Liver Transplantation at a Small-volume Procedure Center—Preliminary Results from Taipei Veterans General Hospital

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Background: Liver transplantation is a challenging procedure that is associated with perioperative morbidity and mortality, so it is justifiable to perform such a procedure in high-volume procedure centers. Organ shortage remains a major issue in Taiwan. Due to the difficulty in establishing a high-volume procedure center, it is important to review the overall outcome of patients undergoing liver transplantation at a small-volume procedure center to determine if performing such a procedure is justified.

Methods: Between April 2001 and May 2005, 26 adults underwent deceased donor liver transplantation at Taipei Veterans General Hospital. The overall outcomes were reviewed in terms of 90-day mortality, 1-year and 3-year survival rates. In addition, the patients were divided into a hepatocellular carcinoma (HCC) group ($n = 12$) and a benign end-stage liver disease (ESLD) group ($n = 14$). The clinical demographics, 90-day mortality, 1-year and 3-year survival rates were reviewed and compared between the 2 groups.

Results: The 90-day mortality was 15.3% in the whole series, 8.3% in the HCC group and 18.7% in the ESLD group. The overall 1-year and 3-year survival rates were 76.9% and 63.5%, respectively, for the whole series. For the 2 groups, the respective 1-year and 3-year survival rates were 83.3% and 71.4% in the HCC group, and 71.4% and 57.1% in the ESLD group. The survival difference was not significant ($p = 0.319$) between the 2 groups. In the HCC group, the 1-year and 3-year disease-free survival rates were 88.9% and 71.1%, respectively.

Conclusion: The survival rates between ESLD and HCC patients undergoing liver transplantation at a small-volume procedure center were comparable. The results of the whole series were not satisfactory, but the results for the HCC group were acceptable. [*J Chin Med Assoc* 2008;71(4):186–190]

Key Words: end-stage liver disease, hepatocellular carcinoma, liver transplantation

Introduction

The first human liver transplantation was performed in 1963, but poor initial results kept liver transplantation an experimental surgery for 20 years before it was accepted as a definitive therapeutic modality for end-stage liver disease (ESLD).[1] Because of the challenging procedure and high perioperative mortality associated with liver transplantation, it has been suggested that this procedure be done in centers with a high volume of procedures to ensure better patient outcome.[2] Organ shortage has long been a significant problem faced by the transplant society, and because of folk beliefs and religions, organ shortage is generally more severe in Asian countries compared with Western ones. The organ donation rate is about 4.7 per million people per year in Taiwan.[3] This number is far behind that in Spain, a country with an organ donation rate of around 24.1 per million people per year.[4] Therefore, it is difficult to establish a center with a high volume of liver transplants in Taiwan. Under these circumstances, we wanted to review the overall outcome of patients who

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underwent liver transplantations at a small-volume procedure center to determine if it is justifiable to perform liver transplantations at such a center. In addition, subgroup analysis was done to compare the outcome between patients with benign ESLD and patients with hepatocellular carcinoma (HCC).

Methods

The study complied with current ethical guidelines of medical research. Between April 2001 and May 2005, 26 adults underwent deceased donor liver transplantation (DDLT) at Taipei Veterans General Hospital (TVGH). There were 17 males and 9 females. The mean age of these patients was 54.0 ± 10.7 years (range, 24–68 years). Nineteen patients had chronic hepatitis B virus (HBV) infection, 3 had chronic hepatitis C virus (HCV) infection, 2 had Wilson's disease, 1 was an alcoholic, and 1 had cryptogenic liver cirrhosis.

Model of end-stage liver disease (MELD) score was introduced into Taiwan's organ allocation system in 2004. Before 2004, waiting time had been a priority for organ allocation except for urgency. Mean MELD score of the subjects in this study was 14.9 ± 7.6 (range, 6–42). Among the 26 patients, 12 had concomitant HCC preoperatively (Table 1). All of the HCC patients included in this study met the Milan criteria[5] before transplantation.

All patients underwent orthotopic liver transplantation without venous-venous bypass. The immunosuppressant regimen consisted of intraoperative induction of methylprednisolone 1 g and then tapering to oral prednisolone 20 mg on the 7th postoperative day. Steroid was withdrawn before 6 months after transplantation. The main maintenance immunosuppressant was tacrolimus (Astellas Pharma, Osaka, Japan). The dosage of tacrolimus was 0.025–0.15 mg/kg/day in 2 divided doses. The trough blood level was kept between 2.5 ng/mL and 20 ng/mL.

The patients' clinical demographic data, operative mortality and pathologic results were reviewed. Operative mortality was defined as death within 30 days of transplantation or during the same period of hospitalization. The median follow-up time was 25.3 months (mean, 28.8 ± 10.7 months; range, 1 day to 69.3 months). The patients' overall survival rate was calculated using the Kaplan-Meier method. In addition, patients were further divided into an HCC group ($n = 12$) and an ESLD group ($n = 14$). The clinical demographic characteristics, surgical outcomes and survival rates were compared between the 2 groups. Continuous variables were compared using Student's t test, and categorical variables were compared using Fisher's exact test. The difference in survival between the HCC and ESLD groups was calculated using log-rank test.

Table 1. Demographic characteristics of 26 adult patients who underwent deceased donor liver transplantation between April 2001 and May 2005 at Taipei Veterans General Hospital

Age (yr)	54.0 ± 10.7
Male/female (*n*)	17/9
MELD score	14.9 ± 7.6
ESLD/HCC	14/12
Etiology (*n*)	
HBV	19
HCV	3
Wilson's disease	2
Alcoholism	1
Cryptogenic liver cirrhosis	1
Median follow-up (mo)	25.3

MELD = model of end-stage liver disease; ESLD = end-stage liver disease; HCC = hepatocellular carcinoma; HBV = hepatitis B virus; HCV = hepatitis C virus.

Results

In this series, 4 patients died within 30 days of transplantation. The causes of mortality in 1 patient each were hemorrhagic shock, small-for-size syndrome, portal vein thrombosis, and intracranial hemorrhage. Operative mortality was 15.3% (4/26). The overall 1-year and 3-year survival rates for the whole series were 76.9% and 63.5%, respectively (Figure 1).

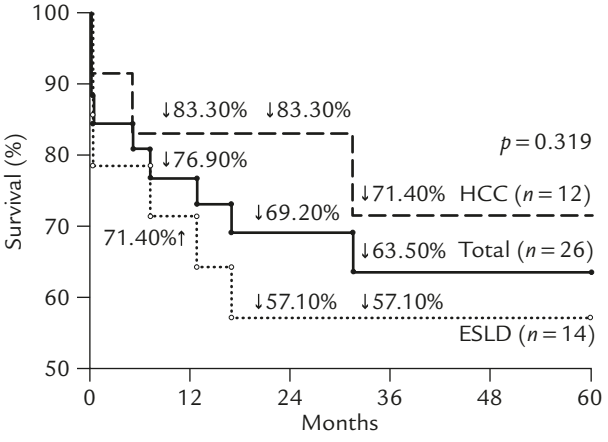

Figure 1. Survival curves for the total number of patients and patients in the end-stage liver disease (ESLD) and hepatocellular carcinoma (HCC) groups.

Table 2. Clinical demographic characteristics of patients with hepatocellular carcinoma (HCC) and patients with end-stage liver disease (ESLD) who underwent deceased donor liver transplantation

	HCC group	ESLD group	*p*
Male/female (*n*)	8/4	9/5	1.000
Age (yr)	58.5±6.6	50.14±12.2	0.039
MELD score	13.33±4.9	16.21±9.2	0.343
Operative mortality (*n*)	1/12	3/14	0.613

MELD = model of end-stage liver disease.

Table 3. Clinical demographic characteristics and outcome of patients with hepatocellular carcinoma who underwent deceased donor liver transplantation

Patient	Age (yr)	Gender	Etiology	MELD score	Status	Follow-up (mo)	Time to recurrence (mo)	COD
1	67	Female	HBV	9	Alive	69	–	–
2	66	Male	HCV	10	Alive	60	–	–
3	57	Male	HBV	14	Alive	51	–	–
4	57	Male	HCV	6	Dead	32	–	Sepsis
5	45	Male	HBV	15	Alive	46	–	–
6	66	Female	HBV	21	Dead	5	–	Sepsis
7	55	Male	HBV	11	Alive	33	23*	–
8	52	Male	HBV	16	Alive	33	32†	–
9	57	Male	HBV	8	Alive	25	–	–
10	62	Female	HBV	22	Alive	23	–	–
11	55	Male	HBV	13	Alive	22	–	–
12	63	Female	HCV	15	Dead	POD9	–	ICH

**Intrahepatic recurrence, peritoneal seeding, lung and spleen metastases; †liver, lung and brain metastases. MELD = model of end-stage liver disease; COD = cause of death; HBV = hepatitis B virus; HCV = hepatitis C virus; POD = postoperative day; ICH = intracranial hemorrhage.*

The male-to-female ratio in the HCC group was 8 to 4, while it was 9 to 5 in the ESLD group (p=1.000). The mean age in the HCC group was 58.5±6.6 years, while it was 50.14±12.2 years in the ESLD group (p=0.039). There was no significant difference in MELD score between the HCC and ESLD groups (13.33±4.9 *vs.* 16.21±9.2, p=0.343). Operative mortality was 8.3% (1/12) in the HCC patients and 18.7% (3/16) in the ESLD patients (Table 2). The 1-year survival rates for the HCC patients and ESLD patients were 83.3% and 71.4%, respectively. The 3-year overall survival rates for the HCC patients and ESLD patients were 71.4% and 57.1% (p=0.319), respectively (Figure 1).

In the HCC group, 1 patient died as a result of post-transplantation intracranial bleeding on post-operative day 9, and 2 died of sepsis, at 5 months and 31 months after transplantation, respectively, without evidence of tumor recurrence (Table 3). In the ESLD group, 6 patients died: 3 were due to surgical complications, and 1 each to hemorrhagic shock, portal vein thrombosis and small-for-size syndrome on postoperative days 1, 3 and 7, respectively. The diagnosis of small-for-size syndrome was made according to the patient's clinical presentations of progressive hyperbilirubinemia without mechanical cause and refractory ascites in the absence of vascular complications within 7 days of liver transplantation. Another 3 patients died of suffocation, sepsis, and suicide, at 7, 13 and 17 months after transplantation, respectively (Table 4). Of the 12 HCC patients, 9 had received pre-transplant treatment (1 surgical resection, 1 surgical resection for primary tumor and transarterial embolization for recurrence, 7 locoregional ablative therapies). During the post-transplantation follow-up period, 2 patients were found to have recurrent tumors. One of the 2 patients had intrahepatic recurrence, peritoneal seeding, and lung and spleen metastases at 23 months after transplantation. The other patient had tumor in the liver, lung and brain at 32 months after transplantation. The recurrence rate was 16.7% (2/12). The 1-year disease-free survival rate was 88.8%, and the 3-year disease-free survival rate was 71.1% (Figure 2).

Discussion

Liver transplantation had been an experimental surgery until 1983, 20 years after the first human liver transplant,

Table 4. Clinical demographic characteristics and outcome of patients with end-stage liver disease who underwent deceased donor liver transplantation

Patient	Age (yr)	Gender	Etiology	MELD score	Status	Follow-up (mo)	COD
1	44	Male	Wilson's disease	11	Dead	13	Sepsis
2	37	Male	HBV	26	Dead	POD1	Hemorrhagic shock
3	56	Male	HBV	17	Alive	64	–
4	68	Female	Cryptogenic liver cirrhosis	23	Dead	7	Suffocation
5	62	Male	HBV	8	Alive	55	–
6	47	Female	HBV	11	Dead	17	Suicide
7	58	Female	HBV	16	Alive	43	–
8	24	Male	HBV	8	Dead	POD7	Small-for-size syndrome
9	46	Male	Alcoholism	13	Alive	36	–
10	63	Male	HBV	19	Dead	POD3	Portal vein thrombosis
11	37	Female	Wilson's disease	8	Alive	32	–
12	47	Male	HBV	13	Alive	26	–
13	63	Male	HBV	42	Alive	23	–
14	60	Female	HBV	12	Alive	20	–

MELD = model of end-stage liver disease; COD = cause of death; HBV = hepatitis B virus; POD = postoperative day.

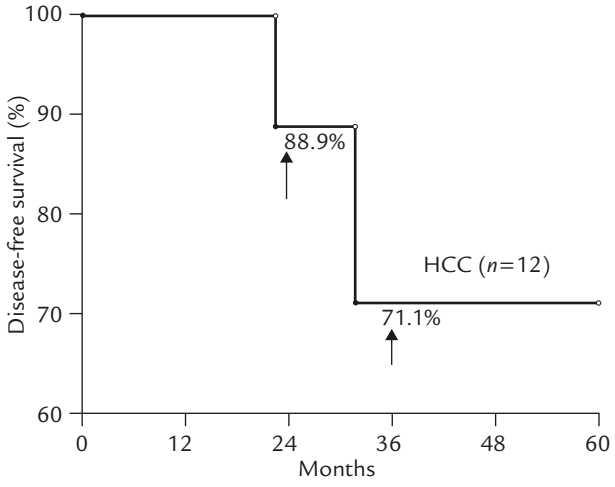

Figure 2. Disease-free survival curve of 12 adults with hepatocellular carcinoma (HCC) who underwent deceased donor liver transplantation.

when experts at the Consensus and Development Conference of the National Institute of Health recommended that liver transplantation be a definitive treatment for ESLD.[1] The first successful human liver transplantation in Asia was performed in Taiwan by Chen et al in 1984.[6] Their successful operation influenced the development of liver transplantation not only in Taiwan but also in other Asian countries. Soon after the first liver transplantation in Asia, the first liver transplantation at TVGH was performed, on March 31, 1985. However, no patient survived for more than 1 year until 1990. Before 2001, there were only 14 liver transplantations done at TVGH over a 16-year period. The learning process has been long and slow. Between January 2001 and December 2005, a total of 33 DDLTs were performed at TVGH, with 14 of the 33 transplants done in 2005. However, by definition, TVGH is still a small-volume center for DDLT.[2]

In spite of an increased number of organ donations in Taiwan during the past decade, there were only 73 liver grafts available from deceased donors in 2005.[3] Under such circumstances, it is difficult to establish a high-volume procedure center in Taiwan. Hence, it is necessary to review the results of a small-volume procedure center to see if it is justifiable to perform liver transplantation.

According to the report of Edwards et al,[2] the 90-day mortality rate at low-volume centers was 20.9%, while it was 14.1% at high-volume centers (>20 procedures/year). The 1-year mortality rate at low-volume centers ranged from 25.9% to 29.9%, and from 20.0% to 25.1% at high-volume centers, according to the different time periods. In our series, the 90-day mortality rate was 15.3%, and the 1-year mortality rate was 23.1%. These results are comparable to those of high-volume centers reported by Edwards et al.[2]

It is generally accepted that the 1-year survival rate is 80% and the 3-year survival rate is 75% for ESLD patients undergoing liver transplantation. Our series showed that ESLD patients undergoing liver transplantation achieved a 1-year survival rate of 71.4% and a 3-year survival rate of 57.1%. These results are not satisfactory. The reason for the unsatisfactory outcome was mainly due to 3 of the 6 cases of mortality occurring within 30 days after transplantation. The mean MELD score in our patients was 14.9 ± 7.6, which means that most of our patients were not critically ill. Refinement

of perioperative care and surgical techniques should decrease surgical mortality and improve patient survival.

Liver transplantation is justified for patients with liver malignancy only when the outcome after transplantation is comparable to that of patients with ESLD, especially in a country with organ shortages. The prognosis of patients with HCC undergoing liver transplantation in the initial series was disappointing. Even in the early 1990s, the 5-year survival rate was 15–48%.[7–10] The tumor recurrence rate was up to 54%.[9] The poor outcome was mainly due to unrestrictive patient selection criteria. In the late 1990s, the survival rate of HCC patients undergoing liver transplantation improved greatly. The most notable result was from the Milan group. In 1996, Mazzaferro et al[5] demonstrated that HCC patients with a single tumor no larger than 5 cm, or with no more than 3 tumors with each tumor being no larger than 3 cm, could achieve a 1-year survival rate of 90% and a 3-year survival rate of 76%. The overall recurrence rate was 8%, and the 4-year disease-free survival rate was 83%. These selection criteria were called the *Milan criteria*. With restrictive patient selection criteria, these satisfactory outcomes were reproducible in other later series.[11–13]

In Taiwan, we follow the Milan criteria for patients with HCC undergoing DDLT. In this series, 12 patients with HCC underwent liver transplantation. Our results showed that the 1-year and 3-year overall survival rates were 83.3% and 71.4%, respectively; 1-year and 3-year disease-free survival rates were 88.9% and 71.1%, respectively. The figures were better than those for our patients with ESLD, although the difference was not statistically significant ($p=0.319$). The outcome was also comparable to results from other larger series.[5,11–13]

The preliminary results of this whole series were not satisfactory but they were acceptable, especially for the HCC group. The results indicate that liver transplantation at a center with a small volume of procedures in Taiwan is justifiable, but there remains much room for further improvement.

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