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• LIVER CANCER •

Total vascular exclusion technique for resection of hepatocellular carcinoma

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Abstract

AIM: To improve the low resection rate, poor prognosis and to control the massive hemorrhage during operation, total vascular exclusion (TVE) technique was used in hepatectomies of advanced and complicated hepatocellular carcinomas (HCCs).

METHODS: Five hundred and thirty patients with HCCs were admitted in our hospital. They were divided into TVE technique group (group A: n=78), Pringle maneuver method group (group B: n=176) and unresectable group (group C: n=276). The clinical, operative, pathological parameters and outcome of the patients were statistically evaluated.

RESULTS: Group A had a significantly higher resection rate than group B (accounting for 47.92 % and 33.21 % respectively). There was no significant difference in blood loss, blood transfusion and perioperative mortality between groups A and B. Both groups had the similar median disease free survival time (14.6 *vs* 16.3 months) and 1 year survival rate (92.9 % *vs* 95.5 %). The TVE group had a medial survival time of 40.5 months and its 5-year survival rate was 34.6 %.

CONCLUSION: As compared with Pringle maneuver method, the total vascular exclusion is a safe and effective technique to increase the total resection rate of advanced and complicated HCCs.

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INTRODUCTION

At present, operations including tumor resection and liver transplantation offer the only chance of cure for the patients with HCCs[1], and hepatectomy remains the normal choice when liver transplantation is not available. HCCs we met were mostly advanced with a low resection rate and had a high risk of lethal blood loss during operation as well as a high mortality after operation especially when the liver was affected by chronic hepatitis or cirrhosis[2-7]. To avoid excessive bleeding and blood transfusion, several methods to limit bleeding have been developed since hepatic portal clamping was successfully performed by Pringle in 1908, which led to the development of total vascular exclusion (TVE) of the liver by Heaney in 1966. Since then, Huguet and his colleagues have better characterized and widely advocated the use of TVE, which can greatly reduce the risk of massive hemorrhage and air embolism[8].

Pringle maneuver method is routinely used in hepatectomy to control blood loss during HCCs operation, TVE is there fore controversial. To the present, no study has documented its safety and efficacy as compared with Pringle maneuver method in resection of HCCs. This study was review our experiences with resection of HCCs by TVE and Pringle maneuver methods.

MATERIALS AND METHODS

Patients

From January 1994 to January 2002, 530 patients with HCCs were admitted in our hospital, they were divided into 3 groups. Group A: 78 patients with complicated HCCs underwent total vascular exclusive hepatectomies. Group B: 176 patients with HCCs underwent Pringle maneuver hepatectomies. Group C: 276 patients with unresectable HCCs underwent conservative treatments such as transhepatic artery embolization.

Diagnosis and vascular exclusion selection

HCCs were diagnosed by examinations such as serum tumor marker α-fetal protein, B-type ultrasound, plain or enhanced spiral computed tomography, magnetic resonance imaging before operation. The diagnosis was confirmed by pathologic examination after operation.

Pringle maneuver method was routinely used in the hepatectomy in our center, and the TVE was only used in advanced and complicated HCC patients such as massive tumors needing major hepatectomy, tumor closing or invading the major blood vessels of liver, tumor in the caudate lobe and multiple tumors.

Perioperative care and treatment

Preoperative care: A venous catheter was introduced one week before operation for routine parenteral nutrition to improve the patient' s liver function, nutritional status and coagulation condition. During perioperative care period, frozen plasma should be infused and blood transfusion must be strictly controlled. Blood loss and ascites production during the operation were balanced by infusing fresh frozen plasma. Intraoperative blood transfusion was given only if the hematocrit value was below 0.30. To prevent bleeding, hemostatic drugs such as fibrinogen and thrombinogen were always intravenously given. The main aim during the first few postoperative days was to restore the liver function and prevent hepatic failure. We used 20 % human albumin 100-200 ml/day to maintain the serum protein level. Glucose solution was given for the energy, and short-term antibiotics, histamine blockers were also administered. Appropriate oral intake was restored as soon as possible. The blood discharge from the drain was

carefully monitored. When bleeding exceeded 100 mL/h, an emergency laparotomy was performed. The patients were taken care of in an intensive care unit for the first 24 to 48 hrs with their the life signs inspected. Immediate postoperative treatments included hemostasis, prophylaxis antibiotic treatment and total parental nutritional support.

Operative technique

The surgical technique was described previously[2,8]. In general, a bilateral subcostal incision with or without an upward midline extension was used, and intraoperative ultrasound was routinely used to determine location of the tumor, or possible tumor modules in the contralateral lobe and the exact relationship between the tumor and the major liver blood vessels. In group A, all the hepatic ligaments were divided to allow complete mobilization of the liver and exposure of the whole retrohepatic vena cava. TVE was prepared by carefully dissecting the suprahepatic and infrahepatic vena cava, and right adrenal veins and accessory hepatic veins were ligated if necessary to allow complete venous control during clamping. Clamps were always applied in the following sequence: hepatoduodenal ligament, infrahepatic vena cava and suprahepatic vena cava. During transection of the liver, 5 min interval was always allowed in every 15-20 min TVE until the transection was over. After the resection was completed, the clamps were removed in reverse order of their application. Pringle maneuver method was applied in group B at the time of liver transection and consisted of cross-clamping the hepatoduodenal ligament until the liver transection was completed. If the time was more than 20 min, the clamp was released for about 5 min until the operation was completed. Hemostasis of the raw surface of the liver was assured by biological fibrin glue and exact suture. Closed drainage was routinely used before closure of the incision.

Data collection and analysis

All medical records of the patients of the three groups were reviewed retrospectively. Major hepatectomy was defined as resection of two or more liver segments according to Goldsmith and Woodburne, while minor hepatectomy was defined as resection of only one segment[2]. Tumor closing or invading the major liver blood vessels was defined as the distance between them which was less than 1 cm.

The values were expressed as median (range) and cases (percent). The overall survival after hepatic resection was calculated by the Kaplan-Meier method. Statistical evaluations were performed by using unpaired Student *t* test and chi-spuare analysis, and comparison was made by log rank analysis. Statistical significance was determined by a *P* value of less than 0.05. Calculations were made with SPSS computer software (Chicago, IL).

RESULTS

As shown in Table 1, the two groups (groups A and B) of patients were similar in terms of age, sex. Both groups had similar high HBV infectious rate. Although the operative time and blood exclusive time were long in TVE group, no significant difference was found in blood loss and blood transfusion between groups A and B. More major hepatectomies and caudate lobe hepatectomies were performed in group A than in group B.

The pathologic data are shown in Table 2. There was a significant difference in the size of tumors between groups A and B. From the data, the rate of tumor closing or invading the major liver blood vessels in group A was higher than that in group B. The patients with HCCs in group A had a higher probability in their advanced stage, about 70 % of the patients were TNM stage 3 or 4 in group A, while only about 32 % in group B. Although higher cirrhosis rate, multiple tumor possibility, more caudate lobe location and higher risk of tumor rupture were found during operation in group A than in group B, the possibilities of tumor free resection margin in the two groups were similar.

Table 1 General clinical data

Clinical parameters	Group A (*n*=78)	Group B (*n*=176)
Age (yr)	51.72 (36-71)	49.66 (14-74)
Male	69 (88.64 %)	147 (83.52 %)
HbsAg (+)	67 (85.89 %)	151 (85.79 %)
Child-Push grade		
Grade A	41 (52.54 %)[a]	124 (70.45 %)
Grade B	28 (35.90 %)[a]	38 (21.59 %)
Grade C	9 (11.53 %)	14 (8.0 %)
Total resection rate	47.92%(254 / 530)[a]	33.21 %(176 / 530)
Procedure time (min)	268 (150-325)[a]	178(128-356)
Blood exclusion time (min)	25.4 (12-55)[a]	14.2(8-28)
Blood loss (ml)	818 (250-2800)	725(180-2400)
Blood transfusion (ml)	690 (0-2400)	620 (0-2600)
Total hospital stay time (d)	29.4 (12-35)	19.8 (10-39)
Re-operation	11 (14.10 %)	16 (9.09 %)
Emergency operation	5 (6.41 %)	9 (5.11 %)
Local hepatectomy	12 (15.38 %)[a]	48 (27.28 %)
Minor hepatectomy	21 (26.92 %)[a]	96 (54.55 %)
Major hepatectomy	45 (57.69 %)[a]	32 (18.19 %)
Caudate lobe hepatectomy	4 (5.13 %)[a]	0 (0)

[a]*P*<0.05 *vs* statistically significant when compared with group B.

Table 2 Pathologic data

Clinical parameters	Group A (*n*=78)	Group B (*n*=176)
The mass		
Median diameter (cm)	11.58 (6.2-24.6)[a]	6.25 (1.8-12.7)
>or =5 cm	72 (92.30 %)[a]	118 (67.05 %)
>or =10 cm	53 (67.95 %)[a]	28 (15.90 %)
Close or invade vana cana	23 (29.49 %)[a]	17 (9.65 %)
Close or invade major hepatic vein	21 (26.92 %)[a]	13 (7.39 %)
Close or invade major bile duct	11 (14.10 %)[a]	8 (4.55 %)
Close or invade major port vein	32 (41.03 %)[a]	22 (12.5 %)
TNM tumor stage		
Stage 1	6 (7.69 %)[a]	49 (27.84 %)
Stage 2	12 (15.38 %)[a]	71 (40.34 %)
Stage 3	36 (46.15 %)[a]	32 (18.19 %)
Stage 4a	20 (25.64 %)[a]	22 (12.5 %)
Stage 4b	4 (5.13 %)[a]	2 (1.14 %)
Cirrhosis	59 (75.64 %)	120 (68.18 %)
Multiple tumor	8 (10.25 %)[a]	6 (3.41 %)
Caudate lobe tumor	4 (5.13 %)[a]	0 (0)
Tumor free resection margin	74 (94.87 %)	173 (98.3 %)
Tumor rupture during operation	11 (14.10 %)[a]	13 (7.39 %)

[a]*P*<0.05 *vs* statistically significant when compared with group B.

Bleeding was most common short-term complication after hepatectomy, but there was no significant difference between the two groups, accounting for 20.5 % and 16.48 %, respectively. Although the complications in group A including bile leakage, ascites, pleural effusion, jaundice, hepatic failure were significantly higher than those in group B, the reoperation

rate within 24 h after operation and perioperative mortality were similar in the two groups. The data are shown in Table 3.

The prognostic data are shown in Table 4. As compared with Pringle maneuver technique, the hepatectomy of TVE might lead to similar median disease-free survival time and short-term survival rate (92.3 % *vs* 95.5 % of one year survival rate, $P>0.05$). The median survival time and long-term survival rate in group A were significantly lower than those in group B, but obviously higher than those in group C. The results showed that the Pringle maneuver group had a higher incidence of remote metastasis than the other two groups.

Table 3 Postoperative complications

Clinical parameters	Group A	Group B
Bleeding	16 (20.51 %)	29 (16.48 %)
Bile leakage	6(7.69 %)[a]	8 (4.55 %)
Infection (including abscess)	12 (15.38 %)	23 (13.68)
Pleural effusion	31 (39.74 %)[a]	34 (19.32 %)
Reoperation within 24 h after operation	3 (3.85 %)	6 (3.40 %)
Ascites	16 (20.51 %)[a]	20 (11.36 %)
Jaundice	6 (7.69 %)[a]	5 (2.84 %)
Hepatic failure	6 (7.69 %)[a]	5 (2.84 %)
Total morbidity	40 (51.28 %)[a]	45 (25.57 %)
Perioperative mortality	2 (2.56 %)	5 (2.84 %)

[a]$P<0.05$ *vs* statistically significant when compared with group B.

Table 4 Outcome after hepatic resection

Clinical parameters	Group A	Group B	Group C
Median disease-free survival (m)	14.6 (8-25)	16.3 (9-37)	-
Median survival (m)	40.5 (28-52)	57.6 (33-84)	8.8 (5-31)
Cumulative survival rate			
1 year survival	92.3 %[b]	95.5 %[b]	29.9 %
3 year survival	51.3 %[ab]	69.6 %[b]	2.9 %
5 year survival	34.6 %[ab]	48.0 %[b]	0
Remote metastasis rate	16.27%[a]	23.9%[b]	14.8 %

[a]$P<0.05$ *vs* statistically significant when compared with group B; [b]$P<0.05$ *vs* statistically significant when compared with group C.

DISCUSSION

With the advances in surgical technique, the mortality rate of hepatectomy today is less than 5 %[2]. Despite of the satisfactory outcome of hepatectomy for HCC[9], hepatectomy of advanced and complicated HCC remains a major surgical challenge, especially when underlying liver cirrhosis is present[10-12]. HCC is mostly resulted from hepatitis virus infection and liver cirrhosis, and the conventional approach used in hepatcetomy will always lead to excessive bleeding and high risk of perioperative mortality[13,14]. Perioperative transfusion has been found to promote recurrence of HCC and to result in short disease-free and overall survivals[15], the highlight of surgery of advanced and complicated HCC is thus to prevent massive bleeding and blood transfusion in hepatectomies[2]. HCCs we met were always in their terminal stage with a diameter larger than 10 cm. Since the Pringle maneuver method does not prevent hepatic venous bleeding or air embolism, new ways of vascular exclusion has to be devised. The TVE technique has been widely accepted in resection of advanced and complicated HCCs since it was introduced by Heaney in 1966 and modified in clinical practice[3,7,8,16]. In general, the TVE technique is used predominantly for major resections or centrally placed lesions or in cases with blood vessels involved.

TVE technique means the total vascular block of the liver during hepatectomy. Though bleeding is decreased in the operation, the TVE technique will prolong the warm ischemia time of the liver, so we must emphasize its safety. Complications were noted in the total vascular exclusive group, which was regarded to be corresponded to the higher incidence of complex resections[17]. Berney and his colleagues showed that the risk factors for postoperative complications were the duration of surgery and the amount of blood transfused[3]. The frequency of perihepatic infected fluid collections has been reported to be 2 % to 20 %, biliary fistulas occurrence was up to 8 % of patients[18]. Brancatisano showed similar perioperative mortality (2.5 %) in radical major hepatic surgery by TVE but with a lower postoperative complication rate (about 46 %) than that of ours[19].

At present, it is generally accepted that liver resection performed under intermittent warm ischema is a safe and well-tolerated modality in patients with and without cirrhotic livers[20]. Huguet and others showed that hepatocytes could tolerate normothermic ischemia in excess of 1 hour, and ischemia up to 2 hour without major detrimental effects other than transient hepatic failure has never been reported[21,22]. Others suggested that the risks related to hemorrhage were of greater concern than those related to the time of ischemia. Thus, for advanced and complicated HCC, it is safer to continue vascular exclusion, within 1 h, until complete resection is achieved, rather than take the risk of significant bleeding for the sake of a shorter period of ischemia. A prospective randomized trial showed that the postoperative outcome of patients who underwent liver resection with Pringle maneuver method was better than that of those who underwent operation with other methods[2]. The results of our data showed that although the TVE group had a high hepatic failure rate and complication occurrence than the Pringle maneuver group, but the perioperative mortality was not significantly higher, suggesting that the hepatic failure and complication occurrence might be transient and recoverable.

Another major problem of TVE is the hemodynamic change during TVE. As reported before, hemodynamic tolerance to TVE was excellent in most patients[3], and we also found that the patients could adapt well and quickly to the haemodynamic changes observed after total vascular exclusion. On the bases of the reported complications of spinal cord ischemia, renal failure or aortic injury after routine aortic clamping[23] and the excellent hemodynamic tolerance obtained without aortic occlusion, we applied the modified TVE without aortic exclusion.

Advanced and complicated HCCs were formerly regarded as contraindications of operation for their high mortality and postoperative recurrent rate, the resection rate of advanced and complicated HCCs was extremely low. It was reported that the resection rate of HCCs was 12-28 %[18, 24,25]. After the use of TVE technique, the resection rate of HCCs increased remarkably, which was also confirmed in our retrospective analysis.

Untreated patiens with HCCs had a median survival time of 6 months, no 5-year survival has been reported. But the surgical treatment prolonged the median survival to 42 months and the 5-year survival to 32 % in some center[26]. Good results could be obtained through an aggressive surgical approach for patients with advanced and complicated HCCs, even for those with tumor thrombi in the portal trunk and vena cava invasion[27]. Comparatively, our perioperative mortality of the patients with advanced and complicated HCCs by TVE was similar to the hepatectomy by Pringle maneuver method and the 5-year survival rate of TVE group after resection was similar to others[28]. The shorter long-term survival rate and median survival time of complicated HCCs by TVE compared with

Pringle maneuver group might be resulted from their poorer conditions such as inflammatory activity, hepatic reserve and tumor characteristics, advanced TNM stage, higher possibility of introgenic tumor rupture, higher rate of metachronous and multicentric liver carcinogenesis[29-31]. However, the long-term survival rate and median survival time of the TVE group were remarkably higher than those of the unresectable group. By the way, the remote metastasis rate of the Pringle maneuver group was higher than that of the TVE group and unresectable group, and this result needs to be further studied. In addition, the potentially harmful effect on the metabolic function of hepatocytes should be mentioned in future study.

In summary, hepatectomy by TVE is a safe and effective technique in surgical treatment of advanced and complicated HCC as compared with Pringle maneuver technique. It can increase the resection rate of HCCs, reduce the massive bleeding during operation and increase the survival rate of advanced and complicated HCCs. This series of HCCs demonstrate that an aggressive policy of liver resection by TVE can be adopted as a feasible therapeutic option without excess mortality.

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