



## Surgical Treatment for Hepatocellular Carcinoma – Choose Liver Resection or Liver Transplantation

Wei-Chen Lee\*

Department of General Surgery, Chang-Gung University College of Medicine, Taiwan

### Abstract

Hepatocellular carcinoma (HCC) is the most common primary malignancy in the liver. In very early/early HCC, surgical treatment is the treatment with the best outcomes. Surgical treatment for HCC included liver resection and liver transplantation. Recently, surgical treatment is toward liver transplantation instead of liver resection because disease-free and overall survival rates are better in liver transplantation than liver resection. However, liver donation is always short and it is impossible to perform primary liver transplantation for every HCC patient. Liver resection can undergo for the patients with low recurrent rate and liver allografts are allocated to the most suitable patients to achieve the best outcomes for all patients. Under this policy, liver resection will be preferred for the patients with solitary tumor and adequate liver function reservation and liver transplantation will be for the patients with multiple tumors, decompensate liver function or compensated liver function with clinical suspicion of portal hypertension.

**Keywords:** Hepatocellular carcinoma; Liver resection; Liver transplantation

### Introduction

Hepatocellular carcinoma (HCC) is the 5<sup>th</sup> most common malignancy in the world [1]. HCC is also the most common primary malignant tumor in the liver. Because the liver is the largest organ in the abdomen, tumors in the liver are always silent and hard to be detected. In the old days, the tumors in the liver were always large when the tumors were found and the prognosis was poor [1]. Currently, the small-sized liver tumors can be found by screening the high risk patients using blood samples and abdominal ultrasonography [2]. Therefore, these patients have the opportunities to receive curative treatments. What is the best treatment for an individual patient? This review focuses on how to choose surgical treatments for early stage HCC.

### Screening of HCC

To find out the patients in early stage of HCC, screening of HCC has to be carried out. Who should be screened for liver tumors? To our knowledge, the etiologies of HCC are not really known until now. But, the presence of liver cirrhosis is a risk to develop HCC. The disease entities leading in liver cirrhosis will be the predisposing diseases contributing to HCC development. Hepatitis B infection, hepatitis C infection, alcoholic hepatitis, hemochromatosis, obesity, primary biliary cirrhosis and so on are all the well-known diseases associated with HCC [3,4]. The patients suffered from these diseases should be followed up and screened by abdominal ultrasonography and alpha-fetoprotein (AFP) regularly [5,6]. Abdominal ultrasonography can detect 85-95% of the lesions when the diameters of the lesions are between 3 and 5 cm. The detection rate will decrease to 60-80% when the diameters of the lesions decrease to 1 cm. AFP can supplement the liver tumor detection and diagnosis. AFP is a biomarker for detecting HCC [7]. Although AFP is not produced by every single HCC, AFP  $\geq 400$ ng/ml is diagnostic for HCC [4]. Even AFP does not reach 400 ng/ml, a rising level of AFP  $\geq 200$  ng/ml with a liver nodule is usually diagnostic for HCC, too [6].

### Available Treatments of HCC

When the liver tumors are diagnosed as HCC based on radiological imaging studies [6], the following issue is how to treat HCC. The therapeutic modalities for HCC include liver resection [8-10], liver transplantation [11,12], radiofrequency ablation (RFA) [13,14], percutaneous ethanol/acetic acid injection [15], transcatheter arterial chemoembolization (TACE) [16,17], molecular targeting therapy [18], immunotherapy [19-21], chemotherapy [22], radiotherapy [23], etc. The guidelines of treatments have been proposed by many medical societies [24-26]. Among them, Barcelona-Clinic-Liver-Cancer (BCLC) guideline is the most widely adopted currently [5]. Based

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#### \*Correspondence:

Wei-Chen Lee, Department of General Surgery, Division of Liver and Transplantation Surgery, Chang-Gung Memorial Hospital, Chang-Gung University College of Medicine, 5, Fu-Hsing Street, Kwei-Shan, Taoyuan, Taiwan, Tel: 886-3-3281200(Ext: 3366); Fax: 886-3-3285818;

E-mail: weichen@cgmh.org.tw

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on BCLC staging system guideline, the tumors in their very early and early stages can be curatively treated by liver resection, liver transplantation and RFA. Nevertheless, liver resection and liver transplantation are the better treatments as they yield the best results among HCC therapeutic modalities [13,27,28].

## Liver Resection

Surgical treatment of HCC includes liver resection and liver transplantation. Because liver donation is always short, liver resection remains a popular operation of HCC treatment. In Asian countries, liver resection for HCC is not limited in very early and early stage of HCC. A large-sized solitary tumor or tumor with ipsilateral portal vein thrombus is also indicated for liver resection if liver function reservation is enough [29].

For liver resection, the critical issue is accurate assessment of liver function and the residual liver volume after liver resection. Currently, the most common liver function assessment in Asia is indocyanine green (ICG) test [30]. Briefly, ICG test was performed by injecting 0.5 mg/kg of ICG into a peripheral vein and drawing a blood sample from another site 15 minutes later. Results were presented as 15-minute retention rate of indocyanine green ( $ICG_{R15}$ ). Makuuchi et al. [31] described the criteria of liver resection based on  $ICG_{R15}$  test. If  $ICG_{R15}$  is normal (<10%), right hepatectomy and trisegmentectomy can be performed safely. If  $ICG_{R15}$  is between 10-19%, left hepatectomy and right segmentectomy can be done. If  $ICG_{R15}$  is between 20-29%, segmentectomy can be done. If  $ICG_{R15}$  test is above 30%, only limited resection can be done. All these criteria are set based on considering the residual volume and liver function of the liver to prevent post-hepatectomy liver failure. For more accurate assessment of the allowed range of liver resection, we established a formula, ratio (%) of residual volume =  $[1.98 \times ICG_{R15} + 0.3672] \times 100\%$  based on  $ICG_{R15}$  to precise range assessment of liver resection [32].

After adequate assessment of liver function and the estimation of the residual liver volume, surgical mortality is less than 5% in most of the centers with well experience in liver resection [33]. In a systemic review of liver resection for early HCC, the 5-year disease-free survival rates ranged from 21% to 57% with a median of 37% and overall survival ranged rates from 27% to 81% with a median of 67% [33]. The overall survival of liver resection for early HCC approached to that of liver transplantation. However, the disease-free survival of liver resection was lower than that of liver transplantation. A high tumor recurrent rate was the most frequent critique of liver resection. Many papers have published the risk factors of tumor recurrence, including severity of cirrhosis, high  $ICG_{R15}$ , high level of AFP, wide range of hepatectomy, limited resection margin, high blood loss, large-sized tumors, non-encapsulation of the tumor, microvascular invasion, presence of daughter nodules and poor differentiation of the tumor [9,34,35]. Most of these risk factors belong to liver function itself or tumor behavior. Therefore, there are two peaks of tumor recurrence after liver resection. The first peak is around the first year after liver resection, which is associated with tumor behavior such as microvascular invasion, AFP, encapsulation of tumor, etc. The second peak is around 4-5 years after liver resection which is associated with hepatitis activities and tumor multicentricity [36]. Thereafter, tumor recurrence seems not to be prevented for some patients. To avoid tumor recurrence, another option of surgical treatment for HCC is liver transplantation which removes HCC and diseased liver simultaneously.

## Liver Transplantation

Liver transplantation is a smart surgical treatment for HCC, which treats liver tumor and cirrhosis simultaneously. In pioneer stage, liver transplantation was considered as an ideal treatment for Unresectable HCC because total hepatectomy could remove the unresectable HCC. However, the tumors recurred easily. Almost 50% of the patients had tumor recurrence within 2 years after transplantation and 5-year survival rate was only 15.2% [37]. Thereafter, HCC was considered as a relative contraindication for liver transplantation.

Until early 1990s, Bismuth et al. [38] compared their patients who received liver resection or liver transplantation for HCC treatment and found that liver transplantation for early or incidental HCC yielded equivalent survival rate to their non-HCC counterparts. In 1996, Mazzaferro et al. [39] publish so-called Milan criteria for HCC. If tumor is single, the diameter is not more than 5 cm. If tumors are multiple, the number of tumor should be not more than 3 and the largest diameter is not more than 3 cm. There are no portal vein invasion and extrahepatic metastasis. Under these criteria, 4-year actuarial survival reached 75%. Since then, Milan criteria become the gold standard of liver transplantation for HCC. However, Milan criteria might be too restrictive to let some patients have their opportunities of liver transplantation. Yao et al. [40] published the so-called University of California San Francisco (UCSF) criteria and extended the diameter to 6.5 cm for single tumor and 4.5 cm for the largest diameter of multiple tumors. The results under UCSF criteria were not inferior to that of Milan criteria. Many centers continued to challenge Milan criteria, set up criteria by themselves and claimed that their results were comparable to that with Milan criteria [41]. However, these criteria like metro tickets in European Metro System "the further the distance, the greater the price" [42]. Mazzaferro et al. [43] themselves extended their criteria to up-to-7 criteria and claimed that the survival of liver transplantation for HCC under up-to-7 criteria was similar to that of Milan criteria.

Currently, liver transplantation yields the bet results for HCC treatment if the tumors meet Milan, UCSF, up-to-7 or other certain restrict criteria. Sapisochin et al. [44] described their data of liver resection or liver transplantation for early and very early HCC. They found 1-, 5- and 10-year tumor recurrent rates were 18%, 69% and 83% for liver resection, compared to 4%, 10% and 29% for liver resection, and thereafter, the 10-year survival rate was 33% for liver resection and 49% for liver transplantation. Morris-Stiff et al. [45] reviewed the surgical treatment for HCC and found that 3- and 5-disease-free and overall survival rates for liver transplantation were much better than liver resection. In a meta-analysis study, the 1-, 3- and 5-year survival rates were higher in liver transplantation than in liver resection for HCC. The 3- and 5-year overall survival rates were also significant higher in liver transplantation than in liver resection [46]. Although liver transplantation can yield good outcomes for HCC treatment, beyond the criteria and microvascular invasion still are the risks of tumor recurrence after liver transplantation [47,48].

## Choice Liver Resection or Liver Transplantation

Because liver transplantation for early HCC yields better disease-free and overall survival rates, surgical treatment for HCC is shifted from liver resection to liver transplantation recently [49]. However, liver allografts are always limited and primary liver transplantation is not possible for every HCC patients. To achieve the best results

of surgical treatment for all HCC patients, we have to choose liver resection or liver transplantation for right HCC patients. Based on our knowledge, choice of liver resection or liver transplantation depends on tumor size, tumor number and liver function.

(A) If liver function is good and liver tumor is solitary, liver resection can be chosen [50].

(B) If liver function is good and tumors are multiple, liver transplantation is preferred because multiple-tumor is the risk factor of tumor recurrence after liver resection.

(C) If liver function is decompensate and liver tumor/tumors is within Milan criteria, liver transplantation is indicated, which is the best treatment [51].

(D) If liver function is decompensate and liver tumor/tumors is outside Milan criteria, TACE or RFA can be performed to downstage the tumor/tumors and followed by liver transplantation [52-54]. The problem is whether the liver function can tolerate TACE or RFA.

However, there is a dilemma to choose liver resection or liver transplantation sometimes when a solitary tumor is in the liver with compensated function but clinical suspicious portal hypertension. Huang et al. [51] analyzed the outcomes of liver resection for solitary HCC with diameter  $\leq 5$  cm in their patients whose liver function was in Child-Push A. The results showed that the patients with moderate/severe cirrhosis had worse disease-free and overall survival rates than the patients with mild cirrhosis or non-cirrhosis. In our previous study, liver cirrhosis and clinical suspicion of portal hypertension with platelet  $\leq 105 \times 10^3/\text{mm}^3$  were both the risk factors of early tumor recurrence [55]. Therefore, liver transplantation will be the optimal choice of treatment for the patients with clinical suspicion of portal hypertension.

### Liver Donor Liver Transplantation

Liver transplantation is the best treatment for cirrhotic liver with liver tumors, however, deceased liver allograft is always short and HCC patients may not have the chance to have liver transplantation. The transplant candidates may be dropped out from the waiting list due to tumor progression. In the literature, a model assessment of transplant candidates of drop out from waiting list was designed [56]. Because the incidence of deceased organ donation is different in different countries, how long the HCC patients can wait in the waiting list before dropped out due to tumor progression is different. Living donor liver transplantation should be considered before the tumors progress and the candidates drop out from the list.

### Salvage Liver Transplantation

Because liver allografts are always limited, it is not possible to perform primary liver transplantation for every early HCC patient. For the patients with well-preserved liver function, liver resection is still the preferred surgical treatment for HCC. However, all HCC patients with liver resection for HCC must be regularly followed up. When recurrent HCC is detected, salvage liver transplantation should be considered [57]. Currently, survival rate of salvage liver transplantation is almost the same as primary liver transplantation. But, during operations, the complication of liver transplantation is higher than primary liver transplantation because of the adhesion of previous hepatectomy [58]. Adhesion protecting attempt may be considered for young HCC patients during liver resection, which may need liver transplantation some days later.

### Conclusion

Liver resection and liver transplantation are both surgical treatments for HCC with better outcomes than other therapeutic modalities. Liver transplantation even has superior disease-free survival to liver resection. However, liver allografts may not be available anytime. Careful selection of liver resection and liver transplantation for the suitable patients will create a best result for HCC patients.

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