Management of Patients with Recurrent Hepatocellular Carcinoma Following Living Donor Liver Transplantation: A Single Center Experience

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Abstract

Objective:
Tumor recurrence is the most important predictive factor for the survival of patients following liver transplantation for hepatocellular carcinoma (HCC). The management of recurrent HCC remains controversial. In this study, we presented the clinical outcomes of patients with recurrent HCC following living donor liver transplantation.

Material and Methods:
Of the 109 patients who underwent liver transplantation due to hepatocellular carcinoma, sixteen (14.7%) developed tumor recurrence and were included in the study. We analyzed the management of patients with recurrent tumors and their outcomes.

Results:
The mean age of patients included in the study was 55.2 ± 7.82 (28–65) years, and 13 patients (81%) were male. The mean follow-up and time to recurrence were 25.8 ± 19.2 (5–78) months and 11 ± 9.4 (4–26) months, respectively. Four patients developed recurrence in the liver graft and 12 (75%) developed recurrence in extrahepatic organs. Of these patients, seven had surgical treatment, seven received chemotherapy, and two did not receive any treatment. All four surviving patients received surgical treatment.

Conclusion:
Recurrence of HCC following liver transplantation generally occurs in the first two years and in extrahepatic organs. The most effective treatment for patients with single and isolated recurrent tumors is surgery. However, the long-term survival differed according to the type of recurrence, depending on which organs recurrence occurred in and whether recurrence was in single or multiple locations. Therefore, the treatment strategy should be individualized for longer survival.

Keywords:
The management of HCC, Recurrent HCC, Living donor liver transplantation

Introduction
Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third most common cause of cancer-related death in the world(1). Most cases of HCC arise from cirrhosis. The most effective treatment for HCC arising from cirrhosis is liver transplantation (LT), because LT eliminates both HCC and the underlying cirrhotic liver(3,4). However, the main risk for patients after LT is HCC recurrence, which dramatically decreases the survival rate(5). Despite strict policies, recurrence rates are still approximately 10–30%(6). Several criteria are used during patient selection to predict the risk of HCC recurrence following LT(7,8). In addition to tumor size and number, the factors that affect HCC recurrence after LT include vascular or microvascular invasion, tumor differentiation, and elevated alpha-fetoprotein (AFP) levels(9,10,11). Recurrence is most likely in the first two years...
after LT, but it can occur earlier in HCC patients with large, poorly differentiated tumors\(^{(12)}\).

Currently, different therapeutic modalities such as surgical resection, radiofrequency ablation, embolization, and systemic treatment have been implemented for recurrent HCC\(^{(5,13,14)}\). However, there is no consensus regarding a standard treatment model in the literature, and the best treatment for recurrent HCC remains unclear. The aim of this study was to report our experience regarding the management of recurrent HCC following living donor liver transplantation (LDLT).

**Patients and Methods**

This study investigated 109 patients with HCC due to liver cirrhosis who underwent right lobe LDLT between July 2004 and July 2012. We reviewed the data for 16 of these patients who developed recurrence of HCC after transplantation. The variables recorded included patient demographics, the number and sizes of pre-transplantation tumors, recurrence dates, treatments used for recurrence, Model for End-Stage Liver Disease (MELD) and Child-Pugh scores, and preoperative AFP levels.

When selecting patients for LDLT, the Milan criteria and the University of California, San Francisco (UCSF) criteria were observed. The Milan criteria were: solitary tumor up to 5 cm in size or a maximum of 3 tumor nodules with each no larger than 3 cm\(^{(7)}\). The UCSF criteria were: 1 tumor with a diameter ≤ 6.5 cm or a maximum of 3 tumor nodules each with a diameter ≤ 4.5 cm, and the sum of the tumor diameters ≤ 8 cm\(^{(8)}\). LDLT was considered for HCC patients if they met the following criteria: HCC was confined to the liver (regardless of tumor size or number), and there was no radiological evidence of vascular invasion.

Pathological staging of liver explants was completed by reviewing pathology reports. The sizes, numbers, and distributions of tumors and the presence of microvascular or macrovascular invasion were noted. Based on the tumor sizes and numbers, each tumor in an explant liver was staged as either meeting or exceeding the Milan and UCSF criteria. The standard immunosuppression protocol used after transplantation was based on an anticalcineurin (ACN) agent (tacrolimus or cyclosporine) combined with mycophenolate and corticosteroids. Patients with HCC recurrence received both surgical resection and systemic treatment with concomitant administration of sorafenib, an inhibitor of multiple tyrosine kinases, and mammalian target of rapamycin (mTOR) inhibitors. The patients were administered a daily dose of 400 mg sorafenib and the mTOR inhibitor sirolimus. The dose of sirolimus was adjusted based on its level. In these patients, the level of immunosuppression agents was kept low.

**Statistics**

The results for continuous variables are given as means ± standard deviations (SD), and results for categorical variables are given as numbers (percents). Results for normally distributed continuous variables were compared by the Student’s t-test. Survival was assessed using the Kaplan–Meier method, with comparisons made using a log-rank test. P-values of < 0.05 were considered significant.

**Results**

The 16 patients who developed recurrent HCC following LDLT were assessed in this study. The mean age of these patients was 55.2 ± 7.82 (28–65) years, and 13 patients (81%) were male. The demographic data are listed in (Table 1). Of the etiologic factors for cirrhosis, 12 patients (75%) had hepatitis B, one had hepatitis C, one had autoimmune hepatitis, and two had cryptogenic cirrhosis. Four patients received treatment prior to transplantation for HCC (Table 2). Pre-transplant treatment included segmentectomy, left and right hepatectomy, and radio frequency ablation (RFA). The mean time from diagnosis of HCC to LDLT was 38.6 ± 29.3 days. The mean tumor number, mean tumor size, and total tumor size were 5.31 ± 6.15 (1–20), 53.75 ± 30.06 (20–140) mm, and 99 ± 50.67 (27–230) mm, respectively. Thirteen (81.3%) patients had HCC with multifocality, and 4 (25%) had vascular invasion. Fourteen (87.5%) had HCC beyond the Milan criteria, and 10 (62.5%) had HCC beyond the UCSF criteria.
left adrenal. One patient underwent combined right adrenalectomy and right nephrectomy and was still alive at the completion of the study, whereas the other two patients underwent only adrenalectomy and both died of recurrence. Two patients had recurrence in the iliac and spinal bones and received chemotherapy, and one of these patients had recurrence in the cranial tissue and received no treatment. Three patients had recurrence in the lung, and all of them underwent lobectomy.

Of the 16 patients who underwent treatment for recurrent HCC, four patients were free of disease at the completion of the study. Of these four patients, three underwent lobectomy due to recurrence in the lung and one underwent surrenalectomy and nephrectomy due to recurrence in the right adrenal gland and right kidney (Table 2). All surviving patients had moderate tumor differentiation. In the four patients who received treatment prior to transplantation, recurrence occurred outside of the transplant liver.

We assessed prognostic factors possibly associated with cancer-related death after HCC recurrence by using univariate and multivariate analyses. No significant associations were found between survival and patient age, cirrhosis etiology, preoperative AFP levels, MELD and Child-Pugh scores, numbers of tumors, tumor multifocality, or tumors that exceeded the Milan and UCSF criteria (all p > 0.05). Patients who died of cancer had significantly larger tumors (51.67 ± 32.49 mm versus 34.56 ± 20.57 mm;
Table 2: The characteristics of patients and tumors

<table>
<thead>
<tr>
<th>No.</th>
<th>Pre-transplant treatment</th>
<th>Follow up (month)</th>
<th>Time to recurrence (month)</th>
<th>Recurrence location</th>
<th>Treatment for recurrence</th>
<th>Survival</th>
<th>Length of Survival after recurrence (month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>32</td>
<td>26</td>
<td>Intra-abdominal</td>
<td>No</td>
<td>Exitus</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>9.5</td>
<td>7</td>
<td>Bone</td>
<td>Chemotherapy</td>
<td>Exitus</td>
<td>2.5</td>
</tr>
<tr>
<td>3</td>
<td>RFA</td>
<td>17.8</td>
<td>6.5</td>
<td>Lung</td>
<td>Lobectomy</td>
<td>Live</td>
<td>11.3</td>
</tr>
<tr>
<td>4</td>
<td>Segmentectomy</td>
<td>11.5</td>
<td>7</td>
<td>Intra-abdominal</td>
<td>Chemotherapy</td>
<td>Exitus</td>
<td>4.5</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>17</td>
<td>13.5</td>
<td>Cranial</td>
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<td>Exitus</td>
<td>3.5</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td>27.4</td>
<td>Liver</td>
<td>Surgical resection and RFA</td>
<td>Exitus</td>
<td>19</td>
</tr>
<tr>
<td>7</td>
<td>Left hepatectomy</td>
<td>47</td>
<td>28.7</td>
<td>Intra-abdominal</td>
<td>Chemotherapy</td>
<td>Exitus</td>
<td>18.3</td>
</tr>
<tr>
<td>8</td>
<td>Right hepatectomy</td>
<td>42</td>
<td>28</td>
<td>Right Surrinal</td>
<td>Surranelectomy</td>
<td>Exitus</td>
<td>14</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>16.5</td>
<td>6.5</td>
<td>Liver</td>
<td>Chemotherapy</td>
<td>Exitus</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>4.9</td>
<td>3.5</td>
<td>Liver</td>
<td>Chemotherapy</td>
<td>Exitus</td>
<td>1.4</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>4.8</td>
<td>2.8</td>
<td>Liver</td>
<td>Chemotherapy</td>
<td>Exitus</td>
<td>2</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>75</td>
<td>24</td>
<td>Lung</td>
<td>Lobectomy</td>
<td>Live</td>
<td>51</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>23</td>
<td>4</td>
<td>Right surrenal+right kidney</td>
<td>Surranelectomi</td>
<td>Live</td>
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<td>14</td>
<td></td>
<td>36.5</td>
<td>9.5</td>
<td>Left surrenal</td>
<td>Surrenalectomy</td>
<td>Exitus</td>
<td>27</td>
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<td>15</td>
<td></td>
<td>21.4</td>
<td>13.7</td>
<td>Lung</td>
<td>Lobectomy</td>
<td>Live</td>
<td>7.7</td>
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<td>16</td>
<td></td>
<td>5.3</td>
<td>2.5</td>
<td>Bone</td>
<td>Chemotherapy</td>
<td>Exitus</td>
<td>2.8</td>
</tr>
</tbody>
</table>

$p = 0.022$ and higher rates of poorly differentiated tumors ($5 (41.7\%)$ versus $9 (9.6\%); p = 0.004$). By multivariate analysis, only poorly differentiated tumors were associated with a lower survival rate (OR = 8.656, 95% CI: 2.01–37.16; p = 0.004).

To show the impact of recurrence on survival, we compared the survival rates of patients with and without recurrence by Kaplan–Meier analysis (Figure 1). The overall patient survival rate was 75.2%. The overall survival rates for those without recurrence and those with recurrence were 83% and 25%, respectively. The survival rate was
significantly lower for patients with recurrence (Figure 1; Kaplan–Meier analysis, log rank test: p < 0.001). The 1-, 3-, and 5-year survival rates for those without HCC recurrence were 85.5%, 79.9%, and 71.7%, respectively, and these rates were 54.3%, 9.04%, and 9.04%, respectively, for patients with HCC recurrence. For all patients, the mean life expectancy was 65 ± 4.3 months (range: 56–73 months), whereas it was 28.6 ± 5.5 months (17–39 months) for patients with HCC recurrence and 74.3 ± 4.2 months (66–83 months) for patients without recurrence. These life expectancies were significantly different. The mean life expectancy was 21.4–14.5 (11.3–51) months in patients who had surgical treatment for recurrent HCC, whereas it was 6.7 ± 6.4 (2–18.3) months in patients who received chemotherapy for recurrent HCC (p = 0.003).

Discussion

Our data showed that the most predictive factor for patient survival is recurrence of HCC after liver transplantation, and these results are consistent with previous reports(5,15). Our results demonstrate that if recurrence is a solitary lesion or if it is amenable to surgery, surgical resection should be the first treatment option because it increases the disease-free survival rate.

The treatment of recurrent HCC after LT is chosen based on the location of the recurrent tumor and the extent the tumor has spread. Kornberg et al. showed that surgical management is the best option for treating a single tumor that has recurred two years following LT(16). In this study, four out of seven (57%) patients survived who underwent surgical treatment for recurrent HCC, whereas no patient survived from those who received systemic chemotherapy. Moreover, patients who underwent surgical resection had a significantly longer life expectancy compared to those who did not undergo surgical treatment in this study. All three patients with recurrence in the lung who then underwent surgical resection survived, and one of these patients was free of disease 51 months after lobectomy for recurrent HCC. The effectiveness of surgical treatment for recurrent HCC in this study was consistent with previous studies, which demonstrated that surgical treatment increases disease-free survival(6,16,17). The recurrence in the lungs, as seen in our patients, is generally a single lesion that likely does not show symptoms and is generally diagnosed during routine follow up(18). When these lesions are diagnosed at an early stage, the patient has an increased chance of successful treatment with surgery and an increased survival rate(19). It is not clear whether the improved surgical treatment results are due to its effectiveness or because the patients who underwent surgery had a single, isolated lesion, which improved their outcomes compared to patients who did not undergo surgical treatment. To examine this issue, there is a need for larger studies in the future. Consistent with previous reports, most of our patients had recurrence of HCC outside of the transplant liver and most were not amenable to surgery(20,21,22). The reason why most recurrence takes place outside of the graft liver may depend on tumor biology, but the exact reason is yet unclear(23).

For the management of recurrence in multiple locations that is not amenable to surgical treatment, it has been reported that sorafenib alone or sorafenib with an mTOR inhibitor could provide an alternative treatment(24,25). The use of sorafenib with an mTOR inhibitor has been shown to be an effective and safe option to treat recurrent HCC(26,27,28). In our study, seven patients with recurrent HCC, who were not amenable to surgery, received an mTOR inhibitor that was switched from a calcineurin inhibitor. They also received sorafenib and the immunosuppression level was kept low. Unfortunately, the outcomes of these patients were not as good as those for patients who underwent surgical treatment. Moreover, it was not clear whether patients who received chemotherapy had a lower life expectancy because of the effectiveness of chemotherapy or because the tumors had already spread out of control. The other nonsurgical treatment options for recurrent HCC include radiation, radiofrequency ablation (RFA), and chemoembolization(29), but we did not use any of these treatments for our patients.

Although the number of patients in this study was very small, and the size could be considered
a limitation, our experience indicates that the best approach to HCC arising from cirrhosis is to perform LT in properly and carefully selected patients in order to prevent recurrence. Despite very strict selection criteria, recurrence still occurs. Therefore, patients have to be followed up regularly after LT because early diagnosis of recurrence can increase the chance of surgical treatment, which can increase the disease-free survival in these patients. During follow up, if recurrence is amenable to surgery, such as for a solitary lesion, surgical management should be the first option. In conclusion, our data demonstrate that surgical management remains the only potential treatment option for long-term survival in patients with recurrent HCC.

References


