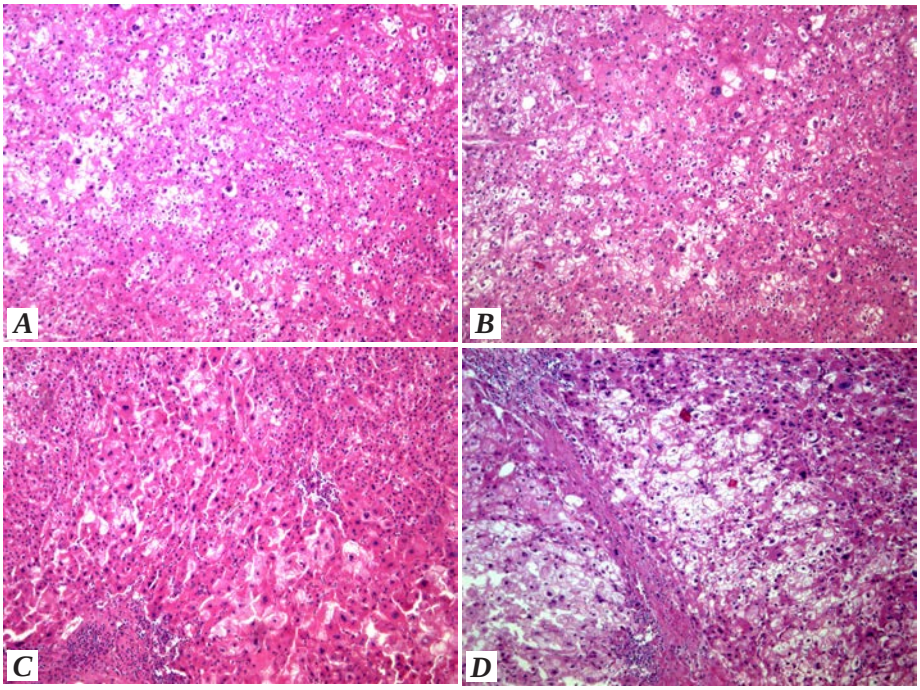

Figure 1. *Hepatocellular carcinoma. A – Tumor cells have larger hyperchromic nuclei.* ***B*** *- The nuclear-cytoplasmic ratio is high;* ***C*** *- Tumor cells's Cytoplasm is granular, have not bile pigment; D - in vascular spaces have separate groups of cells, small foci of necrosis. Degree of malignancy According to the system Edmondson, Steiner - Grade III. (Hematoxylin & Eosin staining. Magnification x200)*

Seven (36.8%) patients had clinical signs of HCC (AFP: 35.5 ± 11.3 u/ml, ALT: 80.6 ± 11.9 u/ml, and total bilirubin 26.2 ± 5.2 μkmol/l), and TACE was performed

One-year survival rate was 89.5% in patients with hepatocellular carcinoma. Survival of less than 1 year was observed in 2 (10.5%) cases after repeated transarterial chemoembolization among patients with hepatocellular carcinoma.

Discussion

Patients in groups at high-risk for development of hepatocellular carcinoma (cirrhosis carries of HBV, patients without cirrhosis with high concentration HBV, patients with HCV-associated or alcohol cirrhosis of the liver) should be included on special monitoring programs for early detection of hepatocellular carcinoma if they are amenable to surgical treatment. Using ultrasound monitoring should be done every 6–12 months, in combination with alfa-fetoprotein monitoring [*Masao Omata, et al. 2017*]. However, we don't have any evidence that early detection of the disease improves patient survival with a Child–Pugh B and C cirrhosis [C*hen CJ, et al, 2006*].

Liver resection R0 (tumor-free marginal resection) surgical treatment should be first in patients with localized and operative tumors but no cirrhosis, or in patients Child–Pugh A with cirrhosis; in 54% of patients with hepatocellular carcinoma, a non-cirrhotic liver provides three-year survival, according to some data in the literature.

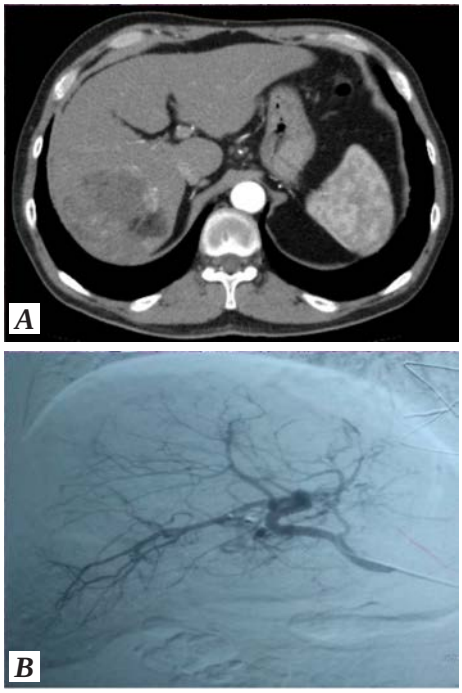

Figure 2. *Transarterial chemoembolization.* ***A*** *- abdominal computer tomography: right lobe of the liver formation size 8.0x7.2x7.5 sm. Right lobe hepatocellular carcinoma;* ***B*** *- transarterial chemoembolization of the right lobe liver formation.*

Today, hepatocellular carcinoma liver transplantation is a surgical treatment method with long-term impacts for patients with hepatocellular carcinoma and cirrhosis, because it offers the possibility to tumor and the main disease treatment, although hepatocellular carcinoma treatment issues in liver transplantation are very controversial [*Michael A. Choti 2009; Sotiropoulos GC, et al. 2009*]. Patients with a single node less than 5 cm or three nodes smaller than 3 cm that are not suitable for resection are encouraged to have liver transplantation. These Milan criteria guarantee a five-year survival rate and a disease-free overall survival rate of more than 65% [*Sotiropoulos GC, et al. 2009*]. In cases when recipients have waited for a donor for a long time (more than 6 months), they are encourage to undergo resection, local ablation, or transarterial chemoembolization to avoid tumor progression risk and to offer a bridge to transplantation [*Reena JS, et al. 2014*].

Transarterial chemoembolization for hepatocellular carcinoma with cirrhosis, or palliative care, are generally accepted standard treatments, like bridge treatments when waiting for transplantation. Transarterial chemoembolization is the intra-arterial injection of a combination of cytotoxic drugs (doxorubicin and/or cisplatin and/or mitomycin) into the hepatic artery, accompanied by injection of Lipiodol for vessel occlusion [*Mario S, et al. 2010; Mituo S, et al. 2008*]. Based on the local distribution of disease and functional liver reserve, transarterial chemoembolization can be provided through a microcatheter as a fully selected or super-selective treatment. Contraindications for transarterial chemoembolization are Child-Pugh B score ≥8; Child–Pugh C cirrhosis; the existence of multifocal, bilobar tumor dissemination; extrahepatic metastases; portal vein thrombosis or arterioportal fistula; and creatinine clearance <30 ml/min [*Jiazhi Li, et al. 2017*]. Transarterial chemoembolization is to be recommended to patients for hepatocellular carcinoma BCLC B stage without vascular invasion and extrahepatic metastases and multi-nodal asymptomatic hepatocellular carcinoma [*Mituo S, et al. 2008*].

Radiofrequency ablation is widely used as a palliative treatment for hepatocellular carcinoma or as a bridge before liver transplantation. The procedure is performed with ultrasound or computer tomography as well as during laparoscopic and open operations.

There are limitations compared with transarterial chemoembolization; it must be performed in the center under three nodes or node maximum diameter under 5 cm. Benefit is realized when 100% tumor necrosis is achieved, but that is very difficult to do [*Andrea V, et al. 2006; Benevento R, et al. 2011*].

Conclusion

The diagnosis and determination of the strategy for surgical treatment of hepatocellular carcinoma should be studied, taking into account the expanded laboratory characteristics of cancer.

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