Review Article

Liver Transplantation for Hepatitis B Virus-related Hepatocellular Carcinoma in Hong Kong

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Abstract

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third most common cause of cancer-related deaths worldwide. Curative resection is frequently limited in Hong Kong by hepatitis B virus-related cirrhosis, and liver transplantation is the treatment of choice. Liver transplantation has been shown to produce superior oncological benefits, when compared to hepatectomy for HCC. New developments in the context of patient selection criteria, modification of organ allocation, bridging therapy, salvage liver transplantation and pharmaceutical breakthrough have improved the survival of HCC patients. In this article, we will share our experience in transplanting hepatitis B virus-related HCC patients in Hong Kong and discuss the recent progress in several areas of liver transplantation.

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Introduction

Hong Kong is one of the endemic regions for hepatitis B virus (HBV) infection. In a population surveillance report from the Health Ministry, 10.4% of males and 7.7% of the females were positive for HBV surface antigen.[1] Chronic HBV infection has been the main etiology for the development of hepatocellular carcinoma (HCC) in this locality.[2] The majority of HCC patients present at an advanced, inoperable stage; furthermore, development of HCC in the background of cirrhosis[3] makes curative resection difficult.

Liver transplantation (LT) represents the last hope for this group of patients (Table 1). Since the landmark publication by Mazzaferro *et al.*[4] in 1996, LT has been regarded as an ideal treatment for HCC, with 5-year overall survival over 70%. This encouraging result was subsequently demonstrated in many other centers around the world. At Queen Mary Hospital—the only liver transplant center in Hong Kong—the median survival after primary (p)LT for HBV-related HCC was 71.2 months (the 1-/5-yr overall and disease-free survival rates were 95%/85% and 80.5%/77.8%, respectively).

In order to reproduce and sustain this good oncological outcome, a well-designed LT protocol for HCC is indispensable. In this article, issues about patient selection criteria, the Model of End-Stage Liver Disease (MELD) exception scoring system and bridging therapy, living donor (LD)LT, small-for-size syndrome (SFSS), salvage LT, and postoperative antiviral and immunosuppressive therapies will be discussed.

Patient selection criteria and prediction of HCC recurrence

Like many other Asian regions, Hong Kong has a small donor pool, with a liver donation rate of about 4 in a million.[5] This organ shortage is probably a result of poor acceptance of the brain death concept, insufficient government funding and cultural barriers.[6] Careful patient selection and a tailor-made organ allocation system are essential to good utilization of this precious organ.

Different patient selection criteria have been advocated by different centers (Table 2).[4,7–16] The majority of criteria still have a focus on tumor factors such as tumor size and number, with some fine adjustment. Our center has adopted the University of California, San Francisco (UCSF) criteria for patient selection for deceased donor DDLT. In recent years, new parameters such as alpha fetoprotein (AFP) level,[14,16] protein-induced vitamin K antagonist-II (PIVKA-II),[12,13] and degree of tumor differentiation[15,16] have been proposed.

Pre-LT liver tumor biopsy is not routinely performed, due to anatomical reasons and concerns of tumor bleeding, seeding and risk of sampling error. Association between post-LT HCC recurrence and level of pre-LT AFP level has been demonstrated, and AFP is incorporated as a predicting parameter in some scoring systems (such as the RETREAT[17] and MORAL[18] scores) and nomograms.[19] However, another study[20] showed that the sensitivity of AFP for recurrent HCC was just around 59%. In our center, around 20–30% of the HCC patients were nonsecretors of AFP; this fact might limit its application in patient selection.

PIVKA-II is currently not available in many centers, including ours. Yet, many studies have demonstrated high

Keywords: Liver transplantation; Hepatitis B; Hepatocellular carcinoma; Review.
Abbreviations: AFP, alpha fetoprotein; CI, confidence interval; DDLT, deceased donor liver transplantation; ESLV, estimated standard liver volume; GW, graft weight; HBIG, hepatitis B immunoglobulin; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HIFU, high-intensity focused ultrasound; IVC, inferior vena cava; LT, liver transplantation; LDLT, living donor liver transplantation; m-TOR, mammalian target of rapamycin inhibitor; MELD, Model for End-Stage Liver Disease; OR, odds ratio; PIVKA-II, protein-induced vitamin K antagonist-II; pLT, primary liver transplantation; RVI, radiogenomic venous invasion; SBRT, stereotactic body radiotherapy; SFSS, small-for-size syndrome; TACE, transarterial chemoembolization; TTV, total tumor volume; UCSF, University of California, San Francisco.
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Table 1. Background information of liver transplantation in Hong Kong in 2016

Total number of liver transplantations, *n*	72
Living donor liver transplantation, *n* (%)	36 (50)
Deceased donor liver transplantation, *n* (%)	36 (50)
Common indications, % • Cirrhosis • Acute/acute on chronic liver failure • Hepatocellular carcinoma	 51.4 27.8 38.9
OT time in min, mean (range) • DDLT • LDLT	 431 (270–929) 621 (374–802)
Blood loss in mL, mean (range)	3500 (300–18000)
Hospital stay in days, mean (range)	19 (8–354)
All-complication rate, %	54.2
Hospital mortality, *n* (%)	1 (1.4)

sensitivity and specificity of PIVKA-II when used alone[20–22] or in combination[23,24] with AFP for the prediction of microvascular invasion and recurrence in HCC. Apart from biochemical markers, promising results in the prediction of microvascular invasion and HCC recurrence have been shown by using new radiological parameters, such as radiogenomic venous invasion (RVI)[25] and total tumor volume (TTV),[26–28] on computed tomography scan and positron emission tomography scan using different isotope tracers (i.e. carbon-11 and 18-fluoro-deoxy-glucose).[29–31] Nonetheless, a majority of these results were from single-center series, and the cut-off values of parameters were not standardized. External validation with multicenter, multiethnic data is necessary before universal acceptance of these new predictive factors.

MELD exception system and bridging therapy

Patients who initially present with HCC beyond UCSF criteria are not eligible for DDLT in Hong Kong. Despite evidence showing that the survival outcomes of patients receiving LT after down-staging treatment for beyond-criteria HCC were comparable to those who received LT for within-criteria HCC,[32–36] these studies had different patient inclusion criteria, modes of down-staging treatment, treatment end-points and rates of successful down-staging. Hence, the results should be interpreted with caution. In addition, there are only around 30–40 deceased-donor organs available each year in Hong Kong, and therefore it is not possible for the system to cater to the overwhelming number of down-staged HCC patients. As such, down-staging therapy is currently not implemented in Hong Kong.

The MELD score system was not intended for the estimation of HCC-related mortality, and most HCC patients have normal or low MELD scores. It has been reported that the drop-out rates for HCC patients on the LT wait list were 25% and 43% for first and second year respectively.[15] Extra bonus score should be granted to HCC patients so as to adjust the estimated mortality risk associated with tumor progression and dissemination while waiting. Since October 2009, patients listed for DDLT who have HCCs that remain at stage 2 for 6 months after confirmation of stage 2 disease by imaging are assigned an arbitrary MELD score of 18. An additional 2 points are added to the MELD score every 3 months if the disease

Table 2. Selection criteria for LT for HCC patients in different centers

Criteria	Tumor size	Tumor number	Additional restriction	Overall 5-yr survival
Mazzerfero[4]	<5 cm <3 cm	Solitary ≤3	-	74% (4-yr OS)
UCSF[7]	<6.5 cm <4.5 cm Total <8 cm	Solitary ≤3	-	75.2%
University of Tokyo[8]	≤5 cm	≤5	-	75%
Chang Guan University[9]	6.5 cm 4.5 cm	1 ≤3	-	90%
Asan[10]	≤5 cm	≤6	-	82%
Up-to-7 (Metroticket)[11]	≤7 cm	≤7	Numerical sum of tumor size and number must be <7	71.2%
Kyoto University[12]	≤5 cm	≤10	PIVKA-II ≤400 mAU/mL	87%
Kyushu University[13]	≤5 cm	Unlimited	PIVKA-II <300 mAU/mL	83%
Hangzhou[14]	Total size ≤8 cm	Unlimited	For total tumor > 8 cm, histological grade must be I or II and AFP must be ≤400 ng/L	72%
Dubay[15]	Unlimited	Unlimited	Only biopsy-confirmed poorly differentiated HCC would be excluded	72%
Extended Toronto[16]	Unlimited	Unlimited	Presence of systemic HCC symptoms/poor tumor grade/AFP > 500 ng/mL	70%

remains at stage 2. There is no upper limit for this bonus score granting; however, bonus granting will be withheld if the disease has progressed to stage III. Patients will be delisted if their disease has progressed to outside UCSF criteria.[37]

Various modes of bridging therapy, such as transarterial chemoembolization (TACE), image-guided local ablation, high-intensity focused ultrasound (HIFU) and stereotactic body radiotherapy (SBRT), are available.[38] In our center, TACE and SBRT are the two most commonly performed bridging therapies. The complete tumor necrosis rate was reported to be around 30%.[39–43] Even if bridging therapy cannot improve the postLT survival or diminish the chance of HCC recurrence when complete pathologic response is not achieved,[44] it serves to stop or slow down disease progression and maximize the chance of LT for wait-listed HCC patients.

LDLT for HCC

Competition between HCC and non-HCC patients for deceased-donor grafts in a tight donor pool has been a "zero-sum" game. LDLT is regarded as the solution to this situation. Given the low donor rate in Hong Kong, most of the LT cases are LDLTs. Conventionally, living donor graft was considered not suitable for patients with high MELD score, which is occasionally seen in HCC patients; however, our recent study suggested that living donor graft could work as well as deceased donor graft.[45]

With the use of living donor graft, which is a dedicated gift from a loved one, concerns about graft utility no longer exist.[46,47] Patients with HCC beyond standard criteria could still be considered for LDLT.[48] Results from our earlier case series[49] and a multicenter study[50] have suggested that LDLT is associated with worse prognostic outcome when compared to DDLT. This worse outcome could be related to the "fast-tracking" effect and possible compromised vascular margin for posteriorly located HCC because the inferior vena cava (IVC) is not resected in total hepatectomy as in the case of DDLT.[51]

Recent studies were not able to confirm the oncological superiority of DDLT for HCC[52,53] and this is probably related to the implementation of the MELD exception scoring system, which leads to a similar "fast-tracking" effect. Up to the moment, convincing evidence is still lacking to suggest superiority of either LDLT or DDLT.

Conquering the small-for-size hurdle in LDLT for HCC

Donor safety is the most concerning part of LDLT. Since the risk for a right lobe donor is 5 times higher (0.5% in right lobe donor vs. 0.1% in left lobe donor),[54] there is a recent trend of increasing use of left lobe graft in many centers, including ours.[55–58] However, left lobe graft is often a small-for-size graft, especially when the recipient is of a size similar to or larger than the donor. This "left shifting" of living donor graft has shifted the risk from donors to recipients and increased the risk of SFSS.[59,60] Despite this, good results have been reported from some centers.[56,57]

In order to reproduce this good outcome, accurate calculation of graft weight (GW) to estimated standard liver volume (ESLV) of the recipient is necessary preoperatively. A validated new formula using patients' body thickness and body weight for ESLV has been proposed by our center, in hopes of minimizing calculation error.[61] Intraoperatively, in addition to the standardized steps,[62,63] we need to shorten the warm ischemic time by expediting graft implantation. Portal venous flow and pressure are measured routinely by flowmeter and pressure transducer in case the GW/ESWL is less than 40%.[64,65] Portal venous modulation might be considered if the portal flow is high (>250 mL/min/100 gm liver) and the portal venous pressure is over 10 mmHg.[65,66] At our center, this is most commonly done by splenic artery ligation.[66,67] Postoperatively, useful measures to avoid SFSS include strict fluid management in the intensive care unit, keeping central venous pressure at 5 cmH_2O by diuretics and albumin, and bed tilting up and right by 5 degrees.

pLT and salvage LT

Debates between the advocates of pLT[68,69] and salvage LT[70] have never ended since Majno *et al.*[43] introduced the concept of salvage LT in 2000. Bhangui *et al.*[71] recently published an intention-to-treat analysis, comparing 130 HCC patients receiving up-front liver resection with 366 HCC patients listed for LT. The authors found that one-third of the patients in the up-front resection group developed nontransplantable recurrence, and both overall and disease-free survival rates were superior in the primary transplant group.

Instead of a universal approach of pLT, some centers advocate primary[10,72]/prophylactic LT[73] for patients with a higher likelihood of recurrence. In areas with organ shortage like Hong Kong, we resect whenever possible, as there are bound to be a significant proportion of patients who can be cured by resection. Moreover, this precludes the need for lifelong immunosuppression, rejection risk and donor risk in LDLT. Close surveillance is important to pick up recurrence at a transplantable stage.

Postoperative viral and immunosuppressive therapy

Adequate antiviral treatment after LT for HCC can reduce the chance of graft loss, hepatitis recurrence and HCC recurrence.[74,75] In the past, due to the high incidence of drug resistance to lamivudine, hepatitis B immunoglobulin (HBIG) was added on, reducing the hepatitis recurrence rate to less than 5%.[76] Since the development a newer antiviral agent, monotherapy using entecavir has been shown to be effective and durable in achieving viral suppression and in preventing HBV-related complications.[77–79]

For immunosuppressive therapy, tacrolimus has been the first-line medication for patients after LT since its development in the 1990s.[80] However, there is the worry that the oncogenic property of this calcineurin inhibitor may predispose patients to HCC recurrence and metastasis.[81,82] Apart from dose minimization,[83] new agents such as sirolimus and everolimus have been shown to have antitumor properties.[84]

Studies from the United States[85] and Canada[86] have demonstrated better post-LT survival in patients with sirolimus. A recent case-controlled study published by Alamo *et al.*,[87] comparing the antitumor efficacy of calcineurin inhibitor and mammalian target of rapamycin inhibitor (m-TOR), showed that the HCC recurrence rate and survival were significantly superior in patients who received either sirolimus or everolimus. In a meta-analysis published by Liang *et al.*,[88] use of a sirolimus-based immunosuppressive regimen was shown to be associated with prolonged overall survival (odds ratio (OR) = 2.47; 95% confidence interval (CI): 1.72–3.55) and decreased tumor recurrence (OR = 0.42; 95% CI: 0.21–0.83), with no increase in frequency of acute rejection and hepatic artery thrombosis. A future randomized controlled

trial is awaited to further define the role of m-TOR in preventing HCC recurrence. Sirolimus should be avoided in the early postoperative period due to the risks of poor tissue healing and hepatic artery thrombosis.

Conclusions

LT is an ideal treatment for HCC as it removes both the tumor and the diseased liver. Careful patient selection and judicious use of the bonus MELD score improve the chance of waitlisted HCC patients. LDLT is equivalent to DDLT in terms of oncological outcomes as treatment for HCC patients. Salvage LT is an ideal approach as part of HCC management, especially in a region with organ shortage. Modern antiviral agents allow for daily oral administration, precluding the need for regular HBIG injection and at the same time providing excellent protection from HBV recurrence. Use of m-TOR inhibitor might have a role in improving survival of selected HCC patients.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Manuscript drafting (KWM), design and supervision of the study (KSHC), provision of information from a hepatologist's perspective (JYYF), senior author, provision of intellectual and knowledge support, supervision of progress of the study (CML).

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