Liver transplantation: would it be the best and last chance of cure for hepatocellular carcinoma with major venous invasion?

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Background: Hepatocellular carcinoma (HCC) with portal vein tumour thrombus (PVTT) signifies advanced disease, whether LT confers any survival superiority over resection remains uncertain.
Methods: A propensity score matched (PSM) analysis of liver transplantation (LT) and liver resection (LR) for HCC with PVTT was performed.
Results: A consecutive series of 88 patients who received either LT (10 DDLTs and 3 LDLTs) or LR (n=75) respectively were recruited. Before PSM, the LT group has a higher MELD score (17.3 *vs.* 7.8, P<0.001), lower serum AFP levels (96 *vs.* 2,164 ng/mL, P=0.017) and smaller tumour size (4 *vs.* 10 cm, P<0.001). The 5-year overall survival for LT and LR were 55.4% and 15.9% respectively (P=0.007). After matching for serum AFP levels and tumour size, 1-, 3- and 5-year overall survival for LT were 81 ng/mL, 3.9 cm, 80%, 70% and 70% and the corresponding rates for LR were 1,417 ng/mL, 5.3 cm, 51.8%, 19,6% and 9.8% (P value =0.12, 0.27 and 0.009 respectively).
Conclusions: LT is associated with significantly better oncological outcomes in HCC patients with PVTT involving the lobar or segmental level. A modest expansion of selection criteria to include small HCC with segmental PVTT should be considered.

Keywords: Liver transplantation (LT); portal vein; tumour thrombus; liver resection (LR)

Introduction

Hepatocellular carcinoma (HCC) is the 5th most common cancer and 3rd most common cause of cancer related death in the world (1). This disease leads to significant burden to the healthcare system in developed countries such as United Stated due to the observed growing incidence and HCC-related death (2). Given the high propensity of portal vein invasion, 10–20% of the HCC presents have concomitant portal vein tumour thrombus (PVTT). According to the latest update of Barcelona Clinic Liver Cancer (BCLC) staging, HCC with portal vein tumour thrombosis (PVTT)

is classified as Grade C advanced HCC (3), meaning that patients of BCLC Grade C can only receive systemic therapy even they have relatively preserved liver function, and the survival is exceedingly limited (4,5).

HCC patients with PVTT are treated more aggressively in many Asian countries. According to the Hong Kong Liver Cancer (HKLC) staging system, HCC patients (solitary tumor and the size is less than 5cm) and with intra-hepatic (i.e., left or right portal vein) PVTT are classified as Stage IIb/IIIa, in which resection can still be offered as a curative treatment (6). Although the long-term survival of HCC patients with PVTT is worse than the PVTT

free counterparts, 3-year survival of up to 20% had been constantly reported in many Asian centres. In comparison to other treatment modalities, the survival outcomes after hepatectomy is still better than trans-arterial chemo-embolization (7,8), trans-arterial radio-embolization (9), external radiotherapy (10), and systemic treatments (11,12).

Liver transplantation (LT) is regarded as the best treatment for HCC. The 5-year overall survival of over 80% is frequently reported by established LT centres (13-16). Since major vascular invasion is considered as an absolute contra-indication for this procedure, data concerning the efficacy of LT in the context of HCC with PVTT treatment is very limited. A recent study suggested that LT was feasible for HCC with segmental PVTT but not for lobar PVTT (17). However, the survival benefit of LT in comparison liver resection (LR) in this context remains uncertain. The aim of this study was to address this issue and to evaluate the oncological feasibility of LT for HCC with PVTT. We present the following article in accordance with the STROBE reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn.2020.03.09/rc).

Methods

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was a retrospective analysis of anonymous clinical data and, according to institutional guidelines, did not require approval by the institutional research ethics board. All patients gave informed consent to surgery as well as use of their anonymous clinical data for research purposes.

Patient background

From January 2000 to December 2016, the clinic-pathological and follow-up data for all patients who received either LT or LR for HCC were reviewed. In the LR group, patients with positive resection margin was excluded from data analysis. This was a retrospective cohort of patients with HCC related major venous thrombosis treated in Queen Mary Hospital, The University of Hong Kong from 2000 to 2016. Patients who received either LR or LT as a treatment with curative intent were included. Paediatric patients, patients with final pathology showing cholangiocarcinoma or mixed cholangio-HCC were excluded from the study. All LTs in this series were performed in Author's centre and no prisoner's organ was

used for transplantation in our centre. Technical details of hepatectomy (18) and LT (19) had been described in previous publications. In short, patients who are eligible for hepatectomy if there is absence of extrahepatic disease, adequate liver function (i.e., indocyanine green retention less than 18% in 15 minutes and the ratio of future liver remnant to estimated standard liver volume more than 30%) and significant comorbidity that preclude major hepatectomy under general anaesthesia. Patients with pathological evidence of PVTT will not receive adjuvant treatment if the resection margin is negative of HCC. Concerning the protocol of LT for HCC patients, Milan criteria (20) was adopted for patient selection for DDLT before 2002. After 2002, University of California at San Francisco (UCSF) criteria was adopted for patient selection (21). Details concerning MELD bonus scoring system, bridging therapy, and immunosuppressive regimen were reported in previous publications (22). However, evidence of major vascular invasion (i.e., portal vein or hepatic vein) on pre-transplant structural imaging represent an absolute contra-indication to proceed. In case of PVTT in explant pathology, m-TOR inhibitor will be started with minimization of calcineurin inhibitor in order to reduce the chance of recurrence. Adjuvant or systemic therapy will only be given in case of the detection of recurrence.

Statistical analyses

Demographic data, preoperative biochemistry, pathological findings and operative outcomes were retrieved from prospectively maintained database. Classification of PVTT followed Liver Cancer Study Group of Japan (LCSGJ) (23). Multi-variate analysis with Cox-regression model was used to determine factors associated with post-transplant survival of the patients. Prior to survival comparison between two groups, univariate analysis was performed to look for presence of heterogeneity. Propensity score matching was performed to reduce bias secondary to the presence of these heterogeneity using the nearest neighbour method. Survivals of patients were analysed using Kaplan-Meier curves and compared with Log-rank test. P value less than 0.05 were considered statistically significant.

Results

Characteristics of study population

From 2000 to 2016, HCC with tumour invasion to the portal vein invasion was confirmed pathologically in 88

patients. Majority (94.3%) of the patients had tumour invasion to the second order branch of the portal vein (Vp2). In patients who received LT, all PVTT were incidental finding in the DDLT group, while 4 out of the 10 LDLT recipient had known PVTT before the operation. The median age at operation was 55 [22–78] years old and male was the predominant gender in the population. Within the whole study population, 88.6% and 4.5% were hepatitis B and hepatitis C carrier respectively. The median AFP level and tumour size was 1,694 [2–1,112,000] ng/L and 8.9 [1.4–21.5] cm respectively. The median follow-up duration was 16 months.

Univariate, multi-variate and propensity score matching

After univariate analysis, size of tumour (P=0.016) and LT (P=0.007) were found to be associated with post-operative survival. After multivariate analysis, only LT was the only independent factor associated with overall survival (P=0.01, OR 0.329, 95% CI: 0.142–0.766). The 3-year overall and disease-free survival of patients in the LT and resection was 69.2% *vs.* 25.1% (P=0.007) and 64% *vs.* 10.4% (P<0.001) respectively.

Comparisons between patients who received resection (n=75) and transplantation (n=13) were therefore made. Characteristic of these two population was shown in *Table 1*. A number of heterogeneities were observed between these two groups, namely pre-operative AFP (P=0.017), platelet count, total bilirubin, MELD score, tumour size, and type of venous invasion (P<0.001). Among these factors, those which were known to be associated with tumour biology were used for propensity score matching. There was no significant heterogeneity between resection and transplantation in all factors associated with worse tumour biology, namely AFP level, tumour size and number, microvascular invasion, tumour differentiation, and type of venous invasion after matching (*Table 1*).

Survival outcomes in propensity score matched (PSM) population and subgroup analysis

There were 10 (7 DDLT and 3 LDLT) and 30 patients in the transplantation and resection group respectively after matching with their characteristics shown in *Table 1*. HCC recurrence was found in 50% and 76.7% of the patients in transplantation and resection group respectively (P=0.133). Patients in the transplantation group had a significantly better disease-free survival (median 62 *vs.*

5.7 months, P<0.001) (*Figure 1*). Superior overall survival was demonstrated in the transplantation group, with median survival of 217 *vs.* 12.3 months (P=0.009) (*Figure 2*). Survival analysis was repeated after excluding patients with pre-operative AFP over 500 ng/mL. A trend of superior overall survival was still observed in the transplantation group (*Figure 3*).

Discussion

Survival analyses in the matched population demonstrated that, patients in the LT group had significantly better disease-free and overall survival when compared to the resection group counterparts (62 and 217 *vs.* 5.7 and 12.3 months respectively). These superior oncological outcomes suggested that LT could be a viable treatment option in selected HCC patients with PVTT.

According to the BCLC staging, which was adopted by many liver cancer centres in the west, presence of PVTT represents an advance disease stage (stage C), as such, hepatectomy is no longer a treatment option. The expected survival of this group of patients is around 3 months. Hepatectomy with portal thrombectomy or en bloc thrombus resection technique had been proven safe and feasible for this group of patients. Despite the aggressiveness of the procedure, the reported median survival after surgery was still limited, ranging from only 8 to 36 (3-year overall survival of 0–49%) months from most series (18,24-29). The efficacy of hepatectomy as a curative treatment modality remains suboptimal.

Concerning LT, presence of PVTT is considered as an absolute contraindication judging from the high recurrence rate (30,31). There were few studies reporting the survival outcomes of LT for HCC patients with PVTT and most of them were from the Korean groups (17,32,33). The reported 5-yr overall survival was ranging from 50.3–63.6%. With these encouraging results, some surgeons advocated that PVTT should no longer be a contraindication for LT (32).

In the regions of organ shortage like many Asian countries (34), deceased liver graft is not allocated to HCC patients with PVTT in view of the anticipated worse outcomes comparing with HCC patients without PVTT. However, this principle of utility does not apply to LDLT in which the liver graft is a dedicated gift from a loved one. In fact, conventional criteria such as Milan Criteria and UCSF Criteria were introduced in more than 2 decades ago, there are many series reporting very good long term

Table 1 Characteristics of the resection group and transplantation group before and after propensity score matching

Factor	Before matching			After matching		
	Transplantation group (n=13)	Resection group (n=75)	P value	Transplantation group (n=10)	Resection group (n=30)	P value
Sex (%male)	84.6	84.0	1.0	80	83.3	1.0
Age (yr)	55 [32–62]	56 [22–78]	0.24	56 [32–62]	56 [29–78]	0.31
HBV carrier (%)	92.3	88.0	1.0	90	93.3	1.0
HCV carrier (%)	7.7	4.0	0.48	10	10	1.0
AFP (ng/mL)	96 [2–38,001]	2,164 [2–1,112,000]	0.017	81 [2–38,001]	1,417 [2–44,237]	0.12
Platelet count (×10^9)	54 [36–130]	191 [75–447]	<0.001	48 [36–114]	157 [75–309]	<0.001
Lymphocyte count (×10^9/L)	0.98	1.29	0.095	0.84	1.3	0.095
Albumin (g/L)	33 [19–52]	40 [20–48]	0.08	33 [19–52]	41 [32–48]	0.08
Bilirubin (mmol/L)	61 [9–436]	11 [3–70]	<0.001	53 [9–436]	11 [3–70]	0.001
MELD	17.3 [6.4–34.1]	7.8 [6.4–15.7]	<0.001	16.2 [6.4–27.3]	7.7 [6.4–15.7]	0.002
Tumor size (cm)	4 [1.4–8]	10 [2–21.5]	<0.001	3.9 [1.4–8]	5.3 [2–8.8]	0.27
Tumor number	2 [1–9]	2 [1–9]	0.653	2 [1–9]	2 [1–9]	0.36
Type of venous invasion (%)			<0.001			0.06
VP2	61.5	100		80	100	
VP3	15.4	0		20	0	
VP4+ HV	15.4	0		0	0	
HV only	7.7	0		0	0	
Microvascular invasion (%)	84.6	94.7	0.21	80	93.3	0.25
Differentiation (%)			0.35			0.45
Well	8.3	2.7		10	6.7	
Moderate	75.0	63.5		80	63.3	
Poor	16.7	33.8		10	30	
Recurrence (%)	61.5	81.3	0.143	50	76.7	0.133
Median survival (month)	58.2	13.7	0.007	217.3	11.5	0.009

survival even transplanting HCC beyond these standard criteria. The message was clear that size and number of HCC represent only a part of the tumour biology, other factors such as alpha fetoprotein level, PIVKA-II level, nuclear differentiation, presence of microvascular and macrovascular invasion should all be put into the calculating formula. In a study by Choi *et al.*, 24 patients with MVI were compared with 27 patients with segmental type PVTT (i.e., VP2). There was no statistical significant difference identified between two groups (3-year overall survival 69.7% *vs.* 60.3%, P=0.48) (17). This result suggested that

HCC with PVTT should be seen as an adverse factor rather than an absolute contraindication for LT.

The best way to tell whether LT is a better treatment option than resection is to perform a randomized controlled trial, yet, this study design is practically not possible. Direct comparison between LT and resection is bound to bias due to obvious heterogeneity between these two populations. A propensity score matching analysis is probably next best methodology. In our study, because of the limited patient number, complete matching for all factors deemed not possible. Therefore, only factors known to be related
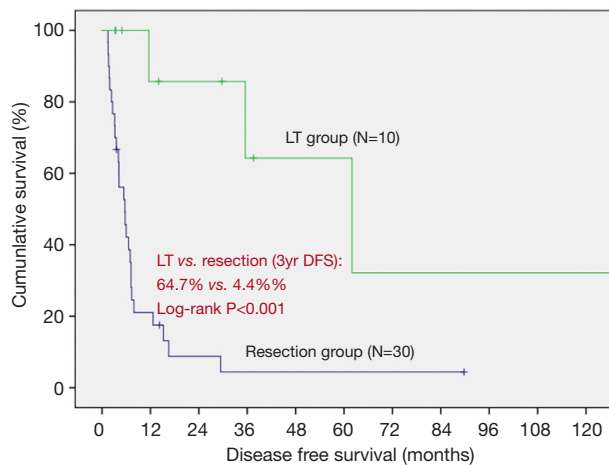
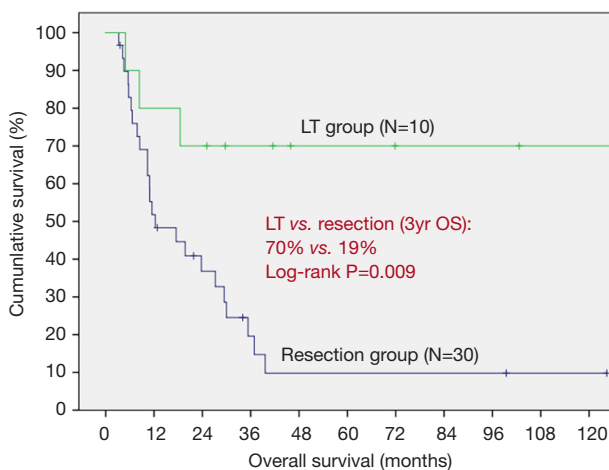**Figure 1** Comparison of disease free survival between LT and resection group.

Figure 3 Comparison of overall survival between LT and resection group in matched population (AFP <500 ng/mL).

Figure 2 Comparison of overall survival between LT and resection group.

The superiority of LT might be confounded by a lower preoperative AFP level. Therefore, a subgroup survival analysis was performed for patients with AFP <500 ng/mL as this is a common cut-off for patient stratification used by many studies. Superiority of LT over resection was apparent from the wide separation of the corresponding Kaplan-Meier curves. An insignificant P value is likely accounted by type II error.

There were limitations concerning this study. The retrospective study design unavoidably subjected this study to selection and recall bias, use of propensity score matching helped to alleviate this weakness to a certain extent. In addition, small study population reduces the power of this study, yet this weakness is common in performing study on rare disease conditions (i.e., LT for HCC with PVTT). A multi-centre study would help to improve these weaknesses and better define the role of LT in the context of PVTT.

Conclusions

HCC with PVTT of Vp2/Vp3 type should be considered a relative contra-indication for LT in view of the potentially better oncological outcomes when compared to hepatectomy.

Acknowledgments

to tumour biology were statistically matched (i.e., AFP, tumour size, type of PVTT). Despite a significantly better pre-operative liver function (i.e., MELD score, albumin level and platelet count) in the resection group population (better liver function is known to associate with better post-operative survival), the oncological outcomes were still inferior to that of the LT group. This implied a significant protective effective using LT as a treatment for HCC patient with PVTT.

It was observed that, despite statistically insignificant, the median AFP level in the resection group was still much higher than the LT group (1,417 *vs.* 87 ng/mL, P=0.12).
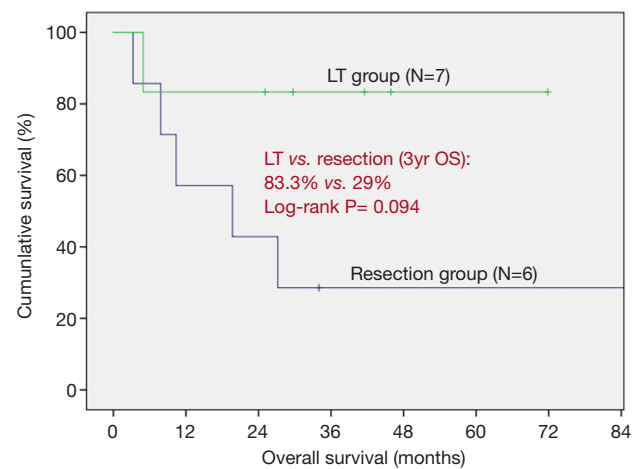
Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn.2020.03.09/rc

Data Sharing Statement: Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn.2020.03.09/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn.2020.03.09/coif). Dr. ACYC and Dr. CML serve as unpaid editorial board members of *Hepatobiliary Surgery and Nutrition*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was a retrospective analysis of anonymous clinical data and, according to institutional guidelines, did not require approval by the institutional research ethics board. All patients gave informed consent to surgery as well as use of their anonymous clinical data for research purposes.

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