Clinical practice guideline on liver transplantation for hepatocellular carcinoma in China (2021 edition)

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Hepatocellular carcinoma (HCC) is the main cause of cancer-related deaths in adult men under the age of 60 years in China.[1] Liver transplantation (LT) is generally recognized as one of the most effective therapeutic approaches for end-stage liver diseases. LT guidelines for HCC were firstly launched in 2014 and were updated in 2018. Recently, further updates are required to adapt to the new situation of LT in China and to continue advancing the recommendations. (Full version in Supplementary file, http://links.lww.com/CM9/B362).

The classification of evidence adopted in the guideline mainly refers to the 2001 Oxford evidence classification (Supplementary Table 1, http://links.lww.com/CM9/B362).

Criteria of LT for HCC

Establishing appropriate LT criteria for HCC patients is key to improving the prognosis and making rational use of the scarce donor-liver resources. The restrictions on tumor size and number render the Milan criteria too restrictive. Hangzhou criteria expand the recipient population safely and combine both tumor biological and pathological characteristics. Salvage LT was feasible for recipients with HCC recurrence after initial partial hepatic resection who met the criteria. The selection criteria for living-related donor LT in HCC candidates can be extended appropriately (Table 1).

Preoperative Downstaging Treatment of HCC for LT

Downstaging treatment is mainly indicated in HCC patients who initially fail to meet the existing LT criteria, and who have no macrovascular invasion and no distant metastasis. Recent increases in the usage of immunotherapeutic drugs and molecular-targeted drugs have provided new options for downstaging. The safe time interval between immunotherapy and LT remains controversial. Moreover, it should be noted that downstaging using immunotherapy might increase the risk of post-LT rejection, and post-LT surveillance should thus be increased and immunosuppressive therapy should also be intensified in these cases if necessary. Molecular-targeted drugs, such as sorafenib and lenvatinib, are also effective downstaging treatments. A multicenter clinical study verified that the Hangzhou criteria was a reliable endpoint of downstaging treatment.[2] (Table 1).

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Table 1: Clinical practice guidelines on liver transplantation for hepatocellular carcinoma.

Items	Recommendations	Evidence grade	Recommendation strength
Criteria of liver transplantation for hepatocellular carcinoma			
1	The Milan criteria are the benchmark for the selection of LT recipients with HCC. However, the criteria can be expanded safely.	II	Strong
2	The Hangzhou criteria are reliable criteria for the selection of LT recipients with HCC, with satisfactory post-LT survival.	II	Strong
3	Patients meeting category A of the Hangzhou criteria (tumor diameter ≤8 cm or tumor diameter >8 cm but AFP level ≤100 ng/mL) have a better prognosis than those meeting category B (tumor diameter >8 cm but AFP level between 100–400 ng/mL).	II	Strong
4	Patients with intrahepatic HCC recurrence after partial hepatic resection who meet the selection criteria are candidates for salvage LT.	II	Weak
5	The selection criteria for HCC recipients of living donor LT can be extended appropriately, but extrahepatic metastasis and major vessel invasion should be excluded. Recipient benefit and donor risk must be evaluated comprehensively, and the social psychology statuses of the donor and recipient must be strictly assessed before LT.	III	Weak
6	If graft loss occurs after living donor LT, retransplantation is feasible for HCC patients who meet the criteria for LT.	III	Weak
7	HCC patients exceeding the criteria for LT in whom initial graft loss occurs due to HCC recurrence after living donor LT are not candidates for cadaveric LT.	V	Strong
8	To minimize donor risk and optimize recipient prognosis, living donor LT should be limited to experienced LT facilities.	V	Strong
Preoperative downstaging treatment of hepatocellular carcinoma for liver transplantation			
9	Downstaging therapy includes TACE, yttrium-90 microsphere TARE, local ablation etc.; local ablation includes radiofrequency ablation, microwave ablation, cryoablation, and percutaneous ethanol injection. The selection of downstaging therapy needs to be individualized.	II	Strong
10	Combination of multiple therapies is considered to have a better downstaging effect than individual therapies.	II	Strong
11	The comprehensive evaluation index of downstaging efficacy should be based on tumor size and number, and changes in serum AFP and PIVKA-II levels	II	Strong
12	Downstaging or bridging treatment should be applied in a timely manner for LT candidates with an estimated waiting time >6 months	II	Strong
13	Hangzhou criteria can be used as the end point of preoperative downstaging treatment.	III	Strong
14	Postoperative surveillance for rejection should be strengthened in LT recipients with successful downstaging treatment using immune checkpoint inhibitors.	IV	Weak
Anti-hepatitis virus therapy in patients with hepatocellular carcinoma receiving liver transplantation			
15	NAs should be adopted in HCC candidates with positive HBV DNA before LT to reduce HBV DNA levels.	I	Strong
16	Potent NAs with a high genetic barrier to resistance should be the first-line treatment in patients with a high HBV load before LT. In the event of NA resistance, appropriate drugs should be selected based on the results of resistance mutation tests. In the case of lamivudine resistance, adefovir dipivoxil can be added or tenofovir can be used instead.	II	Strong
17	HBIG should be administered in the anhepatic phase during surgery in HBV-related HCC patients. Long-term post-LT monitoring of HBV DNA levels and HBV recurrence should be applied.	II	Strong
18	Entecavir/tenofovir combined with low-dose HBIG is the first-line regimen to prevent post-LT HBV recurrence.	II	Strong
19	Entecavir or tenofovir monotherapy is effective for preventing post-LT HBV recurrence.	IV	Strong
20	Timely hepatitis B vaccination for patients on the waiting list combined with postoperative NAs can reduce *de novo* HBV infection following HBcAb-positive LT in non-HBV related LT recipients.	III	Strong
21	A glucocorticoid-free immunosuppression regimen can reduce post-LT HBV recurrence.	IV	Weak
22	Tenofovir alafenamide fumarate is recommended for recipients with chronic renal impairment after LT.	III	Weak
23	Appropriate and timely DAAs should be selected for antiviral treatment in HCC patients on the waiting list who have positive HCV RNA.	III	Strong
Application of immunosuppressants in patients with hepatocellular carcinoma after liver transplantation			
24	The administration of CNIs is an independent risk factor for HCC recurrence after LT.	I	Strong
25	Interleukin-2 receptor blockers, mycophenolic acid, and sirolimus should be used instead of CNIs in recipients with hepatorenal syndrome or renal insufficiency.	I	Strong
26	Low-dose CNIs and early withdrawal of glucocorticoids are recommended for HCC patients after LT.	II	Strong
27	The application of mTOR inhibitors, such as sirolimus and everolimus, reduces post-LT tumor recurrence and metastasis in HCC patients.	I	Strong
28	A glucocorticoid-free immunosuppressive regimen can be used in HCC patients after LT.	II	Weak

(Continued)

Table 1
(Continued)

Items	Recommendations	Evidence grade	Recommendation strength
29	Conversion to an mTOR inhibitor-based immunosuppressive regimen is suggested for patients with HCC recurrence after LT.	III	Weak
Prevention and treatment of post-liver transplantation hepatocellular carcinoma recurrence			
30	Everolimus combined with low-dose tacrolimus can reduce the recurrence rate of HCC in LT recipients exceeding the candidate selection criteria.	III	Weak
31	Surgical resection is the preferred option for resectable recurrent lesions after LT.	III	Strong
32	Local ablation, TACE, molecular-targeted drugs, systemic chemotherapy, or a combination of the above treatment approaches should be selected on an individual basis to prolong the survival of recipients with unresectable recurrent lesions.	IV	Strong

CNIs: Calcineurin inhibitors; DAAs: Direct-acting antiviral drugs; HBIG: Hepatitis B immunoglobulin; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; LT: Liver transplantation; mTOR: Mammalian target of rapamycin; NAs: Nucleoside/nucleotide analogs; AFP: Alpha fetoprotein; HBcAb: Hepatitis B virus core antibody; PIVKA-II: Protein induced by vitamin K absence or antagonist-II; TACE: Transcatheter arterial chemoembolization; TARE: Transarterial radioembolization.

Anti-Hepatitis Virus Therapy in HCC Patients for LT

LT candidates with hepatitis B virus (HBV) infection should receive antiviral drugs as early as possible. The combination of entecavir or tenofovir with low-dose hepatitis B immunoglobulin (HBIG) is currently considered the first-line regimen. The recent widespread use of new high resistance-barrier nucleoside/nucleotide analogs (NAs) has led to decreasing trends in terms of the dosage and duration of HBIG after LT.[3] Steroid-free immunosuppression is also widely accepted to reduce HBV recurrence after LT. Complete discontinuation of NAs after LT is not recommended. For non-HBV-related LT recipients, timely HBV vaccination before LT, combined with postoperative NAs, is a cost-effective prophylaxis of *de novo* HBV infection after receiving HBcAb-positive liver grafts. Studies have pointed out that tenofovir alafenamide fumarate can inhibit HBV and protect renal function more effectively than other NAs. Pre-LT antiviral therapy with appropriate direct-acting antiviral drugs is the best way to prevent post-LT hepatitis C virus (HCV) recurrence in LT candidates with positive HCV RNA (Table 1).

Application of Immunosuppressants in HCC Patients Post-LT

The use of immunosuppressants, such as calcineurin inhibitors (CNIs), is an independent risk factor for HCC recurrence after LT. The use of individualized low-dose immunosuppressive regimens is encouraged. HCC patients who received mammalian target of rapamycin (mTOR) inhibitors were shown to have a significantly lower HCC recurrence rate than patients who received CNIs, and the everolimus-based immunosuppressive regimens have been shown to improve the prognosis of HCC recipients.[4] The regimen may also be converted to an mTOR inhibitor-based immunosuppressive regimen 4–6 weeks after LT, combined with mycophenolic acid or low-dose CNI, to protect renal function. An mTOR inhibitor-based immunosuppressive regimen is recommended for recipients with HCC recurrence after LT (Table 1).

Prevention and Treatment of Post-LT HCC Recurrence

Careful selection of HCC LT recipients is critical for reducing postoperative tumor recurrence. The prevention and treatment of post-LT HCC recurrence and metastasis are critical as well. The early diagnosis of HCC recurrence is beneficial in selecting the treatment strategy and improving treatment efficacy. Surgical resection is the preferred treatment for resectable recurrent lesions. Recipients with negative expression of programmed cell death-1 ligand (PD-L1) in the liver graft had a low incidence of rejection after administration of programmed cell death-1 (PD-1) or PD-L1 antibody. For these recipients, if the recurrent HCC fails to respond to other anti-HCC regimens may thus receive salvage therapy with PD-1 or PD-L1 antibody (Table 1).

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