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Research Article

Management of Recurrent Hepatocellular Carcinoma after Liver Transplant – A Single Center Experience

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Abstract

Background: Hepatocellular carcinoma (HCC) recurs in 10-60% of patients after liver transplantation and carries very dismal prognosis. Optimal management of this condition has yet to be defined.

Patients and Methods: All adult patients with HCC within the UCSF (University of California, San Francisco) criteria who underwent liver transplantation at Queen Mary Hospital during the period from July 1995 to September 2013 were reviewed. Two hundred and fifty-two patients were included in the analysis. They were divided into three groups for comparison: with intrahepatic recurrence (IR), with multiple or extrahepatic recurrence (MR), with no recurrence (NR).

Results: HCC recurrence occurred in 35 (13.9%) patients, 3 with IR and 32 with MR. Patients in the IR and MR groups had a younger age (51 vs. 51 vs. 56 years; p=0.007), a higher pretransplant serum α-fetoprotein level (27 vs. 97.5 vs. 18 ng/mL; p=0.005), more tumor nodules (4 vs. 2 vs. 1; p=0.003) and a higher incidence of lymphovascular permeation (33% vs. 59% vs. 27%; p=0.001) than patients in the NR group. More patients in the IR and MR groups had tumors beyond the UCSF criteria on histopathology (67% vs. 56% vs. 17%) when compared with the NR group. Treatments for IR included hepatectomy, radiofrequency ablation and transarterial chemoembolization. One patient with IR remained alive 3 years after last treatment. Overall survival in the IR group was longer than that in the MR group (59 vs. 30.4 months; p<0.001). Time from transplant to recurrence was similar between the two groups (23.1 vs. 12 months; p=0.141).

Conclusions: Recurrence of HCC after liver transplantation is not uncommon. Aggressive surgical treatment may prolong survival in patients with IR only. Prognosis for patients with MR is dismal. Effective systemic therapy is urgently needed.

Keywords: Hepatocellular carcinoma; Recurrence; Liver resection; Transarterial chemoembolization; Liver transplantation; Targeted therapy

Introduction

Hepatocellular Carcinoma (HCC) is the leading cause of deaths among patients with hepatitis B, hepatitis C or related cirrhosis, and its incidence has increased over the past decade [1]. Liver Transplantation (LT) is the definitive treatment for it and the underlying liver cirrhosis. Unfortunately, HCC recurs in 10-60% of patients after LT [2-6]. The average time for recurrence ranges between 1 and 2 years, and some patients develop recurrence after 5 years [6]. Treatment of recurrent HCC after LT remains a myth. The present study reviews the management of recurrent HCC after LT at our center.

Patients and Methods

Data of all adult patients who underwent LT at Queen Mary Hospital in the period from July 1994 to December 2007 were reviewed. The strategies used for the management and selection of patients with known HCC for LT have been described previously [7]. In brief, normally patients aged 65 years or below with disease not suitable for partial hepatectomy or local ablation were considered for LT. Before 2002, the radiological Milan criteria [2] (solitary tumor up to 5 cm in size, or a maximum of 3 tumor nodules with each no larger than 3 cm) were used for selection, but since 2002 the tumor number and size limits have been expanded to match the UCSF (University of California, San Francisco) criteria [8] (solitary tumor up to 6.5 cm in size, or a maximum of 3 tumor nodules with each no larger than 4.5 cm and a maximum total diameter of 8 cm). Tumor evaluation was done using computed tomography of the abdomen and thorax, as well as radionucleotide bone scan at initial diagnosis. Recently, dual-tracer (carbon-11 acetate and fluoro-18 deoxyglucose) positron emission tomography has been used on selected patients to detect extrahepatic metastasis. For patients with prolonged waiting time, imaging studies were repeated every 3 to 6 months, and transarterial chemoembolization was given to control tumor growth for those with adequate hepatic reserve. Patients whose tumors progressed to beyond the acceptance criteria as seen on serial imaging were excluded from LT. Patients with major vascular invasion, extrahepatic disease or tumors beyond the UCSF criteria were not offered LT.

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Table 1: Comparison of demographic and clinical data of the 3 groups.

	IR (n=3)	MR (n=32)	NR (n=217)	P
Male : Female	3 : 0	29 : 3	179 : 38	0.378
Median age (years) (range)	51 (48 - 56)	51 (40 - 63)	56 (3-72)	0.007
Diagnosis				0.998
Cirrhosis	3	29	194	
Chronic active hepatitis	0	1	4	
Cirrhosis with acute deterioration	0	2	16	
Biliary atresia	0	0	1	
Primary biliary cirrhosis	0	0	2	
Carrier of HBV	3	32	172	0.012
Carrier of HCV	0	0	29	0.071
Carrier of HBV and HCV	0	0	3	0.783
Median pre-LT α-fetoprotein (ng/mL) (range)	27 (21 - 1793)	97.5 (2 - 117850)	18 (1 - 38001)	0.005
Median pre-recurrence α-fetoprotein (ng/mL) (range)	8 (3 - 10)	18 (2 - 307)	--	0.099
Salvage LT	0	17	34	**0.000**

For living-donor LTs, all living donors needed to have compatible ABO blood groups, as well as negative serology for hepatitis B surface antigen and hepatitis C antibody, and no evidence of any acute or chronic illness that would increase the operative risk. Computed tomography with volumetry was performed to determine the size of the donor liver, and the left or right liver lobe was selected to provide a graft larger than 40% of the recipient's standard liver as estimated according to the University of Hong Kong formula [9].

Patients were followed up at our outpatient clinic weekly within the first 3 months of LT, and then every 1 to 3 months depending on their clinical status and results of liver function tests. Routine blood tests including liver and renal function tests were performed at every visit. Serum α-fetoprotein level check, chest X-ray and computed tomography (or magnetic resonance imaging for patients with impaired renal function) were performed every 3 to 6 months within 5 years of LT, and thereafter every 6 to 12 months or when deemed indicated (e.g. if the serum α-fetoprotein level showed a rising trend).

Treatment for intrahepatic recurrence

The selection criteria for resection in liver grafts were the same as those for primary resection [10]. The resection techniques have been described in detail previously [10]. In brief, the criteria were (i) absence of extrahepatic disease, (ii) anatomically suitable disease, (iii) technically feasible disease, and (iv) absence of main portal vein or inferior vena cava tumor thrombus. All resections were conducted by experienced liver transplant surgeons. As a general guideline, sectionectomy or hemihepatectomy was performed for centrally located lesions, and wedge resection was performed for peripherally located lesions. Intraoperative ultrasonography was performed routinely for detecting undetected lesions in the liver. Liver parenchymal transection was performed with a Cavitron ultrasonic surgical aspirator. During liver transection, the central venous pressure was maintained below 5 mmHg by strict control of intravenous fluid administration so as to reduce venous bleeding from the liver. Hemostasis was achieved by suture, electrocautery or argon beam coagulation. Abdominal drain was not routinely deployed.

Patients with a solitary tumor ≤5 cm or ≤3 tumor nodules each ≤ 3 cm who needed resection of large non-tumorous liver or had marginal liver function or difficult anatomical tumor locations (e.g. junction of major vasculatures) were subjected to radiofrequency ablation.

Treatment for multiple or extrahepatic recurrence

Patients with multiple or extrahepatic recurrence were given best medical treatment and referred to the oncology department for consideration for possible systemic or targeted therapies.

Statistical analysis

The patients were divided into 3 groups for comparison: with intrahepatic recurrence (IR), with multiple (>3 intrahepatic recurrences) or extrahepatic recurrence (MR), and with no recurrence (NR). No patients had suspicious extrahepatic metastasis at the time of transplantation. Hospital mortality was defined as death occurring during the same hospital admission for the primary operation. Comparison of categorical variables was performed using Pearson's chi-squared test. Nonparametric continuous variables were compared using independent-samples Kruskal-Wallis test and presented as medians and ranges. Parametric continuous variables were compared using Student's t test and presented as means with standard deviation. Survival was analyzed by the Kaplan-Meier method, and comparison of variables was performed with the log-rank test. P values <0.05 were regarded as statistically significant and all p values were two-tailed. Significant factors ($p<0.1$) were put into a multiple logistic regression to determine independent factors associated with survival.

Results

Two hundred and fifty-two patients were included in the analysis. HCC recurrence occurred in 35 (13.9%) patients, 3 with IR and 32 with MR. Patients in the IR and MR groups had a younger age (51 vs. 51 vs. 56 years; $p=0.007$), a higher pretransplant serum α-fetoprotein level (27 vs. 97.5 vs. 18 ng/mL; $p=0.005$), more tumor nodules on histopathology (4 vs. 2 vs. 1; $p=0.003$) and a higher incidence of lymphovascular permeation (33% vs. 59% vs. 27%; $p=0.001$) than patients in the NR group (Table 1 and Table 2). More patients in the IR and MR groups had tumors beyond the UCSF criteria (67% vs. 56% vs. 17%) and tumors at stage IIIA or above ($p<0.001$) when compared with the NR group (Table 2). The preoperative and postoperative viral loads for infections of hepatitis B virus (HBV) and hepatitis C virus (HCV) are listed in Table 3. Entecavir was given to patients who had a high HBV DNA load, and interferon-based therapy was given to patients with a high HCV RNA load. On multivariate analysis, patient age, salvage LT and tumor status beyond the UCSF criteria are independent risk factors for HCC recurrence (Table 4). Table 5 shows the treatments for recurrence given to patients in the IR and MR groups. The overall 1-year, 3-year and 5-year patient survival rates were 100%, 66.7% and 0% respectively in the IR group, 93.8%, 43.5% and 23.9% respectively in the MR group, and 96.7%, 95% and 92.7% respectively in the NR group. Longer patient survival was found in the IR group when compared with the MR group ($p<0.001$) (Figure).

Table 2: Comparison of tumor characteristics and survival in the 3 groups.

	IR (n=3)	MR (n=32)	NR (n=217)	P
Explant tumor characteristics				
Median tumor number (range)	4 (2 - multiple)	2 (1 - 20)	1 (1 - multiple)	**0.003**
Median largest tumor size (cm) (range)	3.2 (1.8 - 5.0)	3.2 (1.0 - 19.5)	3.7 (0.25 - 8.0)	0.094
Vascular permeation	1	19	58	**0.001**
Differentiation				0.065
Well	2	3	69	
Moderate	0	23	110	
Poor	1	2	12	
Undifferentiated	0	0	2	
Not mentioned	0	4	20	
Milan – within : beyond	1 : 2	13 : 19	149 : 64	**0.002**
UCSF – within : beyond	1 : 2	14 : 18	176 : 37	**0.000**
AJCC staging system (2002, 6th edition)				**0.000**
I	0	7	87	
II	2	16	116	
IIIA	1	9	9	
IIIB	0	0	1	
Patient status – alive : dead	1 : 2	6 : 26	200 : 17	**0.000**
Graft status – functioning : lost	1 : 2	6 : 26	199 : 18	**0.000**
Overall patient survival				**0.000**
1-year	100.0%	93.8%	96.7%	
3-year	66.7%	43.5%	95.0%	
5-year	0%	23.9%	92.7%	
Overall graft survival				**0.000**
1-year	100.0%	93.8%	95.7%	
3-year	66.7%	43.5%	94.6%	
5-year	0%	23.9%	92.4%	
Median survival (months)	59.0	30.4	>222.8	**0.000**
Median follow-up (months) (range)	34.6 (29.7 - 59.0)	28.4 (8.5 - 139.8)	49.6 (0 - 222.8)	**0.030**
Median time from LT to recurrence (months) (range)	23.1 (21.1 - 44.8)	12 (3.3 - 71.2)	--	0.141

AJCC: American Joint Committee on Cancer

Discussion

Around 8% of Hong Kong residents are HBV carriers, and most of the HCC cases in Hong Kong are caused by the virus. According to the *Surveillance of Viral Hepatitis in Hong Kong – 2010 Update Report* conducted in 2011 by the Department of Health of the Hong Kong government, about 10.4% of male adults and 7.7% of female adults were positive of hepatitis B surface antigen. On the other hand, places where HCV infection is epidemic such as Japan and the United States has seen a surge of liver cirrhosis and HCC related to the virus [1,11].

In 2009, the LT program in Hong Kong started to adopt the 'bonus points' system for stage-2 HCC [12]. The system has increased the number of LTs for HCC considerably, which now account for one third of all LTs in Hong Kong. Concomitantly, the incidence of HCC recurrence after LT is on the rise. This desperate issue requires more attention than ever before. Treatments for HCC recurrence are highly variable. Therorectically, all treatments for HCC can be applied to treat its recurrences after LT, but the nature would be different. Treatments for HCC recurrences after LT are palliative in nature since they are 'systemic' recurrences. Nonetheless, aggressive treatment can be offered to patients who have IR only.

In the study, all the 3 patients in the IR group underwent resection of the liver graft and further recurrences were treated by transarterial chemoembolization or radiofrequency ablation. The overall survival of patients with IR was significantly longer than that of patients with MR (59 vs. 30.4 months; p<0.001) although the time of recurrence from transplant was comparable (23.1 vs. 12 months; p=0.141). One patient survived 3 year after treatments for IR.

At out center, patients with IR are subjected to surgical resection or radiofrequency ablation if they have fewer than 3 nodules, otherwise transarterial chemoembolization is administered. The aggressive approach has shown some evidence of prolonging survival. Nonetheless, recurrence pattern also plays an important role in

Table 3: Preoperative and postoperative viral loads for HBV and HCV infections.

	IR (n=3)	MR (n=32)	NR (n=217)
HBV			
Preop HBV DNA			
Positive	2	15	81
Negative	1	17	90
No data	0	0	1
Postop first HBV DNA			
Positive	0	4	13
Negative	3	28	157
No data	0	0	2
HCV			
Preop HCV RNA			
Positive	/	/	8
Negative	/	/	3
No data	/	/	18
Postop first HCV RNA			
Positive	/	/	23
Negative	/	/	5
No data	/	/	1
HBV + HCV			
Preop HBV DNA			
Positive	/	/	2
Negative	/	/	1
Postop first HBV DNA			
Positive	/	/	0
Negative	/	/	3
Preop HCV RNA			
Positive	/	/	0
Negative	/	/	0
No data	/	/	3
Postop first HCV RNA			
Positive	/	/	2
Negative	/	/	1

Table 4: Multivariate analysis of independent risk factors associated with recurrence.

	P	Odds Ratio
Age	0.000	0.891
HBV infection	0.997	1.550
Salvage LT	0.000	5.830
Pre-LT tumor status beyond UCSF criteria	0.000	6.728

determining the prognosis. It seems that a larger number of tumor nodule and the presence of vascular permeation are associated with MR (Table 2). On multivariate analysis, tumor factors and salavge transplant were independent risk factors in survival. The finding echoed our previous report [13]. However, there could be selection bias for salvage transplant for poor-risk patients with failed primary treatment, so the outcome was also poor. Obviously, most patients

Table 5: Treatments for recurrence.

	IR (n=3)	MR (n=32)	P
Liver resection	3†	0	**0.000**
Transarterial chemoembolization	2‡	7	0.156
Systemic chemotherapy	0	13	0.279
Adrenalectomy	0	3	1.000
Lung resection	0	8	1.000
Alcohol injection	0	1	1.000
Interferon	0	3	1.000
Local excision	0	4	1.000
Intramedullary nailing	0	4	1.000
Radiotherapy	0	12	0.536
Percutaneous radiofrequency ablation	1‡	2	0.242
Targeted therapy	1‡	16	1.000
Open reduction and fixation	0	1	1.000
Tamoxifen	0	1	1.000
Thalidomide	0	3	1.000

† For recurrence for the first time
‡ For re-recurrences

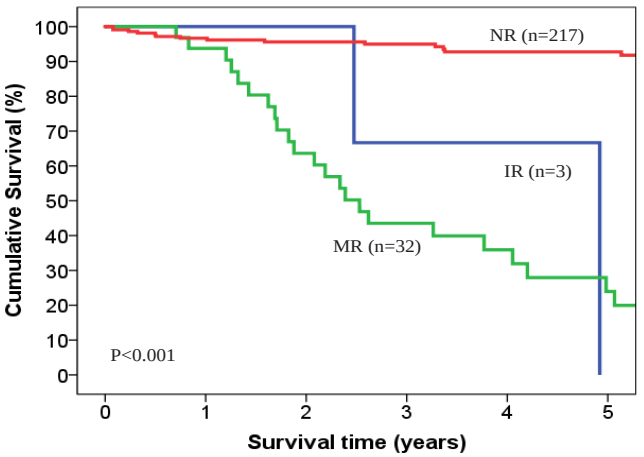

Figure: Comparison of overall patient survival in the 3 groups.

are desperate after failure of their primary treatment and salvage transplant is bound to accept higher-risk patients in this regard, especially if a living donor is available after thorough discussion about the potential risks. Revised or modified patient selection criteria for salvage LT are needed in this context to better stratify the risks.

Patients with MR were treated with various therapies (Table 4). Local excision included excision of solitary retroperitoneal nodule (n=1) and solitary peritoneal nodule (n=1). Two patients received excision of inferior vena cava tumor thrombus. The use of chemotherapy was not standardized and the most commonly used agents were doxorubicin, 5-fluorouracil and carboplatin. At our center, these various therapies are used to treat recurrences after treatment of HCC (LT or non-LT) and have been shown to be beneficial [6].

The drawbacks of this study are its retrospective nature, the small cohort size, and the heterogeneity of the patient population.

Moreover, there could be selection bias as this is a single-center study. However, our center has a strong experience in LT and hepatectomy, so the results may shed some light on the management of HCC recurrence after LT and may serve as a reference of note for other centers.

Conclusion

Aggressive treatment for intrahepatic HCC recurrence after LT may have some survival benefits for selected patients, but prognosis for patients with multiple or extrahepatic recurrence is dismal and effective systemic therapy is urgently needed.

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