Original Article

Salvage transplantation for post-resection recurrence in hepatocellular carcinoma associated with hepatitis C virus etiology: a feasible strategy?

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ABSTRACT

Aim: The aim was to analyze the feasibility of salvage liver transplant after liver resection in hepatocellular carcinoma (HCC) with hepatitis C virus (HCV) etiology. **Methods:** All the patients diagnosed with HCC with HCV etiology who underwent living donor liver transplant from July 2002 to November 2012 were studied. Their recurrence rate, mortality, and prognostic factors were analyzed and compared between primary transplant and salvage transplant for up to 5 years post-transplant. **Results:** One hundred and nine patients underwent a liver transplant for HCC associated with HCV etiology within the University of California, San Francisco criteria. Eighteen were post-hepatectomy salvage transplants and 91 were primary transplants. Median follow-up time was 31 months. One, 3 and 5 years overall survival rates were 76%, 76% and 65% in the salvage group, and 92%, 85% and 85% in primary transplant group respectively. The difference in overall survival rates was statistically significant (P = 0.031). However, recurrence-free survivals for 1, 3 and 5 years were 72%, 72% and 46% for salvage group, and 91%, 73% and 46% for primary transplant group; which were not statistically significant (P = 0.328). **Conclusion**: Salvage transplantation for post-hepatectomy recurrence for patients with HCC associated with HCV-related chronic liver disease seems to offer inferior overall survival rates than primary transplantation.

Key words: Hepatitis C virus; hepatocellular carcinoma; salvage transplantation.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver.[1] There is an ongoing debate about what is the best strategy to treat HCC, particularly in Child A cirrhosis, when the primary option is resection and transplantation. Some reports have suggested that transplantation is a better choice,[2] but the opponents of this approach suggest that resection is better because it can also serve as a bridge to liver transplantation.[3] Many authors have suggested that results of salvage transplantation are comparable to primary transplantation.[4,5] However, there also is controversy over management of HCC associated with hepatitis C virus (HCV) related cirrhosis. Chirica *et al*.[6] suggested that overall and disease-free survival after liver resection for HCV-related HCC is poor and so primary liver transplantation (LT) should be offered to these patients. In this study, we evaluated feasibility of salvage transplantation in HCC patients with HCV-related liver disease.

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The aim of this study was to compare the survival rates and recurrence rates of primary as well as salvage transplantation and also to evaluate prognostic factors affecting survival and recurrence in primary as well as salvage transplantation.

METHODS

Patients selection

All the patients transplanted for hepatitis C related liver disease with HCC were analyzed retrospectively. All the data collected was at the time of liver transplant. Barcelona clinic liver cancer staging criteria were followed to decide treatment options. University of California, San Fransisco (UCSF) criteria were used as transplantation indication.[7] If the tumor was outside UCSF criteria, loco-regional therapies such as transarterial chemoembolization, radiofrequency ablation were used. These patients were scheduled for transplantation when they fulfilled UCSF criteria. Results with down staging are published before.[8] Patients who underwent liver resections before and subsequently transplanted for intrahepatic recurrence were included in salvage transplant group, and other patients who were transplanted without prior resection were included in the primary transplant group. The review board of Chang Gung Memorial Hospital approved this study.

Follow-up

Patients were followed-up every 3 months for the first year, then every 6 months and yearly after that. Follow-up included liver function tests, alpha-fetoprotein (AFP) and triple-phase computed tomography scan, or magnetic resonance imaging.

Statistical analysis

Chi-square test and Fisher's *t*-test whenever appropriate were used for categorical variables and Mann-Whitney *U*-test for continues variables. Kaplan-Meier survival curves were prepared for recurrences and mortality with the Log-rank test. Multivariate analysis was performed using multivariate Cox regression analysis. SPSS version 21 (IBM, Armonk, NY, USA) was used for statistical analysis. Two-tailed significances were taken into consideration. $P < 0.05$ was considered as statistically significant.

RESULTS

One hundred and nine patients underwent living donor LT for HCV-related HCC between July 2002 and November 2012. Median follow-up time was 31 months. Eighteen patients underwent salvage transplantation for intrahepatic recurrence post-hepatectomy; while 91 patients underwent primary transplants. Patients' characteristics are described in Table 1.

As described in Table 1, age of patients in both groups, mean tumor numbers and size were comparable in both the groups. The primary transplant group had statistically significant higher mean model for end-stage liver disease (MELD) score and mean Child-Turcotte-Pugh (CTP) score.

Table 1: Characteristics of 109 patients with hepatitis C virus liver disease and hepatocellular carcinoma undergoing liver transplantation as salvage or primary treatment

	Salvage transplant (n = 18)	Primary transplant (n = 91)	P
Age (years, mean ± SD)	56 ± 5	56 ± 6	0.874
Sex (male, %)	72	63	0.471
MELD (mean ± SD)	9 ± 4.6	11 ± 4.2	0.026
CTP (mean ± SD)	6 ± 1	8 ± 2	0.045
Associated HBV infection (%)	28	15	0.307
Pre-operative interferon and ribaverin treatment (%)	22	37	0.283
Overall recurrence (%)	11	13	0.836
Pre-operative RFA (%)	33	34	0.971
Percutaneous ethanol injection (%)	22	15	0.433
Overall mortality (%)	28	12	0.090
Pre-transplant within Milan (%)	33	55	0.114
Pre-transplant TACE (%)	67	53	0.299
Microvascular invasion on explant histology (%)	11	25	0.178
Moderate to poor differentiation on explant histology (%)	50	25	0.052
Pre-operative viral load = 0 (%)	22	19	0.744
Recurrence months (mean ± SD)	37 ± 32	37 ± 26	0.544
AFP pre-operative (mean ± SD)	40 ± 509	123 ± 86	0.764
Waiting months for transplant (mean ± SD)	9 ± 13	9 ± 12	0.673
Number of tumor (mean ± SD)	1 ± 2	1 ± 1	0.588
Size of largest tumor (cm, mean ± SD)	2.1 ± 1.6	3 ± 1.8	0.116
Pre-operative viral load (mean ± SD)	44,153 ± 146,079	162,459 ± 549,720	0.752

Data are shown as % or mean ± SD. MELD: model for end-stage liver disease; CTP: Child-Turcotte-Pugh; HBV: hepatitis B virus; RFA: radiofrequency ablation; TACE: transarterial chemoembolization; AFP: alpha-fetoprotein; SD: standard deviation

Survival and recurrence rates comparisons in both the groups

The two recurrences occurred in the salvage transplant group that exhibited extrahepatic metastasis. In the primary transplant group, total of 12 recurrences were noted. In two cases the recurrence was intrahepatic, and 10 were extrahepatic metastasis. One, 3 and 5 years recurrence-free survival rates were 72%, 72% and 46% in the salvage transplant group, and 91%, 73% and 46% in the primary transplant group respectively. The difference was not significant statistically ($P = 0.328$ on Log-rank analysis). One-year recurrence-free survival was low in salvage transplant group, but it did not achieve statistically significant level ($P = 0.08$ for 1 year). Kaplan-Meier survival curves were shown in Figure 1. One, 3 and 5 years survival rates were 76%, 76% and 65% in salvage transplant group, and 92%, 85% and 85% in primary transplant group. Kaplan-Meier survival curves were prepared and Log-rank analysis was done [Figure 2]. One, 3 and 5 years survival rates were significantly lower in salvage transplant group ($P = 0.031$).

Analysis of prognostic factors

Prognostic factors were evaluated in all 109 patients. On the log-rank analysis, on univariate analysis high MELD score ($P = 0.01$), no pre-transplant interferon therapy ($P = 0.002$), salvage transplant, no prior transarterial chemoembolization (TACE) ($P = 0.03$) were associated with worse survival rates. On multivariate Cox regression analysis salvage transplantation ($P = 0.04$) and no pre-transplant TACE ($P = 0.02$) were independently associated with worse survival rates. Higher AFP levels were associated with worse recurrence-free survival ($P = 0.005$).

DISCUSSION

Poon *et al*.[9] suggested that 80% of the intrahepatic recurrences after resection are transplantable. Based on this result, many authors such as Belghiti *et al*.[10] suggested that liver resection should be the first line of treatment, followed by salvage transplantation for recurrence. They also showed that 3- and 5-year survival rates were not different between primary transplantation and salvage transplantation. However, Bozorgzadeh *et al*.[11] showed that survival outcome for transplantation for HCC associated with HCV were significantly lower than for other etiology. Chirica *et al*.[6] suggested that overall and disease-free survival after liver resection for HCV-related HCC is poor and so primary LT should be offered to these patients. However Cucchetti *et al*.[12] suggested good outcomes after liver resection for HCV patients.

The aim of our study was to analyze feasibility of salvage transplantation for HCC associated with HCV etiology. In this study both the salvage transplant and the primary transplant groups were comparable however the primary transplant group had significantly higher pre-operative MELD scores as well as CTP scores. MELD scores and CTP scores were not significantly associated with survival or recurrence at any step of the analysis. There were no differences with regard to pre-operative viral load and pre-operative treatment taken between two groups.

In our study, there was not statistical significant difference in recurrence-free survival between salvage transplant and primary transplant group. However, 1-, 3- and 5-year overall survival rates were significantly lower in the salvage transplant group. These results indicate that primary transplant may be a better treatment strategy for transplantable HCC in case of associated HCV etiology. Adam *et al*.[13] also showed inferior overall and recurrence-free survival in the salvage transplant group. However, they did not study HCV etiology separately. Belghiti and Durand[14] in their editorial mentioned that in the study by Chirica

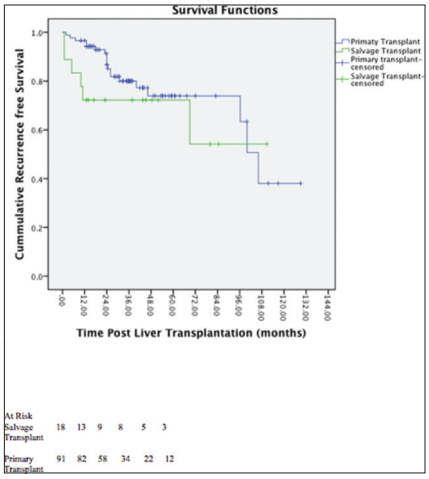

Figure 1: Recurrence free survival salvage transplant *vs.* primary transplant (Log rank test $P = 0.328$)

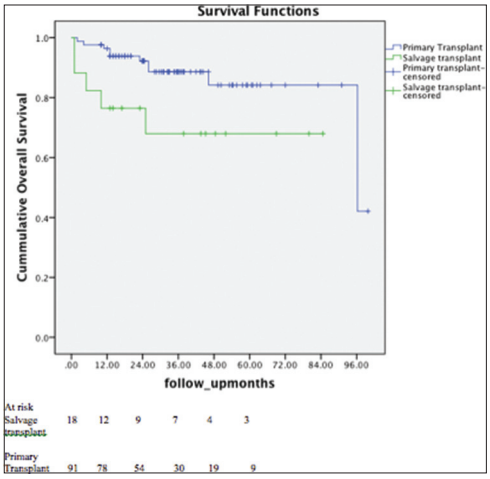

Figure 2: Overall survival in salvage transplant *vs.* primary transplant (Log rank test $P = 0.03$)

et al.[6] tumor recurrences were outside Milan criteria after resection for HCV etiology so they may not be candidates for subsequent transplantation so primary transplant can be a good option for HCV-related HCC.

We also analyzed prognostic factors affecting survival and recurrence in both primary transplant and salvage transplant groups. High pre-operative AFP levels were associated with high recurrence rates. Vibert *et al*.[15] also found pre-operative AFP as a significant prognostic factor for poor survival and recurrence. High MELD score, no pre-transplant interferon therapy, salvage transplant and no prior transarteral chemoembolization was associated with worse survival rates. In multivariate Cox regression, analysis salvage transplant and no prior transcatheter arterial chemoembolization were independent predictors of worse outcome. Shimoda *et al*.[16] suggested that advanced tumor stage and particularly vascular invasion are poor prognostic indicators for tumor recurrence. The authors showed that early pathological tumor-node-metastasis stage, adjuvant chemotherapy, and pre-operative chemoembolization were associated with better outcomes for LT for concomitant HCV and HCC. In our studies, however, factors like vascular invasion, tumor number, tumor size, and presence of vascular invasion, tumor differentiation or histological grade did not achieve statistical significance. HCV viral load did not achieve statistical significance in predicting neither recurrence nor survival ($P = 0.8$ and 0.9 respectively). Pre-operative MELD and CTP scores were significantly higher in the primary transplant group but still these patients achieved better survival rates than the salvage transplant group. Even in advanced underlying disease cases, primary transplant achieved best results. Patients in the salvage transplants had mean CTP of 6, indicating that the majority of them had a compensated, or Child A cirrhosis and their survival was lower than the primary transplant group. There was no statistical difference between recurrence-free survival between primary and salvage transplant group, however 1 year recurrence free survival was 72% in case of salvage transplant and 91% in primary transplant with $P < 0.1$ (though not < 0.05), and most of the death were due to HCV and HCC recurrences. One death was due to post-operative bleeding as salvage transplant is technically more difficult than primary transplant. Pre-operative sustained virological response and pre-operative viral load was less in salvage transplant group though non-significant.

In the era of new and more efficacious anti-HCV drugs, this survival difference will be probably overcome. Thus, patients with HCC and HCV can receive salvage LT but probably they should receive pre-emptive antiviral therapy.

There are certain limitations of this study as this are a retrospective analysis. We also recognize that the numbers of patients in the salvage transplantation group were relatively low and with just two recurrences in salvage transplant group, statistical significance of the recurrence rate is weak. Another limitation is that we did not have complete pathological details of prior liver resection specimens in salvage transplant group as some of them were referred to us after resection; in addition, some patients underwent resection before 2002, and complete pathological analysis was not available.

In conclusion transplantation for post-hepatectomy recurrence for patients with HCC associated with HCV-related chronic liver disease seems to offer inferior overall survival rates than primary transplantation. However, results in the era of new anti-HCV drugs need to be evaluated further.

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