Hepatic Resection for Hepatocellular Carcinoma in Patients With Portal Hypertension

A Long-Term Benefit Compared With Transarterial Chemoembolization and Thermal Ablation

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Abstract: The optimal treatment for hepatocellular carcinoma (HCC) in cirrhotic patients with portal hypertension (PHT) is still controversial. The objective of this study is to compare HCC patients with PHT treated with hepatic resection to those treated with transarterial chemoembolization (TACE) or thermal ablation.

A series of 167 cirrhotic patients with HCC undergoing hepatic resection or TACE/ablation from 2001 to 2008 were retrospectively analyzed. Cirrhotic patients with HCC were divided into 3 groups: hepatic resection in HCC patients with PHT (PHT-R group, n = 58), without PHT (NPHT-R group, n = 67), and TACE or thermal ablation in HCC patients with PHT (PHT-O group, n = 42). The short-term and long-term outcomes of liver function, operative mortality and morbidity, and survival rate were compared.

Baseline characteristics were similar among the 3 groups, except for patients in the PHT-R group had larger spleen (16.0 vs 11.4 cm, P = 0.001) and smaller tumor size (4.8 vs 7.1 cm, P = 0.001) in comparison with those in the NPHT-R group. The PHT-R group had better liver function compared with those in the PHT-O group (patients had Child–Turcotte–Pugh class B liver function: 5.2% vs 31%, P = 0.001). There was no significant difference of operative mortality and morbidity in all groups. The 1-, 3-, and 5-year survival rates were 80.4%, 55.6%, and 28.1% in the PHT-R group; 79.1%, 64.2%, and 24.4% in the NPHT-R group (vs PHT-R, P = 0.001); and 60.7%, 39.8%, and 33.9% in the PHT-O group (vs PHT-R, P = 0.313).

Hepatic resection shows better long-term results for cirrhotic HCC patients with PHT than TACE and thermal ablation.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common malignancy and the third leading cause of cancer-related deaths in the world, and usually arises in the setting of cirrhosis. Esophageal varices is considered a sign of portal hypertension (PHT) and observed in up to 67% of cirrhotic patients. Although hepatic resection for HCC has become a safe procedure due to improved surgical techniques and pre- and post-surgery care, PHT is still considered a contraindication for liver resection according to the EASL (European Association for the Study of the Liver) and AASLD (American Associations for Study of Liver Diseases) published guidelines for HCC management in 2001 and 2011, respectively. Other treatments such as liver transplantation, thermal ablation, and transarterial chemoembolization (TACE) are recommended in these patients.

However, several studies demonstrated that if patients had a similar preoperative liver function, assessed by Child–Turcotte–Pugh (CTP) score or Model for End-Stage Liver Disease (MELD) score, the short- and long-term outcomes were similar in patients with or without PHT. And to the best of our knowledge, whether TACE or thermal ablations for HCC with PHT are superior to hepatic resection is still controversial. The aim of this study is to compare the therapeutic value of hepatic resection with TACE or thermal ablation for HCC in cirrhotic patients with PHT and to reevaluate the current guidelines for HCC management.

METHODS

From May 2001 to December 2008, 167 cirrhotic patients with or without PHT were retrospectively analyzed at the Hepatic Surgery Center, Tongji Hospital, Huazhong University of Science and Technology. This study was approved by the Ethics Committee for Clinical Pharmacology in Tongji Medical College, and all the information of patients were kept private. Patients were divided into 3 groups: presence (PHT-R group, n = 58) or absence (NPHT-R group, n = 67) of PHT at the time of surgery.
of hepatic resection, and those with PHT who were performed other treatments including TACE and thermal ablation (PHT-O group, n = 42). Data were recruited consecutively to address potential sources of bias, and were analyzed retrospectively. The presence of preoperative PHT was defined as esophageal varices detectable at endoscopy or splenomegaly with a platelet count <100 × 10^3/mm^3 according to the Barcelona Clinic Liver Cancer (BCLC) group criteria. The characteristics evaluated to calculate by the formula described by Freeman et al. Patients obtained a tumor-free margin. Major hepatic resection was considered impossible, if patients with single nodule surgery or in whom complete removal of the tumors was performed provided that the liver function permitted. For recurrence occurred within 1 year after resection or inappropriate for reoperation, radiofrequency or microwave ablation, ethanol injection, or TACE was performed.

**STATISTICAL ANALYSIS**
Continuous variables were expressed as mean and standard deviation and differences between groups were compared by the independent-samples t-test or Mann–Whitney U-test, as appropriate; categorical variables were reported as number of cases and prevalence, and differences between groups were compared by the chi-square test or Fisher exact test, as appropriate. The patients’ overall survival was calculated by using the Kaplan–Meier method, and their comparison was performed using the log-rank test. The multivariate analysis was performed using the Cox regression model. P value <0.05 was considered significant in all analysis. Statistical analysis was carried by SPSS 17.0 software.

**RESULTS**

**Preoperative Characteristics and Intraoperative Data**
The clinical characteristics and intraoperative data among the 3 groups are summarized in Tables 2 and 3. In comparison with patients in NPHT-R group, those in the PHT-R group had significant larger spleen (16.0 vs 11.4 cm, P = 0.001), smaller tumor size (4.8 vs 7.1 cm, P = 0.001), lower rate of Pringle maneuver use (46.6% vs 70.1%, P = 0.007), and higher rates of concomitant splenectomy (24.1% vs 0, P < 0.001) or pericardial devascularization surgery (17.2% vs 0, P < 0.001). The CTP classification, MELD score, mean surgical time, blood loss, transfusion rate, and in-hospital stay were all similar between the 2 groups. In the PHT-O group, 24/42 patients underwent microwave ablation, 15/42 patients underwent TACE, and the remaining 3 patients were performed radiofrequency ablation. And patients in the PHT-O group had worse liver function (patients had CTP class B liver function: 31% vs 5.2%, P = 0.001) compared with those in the PHT-R group.

| Variables | PHT-R (n = 58) | NPHT-R (n = 67) | PHT-O (n = 42) |
|-----------|---------------|----------------|---------------|
| Esophageal varices | 28 (48.3%) | 0 | 22 (52.4%) |
| Platelet count <100, 000/mm^3 | 49 (84.5%) | 5 (7.5%) | 37 (89.0%) |
| Platelet count (× 10^3/mm^3; median; range) | 79.0 (21–205) | 146.8 (30–294) | 66.6 (17–309) |
| Splenomegaly | 53 (91.4%) | 19 (28.4%) | 38 (90.5%) |
| Esophageal varices without splenomegaly + platelet count <100, 000/mm^3 | 9 (15.5%) | 0 | 6 (14.3%) |
| Esophageal varices + splenomegaly + platelet count <100,000/mm^3 | 19 (32.8%) | 0 | 16 (38.1%) |
| Splenomegaly + platelet count <100,000/mm^3 without esophageal varices | 30 (51.7%) | 0 | 20 (47.6%) |

NPHT = ?, PHT = portal hypertension.
In the PHT-R group, 1 patient underwent reoperation due to intra-abdominal bleeding 18 hours after the initial surgery. Although bleeding was successfully controlled, the patient died of liver failure on the ninth day after surgery (Table 4). There was no operative death in the other 2 groups. Postoperative complications rate was 32.8% in the PHT-R group, which was similar compared with those in the NPHT-R (34.3%) and PHT-

### TABLE 2. Baseline Characteristics of the Whole Study Population

| Variables                        | PHT-R (n = 58) | NPHT-R (n = 67) | PHT-O (n = 42) | P |
|----------------------------------|----------------|-----------------|---------------|---|
| Age (y)                          | 49.9 ± 11.8    | 46.9 ± 10.0     | 47.7 ± 9.4    | 0.207* 0.312† |
| Male gender                      | 52 (89.7%)     | 64 (95.5%)      | 38 (90.5%)    | 0.207 0.893 |
| Hepatitis serology               |                |                 | 0.618 0.658   |
| Hepatitis B                      | 54 (93.1%)     | 61 (91.0%)      | 37 (88.1%)    | 0.658 |
| Hepatitis C                      | 2 (3.4%)       | 1 (1.5%)        | 3 (7.1%)      | 0.658 |
| Hepatitis B + C                  | 0              | 1 (1.5%)        | 0             | 0.658 |
| Negative                         | 2 (3.4%)       | 4 (6.0%)        | 2 (4.8%)      | 0.658 |
| Albumin (g/L)                    | 38.1 ± 4.4     | 41.0 ± 4.0      | 34.9 ± 6.0    | 0.355 0.108 |
| Total bilirubin (μmol/L)         | 18.8 ± 8.4     | 15.4 ± 6.4      | 24.9 ± 11.5   | 0.175 0.178 |
| CTP classification               |                |                 | 0.336 0.001   |
| Class A                          | 55 (94.8%)     | 66 (98.5%)      | 29 (69.0%)    | 0.658 |
| Class B                          | 3 (5.2%)       | 1 (1.5%)        | 13 (31%)      | 0.658 |
| α-Fetoprotein (ng/mL) < 200      | 34 (58.6%)     | 32 (47.8%)      | 27 (64.3%)    | 0.471 0.425 |
| 200–400                          | 5 (8.6%)       | 8 (11.9%)       | 1 (2.4%)      | 0.471 0.425 |
| >400                             | 19 (32.8%)     | 27 (40.3%)      | 14 (33.3%)    | 0.471 0.425 |
| MELD classification              |                |                 | 0.815 0.649   |
| Score < 9                        | 48 (82.8%)     | 58 (86.6%)      | 32 (76.2%)    | 0.815 0.649 |
| Score 9–10                       | 5 (8.6%)       | 5 (7.5%)        | 6 (14.3%)     | 0.815 0.649 |
| Score >10                        | 5 (8.6%)       | 4 (6.0%)        | 4 (9.5%)      | 0.815 0.649 |
| Tumor size (cm)                  |                |                 | 0.005 0.664   |
| <3                               | 9 (15.5%)      | 7 (10.4%)       | 9 (21.4%)     | 0.005 0.664 |
| 3–5                              | 23 (48.3%)     | 11 (16.4%)      | 18 (42.9%)    | 0.005 0.664 |
| >5                               | 25 (36.2%)     | 49 (73.1%)      | 15 (35.7%)    | 0.005 0.664 |
| Number of nodules                |                |                 | 0.756 0.063   |
| Single                           | 48 (82.8%)     | 54 (80.6%)      | 28 (66.7%)    | 0.756 0.063 |
| Multiple                         | 10 (17.2%)     | 13 (19.4%)      | 14 (33.3%)    | 0.756 0.063 |
| Adjuvant regional chemotherapy   | 35 (60.3%)     | 46 (68.7%)      | —             | 0.332 — |

Continuous variables are reported in mean and standard deviation. CTP = Child–Turcotte–Pugh, MELD = model for end-stage liver disease, NPHT = ?, PHT = portal hypertension.

* This value indicates the comparison results between the patients with (PHT-R group) or without (NPHT-R group) PHT at the time of hepatic resection.

† This value denotes the comparison results between the patients with PHT who underwent hepatic resection (PHT-R group) or other treatments (PHT-O group).

**Short-Term Results**

In the PHT-R group, 1 patient underwent reoperation due to intra-abdominal bleeding 18 hours after the initial surgery. Although bleeding was successfully controlled, the patient died of liver failure on the ninth day after surgery (Table 4). There was no operative death in the other 2 groups. Postoperative complications rate was 32.8% in the PHT-R group, which was similar compared with those in the NPHT-R (34.3%) and PHT-

### TABLE 3. Intraoperative Data of Hepatectomy for Hepatocellular Carcinoma in Cirrhotic Patients With (PHT-R Group) or Without (NPHT-R Group) Portal Hypertension (n = 125)

| Variables                        | PHT-R (n = 58) | NPHT-R (n = 67) | P |
|----------------------------------|----------------|-----------------|---|
| Mean surgical time (min)         | 209.0 ± 58.5   | 186.8 ± 49.3    | 0.197 |
| Mean blood loss (mL)             | 529.3 ± 406.6  | 600.4 ± 547.3   | 0.181 |
| RBC transfusion (mL)             | 19 (32.8%)     | 12 (17.9%)      | 0.055 |
| Anatomic resection               | 51 (87.9%)     | 57 (85.1%)      | 0.642 |
| Extent of hepatectomy            |                |                 | 0.176 |
| Wedge and segmentectomy          | 44 (75.9%)     | 41 (61.2%)      | — |
| Bisegmentectomy                  | 12 (20.7%)     | 20 (29.9%)      | — |
| Major hepatectomy                | 2 (3.4%)       | 6 (9.0%)        | — |
| Pringle maneuver                 | 27 (46.6%)     | 47 (70.1%)      | 0.007 |
| Concomitant splenectomy          | 14 (24.1%)     | 0              | <0.001 |
| Concomitant pericardial devascularization | 10 (17.2%) | 0              | <0.001 |

NPHT = ?, PHT = indicates portal hypertension, RBC = red blood cell.
O (26.2%) groups (P = 0.853 and 0.478, respectively). According to the Clavien–Dindo classification of surgical complication,17 the incidence of grade IIIa or more severe morbidities was also not significantly different between the PHT-R group (17.2%) and the NPHT-R group (19.4%, P = 0.756).

Long-Term Outcomes

Patients with preoperative PHT who were performed hepatic surgery had similar 1-, 3-, and 5-year survival rates compared with those without PHT: 80.4% and 79.1%, 55.6% and 64.2%, and 28.1% and 39.8%, respectively (P = 0.313), which were significantly better than those treated with TACE or thermal ablation (60.7%, 24.4%, and 7.3%, respectively, P < 0.001) (Figure 1). As shown in Figure 2, tumor-free survivals were also comparable in the PHT-R and NPHT-R groups (P = 0.258).

Long-Term Outcomes in CTP Class A Patients

Considering only patients with CTP class A liver function (150 patients: 55 in the PHT-R group, 66 in the NPHT-R group, and 29 in the PHT-O group), patients in the PHT-R group had similar 1-, 3-, and 5-year survival rates compared with those in the NPHT-R group: 81.2% and 78.8%, 57% and 63.6%, and 28.7% and 38.8%, respectively (P = 0.336), which were significantly better than those treated with TACE or local ablation (67.7%, 22.8%, and 9.1%, respectively, P = 0.002) (Figure 3).

Univariate and Multivariate Analysis

Based on the univariate analysis, the best predictors of a poor prognosis for cirrhotic patients with HCC were age over 60 years, splenomegaly, albumin < 35 g/L, multiple number of nodules, and serum AFP level over 200ng/mL (Table 5). Multivariate analysis of these 5 factors showed only AFP level and number of nodules were identified as an independent predicting factors for survival (P = 0.048, 0.030, respectively) (Table 6). Although neither presence of PHT nor elevated serum bilirubin level was associated with overall survivals.

DISCUSSION

Hepatic resection for HCC has become a safe procedure in cirrhotic patients, with lower postoperative mortality, morbidity and improved long-term results.18–20 This progress has been mainly due to improved perioperative managements and better

### TABLE 4. Deaths and Complications After Hepatic Resection or Other Treatments (PHT-O Group) for Hepatocellular Carcinoma in Cirrhotic Patients With (PHT-R Group) or Without (NPHT-R Group) Portal Hypertension

| Variables                        | PHT-R (n = 58) | NPHT-R (n = 67) | PHT-O (n = 42) |
|----------------------------------|---------------|----------------|---------------|
| Deaths                           | 1 (1.7%)      | 0              | 0             |
| Complications                    | 19 (32.8%)    | 23 (34.3%)     | 11 (26.2%)    |
| Liver dysfunction                | 9 (15.5%)     | 6 (9.0%)       | 2 (4.8%)      |
| Ascites                          | 0             | 1 (1.5%)       | 0             |
| Bile leakage                     | 0             | 1 (1.5%)       | 0             |
| Intra-abdominal abscess          | 4 (6.9%)      | 2 (3.0%)       | 2 (4.8%)      |
| Atelectasis                      | 0             | 1 (1.5%)       | 0             |
| Pleural effusion                 | 9 (15.5%)     | 12 (17.9%)     | 3 (7.1%)      |
| Intra-abdominal hemorrhage       | 3 (5.2%)      | 1 (1.5%)       | 0             |
| Wound infection                  | 1 (1.7%)      | 1 (1.5%)       | 0             |
| Pneumonia                        | 0             | 0              | 1 (2.4%)      |
| Wound dehiscence                 | 1 (1.7%)      | 1 (1.5%)       | 0             |
| Gastrointestinal bleeding        | 1 (1.7%)      | 1 (1.5%)       | 0             |
| Pneumothorax                     | 0             | 2 (3.0%)       | 0             |
| Hepatic encephalopathy           | 0             | 0              | 1 (2.4%)      |
| Postembolization syndrome        | 0             | 0              | 2 (4.8%)      |
| Hospital stay (d)                | 20.7 ± 11.8   | 19.1 ± 8.5     | 16.3 ± 10.3   |

NPHT = ??, PHT = indicates portal hypertension.
* Compared with PHT-R group, P = 0.853.
† Compared with PHT-R group, P = 0.478.
‡ Compared with PHT-R group, P = 0.260.
§ Compared with PHT-R group, P = 0.114.
Table 5. Univariate Analysis of Predictive Factors for Overall Survival After Hepatectomy for Hepatocellular Carcinoma in Cirrhotic Patients With (PHT-R Group) or Without (NPHT-R Group) Portal Hypertension (n = 125)

| Variables | No. | P    |
|-----------|-----|------|
| Age > 60 y (yes/no) | 20/105 | 0.045 |
| Gender (male/female) | 116/9 | 0.340 |
| HBsAg (positive/negative) | 116/9 | 0.716 |
| Platelet < 10^9/mm^3 (yes/no) | 73/52 | 0.711 |
| Spleenomegaly (yes/no) | 76/49 | 0.030 |
| Esophageal varices (yes/no) | 27/98 | 0.763 |
| Portal hypertension (yes/no) | 58/67 | 0.313 |
| Albumin > 35 g/L (yes/no) | 106/19 | 0.042 |
| Total bilirubin > 20.5 μmol/L (yes/no) | 34/91 | 0.660 |
| Blood transfusion (yes/no) | 31/94 | 0.418 |
| Tumor diameter > 5 cm (yes/no) | 75/50 | 0.937 |
| Number of nodules (single/multiple) | 102/23 | 0.014 |
| CTP classification (A/B) | 121/4 | 0.882 |
| α-Fetoprotein (ng/mL) > 200 (yes/no) | 58/67 | 0.044 |
| MELD classification score p | 19/106 | 0.778 |
| (Kaplan-Meier method, long > 9 (yes/no)) | | |
| Extent of hepatectomy | 85/40 | 0.211 |

CTP = Child–Turcotte–Pugh, HBsAg = hepatitis B surface antigen, MELD = model for end-stage liver disease.

Table 6. Multivariate Analysis

| Variables | Hazard Ratio | 95% CI | P |
|-----------|--------------|-------|---|
| Tumor number (multiple) | 1.805 | 1.059–3.076 | 0.030 |
| α-Fetoprotein > 200 ng/mL | 1.506 | 1.004–2.259 | 0.048 |

CI = confidence Interval.
treatments. Liver transplantation is recognized as the first choice for cirrhotic patients with HCC within Milan criteria, allowed removing the diseased liver together with the tumor itself, but the current scarcity of organs and extremely high cost restricted only a limited number of candidates to be transplanted at specialized centers. TACE and local ablation are recommended for patients with HCC who were not appropriate for resection or transplantation according to the guidelines. However, the long-term outcomes were not satisfactory enough and there are numerous reports demonstrating that hepatic resection was superior with overall and tumor-free survivals than TACE or thermal ablations for HCC, but whether the result is the same in patients with PHT is still unknown.

As reported by Capussotti et al, operative mortality related to liver function or portal pressure (liver failure, portal vein thrombosis, esophageal bleeding) was significantly higher in patients with PHT. However, recent advances in surgical techniques and perioperative care for patients with cirrhosis have reduced the number of cirrhosis-related complications and deaths. The occurrence of perioperative morbidity was similar in patients who underwent hepatic resection with or without PHT, as was postoperative liver dysfunction. It seems that patients in the PHT-R group had higher rate of postoperative intra-abdominal hemorrhage requiring reoperation compared with those in the NPHT-R group (5.2% vs 1.5%), though the difference was not significant (P = 0.244). But one must bear in mind that patients with PHT usually had prolonged prothrombin time and severe thrombocytopenia, which may be responsible for higher rate of postoperative hemorrhage. For patients in the PHT-R group in this study, there was only 1 case of perioperative death due to liver failure, 8 (13.8%) experienced and 5 (8.6%) died of variceal bleeding during follow-up time, the majority of the deaths were associated with the recurrence of HCC. This was echoed in the study by Ishizawa et al who argued that the benefits of hepatic resection in patients with HCC and PHT might overweight the risks of cirrhosis-related mortality after resection. Moreover, neither PHT nor preoperative bilirubin level was confirmed as an independent predicting factor for survival by multivariate analysis. Our results indicate that liver resection can be performed safely in PHT patients with satisfactory and acceptable 5-year overall survival rate, justifying the surgical indications for HCC with PHT if the liver function was still well compensated.

Patients with PHT who were performed hepatic resection in this study had similar 5-year survivals compared with those reported by Capussotti et al (28.1% and 28.9%, respectively), but were obviously lower than those in the reports by Ishizawa et al (56%) and Cucchielli et al (56.5%). One explanation is that patients in this study had significant larger tumor size. The result was as expected that patients with a more advanced stage of cancer were going to have worse long-term survival. Moreover, most of the patients in our study were HBV related. It was significantly different from the previous published literatures, in which the majority of the patients had HCV as cirrhosis etiology. Patients with HBV or HCV may have distinct clinical profiles and tumor burdens, which have implications for long-term survival.

This study has several limitations. It is a retrospective study with limited number of patients in a single center. A randomized clinical trial with larger number of patients would provide stronger evidence to get a conclusion.

In conclusion, PHT should not be considered as an absolute contraindication to liver resection for HCC in cirrhotic patients with compensated liver functions. Multivariate analysis identifying serum AFP level and number of tumors can be used as independent predicting factors for survival. This study provided important evidence for surgeons that selected HCC patients with PHT could benefit from hepatic resection as compared with TACE or thermal ablation.

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