Hepatic Resection for Bilobar Hepatocellular Carcinoma

Is It Justified?

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Hypothesis: Patients with bilobar stage IVa hepatocellular carcinoma (HCC) are generally considered unsuitable for hepatic resection. Recent data suggest that palliative hepatic resection in selected patients with advanced HCC may result in a favorable survival outcome. The aim of the present study was to evaluate the operative outcome and survival benefits of hepatic resection for patients with bilobar HCC.

Design: Retrospective study.

Setting: Tertiary referral center.

Patients: The study comprised 78 patients who were diagnosed as having unilobar HCC and considered initially suitable candidates for curative hepatic resection on preoperative investigations from 1989 to 2000. Bilobar disease with discrete tumor nodules in the contralateral lobe was diagnosed in these patients on laparoscopy (44 patients) or laparotomy (34 patients) with the help of intraoperative ultrasonography. Fifteen patients (19%) underwent palliative hepatic resection (group A), and hepatic resection was not performed in the remaining 63 patients (81%) (group B).

Main Outcome Measures: The clinicopathologic data and operative and survival outcomes of both groups of patients were compared.

Results: The clinicopathologic parameters were comparable in both groups of patients. In group A, 12 patients (80%) underwent major hepatic resection, and the mean ± SEM size of the resected tumors was 8.3 ± 0.9 cm. The operative morbidity and mortality were 20% and 0%, respectively. Treatment for tumors in the contralateral lobe included wedge excision (5 patients), alcohol injection (5 patients), cryotherapy (2 patients), and transarterial oily chemoembolization (3 patients). In group B, treatment for HCC included transarterial oily chemoembolization (42 patients), systemic chemotherapy (3 patients), transarterial oily chemoembolization and systemic chemotherapy (5 patients), cryotherapy (2 patients), tamoxifen (3 patients), and no treatment (8 patients). The median survival of patients in group A was 19.5 months, with 4 patients surviving for more than 3 years. The survival in group A was significantly better than in group B (median = 7.1 months; \( P = .008 \)). On multivariate analysis, hepatic resection and preoperative serum \( \alpha \)-fetoprotein level were the 2 independent factors that significantly affected patient survival.

Conclusions: Hepatic resection for HCC in patients with stage IVa bilobar disease results in a better survival outcome than nonresectional therapies. It should be considered in selected patients with low operative risks and satisfactory liver function.

Arch Surg. 2003;138:100-104

PATIENTS WITH bilobar hepatocellular carcinoma (HCC) (stage IVa disease by International Union Against Cancer classification) are generally considered unsuitable for hepatic resection. Multidisciplinary treatment has often been performed in these patients, such as transarterial oily chemoembolization (TOCE), radiofrequency ablation, percutaneous ethanol injection, and microwave ablation. However, no generally effective treatment for these patients has yet been reported. Despite recent advances in diagnostic modalities, advanced HCC in some patients is only diagnosed on laparoscopy or laparotomy with the help of intraoperative ultrasonography. When bilobar disease is diagnosed intraoperatively, surgeons face the dilemma of whether to proceed with palliative resection, since the survival benefits of this surgical approach are uncertain. Palliative cytoreduction surgery in patients with advanced HCC has been advocated recently. However, its survival benefits over a nonresectional therapeutic approach in this group of patients have not been documented. The aim of our study was to evaluate the operative outcome and survival benefits of hepatic resection in patients with bilobar HCC.
Table 1. Clinical and Laboratory Data of Patients Who Had Stage IVa Bilobar Hepatocellular Carcinoma and Underwent Hepatic Resection (Group A) and Those Who Did Not Undergo Hepatic Resection (Group B)*

<table>
<thead>
<tr>
<th>Clinical Parameter</th>
<th>Group A</th>
<th>Group B</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>15</td>
<td>63</td>
<td>. .</td>
</tr>
<tr>
<td>Sex (male-female)</td>
<td>14:1</td>
<td>56:7</td>
<td>.61</td>
</tr>
<tr>
<td>Age, y</td>
<td>48.8 ± 4.3</td>
<td>51.6 ± 1.6</td>
<td>.49</td>
</tr>
<tr>
<td>Hepatitis B carrier, No. (%)</td>
<td>14 (93)</td>
<td>54 (86)</td>
<td>.49</td>
</tr>
<tr>
<td>Chronic alcoholic, No. (%)</td>
<td>4 (27)</td>
<td>20 (32)</td>
<td>.70</td>
</tr>
<tr>
<td>Serum AFP, ng/mL</td>
<td>120 915 ± 79 674</td>
<td>42 416 ± 14 838</td>
<td>.28</td>
</tr>
<tr>
<td>Serum albumin, g/dL</td>
<td>3.96 ± 0.13</td>
<td>4.0 ± 0.08</td>
<td>.67</td>
</tr>
<tr>
<td>Serum total bilirubin, mg/dL</td>
<td>0.75 ± 0.09</td>
<td>1.31 ± 0.37</td>
<td>.29</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>55.3 ± 6.7</td>
<td>66.8 ± 15.1</td>
<td>.87</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.1 ± 0.9</td>
<td>12.9 ± 0.5</td>
<td>.58</td>
</tr>
<tr>
<td>Prothrombin time, s</td>
<td>11.7 ± 0.4</td>
<td>11.9 ± 0.2</td>
<td>.70</td>
</tr>
<tr>
<td>ICG retention at 15 min, %</td>
<td>10.6 ± 1.4</td>
<td>14.0 ± 1.2</td>
<td>.12</td>
</tr>
<tr>
<td>Child-Pugh grading*</td>
<td>&gt;.99</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Data are expressed as mean (SEM) unless otherwise indicated.

Abbreviations: AFP, α-fetoprotein; AST, aspartate aminotransferase; ICG, indocyanine green.

Of the 2269 patients who were diagnosed as having HCC from January 1989 to December 2000, 673 were considered as having unilobar disease and were deemed suitable for curative hepatic resection after preoperative evaluation according to a standard protocol. Preoperative investigation of the patients included blood biochemistry, α-fetoprotein (AFP) assay, chest x-ray, percutaneous ultrasonography, computed tomography of the abdomen, and hepatic angiography in selected cases. Preoperative liver function was assessed with an indocyanine green clearance test and Child-Pugh grading. Bilobar HCC with discrete tumor nodules in the contralateral lobe was diagnosed in 78 patients intraoperatively during either laparoscopy (44 patients) or laparotomy (34 patients), with the help of intraoperative ultrasonography. Patients who had satellite lesions around the main tumor or direct extension of the tumor to the contralateral lobe and in whom curative resection could be performed with an extended hepatectomy were excluded from our study. Patients with other contraindications, including peritoneal metastasis and portal vein tumor thrombosis, that precluded curative hepatic resection were also excluded. Fifteen (19%) of the 78 patients underwent palliative hepatic resection (group A). Hepatic resection was abandoned in the remaining 63 patients (81%, group B) and various nonresectional therapies, including TOCE, systemic chemotherapy, cryotherapy, and oral tamoxifen, were provided. The clinicopathologic data and operative and survival outcomes of both groups of patients were compared.

Hepatic resection was performed following the standard technique described previously, and an ultrasonic dissector was used for parenchymal transection. All patients received the same perioperative care by the same team of surgeons and were nursed in the intensive care unit during the early postoperative period after hepatic resection. All intraoperative complications and postoperative morbidities were recorded prospectively. Hospital mortality was defined as death during the same period of hospitalization for the hepatic resection. All patients were followed up with serial AFP assay, and ultrasonography or computed tomography scan of the abdomen was performed every 3 months.

The clinical data on all patients were recorded prospectively in a computerized database by a single research assistant. Statistical analysis was performed by the χ² test or the Fisher exact test to compare discrete variables. The Mann-Whitney test was used to compare continuous variables. Survival analysis was estimated by the Kaplan-Meier survival method. Statistical comparison of survival distributions was analyzed by log-rank tests. Multivariate analysis by the Cox proportional hazard regression model was used to identify independent clinical factors that significantly affected patient survival. Statistical analyses were performed by SPSS for Windows software (SPSS Inc, Chicago, Ill). A P value of less than .05 was considered to indicate statistical significance. Numeric values are expressed as means ± SEM unless otherwise stated.

The study comprised 78 patients who had an intraoperative diagnosis of bilobar HCC with discrete tumor nodules in the contralateral lobe. There were 70 men (90%) and 8 women (10%), with a mean age of 51 ± 2.1 years (range, 13-79 years). Fifteen patients underwent palliative hepatic resection (group A), and hepatic resection was not performed in the remaining 63 patients (group B). The clinicopathologic parameters were comparable in both groups of patients (Table 1).

GROUP A

The extent of hepatic resection in group A is presented in Table 2. Twelve patients (80%) underwent major hepatic resection involving 3 or more Couinaud segments. The mean size of resected tumors was 8.3 ± 0.9
Patients (53%) did not receive blood transfusion. The mean operative blood loss was 1.5 ± 0.3 L, and 8 patients required chest tapping (1 patient), pleural effusion that required chest tapping (2 patients), and wound infection (1 patient). There was no hospital death. The mean postoperative hospital stay was 12.2 ± 1.4 days.

Postoperative complications occurred in 3 patients, resulting in an operative morbidity rate of 20%. The complications included chest infection (1 patient), pleural effusion that required chest tapping (1 patient), and wound infection (1 patient). There were 2 hospital deaths from chest infection and bleeding duodenal ulcer, respectively. The mean postoperative hospital stay was 8.7 ± 1.0 days. Various nonsurgical therapies were provided for patients in group B (Table 6). Forty-two patients (67%) received TOCE, while 5 other patients received both TOCE and systemic chemotherapy. The median number of sessions of TOCE received by each patient was 3 (range, 1-24). Eight patients (13%) refused any form of nonsurgical treatment.

**SURVIVAL RESULTS**

The median survival of patients in group A was 19.5 months. Four patients, including 2 patients with normal noncirrhotic liver, survived for more than 3 years. The survival result was significantly better than that of group B (P = .008). At the time of preparation of the manuscript, 12 patients in group A had died of HCC. Three patients, with a median follow-up of 38 months, were alive with residual disease in the liver and pulmonary metastases. The median survival of patients in group B was 7.1 months (Figure). During the same study period, there were 311 patients with HCC who were found to be unsuitable for curative hepatic resection and did not undergo surgery because of bilobar disease detected on preoperative
evaluation (group C). Among them, 175 patients (56%) received transarterial chemoembolization. The median survival of these 311 patients was 6.4 months, and was not different from that of 7.1 months of the patients in group B ($P= .72$). The survival results were significantly worse than those of the patients in group A ($P=.008$, Figure).

Statistical analysis was performed on all 78 patients to identify clinical factors that significantly affected the survival. Eleven potential prognostic discriminants were examined, which included patient factors (age, sex, hepatitis status, preoperative indocyanine green clearance test, serum total bilirubin level, and prothrombin time), tumor factors (preoperative serum AFP level, location and size of the main tumor, and number of tumor nodules), and the treatment factor (hepatic resection or not). On multivariate analysis, hepatic resection and preoperative serum AFP level were the 2 independent factors that significantly affected patient survival (Table 7).

Hepatic resection remains the treatment of choice for HCC and offers the best chance of long-term survival. However, most patients are considered unsuitable for surgical resection at the time of diagnosis because of advanced disease and the presence of concomitant liver cirrhosis. In patients with bilobar multicentric HCC, hepatic resection is usually not recommended because of the high operative risks and the difficulty of total tumor eradication. Multidisciplinary treatment has often been performed for these patients. However, no effective treatment that results in satisfactory survival has been reported. Total heptectomy with liver transplantation to remove all tumors has been recommended for multiple bilobar HCC, but the results of liver transplantation for large and bilobar multifocal HCC have been poor. In addition, its application to malignant liver disease remains limited by the scarce availability of cadaveric grafts, especially in Eastern countries.

Noncurative hepatic resection (otherwise known as palliative or cytoreduction resection) is a new concept in the treatment of advanced HCC. There is some evidence that suggests that removal of as many tumors as possible from the liver may be an important prognostic factor. This interesting concept in the management of HCC goes against the widely held dogma that hepatic resection should be offered only when curative resection is possible. While most hepatic surgeons will challenge the role of noncurative resection in advanced HCC, such a concept is not without rationale. Yamamoto et al suggested that stage IVa HCC was more likely to have slowly growing intrahepatic tumor clusters, and that removal of rapidly growing tumors from such clusters by cytoreduction surgery might be associated with prolonged survival. In addition, even in patients undergoing hepatic resection with a curative intent, the outcome turned out to be palliative in most instances, as evidenced by a postoperative recurrence of 75% to 100%. Such a high incidence of recurrence, nevertheless, has not been considered a deterrent to hepatic resection for HCC because of the availability of effective treatment for recurrence to prolong survival. Therefore, it appears reasonable to propose that combined cytoreductive hepatic resection for a large tumor and ablation of smaller tumor nodules in the contralateral lobe may be an effective treatment for stage IVa bilobar HCC.

Tanaka et al reported hepatic resection in 55 patients with advanced HCC with tumor thrombi in the portal vein, direct invasion or compression of the inferior vena cava, extraluminal bile duct involvement, or bilobar disease. The extension of surgical indication for these patients with advanced HCC was found to result in satisfactory survival. In 1998, Ikai et al also reported the results of hepatic resection in a selected group of patients with stage IVa HCC without lymph node metastasis, and proposed it as a standard therapy for such patients. Patients who had bilobar disease and underwent hepatic resection had a 5-year survival rate of 20%, which was significantly better than that of 8% in patients who had vascular invasion. Although the survival results of patients who had stage IVa bilobar disease appeared satisfactory, the authors did not directly compare survival of these patients with a comparable group who underwent nonresectional multimodality therapies to justify the operative mortality and morbidity rates of 8.4% and 51%, respectively, reported in their series.

### Table 7. Multivariate Analysis Using Cox Proportional Hazard Regression Model on Factors Affecting Overall Cumulative Survival of the 78 Patients With Bilobar Hepatocellular Carcinoma

<table>
<thead>
<tr>
<th>Independent Factor</th>
<th>$P$ Value</th>
<th>Relative Risk</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum α-fetoprotein level &gt;250 ng/mL</td>
<td>.01</td>
<td>1.957</td>
<td>1.148-3.334</td>
</tr>
<tr>
<td>Hepatic resection</td>
<td>.04</td>
<td>0.493</td>
<td>0.254-0.956</td>
</tr>
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</table>
To justify noncurative hepatic resection for stage IVa bilobar HCC, some prerequisites should be satisfied. First, hepatic resection should be associated with a minimal major operative morbidity and a near-zero operative mortality. Second, effective treatment should be available for the smaller lesions in the contralateral lobe. Third, hepatic resection should result in improved survival compared with nonresectional therapies. In our study, hepatic resection in patients with bilobar HCC was found to be associated with acceptable morbidity and zero operative mortality, which were comparable with those who underwent curative hepatic resection. 25,20 Prolongation of survival in patients with advanced HCC should not be expected with cytoablation surgery alone. Therefore, multidisciplinary treatment, which included wedge excision, local ablative therapy, and postoperative regional chemoembolization, was provided for all patients with tumors in the contralateral lobe. This aggressive surgical approach was also shown to result in satisfactory survival, which was superior to that of patients with comparable clinicopathologic parameters treated by nonresectional therapies (group B).

Major limitations of our study included the small number of patients recruited and the nonrandomized selection of patients with bilobar HCC for hepatic resection. The decision to perform noncurative hepatic resection in group A was made at the time of laparoscopy or laparotomy. This resulted in a potential bias toward selecting patients based on favorable clinical and pathologic parameters. It can be observed that several important clinical parameters, including preoperative indocyanine green and serum bilirubin levels, were worse in group B (Table 1), although the difference did not reach statistical significance. However, on multivariate analysis, hepatic resection was identified to be one of the independent significant factors affecting survival of patients with bilobar HCC. In the future, a prospective randomized study to validate the findings of our study will be performed. Another deficiency of the present retrospective study is that the studied population only included patients with stage IVa bilobar HCC with intraoperative diagnosis of small tumor nodules in the contralateral lobe. Further investigation is required to document whether the results of our study can be extrapolated to patients with a preoperative diagnosis of bilobar disease.

In conclusion, hepatic resection for HCC in patients with bilobar stage IVa disease results in a better survival outcome when compared with those treated by nonresectional therapies. This treatment strategy should be considered in selected patients with low operative risks and satisfactory liver function. Further prospective randomized studies are required to evaluate the survival benefits of this aggressive surgical approach.

Accepted for publication September 8, 2002.

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REFERENCES