Primary Results of Salvage Liver Transplantation in the Patients with Unresectable Recurrent Hepatocellular Carcinoma after Initial Liver Resection

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ABSTRACT

Background/Aims: Salvage liver transplantation (SLT) is a treatment choice for recurrent HCC fulfilling the Milan criteria. However, there is no consensus on the value of SLT for recurrent HCC beyond the Milan criteria, especially for unresectable HCC. Methodology: Eleven patients with recurrent HCC underwent SLT in Tongji Hospital between January 2003 and July 2010. All the 11 patients were considered unresectable because of deteriorated liver function, multiple bilateral tumors or vascular invasion. The outcomes and prognostic factors of these patients were analyzed. Results: At a median follow up of 30 months, six patients were alive. Four patients died from HCC recurrence, and one died from gastrointestinal cancer. The 1-, 2-, and 3-year recurrence and overall survival rates after SLT were 58.4%, 72.3% and 86.1%, respectively, and 90.9%, 40.6% and 40.6%, respectively. Vascular invasion, recurrent HCC beyond the Milan criteria and early recurrence within 18 months after initial resection were negative prognostic factors of SLT for recurrent HCC. Conclusions: SLT can be recommended as an alternative treatment for recurrent HCC fulfilling the Milan criteria. For those beyond the Milan criteria or with vascular invasion, or early recurrence after initial resection, however, SLT is not beneficial and should not be recommended.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide, with a particularly high prevalence in Asia and Africa due to a high incidence of hepatitis B-related and hepatitis C-related cirrhosis.(1, 2) Liver resection and liver transplantation are the potentially curative treatments for HCC.(3) The 5-year survival rates up to 83% have been reported after liver transplantation for HCC within the Milan criteria, which is comparable to those for non-malignant indications.(4) Liver resection also achieved 5-year survivals of 67% in small HCC (≤5cm) and 56% in large HCC (>5cm).(4) Due to organ shortage, Liver resection became an option as initial treatment for the patients with HCC although meeting the Milan criteria. Intrahepatic recurrence is a main cause affecting long-term survival after liver resection. It is reported that 75%-85% of patients experience tumor recurrence within 5 years after resection in the setting of hepatitis B-related and hepatitis C-related cirrhosis.(5, 6) For recurrent HCC repeat liver resection has been reported to be an effective treatment in selected patients. The 5-year survival rates of 30%-69% after repeat resection were reported.(6-9) However, most patients with recurrent HCC are associated with progressive chronic liver disease and poor liver function reserve which usually contraindicate repeat resection.(10) Nonsurgical methods, such as radiofrequency ablation, ethanol injection, and transcatheter chemoembolization (TACE), have been proposed for the treatment of intrahepatic recurrences, but the long-term outcomes by these methods is far from satisfactory.(11-13) Surgical removal is still believed to be the most effective therapy that is potentially curative for recurrent HCC. Recently, several studies have indicated that salvage liver transplantation (SLT) is a choice of treatment for recurrent HCC fulfilling the Milan criteria. (14,15) However, for those with recurrent HCC beyond the Milan criteria, especially for those unresectable HCC, such as insufficient liver function reserve, multiple bilateral tumors and/or vascular invasion, the efficiency of SLT have not been fully evaluated.(16) In this study, we retrospectively analyzed the outcomes of SLT in 11 patients with unresectable recurrent HCC and the prognostic factors associated with SLT.

METHODOLOGY

From January 2003 to July 2010, 11 patients underwent salvage liver transplantation (SLT) for recurrent HCC after initial liver resection for primary HCC in Tongji hospital, Huazhong University of Science and Technology. This study was approved by the medical ethics committee of Tongji Hospital, and in accordance...
with the ethical standards of the Helsinki Declaration. Informed consent was obtained from each patient. Clinicopathological data including patients’ demographic characteristics, liver functional status, tumor status and histopathological findings of the tumors were prospectively collected. All the 11 patients were with recurrent HCC that was unresectable because of deteriorated liver function in two cases, multiple bilobar tumors and/or vascular invasion in nine cases. The mean and median times from initial resection to recurrence were 17.2 and 7 months, respectively. The initial resection of HCC was performed in our hospital (n=8) or other hospitals (n=3) from March 1998 to September 2009.

All patients were followed up regularly, with serum α-fetoprotein (AFP), ultrasonography and chest radiography performed once every 2 months in the first 2 years after surgery and at 3 to 6 month intervals thereafter. Further investigations with computed tomography, magnetic resonance imaging, hepatic digital subtraction angiography or bone scan were performed if tumor recurrence or metastases was suspected. The mean and median follow-up periods were 44.8 and 30 months, respectively, with a range of 13-114 months.

Statistical analysis was performed with SPSS 17.0 software. The recurrence and overall survival curves were calculated by using the Kaplan-Meier method.

RESULTS
The clinicopathological characteristics of patients and the outcomes of salvage liver transplantation

The clinicopathological characteristics of patients undergoing SLT were presented in Table 1. All the 11 patients were male. The median age was 43 years ranging from 37 to 60 years. All the patients were diagnosed with liver cirrhosis histologically, and with positive hepatitis B surface antigen. Six (54.5%) patients were with Child grade A, three (27.3%) with Child grade B and the other two (18.2%) with Child grade C. Among the 11 patients undergoing SLT for HCC recurrence, the mean and median AFP levels were 1674 ng/ml and 110 ng/ml, respectively. Two (18.2%) patients had a solitary recurrent tumor; and nine (81.8%) patients had multiple recurrent tumors (2-6 tumors). The mean and median largest tumor diameters of the recurrent tumors were 4.5 and 3.5 cm, respectively, with a range of 2.8-7.6 cm. Five (45.5%) patients had vascular invasion. Eight patients (72.7%) had recurrent HCC beyond the Milan criteria. The histological grade of recurrent HCC were diagnosis with well differentiation in one patient, moderate differentiation in seven patients and poor differentiation in three patients.

The median waiting time for SLT since tumor recurrence was 2 months (range, 8 days to 21 months). Six patients received TACE as bridging therapy before SLT. The median operating time was 5.7 hours (range, 4.5-8.2 hours). All the patients required transfusion during operation, and the median transfusion was 8U (range, 4-16U). The mortality of this cohort was zero, and morbidity was 5.45% (6/11). Complications included large amount of ascites in 1 patient, pleural effusion and/or pulmonary infection in 4 patients, intra-abdominal hemorrhage in 1 patient, biliary duct stricture in two patients and portal vein thrombosis that required re-operation in one patient.

At a median follow-up of 30 months, 9 of the 11 patients (81.8%) developed recurrence after SLT, including 3 patients within the liver graft and 6 patients with lung metastasis. The recurrence-free time after SLT ranged from 4-49 months. Six patients were alive. Four patients died from HCC recurrence at 8, 14, 16, and 18 postoperative months, respectively, and 1 died from gastric cancer which was irrelevant to HCC recurrence at 13 postoperative months. The survival time after SLT ranged from 8-73 months (Figure 1). The 1-, 2-, and 3-year recurrence rates after SLT were 58.4%, 72.3% and 86.1%, respectively. The 1-, 2-, and 3-year overall survival rates after SLT were 90.9%, 40.6% and 40.6%, respectively (Figure 2).

Prognostic factors of salvage liver transplantation for recurrent HCC

In order to identify the adverse prognostics factors of SLT for recurrent HCC, the 11 patients undergoing SLT for recurrent HCC were then divided into the subgroups by tumor differentiation, vascular invasion, Milan criteria and time from initial resection to recurrence (Table 2). Among the 11 patients, 8 patients were with well or moderate differentiation of recurrent HCC. Two of them died from HCC recurrence at 8 and 18 postoperative months, respectively and 1 died from gastric cancer irrelevant to HCC at 13 postoperative months. Five patients are currently alive for 12, 12, 14, 55 and 73 postoperative months, respectively. The other 3 patients were with poor differentiation of recurrent HCC. Two of them died from HCC recurrence at 14 and 16 postoperative months, respectively, and 1 patient is currently alive for 30 postoperative months. Five patients had recurrent HCC with vascular invasion. Four of them died from HCC recurrence at 8, 14, 16 and 18 months, respectively, and only one patient still alive up to 22 months with lung metastasis. The median survival of the 5 patients with vascular invasion was 16 months. On the contrary, among the 6 patients without vascular invasion, 5 are currently alive for 12, 12, 14, 55 and 73 months, respectively. Only one died from gastric cancer irrelevant to HCC at 13 postoperative months. Three patients had recurrent HCC fulfilling the Milan criteria and they are currently alive for 12, 55 and 73 postoperative months, respectively. Eight patients had recurrent HCC beyond the Milan criteria. Four patients died from HCC recurrence at 8, 14, 16 and 18 postoperative months, respectively. One patient died from gastric cancer at 13 months and the other 3 patients are still alive at 12, 14 and 30 months, respectively. Furthermore, 7 patients had early recurrence occurring in less than or equal to 18 months after initial resection. Three patients died from HCC recurrence at 8, 14 and 18 months after SLT, respectively, and 1 died from gastric cancer at 13 months. The other three patients are alive for 12, 12 and 14 months after operation. The median survival time of the 7 patients with early recurrence was 18 months. Four patients had late recurrence occurring in more than 18 months. One died at 16 months and the other 3 are still alive at 30, 55 and 73 months, respectively. Taken together, vascular invasion, recurrent HCC beyond the Milan criteria and early recurrent HCC occurring within 18 months after initial resection are important prognostic factors for SLT.

DISCUSSION

The concept of SLT was previously advocated to apply to the patients who had developed recurrent HCC fulfill-
ing the Milan criteria or liver failure. Adam reported that the 5-year survival after SLT was poorer than those after primary liver transplantation (41% versus 61%), which might be largely attributed to the much higher operative mortality in the SLT group (28.6% vs 2.1%). In contrast, Belghiti and Del Gaudio have reported that SLT could achieve similar long-term survival as primary liver transplantation, and the operative mortality and morbidity were similar between SLT and primary liver transplantation. These studies suggested that SLT could be an effective treatment in selected patients with early recurrent HCC. Such a strategy, however, is only applicable in the patients with recurrent tumors fulfilling the Milan criteria. In patients with recurrent HCC beyond the Milan criteria, the value of SLT has not been fully investigated. In this cohort, three patients had recurrent HCC fulfilling the Milan criteria, and all of them are currently alive with the follow-up periods of 12, 55 and 73 months after SLT, respectively. This result supports the conclusions that SLT is an effective treatment in selected patients with recurrent HCC fulfilling the Milan criteria. However, the survival of this cohort of patients with recurrent HCC beyond the Milan criteria after SLT was worse than those undergoing primary liver transplantation for HCC beyond the Milan criteria in other studies. This result indicated that SLT may not be suitable for the patients with recurrent HCC beyond the Milan criteria. However, increasing patient numbers and duration of follow-up may further clarify the value of SLT in treatment of these kinds of patients.

Most studies have showed that vascular invasion was an adverse prognostic factor for patients undergoing liver transplantation for HCC. In the present SLT group, the median survival time of the five patients with vascular invasion was only 16 months. Several studies have found that SLT was an effective treatment in the patients with recurrent HCC fulfilling the Milan criteria. In this cohort, seven of eight SLT patients who had beyond Milan criteria recurrence after initial liver resection also showed tumor recurrence after SLT. The survivals of eight patients were poor, with a median survival time of 16 months. Our study suggested that the Milan criteria is still a good indication of SLT for recurrent HCC. The interval time from initial resection to recurrence may signify the underlying pathogenesis of recurrent tumors. In our previous study of 82 patients with intrahepatic recurrence, 88.9% of early recurrences occurring in less than or equal to 18 months after initial resection were classified as intrahepatic metastasis by histological study, whereas 86.5% of the late recurrences occurring in more than 18 months after initial resection were multicentric occurrence due to underlying chronic liver disease. We found that early recurrence occurring in less than or equal to 18 months after initial resection was identified as an independent prognostic factor of overall survival after repeat liver resection. In this study, 7 patients had early recurrence after initial resection and their median survival time was only 18 months. Four patients had late recurrence. One died at 16 months and the other three are still alive at 30, 55, 73 months. There was also a trend that the patients with early recurrence had poorer survival than those with late recurrence after SLT. Our observations were conflicted with the report by Ng who demonstrated that SLT may be more beneficial to patients with early recurrence than nontransplant therapies. However, early recurrence is closely linked to poor tumor differentiation, microvascular invasion, intrahepatic metastasis, or even extrahepatic metastasis. Previous studies had confirmed that patients with early recurrence had poorer survival than those with late recurrence after repeat liver resection. The present study further showed that the patients with early recurrence had poorer survival than those with late recurrence after SLT. Therefore, nonsurgical therapies, but not repeat liver resection or salvage liver transplantation, should be recommended for these patients with early recurrence. However, to provide clinical evidence of high scientific significance on this issue, a large-scale prospective clinical study would be desirable. Collectively, the presence of vascular invasion, recurrent HCC beyond the Milan criteria and early recurrence after initial resection signify a higher aggressiveness of the tumor and poorer prognosis, and SLT should not be recommended for these kinds of patients.

In summary, SLT can achieve long-term survivals in patients with recurrent HCC fulfilling the Milan criteria. The presence of vascular invasion, recurrent HCC beyond the Milan criteria and early recurrence after initial resection may be the adverse prognostics factors of SLT for recurrent HCC, and SLT could not deliver much survival benefit to them. SLT could serve as an alternative treatment for the patients with recurrent HCC fulfilling the Milan criteria, and should not be recommended for those patients who had recurrent HCC with vascular invasion or beyond the Milan criteria, or the patients with early recurrence after initial resection.

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REFERENCES


FIGURE 1. The survival time of each patient after salvage liver transplantation

FIGURE 2. The recurrence (A) and overall survival (B) after salvage liver transplantation
**TABLE 1.** Clinicopathological characteristics of salvage liver transplantation patients.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Gender/Age (yr)</th>
<th>RFS time after IHR (mo)</th>
<th>Milan criteria at SLT</th>
<th>Maximal tumor size (cm)</th>
<th>Number of tumors</th>
<th>Vascular invasion</th>
<th>Cause of unresectability</th>
<th>Recurrence after SLT</th>
<th>RFS time after SLT (mo)</th>
<th>Survival period after SLT (mo)</th>
<th>State</th>
<th>Cause of death</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>M/43</td>
<td>beyond</td>
<td>2</td>
<td>3</td>
<td>present</td>
<td>multiple bilobar tumors</td>
<td>yes</td>
<td>4</td>
<td>8</td>
<td>dead</td>
<td>HCC recurrence</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>M/47</td>
<td>beyond</td>
<td>8.8</td>
<td>3</td>
<td>absent</td>
<td>multiple bilobar tumors</td>
<td>yes</td>
<td>6</td>
<td>12</td>
<td>alive</td>
<td>HCC recurrence</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>M/41</td>
<td>beyond</td>
<td>2</td>
<td>1</td>
<td>absent</td>
<td>deteriorated liver function</td>
<td>multiple bilobar tumors</td>
<td>no</td>
<td>12</td>
<td>alive</td>
<td>HCC recurrence</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>M/60</td>
<td>beyond</td>
<td>4.5</td>
<td>3</td>
<td>absent</td>
<td>multiple bilobar tumors</td>
<td>no</td>
<td>13</td>
<td>13</td>
<td>dead</td>
<td>other disease</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>M/43</td>
<td>beyond</td>
<td>3.5</td>
<td>2</td>
<td>present</td>
<td>multiple bilobar tumors</td>
<td>yes</td>
<td>9</td>
<td>14</td>
<td>dead</td>
<td>HCC recurrence</td>
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</tr>
<tr>
<td>6</td>
<td>M/43</td>
<td>beyond</td>
<td>4.3</td>
<td>6</td>
<td>absent</td>
<td>multiple bilobar tumors</td>
<td>yes</td>
<td>6</td>
<td>14</td>
<td>alive</td>
<td>HCC recurrence</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>M/42</td>
<td>beyond</td>
<td>8</td>
<td>2</td>
<td>absent</td>
<td>multiple bilobar tumors</td>
<td>yes</td>
<td>8</td>
<td>16</td>
<td>dead</td>
<td>HCC recurrence</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>M/55</td>
<td>beyond</td>
<td>3</td>
<td>1</td>
<td>present</td>
<td>major branches of portal vein invasion</td>
<td>multiple bilobar tumors</td>
<td>yes</td>
<td>8</td>
<td>18</td>
<td>dead</td>
<td>HCC recurrence</td>
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<tr>
<td>9</td>
<td>M/37</td>
<td>beyond</td>
<td>8.2</td>
<td>2</td>
<td>present</td>
<td>multiple bilobar tumors</td>
<td>yes</td>
<td>22</td>
<td>30</td>
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<td></td>
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<td>10</td>
<td>M/51</td>
<td>beyond</td>
<td>3</td>
<td>3</td>
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<td>deteriorated liver function</td>
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<td>27</td>
<td>55</td>
<td>alive</td>
<td>HCC recurrence</td>
</tr>
<tr>
<td>11</td>
<td>M/47</td>
<td>within</td>
<td>2.5</td>
<td>2</td>
<td>absent</td>
<td>multiple bilobar tumors</td>
<td>yes</td>
<td>49</td>
<td>73</td>
<td>alive</td>
<td>HCC recurrence</td>
<td></td>
</tr>
</tbody>
</table>

RFS, recurrence-free survival; IHR, initial hepatic resection; SLT, salvage liver transplantation; HCC, hepatocellular carcinoma.
### TABLE 2. Survival analysis of subgroups according to adverse prognostic factors of SLT for recurrent HCC.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Histological grade</th>
<th>Vascular invasion</th>
<th>Milan criteria</th>
<th>Time from initial resection to recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Well/ moderate</td>
<td>poor</td>
<td>absent</td>
<td>present</td>
</tr>
<tr>
<td>Survival time (mo)</td>
<td>1</td>
<td>8</td>
<td>14</td>
<td>12+</td>
</tr>
<tr>
<td>2</td>
<td>12+</td>
<td>16</td>
<td>12+</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>12+</td>
<td>30+</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>14+</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>14+</td>
<td>55+</td>
<td>30+</td>
<td>14+</td>
</tr>
<tr>
<td>6</td>
<td>18</td>
<td>73+</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>7</td>
<td>55+</td>
<td></td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>8</td>
<td>73+</td>
<td></td>
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</tr>
</tbody>
</table>

+: the patient is currently alive.