Hepatectomy for Hepatocellular Carcinoma

The Surgeon’s Role in Long-term Survival

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Hypothesis: The surgeon can contribute substantially to the long-term survival rate of patients undergoing hepatectomy for hepatocellular carcinoma (HCC).

Design: The long-term survival rate of patients with HCC undergoing hepatectomy has improved, but the contribution of the surgeon to the improved survival rate is unknown. We surveyed 211 consecutive patients undergoing hepatectomy for HCC. The clinical, operative, and pathological factors were analyzed to identify factors that were important in affecting long-term survival.

Setting: A tertiary referral center.

Patients: From April 1989 to December 1995, 211 consecutive patients with HCC underwent 153 major and 58 minor hepatectomies.

Main Outcome Measures: Disease-free and overall cumulative survival rate.

Results: The 5-year disease-free survival rate was 27%. By Cox regression analysis, blood transfusion (relative risk [RR], 1.21; 95% confidence interval [CI], 1.05-1.40) and TNM stage (RR, 1.90; 95% CI, 1.47-2.47) were shown to be independent prognostic factors in the 5-year disease-free survival rate. The 5-year overall cumulative survival rate was 37%. By Cox regression analysis, the preoperative indocyanine green retention value at 15 minutes after injection (RR, 1.03; 95% CI, 1.01-1.06), blood transfusion (RR, 1.19; 95% CI, 1.07-1.31), tumor rupture (RR, 1.48; 95% CI, 1.08-2.04), and TNM stage (RR, 1.62; 95% CI, 1.27-2.07) were shown to be significant independent factors that influenced cumulative survival rate.

Conclusions: The long-term survival of patients with HCC after hepatectomy depends on tumor staging, preoperative hepatic functional reserve, history of blood transfusion, and rupture of HCC. Preoperative liver function and tumor staging cannot be altered; however, the surgeon can play an important role in improving the prognosis if blood transfusion and iatrogenic tumor rupture can be avoided and if function of the liver remnant can be preserved.

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RESULTS

There were 179 male and 32 female patients with a median age of 53 years. The size of their HCCs ranged from 0.5 to 25 cm (median, 8 cm). Ninety-eight patients (46%) had underlying cirrhosis, and 71 (34%) had underlying chronic hepatitis.

SURVIVAL

The overall hospital mortality rate was 9.3% (n = 20). However, the hospital mortality rate decreased from 32% in 1989 to 5% in 1995. Recurrence of HCC was detected in 122 patients with a median time of 10.6 months (range, 1-98 months). The 1-, 3-, and 5-year disease-free survival rates were 60%, 38%, and 27% respectively (Figure). The median follow-up period
PATIENTS AND METHODS

From April 1989 to December 1995, 211 consecutive patients with HCC confirmed by histological examination underwent hepatectomies in the Department of Surgery at Queen Mary Hospital, Hong Kong, China. All data were collected prospectively by a single research assistant.

PREOPERATIVE MANAGEMENT

Preoperative evaluation of the tumor was done by ultrasonography, computed tomography, and hepatic arteriography. Hepatic function assessment, including the modification by Pugh et al12 of the Child hepatic function classification system and the indocyanine green (ICG) clearance test,13 were performed after the HCC was considered resectable as determined by imaging studies. The ICG clearance test results are expressed as the percentage of ICG retained in the circulation 15 minutes after intravenous injection of 0.5 g/kg of body weight of ICG.

INTRAOPERATIVE MANAGEMENT

Surgery was performed through a bilateral subcostal incision with an upward midline extension. Thoracic extension was required in 11 patients, because the HCC in the right lobe was large or the tumor was in the right posterior segment.

Intraoperative ultrasonography was performed routinely to detect tumor nodules in the contralateral lobe and/or invasion of the tumor into the major blood vessels and to mark the line of parenchymal transection on the liver surface to obtain the optimal tumor-free resection margin and to avoid a major hepatic vein at the transection plane.

Ipsilateral hilar dissection was performed to control or divide the inflow vasculature. The liver lobe bearing the tumor was then mobilized to control the outflow vasculature. Rotation of the right liver lobe containing the tumor was intermittent to avoid prolonged twisting of the inflow and outflow vasculature of the left lobe.

Liver transection was performed by the finger-fracture technique from 1989 to 1992 and by the ultrasonic dissector after 1992. The Pringle maneuver was employed in 20-minute cycles during parenchymal transection in 111 patients. In the other patients, the Pringle maneuver was not applied. Hemostasis was performed promptly by diathermy coagulation, argon beam coagulation, or fine suturing during parenchymal transection to decrease the volume of blood lost.

After parenchymal transection, bile leakage was identified by injecting methylene blue into the common bile duct via the cystic duct or by pressing the transection surface gently with a piece of clean gauze. A leak, if present, was closed with 3-0 sutures. The falciform ligament was reconstructed for right hepatectomy or lobectomy to prevent the left lobe from rotating into the right subphrenic space, which would produce torsion of the left hepatic vein.14 The transected liver surface was covered, as far as possible, with the greater omentum. A closed vacuum suction drain was inserted into the subphrenic space.

During the operation, blood transfusion was initiated by the anesthetist when the hemoglobin concentration fell below 80 g/L, or in elderly patients when the electrocardiogram showed features of myocardial ischemia.

POSTOPERATIVE CARE

Postoperatively, patients, particularly those with cirrhosis, were monitored in the intensive care unit with attention to oxygenation, tissue perfusion, and fluid balance. Parenteral

Graph showing the disease-free and overall survival rates of hepatocellular carcinoma patients undergoing hepatectomy.

For the overall cumulative survival, the significant adverse factors included preoperative ICG retention value at 15 minutes, serum alkaline phosphatase level, prothrombin time (Table 5), blood loss volume, blood transfusion, fresh frozen plasma infusion, operation time, finding of preexisting rupture of HCC, iatrogenic rupture of the tumor, application of ultrasonic dissector (Table 6), size of the tumor, number of tumor nodules, involve-
COMMENT

This study demonstrated that long-term survival of patients with HCC after hepatectomy depends on the tumor staging, preoperative hepatic functional reserve, history of blood transfusion, and rupture of HCC. Because preoperative liver function and tumor staging cannot be altered, the surgeon can help improve the prognosis if blood transfusion and iatrogenic tumor rupture can be avoided and if the function of the liver remnant can be preserved.

Tumor-node-metastasis staging incorporates all the pathologic information that adversely affects survival, namely, tumor size (>2 cm), multiplicity, presence of venous permeation, involvement of major branches of the portal and hepatic veins, and lymph node and distant metastases. A significant difference in survival time of the resection margin by the tumor, the presence of venous permeation, portal vein involvement, invasion of adjacent organs, and TNM stage (Table 7). By Cox regression analysis, ICG retention value at 15 minutes, blood transfusion, tumor rupture (including iatrogenic and spontaneous rupture), and TNM stage were independent significant factors that influenced the overall cumulative survival (Table 4).

Has been demonstrated in between different TNM stages. By itself, TNM stage should provide the simplest, yet most accurate, information about long-term survival.

Because HCC often develops on top of cirrhosis, hepatic function reserve is frequently suboptimal. Preoperative evaluation of liver function is, therefore, an important aspect of selecting patients with adequate function for hepatectomy. Of the types of hepatic function tests, the ICG clearance test alone or in combination with other parameters is accepted as a means to select patients for hepatectomy. An ICG retention level of 10% or 14% at 15 minutes was used as a cutoff value for a major hepatectomy, but a higher threshold was adopted at an experienced center. However, a higher ICG cutoff should only be adopted when the surgeon is experienced and the volume of nontumorous liver to be resected is minimal because, even if the patient has an ICG retention value of less than 14% at 15 minutes, liver failure, ascites, infection, and bleeding esophageal varices would still occur if the liver remnant sustains hypoxic injury during and after the hepatectomy. Such hypoxic injury may be a result of massive bleeding, prolonged rotation of the liver for exposure and division of the hepatic veins, prolonged and continuous Pringle maneuver, prolonged inadvertent compression of the portal vein...
Management. Liver regeneration after hepatectomy, remnant during the operation, and the postoperative involved liver resected, the degree of insult to the liver circulation 15 minutes after injection.

Patients with satisfactory liver function.

Liver failure has been shown in previous if the blood loss is as much as 10 L,20 this should not be regarded as an advance in hepatic surgery, because blood transfusion of any amount, as shown by this and other studies,33,34 is related to a shortening of the disease-free periods, further deterioration of liver function may occur as the degree of cirrhosis increases. It seems that there are no effective measures to prevent progression of liver cirrhosis apart from the suggestion that oral supplementation with branched-chain amino acid–enriched solution can preserve liver function.28 Another possible approach is to control the hepatitis B virus with nucleoside analogs after hepatectomy, but a study of this approach has not been done. Interferon may be effective in controlling hepatitis C virus,29 but its use in cirrhotic patients can be dangerous.

Bleeding remains a major problem in hepatectomy. Bleeding may occur during mobilization of the tumor from tearing of the collateral that supplies the tumor, rough handling of the tumor leading to iatrogenic rupture, or laceration of the hepatic vein or during parenchymal transection from intrahepatic branches of the hepatic vein. Previously bleeding of 4 L or more was shown to be detrimental.31,32 Although some patients can survive even though possible in patients with mild cirrhosis,27 is unlikely in patients with moderate cirrhosis or may be insufficient if major damage to the liver remnant has occurred during the hepatectomy. During the follow-up periods, further deterioration of liver function may occur as the degree of cirrhosis increases. It seems that there are no effective measures to prevent progression of liver cirrhosis apart from the suggestion that oral supplementation with branched-chain amino acid–enriched solution can preserve liver function.28 Another possible approach is to control the hepatitis B virus with nucleoside analogs after hepatectomy, but a study of this approach has not been done. Interferon may be effective in controlling hepatitis C virus,29 but its use in cirrhotic patients can be dangerous.

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Table 3. Univariate Analysis of the Influence of Pathological Factors on Disease-Free Survival

<table>
<thead>
<tr>
<th>Factor</th>
<th>Median Survival (SE), mo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size, cm</td>
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</tr>
<tr>
<td>≤2 (n = 14)</td>
<td>61.0 (17.40)</td>
<td>.06</td>
</tr>
<tr>
<td>&gt;2 (n = 60)</td>
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<tr>
<td>No. of tumor nodules</td>
<td></td>
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<td>.02</td>
</tr>
<tr>
<td>Multiple (n = 45)</td>
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<td></td>
</tr>
<tr>
<td>Resection margin, cm</td>
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<td></td>
</tr>
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<td>.53</td>
</tr>
<tr>
<td>&gt;1 (n = 72)</td>
<td>24.7 (5.74)</td>
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<td>Resection margin involved by</td>
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</tr>
<tr>
<td>hepatocellular carcinoma</td>
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<td></td>
</tr>
<tr>
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<td>.04</td>
</tr>
<tr>
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<tr>
<td>Tumor capsule</td>
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</tr>
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<td>Venous permeation</td>
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<td></td>
</tr>
<tr>
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</tr>
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<td>25.9 (4.22)</td>
<td>.066</td>
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<td>Yes (n = 78)</td>
<td>8.3 (2.65)</td>
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<td>Adjacent organ invasion</td>
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<td>.02</td>
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<td>Chronic hepatitis</td>
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<td>No (n = 111)</td>
<td>20.3 (3.92)</td>
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<td>Yes (n = 63)</td>
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<td>TNM stage</td>
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<td>&gt;62.9 (7.21)</td>
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</tr>
<tr>
<td>II (n = 68)</td>
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<td></td>
</tr>
<tr>
<td>III (n = 75)</td>
<td>10.8 (2.74)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>IVA + IVB (n = 19)</td>
<td>5.6 (1.04)</td>
<td></td>
</tr>
</tbody>
</table>

To reduce bleeding during mobilization of the tumor, adequate and wide exposure by a generous incision and adequate illumination of the operative field (eg, by wearing a headlamp) are essential. Adequate exposure is likely to be difficult for a large right-lobe HCC that occupies the entire right subphrenic cavity and is soft owing to extensive necrosis. Apart from the risk of cancer cells disseminating into the systemic circulation, the forceful mobilization of a large right-lobe HCC may lead to iatrogenic rupture of the tumor or tearing of the right hepatic vein. In such a circumstance, a thoracotomy will allow adequate space for mobilization and easy access to the space between the inferior vena cava and posterior surface of the liver, and this will reduce the chance of bleeding. In addition, for segmentectomy of segment 6, 7, or 8, thoracotomy allows the liver transection plane to be perpendicular to the wound, making liver transection more expeditious.

During parenchymal transection, bleeding may occur from branches of the inflow or outflow vasculature. Intermittent use of the Pringle maneuver38 and the ultrasonic dissector37 are effective in reducing blood loss, but cannot prevent bleeding entirely because the ultrasonic dissector may damage the hepatic vein and the Pringle maneuver cannot control bleeding from the hepatic vein. To provide a completely avascular field, total vascular occlusion has been suggested, but total vascular occlusion was shown to be harmful to the liver when compared with the Pringle maneuver in a prospective randomized trial. The difference between these 2 vascular control methods is that the liver cells continue to be nourished by venous backflow during the Pringle maneuver. Thus, function of liver cells is not seriously impaired. Therefore, slow and cautious application of the ultrasonic dissector with intermittent use of the Pringle maneuver is recommended.

To reduce venous bleeding, reduction of central venous pressure to less than 6 mm Hg would be benefi-
However, our patients did not benefit from such a maneuver, because the anesthetists worried that an air embolism was more difficult to manage than the bleeding itself. To reduce the volume of bleeding from the transection surface, prompt hemostasis by suturing is essential. Suturing of individual bleeding points from branches of the hepatic vein is more effective than argon beam coagulation, but suturing, if not performed carefully, can lead to tearing of the hepatic vein and liver parenchyma, and therefore more bleeding. Accurate placement of sutures and cautious knotting are required to prevent iatrogenic induction of further bleeding. Forceful insertion of gauze to pack the space between the transection planes to stop venous bleeding is another iatrogenic cause of bleeding from tearing of branches of the hepatic vein and should be avoided.

To our knowledge, this study shows for the first time that rupture of HCC adversely affects the outcome of hepatectomy. Rupture may be spontaneous, occurring before surgery or during tumor mobilization. The cause of spontaneous rupture is not known, but iatrogenic rupture is likely due to rough handling or forceful mobilization of the tumor in the presence of inadequate wound exposure. Rupture of the tumor can lead to massive bleeding, hypoperfusion of the liver, and seeding of cancer cells into the peritoneal cavity. In an effort to remove a ruptured tumor quickly, a hepatectomy becomes rushed, which leads to even more bleeding and an inadequate tumor-free resection margin. Iatrogenic rupture is more likely if a large right lobe tumor infiltrates into the diaphragm. To prevent such a situation, an added thoracotomy incision will improve the exposure and excision of the diaphragm together with the main bulk of the tumor.

Another important aspect that can influence the long-term survival period is the width of the resection margin. A greater extent of resection, especially major hepatectomy, seems to have a positive impact on long-term survival. Blood loss also seems to play a role, because both blood transfusion and fresh plasma infusion seem to be associated with reduced survival. Operation time is another factor that can influence the surgical outcome. The Pringle maneuver is performed to control arterial inflow to the liver during cancer resection, which results in ischemia of the tumor. However, the Pringle maneuver can cause liver atrophy and damage to the tumor, and therefore it can also lead to tumor rupture.

TNM stage is another important factor that can influence the surgical outcome. Patients with TNM stage I or II seem to have a better survival rate than patients with TNM stage III or IV, especially patients with TNM stage IVB. Cirrhosis is another factor that can influence the surgical outcome. Patients with cirrhosis seem to have a worse survival rate than patients without cirrhosis.

Table 5. Univariate Analysis of the Influence of Surgical Factors on Overall Cumulative Survival

<table>
<thead>
<tr>
<th>Factor</th>
<th>Median Survival (SE), mo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extent of resection</td>
<td></td>
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</tr>
<tr>
<td>Major hepatectomy (n = 153)</td>
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<td>.08</td>
</tr>
<tr>
<td>Minor hepatectomy (n = 58)</td>
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<td>Blood loss, L</td>
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<td></td>
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<tr>
<td>≤4 (n = 174)</td>
<td>42.8 (6.30)</td>
<td>.02</td>
</tr>
<tr>
<td>&gt;4 (n = 37)</td>
<td>9.4 (2.40)</td>
<td></td>
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<tr>
<td>Blood transfusion</td>
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<td>No (n = 60)</td>
<td>85.5 (0)</td>
<td>.04</td>
</tr>
<tr>
<td>Yes (n = 151)</td>
<td>26.1 (4.96)</td>
<td></td>
</tr>
<tr>
<td>Fresh frozen plasma infusion</td>
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<td></td>
</tr>
<tr>
<td>No (n = 157)</td>
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<td></td>
</tr>
<tr>
<td>Yes (n = 54)</td>
<td>11.5 (5.78)</td>
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<td>Operation time, h</td>
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<tr>
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<td>51.9 (7.66)</td>
<td>.04</td>
</tr>
<tr>
<td>&gt;5 (n = 110)</td>
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<td>Pringle maneuver</td>
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<td>49.2 (13.30)</td>
<td>.11</td>
</tr>
<tr>
<td>Yes (n = 111)</td>
<td>28.3 (7.20)</td>
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<td>Ultrasonic dissector</td>
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<td>21.6 (6.37)</td>
<td>.03</td>
</tr>
<tr>
<td>Yes (n = 116)</td>
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<tr>
<td>Preexisting rupture</td>
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<td>.07</td>
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<td>Yes (n = 25)</td>
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<tr>
<td>Iatrogenic rupture</td>
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<tr>
<td>No (n = 177)</td>
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<tr>
<td>Yes (n = 8)</td>
<td>11.5 (11.8)</td>
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Table 6. Univariate Analysis of the Influence of Pathologic Factors on Overall Cumulative Survival

<table>
<thead>
<tr>
<th>Factor</th>
<th>Median Survival (SE)</th>
<th>P</th>
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<tbody>
<tr>
<td>Tumor size, cm</td>
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<tr>
<td>≤2 (n = 15)</td>
<td>89.3 (NA)*</td>
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<td>&gt;2 (n = 196)</td>
<td>31.0 (6.61)</td>
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<td>No. of tumor nodules</td>
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<td>&lt;.001</td>
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<tr>
<td>Multiple (n = 62)</td>
<td>12.0 (2.74)</td>
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<tr>
<td>Resection margin, cm</td>
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<td>.09</td>
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<td>&gt;1 (n = 81)</td>
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<tr>
<td>Resection margin involved by hepatocellular carcinoma</td>
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<td></td>
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<td>No (n = 188)</td>
<td>42.3 (6.97)</td>
<td>.04</td>
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<td>Yes (n = 23)</td>
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<td>Tumor capsule</td>
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<td>Yes (n = 98)</td>
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<td>TNM stage</td>
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<td>I (n = 13)</td>
<td>&gt;89.3 (NA)</td>
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<tr>
<td>II (n = 75)</td>
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<td>III (n = 89)</td>
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<td>IV A + IV B (n = 34)</td>
<td>10.6 (1.92)</td>
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Table 7. Cox Regression Analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Relative Risk (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-Free Survival Rate</td>
<td></td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>1.21 (1.053-1.396)</td>
</tr>
<tr>
<td>TNM stage</td>
<td>1.90 (1.467-2.467)</td>
</tr>
<tr>
<td>Overall Cumulative Survival Rate</td>
<td></td>
</tr>
<tr>
<td>Indocyanine green clearance test</td>
<td>1.036 (1.014-1.059)</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>1.191 (1.078-1.316)</td>
</tr>
<tr>
<td>Tumor rupture</td>
<td>1.482 (1.079-2.037)</td>
</tr>
<tr>
<td>TNM stage</td>
<td>1.621 (1.268-2.071)</td>
</tr>
</tbody>
</table>

*NA indicates not applicable.
gin. The optimal width of the resection margin in hepatectomy for HCC is controversial and was shown to have an adverse effect or none at all. A curative hepatectomy is defined as resection with a tumor-free margin of more than 1 cm. However, recurrence of HCC tends to be multicentric in the liver remnant far from the resection margin and is related to the carcinogenic potential of all hepatocytes affected by the hepatitis B or C virus. Attempts to increase the tumor-free resection margin will necessitate resection of more non-tumorous liver. A fine balance and sound judgement by the surgeon is necessary. During the course of liver transaction, repeated intraoperative ultrasound examination of the tumor in relation to the transaction plane is useful in determining the appropriate margin.

In conclusion, surgical technique is as important as preoperative liver function and tumor staging in the long-term survival of patients with HCC after hepatectomy. The surgeon’s ability to avoid blood transfusion and iatrogenic rupture of the tumor and to preserve liver function will improve the outcome of hepatectomy for HCC. With increased experience and improved surgical technique, many surgeons can perform hepatectomies for HCC without blood transfusions and with a very low hospital mortality rate. Apart from careful selection of patients through liver function screening, refined surgical technique is most likely responsible for the improved outcome of hepatectomy for HCC in recent years.

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REFERENCES