Liver Transplant in Hepatocellular Carcinoma: Indication and Prognostic Factors

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ABSTRACT

Hepatocellular carcinoma (HCC) is the most common type of liver cancer. There are several treatment modalities according to Barcelona treatment algorithm. Liver transplant is one of the curative option treatments, with its indication and prognostic factors. Carefully selected patients for liver transplant in HCC case will result in the same or slightly inferior survival rate compare with liver transplant in non-malignancy case.

Keywords: *liver transplant, hepatocellular carcinoma, indication, prognostic factors*

ABSTRAK

Karsinoma hepatoseluler (KHS) adalah jenis kanker hati tersering. Terdapat beberapa modalitas terapi pada KHS menurut algoritme terapi Barcelona. Transplantasi hati adalah salah satu modalitas terapi kuratif dengan indikasi dan factor prognostic tersendiri. Pemilihan pasien yang cermat untuk transplantasi hati pada kasus KHS akan menghasilkan tingkat ketahanan hidup yang sama atau sedikit lebih rendah dibandingkan transplantasi hati pada kasus bukan keganasan.

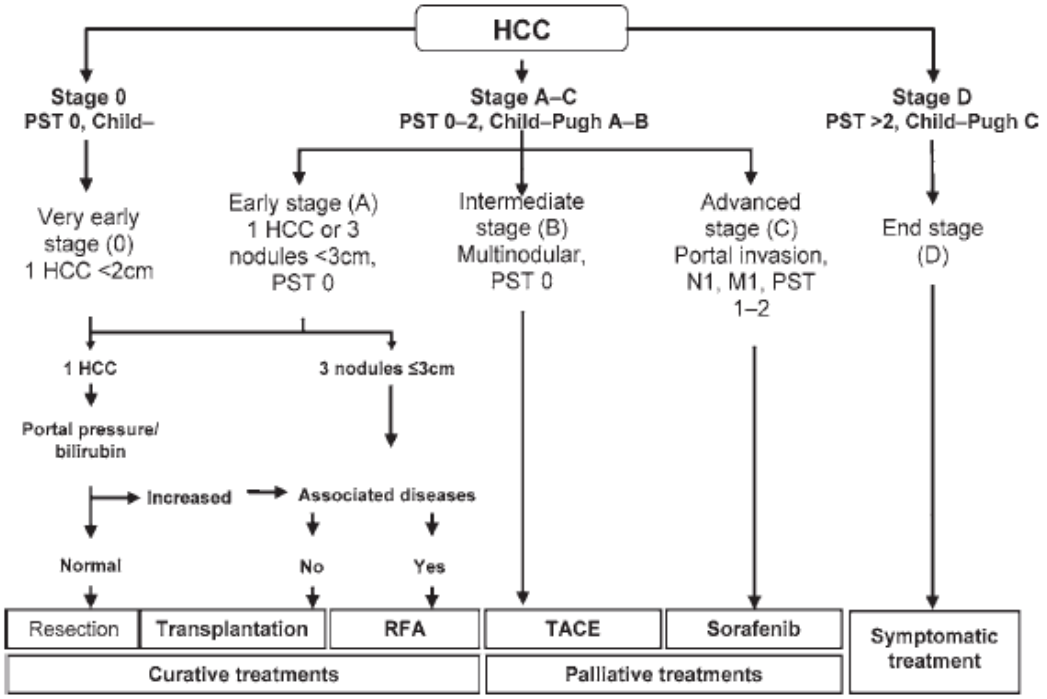
Kata kunci: *transplantasi hati, karsinoma hepatoselular, indikasi, faktor prognosis*

INTRODUCTION

Hepatocellular carcinoma (HCC) is an aggressive tumor in the course of chronic liver disease and cirrhosis. It is usually late diagnosed and has poor median survival rate, with average of 8 months.[1] The optimal treatment modality is resection in non-cirrhotic or minimal cirrhosis patient and liver transplant in advanced cirrhotic patient. Unfortunately, majority of the patients are not suitable for liver transplant due to tumor metastasis, liver dysfunction, and shortage of donor organs. Therefore some experts developed various methods for local tumor ablation.

There are some treatment options for local HCC. A treatment algorithm was published by Barcelona study (Figure 1).[2] Liver transplant for HCC treatment is interesting since the cancer resection can be done together with cirrhotic liver replacement. However, the result of early studies of liver transplant in local HCC was disappointing. It had a high 90-day mortality rate, up to 80% tumor recurrence rate, and low long term survival rate compared with organ transplant in other malignancy cases, which reflected the nature of the disease.[3,4]

The philosophy of liver transplant in HCC has changed due to finding that HCC patient with small nodule undergoing liver transplant had similar survival rate compared with liver transplant in non-malignant case.[5] Moreover, there were increasing retrospective



HCC: hepatocellular carcinoma; PST: performance status; RFA: radio frequency ablation; TACE: transarterial chemoembolization

Figure 1. The Barcelona staging system and treatment algorithym[2]

studies showed liver transplant was one of the effective option and might be more effective than other therapies in some group of patients.

INDICATION

Early study by Mazzaferro in 1996 emphasized cadaver donor for liver transplant (orthotopic liver transplant, OLT) was a good treatment for HCC.[6] It showed that liver transplant to early stage HCC (single lesion ≤ 5 cm, up to 3 separate lesions smaller than 3 cm, no evidence of vascular invasion, and no regional node involvement or distant metastasis) had 75% overall actuarial four-year survival rate and 83% four-year recurrence-free survival rate (Figure 2). This criteria were then widely known as Milan criteria and had been applied in all over the world in selecting HCC patients for liver transplant candidates.[6]

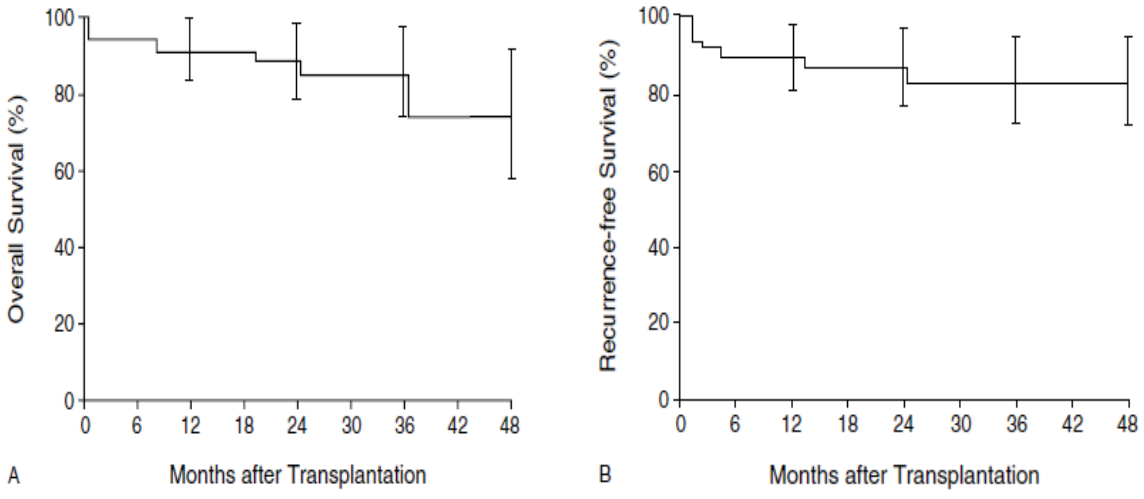


Figure 2. Overall survival (panel A) and recurrence-free survival (panel B) after liver transplantation[6]

SURVIVAL RATE IN HCC LIVER TRANSPLANT

The survival rate of OLT in carefully selected HCC patients was the same or slightly lower than OLT in non-malignant patients.[7] Report from the United Network for Organ Sharing (UNOS) focused on 34,324 liver transplantation cases done between 1987 and 2001; 985 of which were done due to HCC.[8] The five-year survival rate of OLT in HCC increased significantly (25%, 47%, and 61%, respectively) in the 3 different periods (1987-1991, 1992-1995, 1996-2001) although the average waiting time to get the liver donor was increased (37 days, 103 days, 215 days, respectively). Nevertheless, the five-year survival rate of OLT for non-malignancy indication was 71% with no changes over the study period. This study showed that a better outcome of OLT in HCC patients was more likely due to improvement in patient selection rather than technique and post transplant care.

SURVIVAL RATE IN COMPARISON WITH OTHER TREATMENT MODALITIES

No random large scale studies directly comparing OLT with other type of treatments for early HCC. For anatomically operable HCC with adequate liver reserve, resection is the standard method to be compared with other treatment modalities. Some observational studies showed long term outcome after liver transplant was at least the same of slight superior than resection in some groups.[9-13]

The report from Pittsburgh including 181 HCC patients, of which 105 patients underwent OLT and the rest had liver resection.[10] After 37 to 53 months of follow up, there was no significant different in survival rate of both groups if non-cirrhosis patients were included. However, when HCC was associated with cirrhosis of the liver, the survival rates after OLT were significantly better than those after resection at each stage of classification. Similar result was found in a study with 102 HCC patients, 50 patients of which underwent liver transplant and 52 patients had liver resection.[14] Three-year survival rate and recurrence rate was similar in both groups. However, OLT was associated with better three-year survival rate in cirrhosis patients (48% vs. 23%) and patients having tumor greater than 3 cm (76% vs. 33%). Other study in 120 cirrhotic HCC patients showed similar result.[12] Groups of patients in this study had the same underlying disease criteria, age, and tumor size. The rate for survival without recurrence was better in liver transplant group than resection group (46% vs. 27%). In patients with small uninodular or binodular tumors (less than 3 cm), transplantation had better outcome than resection (survival without recurrence, 83% vs. 18%). Transplantation also recommended in a study of 533 HCC patients with different treatments: OLT, resection, transarterial chemoembolization (TACE), percutaneus ethanol injection (PEI).[11] Analysis was done based on number of lesion, stadium of the disease, alphafetoprotein (AFP) level, Child-Pugh lass, etiology of cirrhosis. Survival rate was better in patient undergoing OLT compared with other treatments (three-year and five-year survival rate were 72% and 68% for OLT, 64% and 44% for resection, 54% and 36% for PEI, 32% and 22% for TACE). OLT seemed to be treatment of choice for HCC patients having monofocal lesion less than 5 cm. Although many studies showed the benefit of liver transplant, especially in cirrhosis patient with small tumor, the number of HCC patients who are candidates for OLT and truly accept graft (no graft rejection) are very small.

For patients having HCC which are not candidate for resection, OLT is the suitable strategy for patients with single nodule less or equal than 5 cm, up to 3 separate lesions smaller than 3 cm in size and no evidence of vascular invasion, no regional node involvement or distant metastasis. If the criteria are strictly applied, 75% of higher of five-year survival can be achieved. Survival rate for OLT in carefully selected HCC patients is the same or slightly inferior than OLT in non-malignant case. Although random trial is not available yet, some uncontrolled studies showed that survival rate in patients having OLT was good or better than other treatment modalities in HCC patients with some criteria.

PROGNOSTIC FACTOR

Some studies had identified variables involving patients and tumor which were associated with prognosis after OLT in HCC.[9,10,12-25] Some important factors were the number, size, location of tumor, disease stadium according to modified American Liver Tumor Study Group (ALTSG) (Table 1), histological differentiation grade, macro and microvascular invasion, and extrahepatic metastasis. The most consistent association was shown in the size of tumor.[13]

However, we have to remember that majority of the result here was based on analysis of patients undergoing liver transplant and not included all HCC patients eligible for liver transplant but died before the transplantation. Thus, the result depends on the short waiting time between diagnosis and actual transplantation.

T1: 1 nodule < 1.9 cm
T2: 1 nodule 2.0-5.0 cm; 2 or 3 nodules all < 3.0 cm
T3: 1 nodule > 5.0 cm; 2 or 3 nodules, at least one > 3.0 cm
T4a: 4 or more nodules, any size
T4b: T2, T3, or T4a plus gross intrahepatic portal or hepatic vein involvement as indicated by CT, MRI, or ultrasound
N1: Regional (porta hepatis) nodes involved
M1: Metastatic disease, including extrahepatic portal or hepatic vein involvement

Stage I	T1
Stage II	T2
Stage III	T3
Stage IV A1	T4a
Stage IV A2	T4b
Stage IVB	Any N1, any M1

Figure 3. American Liver Tumor Study Group (ALTSG) modified tumor-node-metastasis (TNM) staging classification[17]

The underlying etiology might become selection criterion for OLT. Patients with chronic hepatitis C virus (HCV) infection needed OLT for HCC more frequently than patients with chronic hepatitis B virus (HBV) infection. HCC patients with chronic HBV infection might be candidate for resection based on liver function and better tumor individual characteristic compared with chronic HCV infection. Since HCV patients had worse clinical condition and liver function, they had higher recurrence rate and shorter survival rate after resection or OLT in comparison with cirrhosis HBV patients or alcohol-induced HCC patients.[26]

IMMUNOSUPPRESSIVE AND ADJUVANT TREATMENT

Since immunosuppressive drug had been associated with higher risk of tumor recurrence, efforts were done to reduce the dose to the minimum effective dose.[27,28]

This approach was suggested in a retrospective study in 70 patients undergone OLT for HCC receiving cyclosporine (CSA) based immunosuppressant drug.[28] Serum CSA was significantly higher in those having tumor recurrence compared with free tumor recurrence (278 vs. 170 ng/mL, respectively). ROC analysis identified 190 ng/mL as an optimal cut off value; higher exposure increased the recurrence rate to 33% (7 from 21 patients) compared with none of the 49 patients having lower serum level of CSA. Immunosuppressive agent with promising prospect in HCC transplant patient was sirolimus. In vivo study showed this agent could prevent the development of some tumor, included HCC.[29] In a retrospective study in 40 HCC liver transplant patients (50% met the Milan criteria, the rest was classified as "extended" criteria), sirolimus based immunosuppressive protocol seemed to have acceptable toxicity and rejection rate.[30] Four year disease-free survival rate was better (81% and 77% for patients met Milan criteria and extended, respectively) compared with other studies. Although this data was promising, more data on long term successful rate of sirolimus based immunosuppressive therapy and toxicity were still needed.

Adjuvant therapy after OLT has not been well studied.[31] Theoretically, adjuvant therapy may be helpful for patients undergoing OLT since the liver resection process involves extensive manipulation and may spread the tumor intra operatively. Moreover, the immunosuppressive therapy might facilitate tumor growth resulting in post transplant tumor recurrence. A study reported significantly shorter tumor doubling time in post OLT patients compared with post resection patients (40 days vs. 270 days).[15] Some uncontrolled studies had suggested the benefit of adjuvant chemotherapy post OLT in HCC. However, in a 60 patients case control study, chemotherapy (doxorubicin given as single agent to be given pre, intra, and post operatively) was not associated with significant better five-year survival rate (38 vs. 40%).[31]

Moreover, there was a question regarding the harmful effect of chemotherapy associated with recurrence of HCV. In a study of 48 patients undergoing OLT for HCC, 21 patients got chemotherapy and 27 patients did not get chemotherapy. The three-month, six-month, and twelve-month disease-free survival rate were 29%, 14%, and 0% respectively in chemotherapy group compared with 76%, 38%, and 25% respectively in no chemotherapy group.[32] On the other hand, promising result was reported by a small placebo controlled, double blind study in China using radioimmunologic agent (Licartin, a 131-I-radiolabeled murine monoclonal antibody targeting specific HCC molecule HAb18G/CD147).[33] Sixty patients having pre transplant biopsy positive of HAb18G/CD147 immunohistochemistry expression were randomly given 3 doses of monthly Licartin or placebo injection started 4 weeks after OLT. In 12 months follow up, Licartin group had significant reduction of recurrent rate (27% vs. 57% in a year) and survival rate (83 vs. 62% in a year). No special side effect occurred in the study. Further study with longer duration and greater sample size are needed prior concluding the benefit of Licartin post OLT. Due to low successful rate and risk of HCV recurrence, systemic adjuvant therapy is not recommended for patients undergoing liver transplantation for HCC, except in clinical trial.

CONCLUSION

OLT is a curative treatment option in selected HCC patients, consisted of cadaver donor and live donor. The survival rate and disease recurrence rate after OLT in selected patients were the same or slightly inferior than other patients undergoing OLT for non malignant indication. Moreover, some retrospective studies showed post OLT survival rate was the same or better compared with other modalities.

Indication for OLT are not candidate for resection, having a single lesion less or equal than 5 cm, less than 3 separate lesions with less or equal than 3 cm, no vascular involvement, no regional node involvement or distant metastasis. The five-year survival rate may increase up to 75% if the criteria are met.

Prognostic factors for the success of liver transplant are the number, size, and location of tumor (especially bilobar distribution), disease stadium according to modified ALTSG, histological differentiation grade, macro and microvascular invasion, and extrahepatic metastasis.

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