



RAPID COMMUNICATION

Perioperative management of primary liver cancer

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Abstract

AIM: To minimize the complications and mortality and improve the survival in primary liver cancer (PLC) patients undergoing hepatic resection.

METHODS: We conducted a retrospective analysis of 2143 PLC patients treated from January 1990 to January 2004. The patients were divided into two groups using January 1997 as a cut-off. Small tumor size (< 5 cm), preoperative redox tolerance index (RTI), vascular control method, and postoperative arterial ketone body ratio (AKBR) were used as indicators of surgical outcome.

RESULTS: Small tumors had less complications and lower mortality and higher overall survival rate. Use of RTI for selecting patients and types of hepatectomy, reduced complications (21.1% vs 11.0%) and mortality (1.6% vs 0.3%). The half liver vascular occlusion protocol ($n = 523$) versus the Pringle method ($n = 476$) showed that the former significantly reduced the postoperative complications (25.8% vs 11.9%) and mortality (2.3% vs 0.6%) respectively, and cut mean hospital stay was 3.5 d. Postoperative AKBR was a reliable indicator of the energy status in survivors.

CONCLUSION: RTI is of value in predicting hepatic functional reserve, half liver occlusion could protect the residual liver function, and AKBR measurement is a simple and accurate means of assessing the state of postoperative metabolism. Optimal perioperative management is an important factor for minimizing complications and mortality in patients undergoing hepatic resection.

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Key words: Liver cancer; Hepatectomy; Optimal

INTRODUCTION

Primary liver cancer (PLC) is one of the most common malignant tumors in China. Its prognosis has been greatly improved due to the major advances in its clinical treatment and basic research since 1950's^[1]. Surgical resection is still the primary means of achieving long-term survival of PLC patients^[2-4]. Massive bleeding and liver failure are the leading risk factors in hepatic resection of PLC patients. The development of various effective vascular control measures^[5-7], thanks to the recent technical innovations, has reduced the number of patients with intraoperative massive hemorrhage. However, postoperative liver failure is still a major impediment to hepatic resection, especially in patients with compromised liver. Although a variety of methods for estimating hepatic function have been described, accurate prediction of hepatic functional reserve and assessment of postoperative risk remains a challenge^[8]. To establish a simple and practical system for assessing hepatic functional reserve to guide the decision-making process in treating PLC patients, we have conducted a systematic clinical study on hepatic energy metabolism since 1980s. This hepatic functional reserve predictive system is of value in terms of minimizing unnecessary invasive hepatic excision and designing optimal strategies for the perioperative and postoperative management of individual PLC patients.

MATERIALS AND METHODS

Patients

We reviewed the hospital records of all the hepatic tumor patients treated at the Department of General Surgery, West China Hospital, Sichuan University between January 1990 and January 2004. A retrospective analysis 2143 patients with intact records who were clinically diagnosed as PLC and underwent surgical treatment was conducted. The review covered sex, age, time of operation, diagnosis,

liver function test, kidney function test, hepatitis marker, tumor marker, arterial ketone body ratio (AKBR), redox tolerance index (RTI), Child-Pugh classification, preoperative management, preoperative evaluation, operation approach, postoperative measurement of AKBR, and therapy protocols. Postoperative clinical course, calculation of incidence of complications, operation mortality and evaluation of follow-up visits were also included. Operation mortality was defined as death during operation or within one month after operation.

Preoperative measurement of RTI

Each patient received 75 g glucose orally in the morning. Arterial blood samples were collected respectively at 30, 60, 90, and 120 min before and after the glucose intake. The following biochemical parameters including the levels of acetoacetate and β -hydroxybutyrate, AKBR, blood glucose, insulin and serum free fatty acids were measured as previously described^[9-12]. The corresponding data obtained were used to plot the oral glucose tolerance test (OGTT) and AKBR curve. The area covered by the respective curve (Δ OGTT and Δ AKBR) was calculated. The value of RTI was determined according to the following equation:

$$\text{ARTI} = \Delta\text{AKBR} / \Delta\text{OGTT} \times 5.6$$

The extent of liver cirrhosis and hepatic functional reserve were judged based on the measured value of RTI. A value of RTI > 0.65 predicted that damage to the liver was mild and the patient had a relatively good hepatic functional reserve and could tolerate various types of hepatectomy. A value of RTI < 0.65 indicated that damage to the liver was either moderate or severe and that the hepatic functional reserve of the patient was apparently compromised. For PLC patients undergoing hepatic resection in this category, special consideration needed to be taken with regard to the extent of hepatic resection. In case of RTI < 0.50, the patient would not be a suitable candidate for more than half liver resection and meticulous perioperative management care should be implemented.

Blood inflow occlusion of the half live

The procedure began with excision of the abdomen, and subsequent exposure of the hepatoduodenal ligament, followed by explorations proceeding upwards along the common hepatic duct until reaching the confluence of the left and right duct. On the visceral envelope overlying the confluence, a small hole was made using a sharp blade and a right-angle forceps was inserted to gently mobilize within liver parenchyma outside the Glisson sheath. To avoid damage to the portal vein and the small branches of caudate portal vein, the right-angle forceps should mobilize in the liver parenchyma towards the caudate lobe in such a way that there was no feel of resistance. Finally, the sharp ends of the forceps were passed through the confluence of the posterior branching part of portal vein and the caudate lobe, and an 8 gauge catheter was introduced. Vascular exclusion to the left or right half of the liver was achieved by tightening the catheter during hepatic resection^[13].

For hepatic resection involving no more than half the liver, the half liver occlusion technique was routinely

employed to keep the blood supply to the contralateral half and to minimize postoperative liver failure and complications^[5]. In cases that big liver tumors involving more than half the liver or tumors located in the middle part of, or crossing the left- and the right half liver or tumors encroaching the hepatoduodenal ligament or patients with apparent anatomic variations of the hilum hepatis, the whole liver vascular exclusion was used (Pringle method).

Regular postoperative measurement of AKBR

Measurement of AKBR and routine hepatic function tests were performed postoperatively on d 1, 3, 5, 7 until stabilization of the patient's condition. For patients developing postoperative complications, the monitoring time course was extended until stabilization of the patient's condition or death. The levels of AKBR were determined using a modified Mellamby approach^[5]. Briefly, all patients received intravenous injection of 10% glucose to allow the blood glucose level to reach at 6.72-11.2 mmol/L one hour later, followed by collection of 4 mL of arterial blood from each patient. The blood samples were centrifuged and 1 mL of blood plasma was collected, then 2 mL of 0.15 mol/L Ba(OH)₂ and 2 mL of 5% H₂SO₄ were gradually added. After mixing, the suspensions were centrifuged at 3000 r/min for 10 min and the supernatants were collected, then 0.15 mol/L Ba(OH)₂ was continuously added and thoroughly mixed until the solution became alkaline. The resultant solutions were put inside the modified distiller and distillates collected later. The amounts of acetoacetate and β -hydroxybutyrate in the collected distillates were respectively determined by salicylic acid colorimetric method and the arterial ketone body ratio was calculated^[14,15].

Patients were classified into three groups: group A including patients with a consistent postoperative AKBR > 0.7, group B with AKBR in the range of 0.4-0.7, group C with the level of AKBR gradually dropped to below 0.4 after operation. For postoperative therapy, standard treatment was applied to group A patients. Because of impaired hepatic function, group B patients received treatment with side chain-containing amino acids and long chain fatty acids and middle- and long chain fatty-containing cream, and large dose of Danshen injection (90 mL/d), as well as liver protection therapy to enhance the recovery of microcirculation in the impaired liver. Since patients in group C could utilize neither glucose nor fatty acids as substrates for energy production because of their severe liver dysfunction and deteriorated energy metabolism, they might ultimately die of the dysfunction of multiple organs. The patients in this group were difficult to treat and liver transplantation or temporal support by artificial liver could be a viable option.

Statistical analysis

Small tumor size, preoperative RTI, vascular control method, and postoperative AKBR were compared by the Wilcoxon tests in two groups. Survival analysis was performed to evaluate the impact of different variables. Cox model was used for univariate analysis,

Table 1 Operation approach for patients in two groups

Operative approach	Earlier period group (%)	Later period group (%)
Resection group		
Right trisectionectomy	6 (0.8)	19 (1.3)
Right hepatectomy	82 (11.2)	73 (5.2)
Right posterior sectionectomy	26 (3.6)	125 (8.9)
Right anterior sectionectomy	13 (1.8)	131 (9.3)
Middle sectionectomy	11 (1.5)	44 (3.1)
Left trisectionectomy	8 (1.1)	24 (1.7)
Left hepatectomy	27 (3.7)	129 (9.1)
Left lateral sectionectomy	31 (4.2)	88 (6.2)
Candate lobectomy	5 (0.7)	38 (2.7)
Segmentectomy	103 (14.1)	306 (21.7)
Total	312 (42.7)	977 (69.2)
Non-resection group		
Hepatic artery ligation or pump	251 (34.3)	143 (10.1)
Intro arterial ¹³¹ I resin form embolization	96 (13.1)	49 (3.5)
Intro-arterial ³² P-GMS embolization ¹	28 (3.8)	36 (2.5)
Cryosurgical ablation	24 (3.3)	82 (5.8)
Radiofrequency ablation	0 (0)	102 (7.2)
Laparotomy	20 (2.7)	23 (1.6)
Total	419 (57.3)	435 (30.8)

¹³²P-GMS: Phosphorus 32 glass microspheres; ARFA: Radiofrequency ablation.

which incorporates the quantitative variables assumed to determine the outcome. Statistical analysis was performed with SPSS software package.

RESULTS

General characteristics of the patients

Of the 2143 PLC patients undergoing surgical treatment between January 1990 to January 2004 in our institution, 1869 were men and 274 were women (male/female ratio: 6.8) with a median age of 46.3 (range 12 to 84) years. In 2037 cases of hepatocellular carcinoma (95.1%), 82 were found to have cholangiocellular carcinoma (3.8%), and 24 mixed type of both carcinomas (1.1%). In 1724 cases of cirrhosis (80.0%), 72% were HBsAg positive, 56.6% had their AFP ≥ 100 $\mu\text{g/L}$. A total of 1289 patients (60.1%) underwent hepatic tumor resection with an operative mortality of 1.6% (21/1289), and postoperative complications of 21.1% (272/1289). A total of 1198 (92.9%) patients were followed up for 6 mo -10.5 years. The 1-, 3-, and 5-year survival rate was 82.1%, 59.4%, and 37.6%, respectively. The remaining 854 cases underwent non-resection surgical treatment with a mortality of 2.1% (18/854), and complications were found in 19.9% (170/854). Operation approaches for all the patients are listed in Table 1.

Comparison of patients in two groups

Using January 1997 as a cut-off, the patients were assigned to two groups^[16]. The earlier period group (January 1990 to January 1997) contained 731 patients including 647 men and 84 women, their age ranged from 16 to 84 years (median 47.4). The tumor size was ≤ 5 cm in diameter in 52 cases (7.1%), and ≤ 3 cm in diameter in 19 cases (2.6%). A total of 312 patients (42.7%) underwent hepatic resection

Table 2 Comparison of mortality, complication, and survival rate in two groups after hepatectomy (%)

Group	Operative mortality	Complication rate	Survival rate		
			1 yr	3 yr	5 yr
Earlier period group	2.2	23.7	73.1	54.2	34
Later period group	1.4	20.3	84.9	61.1	38.7

and 419 (57.3%) received non-resection treatment. The later period group (January 1997 to January 2004) included 1412 cases (1222 men, 190 women, male/female: 6.4; age range 12 to 78 years, median 46.9). The tumor size was ≤ 5 cm in diameter in 298 (21.1%) patients and ≤ 3 cm in diameter in 183 (13.0%) patients. A total of 977 (69.2%) patients underwent hepatic resection, 435 (30.8%) received non-resection treatment. Operation approaches in the two groups of patients are listed in Table 1. Mortality, complications, and the 1-, 3- and 5-year survival rates are listed in Table 2. The mortality and complication rates after non-resection treatment were 2.1% and 22.6% in the first group, and 2.1% and 17.2% in the second group.

Measurement of RTI

RTI was measured in 336 patients, including 288 men and 48 women (age range 28-65 years, median 48.1). Operation approaches included hepatic lobectomy in 287 patients (left or right trisectionectomy in 9, left or right hepatectomy in 14, sectionectomy 112, segmentectomy in 152), hepatic artery ligation or pump in 49 cases. Of the 253 (75.3%) patients with a measured value of RTI ≥ 0.65 , 9 underwent left or right trisectionectomy, 14 left or right hepatectomy, 223 sectionectomy or segmentectomy, and 7 hepatic artery ligation or pump when the tumors were unresectable during operation. Postoperative complication rate was 10.3% (26/253), with no death occurred during operation. Of the 83 patients with a RTI < 0.65 , 41 underwent sectionectomy or segmentectomy, 42 hepatic artery ligation or pump. The postoperative complication rate was 13.3% (11.83) and one patient died of liver failure on d 29. The overall complication rate was 11.0% (37/336) and mortality rate during operation was 0.3%.

Half liver vascular occlusion

The half liver vascular occlusion protocol was employed in 523 (40.6%) of 1289 patients undergoing hepatic lobectomy. Of these 523 patients, 105 underwent either left or right hepatectomy, 418 sectionectomy or segmentectomy. The duration of the half liver occlusion ranged from 12 to 63 min, with a mean of 25.2 min. The amount of blood transfusion was 0 to 3200 mL, averaged of 306 mL. Three patients died after operation (1 due to hepatic failure, and 2 due to infection and MOF). The postoperative mortality was 0.6%, complication rate was 11.9% (62/523), postoperative hospital stay was 8-45 d (mean 18.2 d).

Of 476 patients undergoing hepatic resection using the routine Pringle procedure, 55 received either left or right trisectionectomy, 173 left or right hepatectomy, 42 middle sectionectomy, and 206 sectionectomy or segmentectomy.

The duration of blood occlusion was 11-48 min. Occlusion was performed twice in 37 cases, the mean duration was 24.8 min, the amount of blood transfusion was 0-3600 mL, averaged 383 mL. Postoperative complications were found in 123 cases (25.8%). The postoperative mortality was 2.3% (11/476), and postoperative stay was 8-45 d, averaged 18.2 d.

Regular postoperative measurement of AKBR was conducted in 635 cases (49.3%) undergoing hepatic resection. Based on the AKBR, 472 (74.5%) cases were assigned to group A, 149 (23.5%) to group B, and 13 (2.0%) to group C. The complication rate was 5.9% in group A ($n = 28$), 71.8% in group B ($n = 107$) with 1 patient died due to MOF (0.9%), and 100% in group C with a mortality rate of 69.2% due to infection and MOF.

DISCUSSION

PLC accounted for 95.1% of the 2143 cases, and 80.4% of patients were associated with cirrhosis, 72.0% were HBsAg positive, and only 56.6% were AFP positive, which are consistent with the reported results in China. Based on the outcome of this series, surgical treatment is still the primary choice of treatment for patients with liver cancer. The major progress made in PLC could be attributed to the following factors: (1) early diagnosis of hepatic tumor, as reflected by the higher percentage of cases with small tumor (< 5 cm in diameter) in the later period group than in the earlier period group (21.1% *vs* 7.1%); (2) increased percentage of patients with complete resection as evidenced by 42.7% in the earlier group compared to 69.2% in the later group; (3) long-term survival of liver cancer patients due to the improved perioperative management and refined surgical techniques; (4) improved safety and efficacy due to the implementation of standardized treatment protocol and development of non-resection treatment such as intra-arterial embolization, cryosurgical ablation, radiofrequency ablation.

Liver failure is the leading cause of postoperative death^[17]. There is still no reliable way for estimating hepatic functional reserve in diseased liver^[18-21]. Routine hepatic function test, assay of metabolic proteins and amino acids, clearance capacity test, excretion function test, liver blood in-flow measurement, etc, can only detect the specific function of liver and cannot be used to determine the tolerance of diseased liver to surgical resection. Since any activity of the liver requires consumption of energy and insufficient energy metabolism and compromise the liver function, our previous studies^[22,23] showed that OGTT and AKBR can be used to determine the energy metabolism status in the liver and thus are good indicators of hepatic function reserve. Therefore, we adopted the redox tolerance test (RIT), which reflects the changing pattern of OGTT and AKBR, to compare the diseased liver tissue preoperatively and postoperatively^[9,10], and the data of our current series further confirmed that RTI could reflect the hepatic functional reserve. Our predictive system for hepatic functional reserve is based on the following criteria: (1) when $RTI > 0.65$, the liver function is considered to be good or only mildly affects functional reserve and should be capable of tolerating

more than half the liver resection; (2) a value of $RTI < 0.65$ suggests either a moderate or severe liver tissue damage; (3) if $RTI < 0.5$, the hepatic function is judged to be substantially compromised, and the patients should not be suitable for more than half the liver resection. In this series, the system was used for estimating the residual hepatic functional reserve in 366 cases and for guiding the choice of resection type, resulting in marked improvement in complications from 21.1% to 11.0%, and mortality from 1.6% to 0.3, demonstrating that RTI is a valid indicator of hepatic functional reserve.

The Pringle maneuver under normothermic condition is still routinely employed in hepatic resection^[6], which tends to compromise the function of spared liver tissue, especially in patients with cirrhosis, eventually leading to high occurrence of liver failure^[17]. To overcome this drawback, based on observations through B ultrasonic wave and anatomical study of the hilum, we devised the half-liver vascular occlusion protocol in 1991^[5,13]. The subsequent use of this procedure in 63 patients undergoing hepatectomy, as opposed to 42 cases using the Pringle protocol, showed that half liver occlusion method being was superior to the whole Pringle procedure in terms of diminished adverse effects on energy metabolism in the liver and less invasive nature, and rapid postoperative recovery^[24]. The half liver blood occlusion does not require the dissection of porta hepatis, and a right-angle forceps is passed into the liver to introduce a catheter around the Glisson sheath to achieve vascular occlusion of the half liver, thus this procedure is simple, safe and can be easily adopted. Its benefit was better in 523 cases than that of the Pringle maneuver in 476 cases, as demonstrated by significant reduction in postoperative mortality (0.6% *vs* 2.3%) and complications (11.9% *vs* 25.8%) in patients undergoing hepatectomy. However, it was not until 2001 that Horgan *et al*^[7] proposed a similar protocol for partial vascular control, termed the half Pringle technique.

AKBR measurement and liver function tests were done in 93 patients after undergoing hepatectomy in our previous study^[15]. Based on the measured value of AKBR, the 93 patients were classified into 3 groups. Group A (AKBR > 0.7) had a postoperative complication rate of 4.8%, group B (AKBR 0.4-0.7) 39%, and group C (AKBR < 0.4) consisting of only 3 patients who died of MOF. However, routine live function test failed to show any significant differences in patients of the three groups, indicating that AKBR cannot reveal the degree of damage to the liver. In contrast, AKBR can reflect the redox status in liver mitochondria. The patients in group A had normal functional mitochondria and could utilize glucose for energy production, and metabolism was normal. The patients in group B with severely damaged liver function combined with the subsequent surgical stress, had impaired mitochondria and therefore could not efficiently utilize glucose for the entire energy need and could compensate for the insufficiency when fatty acids were used for energy production, dropping AKBR to 0.4-0.7. With proper management, the mitochondrial function could gradually recover and AKBR could increase to above 0.7 and the patients would recover gradually. If the function of mitochondria fails to recover, AKBR would drop to below

0.4, suggesting that damage to the mitochondria is severe and the oxidative phosphorylation process would stop and patients could use neither glucose nor fatty acids as energy substrates, and the energy metabolism would deteriorate, ultimately leading to multiorgan failure, MOF and death.

In this study, we continuously monitored the postoperative AKBR in 635 patients and the complication rate in groups A-C was 5.9%, 71.8%, and 100%, and the postoperative mortality was 0%, 0.9% and 69.2% respectively, demonstrating that continuous monitoring of AKBR levels can reveal the energy metabolism status and is a simple, sensitive and practical indicator of hepatic functional reserve and a valuable tool for the management and prevention of liver failure.

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