Does Transarterial Embolization Improve Survival for Recurrent Hepatocellular Carcinoma after Living Donor Liver Transplantation?

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ABSTRACT

Hepatocellular carcinoma (HCC) is the second leading cause of cancer related death in Taiwan. However, HCC recurrence after living donor liver transplantation (LDLT) is an undesirable outcome, and the treatment is controversial due to different recurrent patterns. The aim of this study is to evaluate the efficacy of transarterial embolization (TAE) for HCC recurrence after LDLT.

From March 2003 to February 2011, 217 patients received LDLT for HCC under Milan/UCSF criteria in Kaohsiung Chang Gung Memorial Hospital. The clinical profiles, imaging features, histopathologic diagnosis, treatment methods and outcomes of HCC recurrence after LDLT were retrospectively analyzed. TAE was performed with a microcatheter system to protect hepatic artery anastomosis. The endpoint of this study was survival from time of recurrence.

Recurrences were found in 15 patients (6.9%) with LDLT for HCC, and were divided into three groups by treatment. Group 1 (n=2) was surgical resection for localized extrahepatic recurrence. Group 2 (n=4) was TAE for intrahepatic recurrence. Group 3 (n=9) was systemic chemotherapy, radiation therapy or conservative treatment for multiple intrahepatic or extrahepatic recurrence. Kaplan-Meier survival estimates showed that the 6- and 12-months survival after recurrence in group 1, 2, 3 was 100%, 75%, 55.5% and 100%, 37.5%, 0%

Surgery had significant benefit on survival after recurrence for solitary or localized resectable recurrence. TAE may have an effect in the loco-regional control of intrahepatic recurrence to prolong survival, even where limited extrahepatic metastasis could be controlled by other treatment. Multiple metastasis was usually unresponsive to chemotherapy and/or radiation therapy with shorter survival after recurrence.

Hepatocellular carcinoma (HCC) is the second leading cause of cancer related death in Taiwan. The major causes are chronic hepatitis B and C infections. In Asia, the indications of living donor liver transplantation (LDLT) have been expanded to include advanced HCC without extrahepatic spread and vascular invasion detectable on pre-operative imaging, irrespective of tumor size and number [1]. However, HCC recurrence after LDLT is an undesirable outcome and occurs more frequently than in deceased donor liver transplantation [2]. For extrahepatic recurrence, the treatment is controversial including chemotherapy, radiation therapy and surgery. Transarterial embolization (TAE) and radiofrequency ablation (RFA) are considered as loco-regional therapy for intrahepatic recurrence. The aim of this study is to evaluate the efficacy of TAE for HCC recurrence after LDLT.
METHODS

From March 2003 to February 2011, a total of 507 patients underwent LDLT in Kaohsiung Chang Gung Memorial Hospital. 217 (42.8%; 179 men, 38 women) patients received LDLT for HCC under Milan or UCSF criteria. Color Doppler ultrasonography (US) was performed daily for the first 2 weeks after operation, and then at a regular follow-up every 3 months. Furthermore, computed tomography (CT) and magnetic resonance imaging (MRI) were alternatively used as periodic screening for possible recurrence. The definite diagnosis of post-operative recurrence was confirmed by imaging study, biopsy or surgery. The clinical profiles, imaging features, histopathologic diagnosis, treatment methods and outcomes of HCC recurrence after LDLT were retrospectively analyzed. As for TAE procedure, complete celiac and superior mesenteric artery injections by using a 4F catheter were performed on patients with sufficient hepatic function to locate hypervascular tumors. A coaxial microcatheter system (Tracker 18 Vascular Access System; Target, San Jose, Calif, USA) was used to protect hepatic artery anastomosis. After pre-treatment by infusion of 3 to 5 mL of 1% lidocaine to prevent pain and arterial spasms, a mixture of ethanol (99.5%) and iodized oil (ratio=1:2) was infused continuously at the rate of 0.5 to 1 mL/min until the adjacent segmental or lobar portal branches were opacified (Fig. 1). The endpoint of this study was survival from time of recurrence.

RESULTS

In this study, recurrences were found in 15 (6.9%) of 217 patients with LDLT for HCC. Sites of the initial recurrence included the liver (n=7), lung (n=6), bone (n=3), adrenal gland (n=1), regional lymph node (n=8), and other sites (n=4). These 15 patients were divided into three groups by treatment methods (Table 1). Group 1 (n=2) was surgical resection for localized extrahepatic recurrence. Group 2 (n=4) was TAE for intrahepatic recurrence. Group 3 (n=9) was systemic chemotherapy, radiation therapy or conservative treatment for multiple intrahepatic or extrahepatic recurrence.

The treatment after recurrence included surgery (n=5), TAE (n=4), RFA (n=1), chemotherapy (n=6) and radiation therapy (n=8). In group 1, one patient had localized lung metastasis consisting of two small pulmonary nodules in the right lung; and the other had solitary adrenal metastasis. Both patients accepted operation for tumor resection reinforced by radiation therapy. In group 2, three patients had intrahepatic recurrence with or without regional lymph node metastasis, and one patient had multiple lung metastasis with subsequent liver involvement about 3 months later. All four patients received TAE as loco-regional therapy with an average of 2.8 times. According to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) guideline, complete or partial tumor response (at least 30% decrease in arterial enhancement of viable lesions) after TAE
was observed in all patients by the following CT studies (Fig. 2). In group 3, systemic chemotherapy was applied as the principal treatment for multiple metastasis, and radiation therapy played a role in regional control of recurrence.

The mean time until the initial recurrence after LDLT was 9.6 months (range 1.8-24.0 months). The mean follow-up period was 17.1 months (till July 2011, range from 2.4-36.9 months). Two patients in group 1 survived for 28.7 and 20.7 months after LT till the end of this study without disease progression. Of four patients with TAE in group 2, two survived for 36.9 and 17.6 months after LT till the end of this study. Among these nine patients in group 3, eight received chemotherapy, radiation therapy, conservative treatment or none with survival after recurrence with mean of 5.7 months (range 0.6-11.9 months). Kaplan-Meier survival estimates showed that the 6- and 12-months survival after recurrence in group 1, 2, 3 was 100%, 75%, 55.5% and 100%, 37.5%, 0% (Fig. 3).

**DISCUSSION**

Owing to improvements in the selection criteria, the incidence of HCC recurrence after LDLT has been reduced, but the treatment is controversial due to different patterns of recurrence. In this study, reviewing 217 patients with LDLT for HCC, 15 patients (6.9%) were eventually diagnosed with HCC recurrence on the basis of imaging and pathology.

Like primary HCC, no single available therapy is applicable to all patients, so the treatment for HCC recurrence after LDLT should be tailored to the clinical state of the individual patient. Roayaie et al. reported that the surgical treatment of the recurrence was independently associated with significantly longer survival [3]. Taketomi A also described that the eligibility of surgical resection had a beneficial impact on survival from tumor recurrence, and overall survival rate is similar to patient without HCC recurrence [4]. With regard to a solitary or localized recurrence, surgery was invariably considered as the first choice.

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**Table 1. Group classification by different recurrent patterns and treatment methods.**

<table>
<thead>
<tr>
<th>Group 1</th>
<th>n=2</th>
<th>Surgical resection for localized extrahepatic recurrence</th>
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<tbody>
<tr>
<td>Group 2</td>
<td>n=4</td>
<td>TAE for intrahepatic recurrence</td>
</tr>
<tr>
<td>Group 3</td>
<td>n=9</td>
<td>Systemic chemotherapy / radiation therapy / conservative treatment for multiple intrahepatic or extrahepatic recurrence</td>
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**Figure 2.** Computed tomography (CT) evaluation after transarterial embolization (TAE). No definite arterial enhancement of post-TAE HCCs revealed complete tumor response (white arrows).
choice for curative respectability. Indeed, surgical resection obtained good results for a solitary or localized extrahepatic recurrence in the group 1. Both patients were alive without evidence of recurrence till the endpoint in this study. This fact proved that adequate surgery for resectable recurrence brings a better prognosis than conservative treatment.

Patients with preserved liver function and multinodular HCC without vascular invasion would seem to be the best target population for TAE, and survival benefits were identified with chemoembolization [5]. For unresectable primary HCC, meta-analysis of nine randomized controlled trials (RCTs) confirmed that TACE improves survival, and a meta-analysis of TACE versus TAE alone (3 RCTs, 412 patients) demonstrated no survival difference [6]. With the results from the above studies, TAE may become the optimal treatment to prolong survival after recurrence for LDLT patients with liver recurrence. All four patients in group 2 received TAE with mean of 14 months after LDLT. It is noteworthy that TAE should be carefully performed in patients who have received LDLT due to hepatic artery anastomosis. A microcatheter is routinely used for superselective catheterization of the tumor feeding artery with the purpose of protecting the hepatic artery. Vessel injury related to manipulation may cause occlusion to induce ischemia or necrosis of the transplant graft.

Because there are too few patients with recurrence after LDLT to establish statistical data, the differences in survival between patients receiving surgery/TAE/chemotherapy were difficult to analyze respectively. The purpose of this study is to assess the role of TAE for HCC recurrence after LDLT by retrospectively reviewing different patterns, treatment course and survival after recurrence. In conclusion, surgery had significant benefit on survival after recurrence for solitary or localized resectable recurrence. TAE may have an effect in the loco-regional control of intrahepatic recurrence to prolong survival, even where limited extrahepatic metastasis could be controlled by other treatment. Multiple metastasis did not usually respond to by chemotherapy and/or radiation therapy leading to a shorter survival after recurrence.

REFERENCES