

ORIGINAL ARTICLE

Evaluation of the significance of hepatic functional reserve for the operation of liver cancer complicated with cirrhosis

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Summary

Purpose: To evaluate the significance of hepatic functional reserve for the operation of liver cancer complicated with cirrhosis.

Methods: Fifty-six patients suffering from liver cancer complicated with cirrhosis were divided into three levels, A, B and C, according to Child-Pugh grading system. Based on indocyanine green retention rate at 15 min (ICGR₁₅) value, patients were divided into three intervals, $\leq 15\%$, 15-25% and $\geq 25\%$. According to the existence of complications, patients were divided into the complication group and the no complication group.

Results: Child-Pugh grading included 50 cases of level A, 45 cases of B and 29 cases of C. ICGR₁₅ value included 47 cases of $\leq 15\%$ interval, 47 cases of 15-25% and 30 cases of $\geq 25\%$. As the ICGR₁₅ value increased, the levels of all indicators were obviously increased. Among the 124 patients, 35

cases (28.23%) suffered complications. The median follow-up time was 25.0 months. The survival rate of the complication group was 60.00% (21 cases), significantly lower than that of the no complication group (84.27%). Child-Pugh grading of the complication group included 4 cases of level A, 12 cases of B and 19 cases of C. ICGR₁₅ value included 15 cases of 15-25% interval and 20 cases of $\geq 25\%$.

Conclusion: Child-Pugh grading and ICGR₁₅ value can both reflect hepatic functional reserve and are of great clinical significance for complication and survival. There is a fairly good relevance between ICGR₁₅ and levels of AFP, ALT and indicators of liver fibrosis.

Key words: Child-Pugh, hepatic functional reserve, ICGR₁₅, liver cancer, liver cirrhosis

Introduction

At present, surgical excision still serves as the main treatment for liver cancer complicated with cirrhosis. The rest liver of patients suffering of liver cancer complicated with cirrhosis has low regeneration ability and their hepatic functional reserve is damaged [1]. Good hepatic functional reserve can reduce postoperative damage to liver function, secure surgical success and serve as the key for reducing postoperative complications [2]. Therefore, correct evaluation of patient hepatic

functional reserve before operation is critical for a reasonable surgical plan, exact excision extension, increased survival rate and effective prevention of both damage to liver function and complications. Measurement of hepatic functional reserve uses Child-Pugh grading [3] and ICGR₁₅ [4]. Japanese authors, based on blood-oxygen theory, have invented PDD (Pulse Dye Densitometry), which can detect the concentration of indocyanine green in arterial blood in succession without trauma. This

method is easy and convenient and $ICGR_{15}$ value can be used to better evaluate the hepatic functional reserve [5].

This study has retrospectively analyzed the clinical data of liver cancer patients complicated with cirrhosis treated in our hospital. Besides, the application value of Child-Pugh grading and $ICGR_{15}$ for evaluating hepatic functional reserve were also analysed and discussed.

Methods

Patient data

124 patients suffering of liver cancer with cirrhosis treated with partial liver resection in our hospital from January, 2011 to January, 2016 were selected in succession. Preoperatively, patients had definite resectable tumor lesions and no metastasis outside the liver. Liver functions were corrected to normal levels. The operation was successful and the clinical data were perfect. Patients with metastatic tumor and basic diseases, such as organ dysfunctions of heart, kidney, lung and brain, were excluded. This study has been approved by the Ethics Committee of our hospital and informed consent was provided by the patients and their families.

Research methods

This research was carried out by the same team of operation and nursing staff and completed according to the Standard Medical Procedures. Patients were divided into three levels, A, B and C, according to their Child-Pugh grading. Also, based on $ICGR_{15}$ value, patients were divided into three intervals, $\leq 15\%$, 15-25% and $\geq 25\%$. According to the existence of complications, including ascites and pleural effusion, liver-renal functional dysfunction, alimentary tract hemorrhage and bile fistula, patients were divided into the complication group and the no complication group. Child-Pugh grading criteria: 5-6 was level A; 7-8 was B level; ≥ 10 was C level. Higher level suggested higher operation risk (Table 1).

Table 1. Child-Pugh grading criteria

Clinical Biochemical Index	1 point	2 points	3 points
Hepatic encephalopathy (level)	none	1-2	3-4
Ascites	none	light	Moderate-severe
Total bilirubin ($\mu\text{mol/L}$)	<34	34-51	>51
Albumin (g/L)	>35	28-35	<28
Prothrombin time extension(s)	<4	4-6	<6

$ICGR_{15}$ detection

DDG-3300K liver function analysis meter, purchased from Nihon Kohden, was used. ICG agents (25 mg/bottle) were purchased from Dandong Yichuang Pharmaceutical Co., Ltd. Before detection, 25 mg of ICG agents were diluted in 5 ml of sterile water for injection to make ICG solution concentration of 5 mg/ml. Patients should fast for 8 hrs and be asked if they had ever been allergic to iodine. When patients were at fasting status in the morning and rested at prone position, venipuncture was performed at one elbow to place intravenous needle and ICG was injected within 5s and the results of patient's weight (kg), height (cm) and hemoglobin concentration (g/l) were input into the analysis meter. Normal saline was applied for tube washing. Liver function detector calculated the $ICGR_{15}$ value automatically within 5 min.

Detection of AFP, ALT and liver fibrosis indicator

AFP, ALT and liver fibrosis indicator were detected preoperatively, including hyaluronic acid (HA), laminin (LN), procollagen peptide III (PIIIP) and collagen IV (CIV). AFP and liver fibrosis indicators were detected by radioimmunoassay. Kits were bought from Beijing North Biotechnology Institute. The equipment was FJ-2008P fully automated immunity analyzer (Xi'an Nuclear Instrument Factory). The reference range of AFP was $<20\mu\text{g/L}$. Twenty-five to $100\mu\text{g/L}$ was regarded as light increase, $100-500\mu\text{g/L}$ as moderate increase and $>500\mu\text{g/L}$ as high increase. The reference range of HA was $<110\text{mg/L}$; for LN it was $<130\mu\text{g/ml}$; for PIIIP it was $<120\mu\text{g/L}$; and for CIV it was $<75\mu\text{g/L}$. ALT was detected by standard fully automated biochemical detector and its reference range was $<40\text{IU/L}$.

Statistics

SPSS 20.0 software was used for statistical analysis and processing. Measured data was expressed by mean \pm standard deviation. One way ANOVA analysis was applied for comparison among groups. LSD-t testing was applied to pair comparison. Enumeration data was expressed by case (%). Chi-square test was applied for comparisons among groups. $P < 0.05$ was regarded as being statistically significant.

Results

Comparison among groups in the baseline data of Child -Pugh grading

Baseline data of the three groups of Child-Pugh grading were comparable (Table 2).

Comparison of AFP, ALT and liver fibrosis indicators of $ICGR_{15}$ groups

Comparison among the three groups in their AFP, ALT, and indicators of liver fibrosis revealed statistical significance. As the $ICGR_{15}$ value increased, the levels of all indicators were obviously increased (Table 3).

Table 2. Comparison among groups in the baseline data of Child-Pugh grading

Group	A Level (n=50)	B Level (n=45) Mean ±SD	C Level (n=29)	F/x ²	p
Male/Female	27/23	23/22	16/13	0.137	0.934
Age (y)	53.6 ±7.4	54.2 ±6.9	53.8 ±7.5	0.162	0.867
Tumor maximum diameter (cm)	2.8±0.7	3.0±0.8	2.9±0.8	0.234	0.785
Tumor number	1.3±0.4	1.2±0.3	1.4±0.5	0.067	0.958
Operation time (min)	135.4 ±23.6	142.5 ±25.7	138.7 ±28.4	0.326	0.762
Intraoperative hemorrhage (ml)	326.8 ±32.6	346.5 ±35.7	352.6 ±42.5	0.267	0.834
Postoperative drainage (ml)	452.4 ±43.5	462.7 ±45.7	482.5 ±48.3	0.432	0.569

Table 3. Comparison of AFP, ALT and liver fibrosis indicators of ICGR₁₅ groups

Group	≤15% (n=47)	15-25% (n=47) Mean ±SD	≥25% (n=30)	F	p
AFP(μg/L)	653.9 ±72.4	824.4 ±84.3	1232.5 ±156.3	8.234	0.000
ALT(IU/L)	56.2 ±8.3	72.8 ±10.2	94.2 ±13.4	7.352	0.013
HA(mg/L)	132.6 ±32.5	175.4 ±42.3	232.5 ±47.8	7.128	0.016
LN(μg/ml)	156.7 ±42.6	182.9 ±48.7	231.5 ±52.3	6.598	0.022
PIIIP(μg/L)	142.3 ±32.5	166.5 ±36.6	189.7 ±38.7	5.867	0.030
CIV(μg/L)	86.7 ±13.5	113.2 ±21.3	154.6 ±25.7	6.237	0.025

For abbreviations see text

Comparison of complication incidence

Among 124 patients, 35 developed complications, including 12 cases of severe pleural effusions or ascites, 10 cases of liver and/or renal dysfunction, and 7 cases of bile fistula. The follow-up time ranged from 5 to 40 months (median 25.0). The overall survival rate of the complication group was 60.00% (21/35), significantly lower than the no complication group (84.27%,75/89), with statistically significant difference ($\chi^2=8.464$, $p=0.004$). The Child-Pugh grading of the complication group included 4 cases of A level, 12 cases of B level, and 19 cases of C level. ICGR₁₅ grouping included 15 cases of 15-25% interval, and 20 cases of ≥25% interval.

Discussion

Normal liver has relatively strong reserve and regeneration capabilities and is tolerant to excision of at least 70% of the liver volume [6]. However, liver tumor and liver cirrhosis can result in serious liver cell necrosis or apoptosis and poor regeneration capacity. Meanwhile, loss of regeneration conditions, including extracellular matrix components and various cytokines (like vascular endothelial growth factor) can result in insufficient regeneration capacity [7]. Insufficient preoperative evaluation of hepatic functional reserve and excessive excision of liver tissue may result in postoperative acute liver failure, various complications and poor prognosis [8].

ICG, a kind of blue dye, is non-toxic. It can be selectively absorbed by liver after intravenous injection and then be secreted to bile, with no participation of the enterohepatic circulation or internal chemical reaction. Meanwhile, ICG will not go through renal excretion. The speed of renal excretion of ICG can reflect the number of hepatic cell receptors, the liver cell metabolism function and can be applied for dynamic evaluation of hepatic functional reserve [9]. When the liver cell number and blood flow reduce, ICGR₁₅ is increased. When ICGR₁₅ is lower than 12%, a relatively large-scale of liver excision enjoys a higher level of safety [10]. This research concluded that according to Child-Pugh grading, baseline data among groups were not significantly different, but according to ICGR₁₅, A level group had relatively higher value (25%), while C level group had lower value (15%). Levels of AFP, ALT and liver fibrosis indicators among groups were increased as the ICGR₁₅ increased. To be mentioned, ICGR₁₅ can be used to better reflect the real-time metabolism function of the liver, and its detection is easy and convenient to be performed and can be applied to repeated quantitative detection. By great sample data analysis, the evaluation range can be assessed that can better meet the requirements of surgical excision to facilitate clinical dynamic analysis [11].

This research has found that if the patient has A level liver function and his ICGR₁₅ is ≤15% before operation, performance of large-scale liver excision is accompanied with far lower complication incidence compared with patients whose ICGR₁₅ is >15%, and this is in accordance with the basic ideas of Lodge [12]. When ICGR₁₅ <10%, two or more hepatic segments can be excised and the complication incidence can be reduced to the maximum extent. When ICGR₁₅ is between 10-20%, it is safe to cut one hepatic segment. Excision of more than two hepatic segments requires extreme

care and may increase the complication incidence. When $ICGR_{15}$ is $>20\%$, excision of one hepatic segment may be considered or the patients may be advised not to be subjected to surgical excision [13]. As $ICGR_{15}$ increases, patients with liver cancer complicated with cirrhosis become less tolerant to operation. Their liver functions are seriously damaged after operation and the complication incidence is significantly increased [14]. This research has concluded that the survival rate of the complication group is obviously lower than that of the no complication group. The Child-Pugh grading of the complication group included 4 cases of A level, 12 cases of B level and 19 cases of C level; the condition of $ICGR_{15}$ grouping included 15 cases of 15-25% interval and 20 cases of $\geq 25\%$ interval. To be mentioned, when $ICGR_{15} > 15\%$ interval, the complication incidence is the highest.

In addition, the detection of liver volume

is also an important indicator for evaluation of the preoperative hepatic functional reserve [15]. $ICGR_{15}$ can reflect the metabolic function of the liver and liver volume can reflect the liver cell number and volume. The combined detection of $ICGR_{15}$ and liver volume can reflect the general liver function more objectively and more efficiently, thus it can provide more complete information of the liver for surgical plans [16].

In conclusion, Child-Pugh grading and $ICGR_{15}$ value can both reflect the hepatic functional reserve and are of great clinical significance for evaluating surgical complications and survival results. There is a fairly good relevance between $ICGR_{15}$ and AFP, ALT and liver fibrosis.

Conflict of interests

The authors declare no conflict of interests.

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