Liver transplantation for hepatocellular carcinoma in Singapore

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ABSTRACT

Introduction: The prognosis of patients with hepatocellular carcinoma (HCC) is poor. Surgical resection offers the benefit of removal of the tumour but is associated with liver decompensation and tumour recurrence, even after successful surgery. Liver transplantation offers the benefits of complete tumour removal with prevention of both decompensation and recurrence post-operation. This paper aims to review results of liver transplantation for patients with HCC in Singapore.

Methods: All adult patients with HCC accepted on the waiting list for liver transplantation (based on the Milan criteria) from 1996 to 2004 in Singapore were reviewed. Patients' HCC were managed with either transarterial chemoembolisation or percutaneous radiofrequency ablation while they were on the waiting list. Post-transplant survival and factors associated with mortality were analysed by Cox regression analysis.

Results: 41 patients with HCC were accepted onto the waiting list over the nine-year period. 22 underwent transplantation and 19 did not, with a one-year survival of 91 percent versus 24 percent, respectively. (p-value is less than 0.001). Mean waiting time for transplant was 39 weeks. Post-transplant HCC recurrence was 2/22 (nine percent). Among all patients, mortality was significantly related to baseline white cell counts, prothrombin time, age, alpha-foetoprotein level, Child-Pugh score, and whether patients underwent transplant.

Conclusion: Despite the relatively long waiting time of a mean of 39 weeks, post-transplant recurrence of HCC was relatively low at nine percent. Liver transplant is an effective treatment for patients with a HCC, with a reasonable long-term survival.

Keywords: chronic hepatitis B, chronic hepatitis C, cirrhosis, hepatocellular carcinoma, liver transplantation

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth commonest cancer worldwide[1]. Major risk factors for development of HCC include liver cirrhosis from any cause, as well as chronic hepatitis B (CHB). As 4.1% of Singaporeans are carriers of hepatitis B virus (HBV), HCC is also the third commonest cancer in Singapore males, with more than 1,500 cases diagnosed annually[2]. Curative treatment of HCC includes surgical resection and liver transplantation[3]. Unfortunately, most cases of HCC are diagnosed in the advanced stage, or in patients with advanced liver cirrhosis. Hence, only 30-40% of newly-diagnosed HCC are amendable to curative therapies[4].

Decompensation of liver function and mortality post-surgical resection occur frequently in patients with advanced cirrhosis and hence, surgical resection is usually reserved for patients with compensated cirrhosis[5]. Even after successful resection, recurrence of HCC in the remnant cirrhotic liver is as high as 70% at five years[6,7]. Liver transplantation is considered the best treatment option for HCC, as it removes the tumour as well as the cirrhotic liver[8]. In suitable candidates with HCC and advanced cirrhosis, i.e., patients with a single HCC nodule <5 cm, or with a maximum of three nodules, each with a maximum size of 3 cm, five-year survival rates were more than 70% and recurrence rates were less than 15%[9-11]. HCC is one of the commonest indications for liver transplant in Singapore[12]. In this paper, we aim to review the results of liver transplant for HCC in Singapore.

METHODS

All adult patients accepted on the waiting list for liver transplantation at the Liver Transplant Programme at the National University Hospital (NUH) for the

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indication of HCC were reviewed. Indications for transplant included unresectable HCC without portal vein or inferior vena cava invasion, regional or systemic metastasis. Since 1999, the criteria was further restricted according to the Milan criteria, where patients with HCC were accepted if the size of the tumour was less than 5 cm for a single nodule, or maximum size was less than 9 cm for a maximum of three tumour nodules[13]. The Milan criteria were chosen as it has been shown to reduce recurrence-free survival to 92% at four years for those within the Milan criteria. Diagnosis of HCC was based on presence of an arterially-enhancing lesion in a cirrhotic liver, with or without elevation of alpha-foetoprotein (AFP) level. Biopsy was not routinely performed at our centre. Patients with chronic hepatitis B were given oral lamivudine 100-300 mg daily for at least four weeks prior to transplant.

Once patients were listed on the waiting list, their HCC were controlled temporarily by locoregional ablative therapy, consisting of either transarterial chemoembolisation (TACE) or percutaneous radiofrequency ablation (RFA), or both, depending on the location of the tumour and the suitability of either therapy. Computed tomography (CT) of the liver were performed four to 12 weeks after either locoregional ablative therapy, to decide if further treatment was needed. Subsequent CT was performed at a 12-week interval to examine tumour progression. Patients were taken off the transplant waiting list if there was tumour progression beyond the Milan criteria. Selection of patients for transplant was based on blood group matching, severity of underlying liver disease, and size match of the liver. Patients with HCC were given priority over patients with an equivalent stage of liver disease.

Data were expressed in mean ± standard error (SE) of mean. Categorical and continuous variables were compared by Chi square test, Fisher's exact test, or Mann-Whitney U test, as appropriate. Survival between those transplanted and not transplanted were analysed by Kaplan-Meier analysis, and compared by the log rank test. To avoid bias, survival for both groups were calculated from time of being accepted for transplant. Factors associated with mortality were analysed by Cox regression analysis.

RESULTS

From Jan 1996 till Dec 2004, 41 subjects with HCC were accepted to the Liver Transplant Programme at NUH. Follow-up after listing for transplant was 114 ± 19 weeks. 22 patients underwent liver transplantation: 21 orthotopic liver transplant and one left lobe living-related liver transplant. The waiting time for liver

Table I. Patient characteristics comparing those that underwent liver transplantation and those that did not.

	Transplanted n=22	Not transplanted n=19
Age (in years)	53.3 ± 1.4	56.6 ± 1.6
Chinese ethnicity (%)	18 (82)	15 (79)
Underlying liver diseases		
Chronic hepatitis B	13	10
Chronic hepatitis C	6	3
Alcoholic liver disease	2	3
Cryptogenic cirrhosis	0	1
Autoimmune hepatitis	0	1
Wilson's disease	0	1
Citrullinaemia	1	0
Bilirubin (uM)	35 ± 6	51 ± 12
Albumin (g/L)	30 ± 1	25 ± 2
Haemoglobin (g/dL)[a]	11.5 ± 0.4	9.9 ± 0.5
Platelets (x10^9/L)[b]	59 ± 10	84 ± 9
White cell count (x10^9/L)	4.0 ± 0.3	4.8 ± 0.8
Creatinine (uM)[c]	75 ± 3	95 ± 7
Child-Pugh score	8.4 ± 0.5	8.8 ± 0.6
Alpha-foetoprotein level (ng/L)	97 ± 40	164 ± 104
No. of HCC nodules	1.4 ± 0.1	1.5 ± 0.2
Total size of HCC nodules	4.5 ± 0.9	3.1 ± 0.4
No. of prior TACE or RFA	1.8 ± 0.3	1.5 ± 0.3

[a]p=0.31, [b]p=0.34, [c]p=0.33

Data are expressed in mean ± SE.

Table II. Causes of death of all patients.

Causes of death of transplanted patients	Time post-transplant (weeks)
1. HCC recurrence (2 patients)	28, 114
2. Hepatic artery thrombosis and sepsis	2
3. Cerebrovascular accident	56
4. Sepsis	44
5. Liver failure from flare due to non-compliance	173
6. Primary non-function	0.4
Causes of death of non-transplanted patients	**Time after being listed for transplant (weeks)**
1. Septicaemia	52
2. Variceal bleeding (3 patients)	5, 12, 27
3. Liver failure (6 patients)	2, 7, 8, 12, 36, 46
4. Ruptured HCC	33
5. Unknown (2 patients)	1, 45

transplant was 39 ± 8 weeks. Characteristics between those who were transplanted and those who were not are shown in Table I. The two groups were similar in their baseline features at time of assessment, except for haemoglobin, platelets, and creatinine levels. 21 patients (51%) were still alive at their last follow-up. Causes of death were listed in Table II. Causes of death for non-transplanted patients were mainly related to liver failure.

The survival analysis of those with and without transplant is shown in Fig. 1. From the time of being listed for liver transplant, the one-year survival of transplanted patients was 91%, versus 24% of those without transplant (p<0.001). When baseline features were analysed by backwards Cox regression analysis, baseline white cell count, prothrombin time (PT), AFP levels, Child-Pugh score, and whether patient underwent transplantation, were the only significant factors associated with survival (Table III).

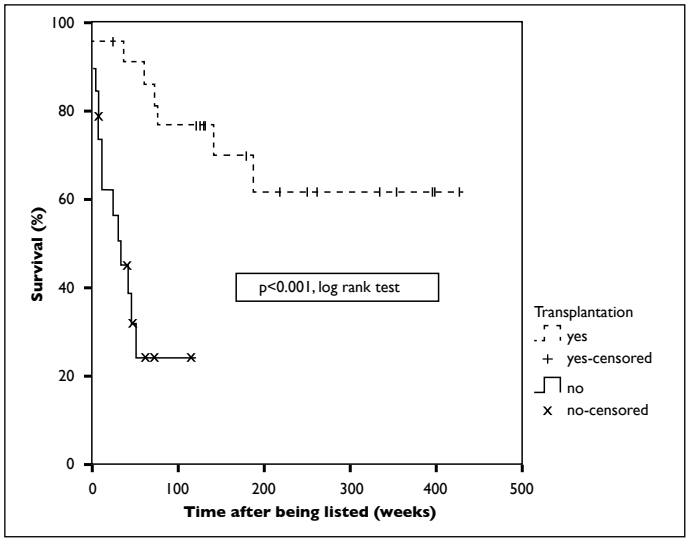

Fig. 1 Survival curves of those who were transplanted and those who were not transplanted.

Table III. Factors associated with survival by Cox regression analysis.

Factors	Hazardous ratio (95% CI)	p-value
Age	1.11 (1.02-1.22)	0.022
White cells count	1.93 (1.25-2.99)	0.003
Prothrombin time	0.98 (0.97-1.00)	0.023
AFP level	1.002 (1.001-1.004)	0.001
Child-Pugh score	1.82 (1.23-2.16)	0.001
Transplantation	9.96 (2.51-39.59)	0.001

DISCUSSION

HCC is an important disease in Singapore as well as other parts of the world, as it is one of the commonest cancers worldwide. Prognosis is generally poor, as many HCC patients were diagnosed at the advanced stage with local or regional spread. In patients with localised lesions, many have concomitant advanced liver cirrhosis, making surgical resection risky. Finally, even in patients who successfully underwent surgical resection, post-surgical relapse of HCC is 50-70% at five years. Liver transplantation offers the dual advantage of complete removal of the tumour, with replacement of the diseased cirrhotic liver. Liver transplantation avoids the risk of post-surgical decompensation as well as tumour relapse.

Results from our centre, with one- and three-year survival rates of 91% and 76%, respectively, for transplanted patients, mirrored those reported by other institutions[14-16]. Among the 22 transplanted patients, recurrence occurred in only two (9%) of patients, occurring at 28 and 114 weeks post-transplant. Surgery-related complications, primary non-function and hepatic artery thrombosis, occurred in another two patients and both died during the early post-operative period.

In patients who were not transplanted, survival is dismal, with only 24% one-year survival. Only three patients survived beyond one year. Their Child-Pugh scores at time of referral were 5, 5 and 12, respectively. Two patients received one session of TACE, while the past patient had five sessions of TACE. It is likely that their liver disease was stable while progression of the HCC was controlled by TACE. Liver failure-related causes are the main cause of death. This is not surprising as liver function often worsens in patients with progressive tumour, which often causes liver failure eventually[17].

Despite our relatively long waiting time for liver transplantation of about 40 weeks, our post-transplant survival was reasonably high and recurrence post-transplant was relatively low. This could be due to the routine use of TACE or RFA in temporarily controlling the tumour, while waiting for the liver graft. Although TACE is potentially associated with risk of hepatic artery injury leading to post-transplant hepatic artery thrombosis, we only saw one case of hepatic artery thrombosis. This is likely to be due to routine use of superselective hepatic angiogram during TACE[18].

We found age, prothrombin time, AFP level, Child-Pugh score, and having undergone transplantation, significantly related to mortality at multivariate analysis, of which having undergone transplantation had the largest hazardous ratio. (Table III and Fig. 1) However, our small sample size of 41 patients, and mortality of only 20 (49%) patients may make results of multivariate analysis invalid.

Nevertheless, our results suggest that patients with older age, worsening liver function, and higher AFP score may be related to poor prognosis without liver transplant, underscoring the need for transplant for such patients. Although our local results were consistent with overseas results on liver transplantation for patients with HCC, we did show that despite the low rate of liver transplant and relatively long waiting time in Singapore, we were able to show good survival in the group of patients who successfully underwent liver transplantation.

In summary, the prognosis of patients with HCC without liver transplant is poor. Loco-regional therapy by either TACE or RFA probably helps reduce the risk of recurrence post-transplant despite our relatively long waiting time. For patients with HCC within the Milan criteria, liver transplantation is effective and is associated with good long-term prognosis.

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