Mini-Review

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Liver transplantation for patients with hepatocellular carcinoma: Its current status and advances

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SUMMARY Liver transplantation is one of the best treatment options for selected patients with hepatocellular carcinoma (HCC). The Milan criteria (a single tumor with a maximum size of 5 cm or two or three tumors with a maximum size of 3 cm without evidence of vascular or extrahepatic involvement or metastasis) are one of the most common criteria to select patients with HCC for transplantation, though they are considered too restrictive. A moderate expansion of the criteria has been found to yield comparable recurrence-free survival rates. HCC will recur in approximately 10% of patients, and mostly within the first 2 years after transplantation. The preoperative level of alpha-fetoprotein, macrovascular invasion, tumor size, and tumor number are prognostic factors for recurrence. Recurrence of HCC after transplantation results in a poor prognosis.

Keywords liver transplantation, Milan criteria, hepatocellular carcinoma

1. Introduction

Liver transplantation has been one of the standard treatment options for patients with early-stage hepatocellular carcinoma (HCC) (*1*). Liver transplantation would be an ideal treatment for HCC since it can treat both the tumor and the damaged liver in the background, providing a higher chance of a cure than other treatments.

Currently, liver transplantation to treat HCC represents approximately15% of all liver transplants (*2*). Since liver transplantation is an excellent treatment option for HCC, the number of candidates exceeds that of available donors (*3*). A more advanced tumor is presumed to result in a poorer outcome. Patients who would receive a major survival benefit from liver transplantation need to be selected. Therefore, the selection criteria for candidates are an important topic (*4*).

The current review describes the current status of liver transplantation for HCC. The selection criteria that will result in the maximum recurrence-free survival are described. Immunosuppressor regimens are also reviewed. Finally, the management of HCC recurrence after liver transplantation is described.

2. Selection criteria

In the past, liver transplantation for HCC had poor outcomes (*5*) because of the high incidence of recurrence. Later, Mazzaferro *et al*. (*6*) proposed criteria for the stage of HCC: a single tumor ≤ 5 cm or two or three tumors ≤ 3 cm without major vessel invasion or extrahepatic tumor spread based on imaging studies. When the criteria were met, the 4-year patient survival was 75% and the recurrence-free survival was 83%. The criteria have been adopted for deceased donor liver transplantation and living donor liver transplantation (LDLT) in many centers all over the world. The criteria, however, are believed to be too strict, preventing many patients from undergoing transplantation. The most commonly used extended criteria are shown in Table 1.

Unlike in the West, in East Asian countries (*7*) including Japan, most transplants have been LDLTs (*8*). LDLT is a private issue between patients and their families, and the indications for LDLT in terms of tumor status can be considered on a case-by-case basis Many transplantation centers performing LDLT have adopted expanded criteria (*9*). This might enable more patients to receive transplants without significantly increasing the rate of HCC recurrence.

In Japan, the Japanese Organ Transplantation Act was enacted in 1997 and amended in 2006. However, there are still not enough deceased donor livers. By the end of 2020, 658 deceased donor liver transplantations and 9760 LDLTs have been performed. Of these, 1,747 were performed to treat HCC. LDLT for HCC has a 1-year survival rate of 85%, a 3-year survival rate of 76%, a 5-year survival rate of 71%, a 10-year survival

Table 1 The extended criteria

Criteria & year	Disease-free survival	Disease-free survival	Overall survival
Milan (*6*), 1996	a single tumor ≤ 5 cm or two or three tumors ≤ 3 cm without major vessel invasion or extrahepatic tumor spread	92% at 4 years	85% at 4 years
USCF (*43*) , 2007	a single tumor ≤ 5 cm or 3 tumors ≤ 4.5 cm with total ≤ 8 cm	91% at 5 years	81% at 5 years
Up-to-7 (*44*), 2009	Tumor number and sum of tumor diameter < 7	64% at 5 years	71% at 5 years
Total tumor volume (*45*), 2015	≤ 115 cm^3, AFP ≤ 400 ng/mL	68% at 4 years	78% at 4 years
Extended Toronto (*23*), 2016	Not poorly differentiated, without major vessel invasion or extrahepatic tumor spread	30% at 5 years	68% at 5 years
5-5-500 (*10*), 2019	Tumor number ≤ 5, Tumor size ≤ 5 cm, AFP ≤ 500 ng/mL	73% at 5 years	76% at 5 years

AFP. alpha-fetoprotein

rate of 63%, a 15- year survival rate of 56%, and a 20-year survival rate of 46%.

A recent study of a database (*10*) examined 965 patients who underwent LDLT for HCC between 1990 and 2005. Of those patients, 664 were within the Milan criteria and 301 were outside those criteria. New criteria were proposed (the 5-5-500 rule) consisting of a tumor number ≤ 5, a tumor size ≤ 5 cm in diameter, and a serum alpha-fetoprotein (AFP) level ≤ 500 ng/mL. This enables more candidates (n = 725) to receive a transplant and it results in a 5-year recurrence rate of less than 10%. The insurance system of the Japanese Ministry of Health, Labor, and Welfare has now covered the cost of the transplantation within the 5-5-500 rule for deceased donor liver transplantation and LDLT.

3. Resection and partial liver segment 2-3 transplantation with delayed total hepatectomy (RAPID) procedure or auxiliary partial orthotopic liver transplantation (APOLT)

RAPID is a new but an extrapolated concept of auxiliary partial orthotopic liver transplantation (APOLT), which is a long-used procedure (*11*).

Few patients have undergone RAPID thus far (*12*), and few of those patients had HCC (13). Indications for RAPID are HCC located in the left lobe of the liver, cirrhosis with a low MELD score, and moderate portal hypertension (*14*). A recent case reported by Balci *et al*. (*15*) suggested that RAPID is effective and safe in a patient with a MELD score of 27.

4. Immunosuppression

Patients at high risk of HCC recurrence may benefit from adjustment of immunosuppression. A high level of calcineurin exposure has been found to be related to HCC recurrence after transplantation. One hypothesis that over-exposure to calcineurin inhibitors in the early postoperative period might prevent the immune system from detecting and destroying remaining HCC cells (*16*).

The mammalian target of rapamycin (mTOR) inhibitors (sirolimus and everolimus) are considered to have anti-neoplastic effects on HCC (*17*). Their use might be related to lower rate of HCC recurrence (*18*). A prospective, randomized, open-label, international multicenter trial was conducted with 525 transplant recipients with HCC (*19*). Results indicated that sirolimus was associated with a statistically better recurrence-free survival at 3 and 5 years after liver transplantation. An analysis (*20*) of the Scientific Registry of Transplant Recipients database indicated a survival benefit of immunosuppression regimens that included sirolimus. A prospective study (*21*), however, revealed that everolimus had no significant effect on HCC recurrence. The effectiveness of mTOR inhibitors on the recurrence of HCC has yet to be confirmed.

5. HCC recurrence

With careful patient selection, the rate of HCC recurrence ranges between 10-20% (*22-24*). Most recurrence occurs within 2 years of transplantation (*25*). The average time to recurrence ranges from 16 to 18 months (*26-28*). The sites of extrahepatic lesions (around 60%) include the lungs, bone, the peritoneum, and lymph nodes, followed by the liver (around 30%) (*29,30*).

6. Treatment and prognosis

Survival time from the diagnosis of recurrence ranges between 10 and 12 months (*26,27*). Treatment of lesions is largely the same as that for the patients who have not undergone transplantation (*27,31,32*). If technically feasible, the most effective radical treatment for recurrence is resection of the lesion (*33*). Ablation therapy can be indicated if the lesion is small and limited to the liver. The 1-year survival rate after radical

resection to treat recurrence is 94% and the 2-year survival rate is 53% (*34*).

If radical treatment is not feasible, trans-arterial chemotherapy with sorafenib or lenvatinib will be considered. Patients who received sorafenib or lenvatinib and who tolerated it well had a survival of 20 months (*34*). Immune checkpoint inhibitors (nivolumab and pembrolizumab) are now being tried as a second-line therapy for recurrence (*34,35*). Their effectiveness has yet to be confirmed.

Conversion to sirolimus is one therapy (*36*). In one study (*36*), patients receiving sirolimus from the moment that recurrence was diagnosed had a survival of 12 months while those receiving unmodified immunosuppressants had a survival of 8 months. Patients receiving symptomatic treatment did not survive 1 year (*27*).

7. Predictors of recurrence

Tumor factors are the most relevant to tumor recurrence. They are followed by preoperative levels of the tumor markers AFP and DCP, which are used to exclude patients from eligibility or the waiting list.

Models of the risk of recurrence are useful at devising protocols for postoperative screening. The RETREAT score (*37*) consists of 3 variables: microvascular invasion, preoperative level of AFP, and the sum of the largest viable tumor diameter and the number of viable tumors on explant. Scores range from 0 to 5 or higher. A higher score indicates a higher risk of recurrence; the possibility of recurrence is < 3% with a score of 0 and > 75% with a score of 5 or higher.

The post-MORAL score (*38*) consists of four independent predictors of recurrence: grade 4, vascular invasion, size > 3 cm, and number > 3 (all are postoperative). A study by UCLA (*27*) revealed that predictors of mortality following recurrence included the model for end-stage liver disease at transplantation > 23, time to recurrence, > 3 recurrent nodules, the maximum size of the recurrent lesion, bone recurrence, the AFP level at recurrence, donor serum sodium, and the pretransplant recipient neutrophil-lymphocyte ratio. Sapisochin *et al*. (*32*) identified three significant predictors: the lack of the potential for radical treatment (resection or thermos-ablation), an AFP level at the time of diagnosis > 100 ng/mL and early recurrence within a year after transplantation. Those predictors were confirmed by multicenter data (*29*).

8. Surveillance of recurrence

Postoperative screening will allow early detection of recurrence. It can help to identify patients who are eligible for radical treatment. Screening is related to an increased chance of survival (*25,30,31*). Although there are no universal protocols to screen for recurrence (*29,31*), some experts recommend performing computed tomography of the abdomen and chest with contrast medium, bone scintigraphy, and measuring the AFP level every 3-6 months for 2-3 years. Thereafter, the test interval can be prolonged to 6-12 months (*25,32,39*). Postoperative screening should be performed for each patient (*25*).

9. Perspectives for the future

The appearance of direct-acting antivirals (DAAs) to treat hepatitis C virus (HCV) has improved the prognosis for patients with HCV. A recent study (*40*) indicated that approximately 20% of cirrhotic patients infected with HCV with or without HCC might be delisted because of improved liver function after therapy. The appearance of DAAs should decrease patients undergoing liver transplantation for HCV and HCC.

In contrast, the increase of non-alcoholic steatohepatitis (NASH) has led to an increase in the number of liver transplants for NASH with or without HCC (*41*). The number of liver transplants for NASH with HCC is expected to fill "the vacancy" left by the decrease in the number of transplants for HCV with HCC (*42*).

10. Conclusion

Liver transplantation is an established treatment for patients with early-stage HCC. However, the shortage of available organs necessitates the adoption of criteria to ensure the optimal use of donor organs. In the LDLT setting, some restrictive criteria are needed from an ethical point of view to ensure a satisfactory recurrence-free survival after liver transplantation.

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