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Practice Guidelines

Clinical practice guidelines on liver transplantation for hepatocellular carcinoma in China (2018 edition)

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Introduction

Over 3 00 000 people in China die each year of hepatocellular carcinoma (HCC), which accounts for approximately half of HCC-related deaths worldwide. Liver transplantation (LT) is generally recognized as one of the most effective therapeutic approaches for end-stage liver diseases. Since the beginning of the second LT boom in the 1990s, LT in China has been developed rapidly with professional and large-scale trends, and it is approaching or has reached the level of developed countries in terms of quantity and quality. According to the China Liver Transplant Registry, the number of transplants for HCC accounted for 36.8% of the total number of LT cases during the past 5 years in the mainland of China. In order to develop an effective, safe and standardized protocol to guide the national LT practice, the clinical guidelines of LT for HCC was launched in 2014 by multidisciplinary experts from Chinese Society of Organ Transplantation, Chinese Medical Association and Chinese Association of Organ Transplantation, Chinese Medical Doctor Association. Recently, there have been new clinical and scientific advances in the field of LT and to keep abreast of these achievements, the original clinical practice guidelines need to be updated.

This guideline is covering the following aspects: criteria for LT in HCC patients, preoperative downstaging treatment, antiviral therapy, application of immunosuppressants and prevention and treatment of post-LT HCC recurrence. The adopted classification of evidence in this guideline mainly refers to the 2001 Oxford evidence classification (Table 1), and the strength of recommendation mainly refers to the Grading of Recommendations Assessment, Development, and Evaluation system (GRADE) [1–3].

Criteria of LT for HCC (Table 2)

The shortage of donor livers remains a serious problem worldwide. Although this shortage has been slightly eased in China due to the propagation of donation after citizen's death (DCD), the number of donor livers is still far from meeting the demands. To overcome this challenge, Mazzaferro et al. proposed the so-called Milan criteria by selection of HCC patients complicated with liver cirrhosis for LT. The Milan criteria requires, in addition to the absence of intrahepatic macrovascular invasion and distance metastasis; a solitary nodule ≤5 cm or no more than 3 nodules (each nodule ≤3 cm) [4]. HCC patients meeting Milan criteria achieved a long-term post-LT survival [4–7]. However, the restrictions on the size and number of tumors render Milan criteria too restrictive. Some of the HCC patients who should have an opportunity to be LT candidate were excluded. Therefore, new LT criteria for HCC patients, such as University of California, San Francisco (UCSF) criteria, Up-to-seven criteria, etc., have been established. These new criteria have been clinically validated to expand the recipient population with similar prognosis as the Milan criteria [8,9]. However, the biological characteristics of the tumor have not been included by the above criteria. In 2008, the Hangzhou criteria was proposed in China which was the first criteria to combine both tumor biological and pathological characteristics to select HCC candidates for LT. Hangzhou criteria was a breakthrough from the previous selection criteria that were limited to the tumor characteristics only. Comparing to the Milan criteria, Hangzhou criteria expanded the tumor size to ≤8 cm or >8 cm with alpha-fetoprotein (AFP) level ≤400 ng/mL and a well/moderately differentiated tumor. Accumulative evidences from many clinical studies confirmed that HCC patients within the Hangzhou criteria are suitable for LT and the post-LT survivals are equivalent to those within Milan criteria [10–16]. According to the outcomes of national multicenter clinical studies, the Hangzhou criteria can be further

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Table 1
Classification of evidence-based medicine-levels of evidence.

Level of evidence	Definition
I	Systemic evaluation of homogenous randomized controlled trial (RCT)
	Single RCT (narrow confidence interval)
	Serial research with complete or no medical records
II	Systemic evaluation of homogeneous cohort study
	Single cohort study (including low-quality RCT, e.g., follow-up rate <80%)
	Outcome research, ecological research
III	Systemic evaluation of homogeneous case-control study
	Single case-control study
IV	Serial research on cases (including low-quality cohort and case-control study)
V	Expert opinion based on experience not on strictly proven results

divided into two categories as follows: tumor diameter ≤8 cm or tumor diameter >8 cm but AFP level ≤100 ng/mL (category A); and tumor diameter >8 cm but AFP level between 100 ng/mL and 400 ng/mL (category B). Patients meeting category A had a better prognosis [17]. For recipients with HCC recurrence after initial partial hepatic resection, salvage LT was feasible if meeting the criteria [18–20]. For recipients suffered from graft loss after LT, re-transplantation can be performed with caution [20].

Preoperative downstaging treatment of HCC for LT (Table 3)

Preoperative downstaging treatment of HCC should be applied to reduce tumor burden and stage, enabling candidates who exceed the LT criteria to obtain the opportunity of LT. The downstaging treatment is mainly indicated to HCC patients who do not meet the existing LT criteria and have no macrovascular invasion in portal vein or inferior vena cava and no distant metastasis [20–23].

The effective downstaging treatment mainly includes transcatheter arterial chemoembolization (TACE) [20,22,24], yttrium-90 microsphere transarterial radioembolization (TARE) [24,25], and local ablation, etc. TARE is a satisfactory downstaging method and superior to TACE in reducing hospitalization and complications [21,24,25]. Local ablation includes radiofrequency ablation, microwave ablation, cryoablation and percutaneous ethanol injection. The combination of multiple adjuvant therapies is considered to have a better downstaging effect.

The comprehensive evaluation of downstaging efficacy is mainly based on imaging study, i.e., contrast-enhanced CT and MRI, and blood tumor biomarker tests to assess tumor size, number and change of AFP level [26–32]. For some HCC patients exceeding the criteria of LT who met the criteria after receiving downstaging treatment and underwent LT, their post-LT survival is similar to that of recipients meeting the criteria originally [33,34]. Other well-known clinical guidelines recommended that downstaging or bridging therapy should be applied in a timely manner for HCC patients on LT waiting list with an estimated waiting time longer than 6 months [35,36].

Antiviral therapy of HCC patients for LT (Table 4)

More than 90% of HCC patients in China are infected with hepatitis B virus (HBV). Recipients with recurrent HBV infection or high HBV load before LT are at higher risk of HCC recurrence. Therefore, to reduce the risk of HBV recurrence and improve long-term survival after LT, antiviral drugs should be administered for LT candidates with HBV infection as early as possible [37–39]. Hepatitis B immunoglobulin (HBIG) should be administered in the anhepatic phase during the operation. The main post-LT antiviral regimen is the nucleotide analogs (NAs) combined with low-dose HBIG. The combination of entecavir or tenofovir with low-dose HBIG is currently considered the first line regimen with reliable effect on preventing HBV recurrence [40–45]. However, a study conducted by the University of Hong Kong discovered that for LT recipients who had chronic HBV infection without lamivudine resistance, the entecavir monotherapy had achieved an HBsAg-negative rate of 92% and an HBV DNA negative rate of 100% at 8-year after LT [46]. This regimen is cheaper and more convenient without reducing the efficacy and could be used as a supplement of NAs with low-dose HBIG. Recent studies [47,48] also showed that steroid-free immunosuppression regimen can reduce HBV recurrence after LT. Additionally, HBV vaccination after LT has been reported to prevent the recurrence of HBV infection, whereas its clinical application is still controversial [49–51].

In China, the incidence of hepatitis C virus (HCV) infection is on the rise. Direct-acting antivirals (DAAs) treatment can achieve close to 100% sustained virologic response (SVR) without severe side effects [52–55]. Pre-LT antiviral therapy is the best way to prevent post-LT HCV recurrence for LT candidates with compensated cirrhosis and elevated HCV RNA [56–58]. DAAs should be used as early as possible in all LT recipients with post-LT HCV recurrence in order to obtain SVR, attenuate cirrhosis progression and reduce HCC recurrence. The recommended treatment should be start 3–6 months after LT [58–62].

Table 2
Criteria of LT for HCC.

Items	Recommendations	Evidence grade	Recommendation strength
1	The Milan criteria is the benchmark for the selection of LT recipients with HCC.	II	Strong
2	The Hangzhou criteria is a reliable criteria for the selection in patients with HCC, and the post-LT survival is satisfactory.	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 better prognosis than those meeting category B (tumor diameter >8 cm but AFP level between 100 ng/mL and 400 ng/mL).	II	Strong
4	Any criteria achieving similar outcomes as Milan criteria and validated by a multicenter large sample study is applicable in clinical practice.	II	Weak
5	Patients suffering intrahepatic HCC recurrence after partial hepatic resection and meeting the selection criteria are candidates of salvage LT.	II	Weak
6	HCC patients meeting the selection criteria can receive living donor LT, and the social psychology status of the donor and recipient must be strictly assessed before LT.	III	Weak
7	If a graft loss occurs after living donor LT, cadaveric LT is feasible for HCC patients within the criteria of LT.	III	Weak
8	HCC patient exceeding the criteria for LT, if the initial graft loss occurs due to the HCC recurrence after living donor LT, is not a candidate for cadaveric LT.	V	Strong
9	In order to minimize donor risk and optimize recipient prognosis, living donor LT should be limited to the matured LT facilities.	V	Strong

Table 3
Preoperative downstaging treatment of HCC for LT.

Items	Recommendations	Evidence grade	Recommendation strength
10	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
11	Combination of multiple therapies is considered to have a better downstaging effect.	II	Strong
12	The comprehensive evaluation index of downstaging efficacy should base on tumor size, number and the change of serum AFP level.	II	Strong
13	For LT candidates with an estimated waiting time longer than 6 months, downstaging or bridging treatment should be applied in a timely manner.	II	Strong

Table 4
Antiviral therapy of HCC patients for LT.

Items	Recommendations	Evidence grade	Recommendation strength
14	NAs should be adopted in HCC candidates with positive HBV DNA before LT to reduce the HBV DNA level.	I	Strong
15	Potent NAs with high genetic barrier to resistance should be the first line if the HBV load is high before LT; for NAs resistance, appropriate drug should be selected based on the results of resistance mutation test.	II	Strong
16	HBIG should be administered in the anhepatic phase during the operation in HBV-related HCC patients; long-term post-LT monitoring as well as NAs and HBIG adoption should be applied to prevent HBV recurrence.	II	Strong
17	Entecavir/tenofovir combined with low-dose HBIG are the first line regimen to prevent post-LT HBV recurrence.	II	Strong
18	Entecavir monotherapy regimen is effective for preventing post-LT HBV recurrence.	IV	Strong
19	The steroid-free immunosuppression regimen can reduce post-LT HBV recurrence.	IV	Weak

Table 5
Application of immunosuppressants to HCC patients after LT.

Items	Recommendations	Evidence grade	Recommendation strength
20	The application of CNI is an independent risk factor for HCC recurrence after LT.	I	Strong
21	For recipients with hepatorenal syndrome or renal insufficiency, interleukin-2 receptor blocker, mycophenolate mofetil and sirolimus should be used instead of CNI.	I	Strong
22	Low-dose of CNI and early withdrawal of glucocorticoids are recommended for HCC patients after LT.	II	Strong
23	The application of mTOR inhibitors, such as sirolimus, in HCC patients post-LT reduces tumor recurrence and metastasis.	I	Strong
24	A glucocorticoid-free immunosuppressive regimen can be used in HCC patients after LT.	II	Weak
25	Conversion to sirolimus-based immunosuppressive regimen is suggested to patients with HCC recurrence after LT.	III	Weak

Table 6
Prevention and treatment of post-LT HCC recurrence.

Items	Recommendations	Evidence grade	Recommendation strength
26	Post-LT TARE can reduce the recurrence rate of HCC, increase the survival rate in LT recipients exceeding the Milan criteria.	II	Weak
27	Surgical resection is the preferred option for resectable recurrent lesions after LT.	III	Strong
28	For unresectable recurrent lesions, local ablation, TACE, molecular-targeted drugs, such as sorafenib, or a combination of the above treatment approaches should be selected individually to prolong the survival of recipients.	IV	Strong

Application of immunosuppressants to HCC patients post-LT (Table 5)

Usage of immunosuppressants such as calcineurin inhibitor (CNI) is an independent risk factor for HCC recurrence after LT. For LT recipients with HCC, the risk of HCC recurrence is related to the invasiveness of the tumor and the immune homeostasis of the body. When the recipients receive high-dose immunosuppressants, their homeostasis of immune system were disturbed which promote tumor recurrence and metastasis; on the other hand, if the immunosuppressant dose is insufficient, the grafts will be rejected. Currently, there is no uniform clinical strategy or monitoring system on how to maintain the immune homeostasis. Complete withdrawal of immunosuppressants for HCC patients after LT is not recommended but we encourage the usage of individualized low-dose immunosuppressive regimens [63]. Currently, the major clinical immunosuppressive regimens are as follows: (i) tacrolimus or ciclosporin + mycophenolate mofetil + glucocorticoids; (ii) interleukin-2 receptor blocker + sirolimus + mycophenolate mofetil + glucocorticoids; and (iii) interleukin-2 receptor blocker + mycophenolate mofetil + tacrolimus/sirolimus. The early withdrawal of glucocorticoids, glucocorticoid-free regimens and the use of tumor-suppressive mTOR inhibitors (e.g., sirolimus) have been recently reported to be successful in clinical applications [64–70]. Immune-inductive therapy using interleukin-2 receptor blockers, as well as the delayed and reduced use of CNI, is recommended during the early withdrawal of glucocorticoids and glucocorticoid-free regimens. Studies [71,72] demonstrated that HCC patients who received mTOR inhibitors have a significant lower HCC recurrence rate compared to those who received CNI. Interestingly, among mTOR inhibitor group, recipients who used everolimus had a lower HCC recurrence rate compared to those who use sirolimus. The regimen may also be converted to a sirolimus-based immunosuppressive regimen in 4–6 weeks after LT, combined with mycophenolate mofetil or low-dose CNI. For recipients with HCC recurrence after

LT, a sirolimus-based immunosuppressive regimen is recommended [72–74].

Prevention and treatment of post-LT HCC recurrence (Table 6)

Among different studies, the 5-year recurrence rate of HCC after LT ranged between 20% and 57.8% [17,29,73]. Thus, a proper management of HCC patients after LT is critical to reduce the postoperative recurrence. With the global trend of continuous attempts to expand LT indications of HCC, an increase in the recurrence rate after transplantation is inevitable [72]. The most common HCC recurrence sites after LT are lung (37.2%–55.7%), transplanted liver (37.8%–47.9%), abdomen (27.3%–37.7%) and bone (22.3%–25.5%) [75,76]. The median survival for recipients with HCC recurrence is 10.6–12.2 months [75,76]. Therefore, the prevention and treatment of post-LT HCC recurrence and metastasis are critical, and the preventive strategies should be individualized based on the morphological characteristics (i.e., size, number, macro- and microvascular invasion, histological grading) and biological characteristics of HCC.

The prevention strategy of recurrence after LT for HCC mainly includes management of immunosuppressive regimen and adjuvant therapy. Currently, adjuvant therapies for the prevention of HCC recurrence include radiotherapy with iodine-131 metuximab, sorafenib and systemic chemotherapy (e.g., oxaliplatin + calcium folic acid + fluorouracil). These adjuvant therapies provide certain survival benefits for some recipients, especially for those who exceed the Milan criteria [77–81]. However, the number of relevant studies is still limited, and the evidence grade is low. Also, there are some studies [82,83] claiming that the prophylactic use of sorafenib cannot prolong the survival of recipients with a high-risk of HCC recurrence after LT.

Early diagnosis of HCC recurrence is beneficial to the selection of a treatment strategy and an improvement in treatment efficacy. Surgical resection is the preferred treatment option for resectable recurrent lesions, with a 3-year postoperative survival rate of 60% [75,76]. When recurrent lesions are unresectable, local ablation, TACE, molecular-targeted drugs (e.g., sorafenib), or a combination of the above treatment approaches should be selected individually to prolong the survival of recipients [75,76,84–86]. For recipients with advanced disease, minimized usage or withdrawal of immunosuppressants may be considered.

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Competing interest

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References

[1] Schünemann HJ, Oxman AD, Brozek J, Glasziou P, Jaeschke R, Vist GE, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. BMJ 2008;336:1106–1110.
[2] Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–926.
[3] Oxford centre for evidence-based medicine-levels of evidence (March 2009). Oxford centre for evidence-based medicine, 2009 [cited 2018-11-01]. Available from: http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/.
[4] Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693–699.
[5] Mazzaferro V, Bhoori S, Sposito C, Bongini M, Langer M, Miceli R, et al. Milan criteria in liver transplantation for hepatocellular carcinoma: an evidence-based analysis of 15 years of experience. Liver Transpl 2011;17:S44–S57.
[6] European Liver Transplant Registry results. European liver transplant registry, 2011 [cited 2018-11-01]. Available from: http://www.eltr.org/.
[7] OPTN/SRTR annual report. Organ procurement and transplantation network, 2011 [cited 2018-11-01]. Available from: http://www.ustransplant.org/.
[8] Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology 2001;33:1394–1403.
[9] Mazzaferro V, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol 2009;10:35–43.
[10] Zheng SS, Xu X, Wu J, Chen J, Wang WL, Zhang M, et al. Liver transplantation for hepatocellular carcinoma: Hangzhou experiences. Transplantation 2008;85:1726–1732.
[11] Audet M, Panaro F, Piardi T, Wolf P. Are the Hangzhou criteria adaptable to hepatocellular carcinoma patients for liver transplantation in Western countries? Liver Transpl 2009;15:822–826.
[12] Chen J, Xu X, Wu J, Ling Q, Wang K, Wang W, et al. The stratifying value of Hangzhou criteria in liver transplantation for hepatocellular carcinoma. PLoS ONE 2014;9:e93128.
[13] Xu X, Yang JY, Zhong L, Lu D, Zhuang RZ, Tu ZH, et al. The clinical value of "Hangzhou Criteria" in the selection of patients with hepatocellular carcinoma for liver transplantation: a report of 1163 cases on a multicenter basis. Chin J Organ Transplant 2013;34:524–527.
[14] Lei JY, Wang WT, Yan LN. Hangzhou criteria for liver transplantation in hepatocellular carcinoma: a single-center experience. Eur J Gastroenterol Hepatol 2014;26:200–204.
[15] Xiao GQ, Yang JY, Yan LN. Combined Hangzhou criteria with neutrophil-lymphocyte ratio is superior to other criteria in selecting liver transplantation candidates with HBV-related hepatocellular carcinoma. Hepatobiliary Pancreat Dis Int 2015;14:588–595.
[16] Fu H, Zheng J, Cai J, Zeng K, Yao J, Chen L, et al. Systemic immune-inflammation index (SII) is useful to predict survival outcomes in patients after liver transplantation for hepatocellular carcinoma within Hangzhou criteria. Cell Physiol Biochem 2018;47:293–301.
[17] Xu X, Lu D, Ling Q, Wei X, Wu J, Zhou L, et al. Liver transplantation for hepatocellular carcinoma beyond the Milan criteria. Gut 2016;65:1035–1041.
[18] Zhang X, Li C, Wen T, Peng W, Yan L, Yang J. Outcomes of salvage liver transplantation and re-resection/radiofrequency ablation for intrahepatic recurrent hepatocellular carcinoma: a new surgical strategy based on recurrence pattern. Dig Dis Sci 2018;63:502–514.
[19] Hu Z, Wang W, Li Z, Ye S, Zheng SS. Recipient outcomes of salvage liver transplantation versus primary liver transplantation: a systematic review and meta-analysis. Liver Transpl 2012;18:1316–1323.
[20] Clavien PA, Lesurtel M, Bossuyt PM, Gores GJ, Langer B, Perrier A, et al. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. Lancet Oncol 2012;13:e11–e22.
[21] Chapman WC, Garcia-Aroz S, Vachharajani N, Fowler K, Saad N, Lin Y, et al. Liver transplantation for advanced hepatocellular carcinoma after downstaging without up-front stage restrictions. J Am Coll Surg 2017;224:610–621.
[22] Galuppo R, McCall A, Gedaly R. The role of bridging therapy in hepatocellular carcinoma. Int J Hepatol 2013;2013:419302.

[23] European Association for the Study of the Liver; European Organisation for Research and Treatment of Cancer EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908–943.
[24] Salem R, Gordon AC, Mouli S, Hickey R, Kallini J, Gabr A, et al. Y90 radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology 2016;151:1155–1163 e2.
[25] Klompenhouwer EG, Dresen RC, Verslype C, Laenen A, De Hertogh G, Deroose CM, et al. Safety and efficacy of transarterial radioembolisation in patients with intermediate or advanced stage hepatocellular carcinoma refractory to chemoembolisation. Cardiovasc Intervent Radiol 2017;40:1882–1890.
[26] Graziadei I, Zoller H, Fickert P, Schneeberger S, Finkenstedt A, Peck-Radosavljevic M, et al. Indications for liver transplantation in adults: recommendations of the Austrian Society for Gastroenterology and Hepatology (OGGH) in cooperation with the Austrian Society for Transplantation, Transfusion and Genetics (ATX). Wien Klin Wochenschr 2016;128:679–690.
[27] Samoylova ML, Dodge JL, Yao FY, Roberts JP. Time to transplantation as a predictor of hepatocellular carcinoma recurrence after liver transplantation. Liver Transpl 2014;20:937–944.
[28] Lai Q, Avolio AW, Graziadei I, Otto G, Rossi M, Tisone G, et al. Alpha-fetoprotein and modified response evaluation criteria in solid tumors progression after locoregional therapy as predictors of hepatocellular cancer recurrence and death after transplantation. Liver Transpl 2013;19:1108–1118.
[29] Duvoux C, Roudot-Thoraval F, Decaens T, Pessione F, Badran H, Piardi T, et al. Liver transplantation for hepatocellular carcinoma: a model including α-fetoprotein improves the performance of Milan criteria. Gastroenterology 2012;143:986–994 e3; quiz e14-15.
[30] Ashoori N, Bamberg F, Paprottka P, Rentsch M, Kolligs FT, Siegert S, et al. Multimodality treatment for early-stage hepatocellular carcinoma: a bridging therapy for liver transplantation. Digestion 2012;86:338–348.
[31] Merani S, Majno P, Kneteman NM, Berney T, Morel P, Mentha G, et al. The impact of waiting list alpha-fetoprotein changes on the outcome of liver transplant for hepatocellular carcinoma. J Hepatol 2011;55:814–819.
[32] Mailey B, Artinyan A, Khalili J, Denitz J, Sanchez-Luege N, Sun CL, et al. Evaluation of absolute serum α-fetoprotein levels in liver transplant for hepatocellular cancer. Arch Surg 2011;146:26–33.
[33] Mehta N, Yao FY. Living donor liver transplantation for hepatocellular carcinoma: to expand (beyond Milan) or downstage (to Milan)? Liver Transpl 2018;24:327–329.
[34] Llovet JM, Pavel M, Rimola J, Diaz MA, Colmenero J, Saavedra-Perez D, et al. Pilot study of living donor liver transplantation for patients with hepatocellular carcinoma exceeding Milan criteria (Barcelona clinic liver cancer extended criteria). Liver Transpl 2018;24:369–379.
[35] European Association for the Study of the Liver EASL clinical practice guidelines: liver transplantation. J Hepatol 2016;64:433–485.
[36] Sastre J, Díaz-Beveridge R, García-Foncillas J, Guardeño R, López C, Pazo R, et al. Clinical guideline SEOM: hepatocellular carcinoma. Clin Transl Oncol 2015;17:988–995.
[37] Qu LS, Liu JX, Zhu J, Lu CH. Risk factors for prognosis of hepatocellular carcinoma after curative resection in patients with low hepatitis B viral load. Ann Hepatol 2017;16:412–420.
[38] Wong JS, Wong GL, Tsoi KK, Wong VW, Cheung SY, Chong CN, et al. Meta-analysis: the efficacy of anti-viral therapy in prevention of recurrence after curative treatment of chronic hepatitis B-related hepatocellular carcinoma. Aliment Pharmacol Ther 2011;33:1104–1112.
[39] Koda M, Nagahara T, Matono T, Sugihara T, Mandai M, Ueki M, et al. Nucleotide analogs for patients with HBV-related hepatocellular carcinoma increase the survival rate through improved liver function. Intern Med 2009;48:11–17.
[40] European Association for the Study of the Liver EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67:370–398.
[41] Hu TH, Chen CL, Lin CC, Wang CC, Chiu KW, Yong CC, et al. Section 14. Combination of entecavir plus low-dose on-demand hepatitis B immunoglobulin is effective with very low hepatitis B recurrence after liver transplantation. Transplantation 2014;97:S53–S59.
[42] Yin J, Li N, Han Y, Xue J, Deng Y, Shi J, et al. Effect of antiviral treatment with nucleotide/nucleoside analogs on postoperative prognosis of hepatitis B virus-related hepatocellular carcinoma: a two-stage longitudinal clinical study. J Clin Oncol 2013;31:3647–3655.
[43] Lai CL, Yuen MF. Prevention of hepatitis B virus-related hepatocellular carcinoma with antiviral therapy. Hepatology 2013;57:399–408.
[44] Huang G, Lai EC, Lau WY, Zhou WP, Shen F, Pan ZY, et al. Posthepatectomy HBV reactivation in hepatitis B-related hepatocellular carcinoma influences postoperative survival in patients with preoperative low HBV-DNA levels. Ann Surg 2013;257:490–505.
[45] Chen CJ, Yang HI, Iloeje UHREVEAL-HBV Study Group. Hepatitis B virus DNA levels and outcomes in chronic hepatitis B. Hepatology 2009;49:S72–S84.
[46] Fung J, Wong T, Chok K, Chan A, Cheung TT, Dai JW, et al. Long-term outcomes of entecavir monotherapy for chronic hepatitis B after liver transplantation: results up to 8 years. Hepatology 2017;66:1036–1044.
[47] Kim JM, Joh JW, Kim SJ, Kwon CH, Song S, Shin M, et al. Steroid withdrawal in adult liver transplantation: occurrence at a single center. Transplant Proc 2010;42:4132–4136.
[48] Wei Q, Xu X, Wang C, Zhuang R, Zhuang L, Zhou L, et al. Efficacy and safety of a steroid-free immunosuppressive regimen after liver transplantation for hepatocellular carcinoma. Gut Liver 2016;10:604–610.
[49] Lo CM, Lau GK, Chan SC, Fan ST, Wong J. Efficacy of a pre-S containing vaccine in patients receiving lamivudine prophylaxis after liver transplantation for chronic hepatitis B. Am J Transpl 2007;7:434–439.
[50] Lo CM, Liu CL, Chan SC, Lau GK, Fan ST. Failure of hepatitis B vaccination in patients receiving lamivudine prophylaxis after liver transplantation for chronic hepatitis B. J Hepatol 2005;43:283–287.
[51] Sánchez-Fueyo A, Rimola A, Grande L, Costa J, Mas A, Navasa M, et al. Hepatitis B immunoglobulin discontinuation followed by hepatitis B virus vaccination: a new strategy in the prophylaxis of hepatitis B virus recurrence after liver transplantation. Hepatology 2000;31:496–501.
[52] Younossi ZM, Stepanova M, Sulkowski M, Wyles D, Kottilil S, Hunt S. Patient-reported outcomes in patients co-infected with hepatitis C virus and human immunodeficiency virus treated with sofosbuvir and velpatasvir: the ASTRAL-5 study. Liver Int 2017;37:1796–1804.
[53] Younossi ZM, Stepanova M, Sulkowski M, Foster GR, Reau N, Mangia A, et al. Ribavirin-Free regimen with sofosbuvir and velpatasvir is associated with high efficacy and improvement of patient-reported outcomes in patients with genotypes 2 and 3 chronic hepatitis C: results from Astral-2 and -3 clinical trials. Clin Infect Dis 2016;63:1042–1048.
[54] Younossi ZM, Stepanova M, Feld J, Zeuzem S, Jacobson I, Agarwal K, et al. Sofosbuvir/velpatasvir improves patient-reported outcomes in HCV patients: results from ASTRAL-1 placebo-controlled trial. J Hepatol 2016;65:33–39.
[55] Younossi ZM, Stepanova M, Charlton M, Curry MP, O'Leary JG, Brown RS, et al. Patient-reported outcomes with sofosbuvir and velpatasvir with or without ribavirin for hepatitis C virus-related decompensated cirrhosis: an exploratory analysis from the randomised, open-label ASTRAL-4 phase 3 trial. Lancet Gastroenterol Hepatol 2016;1:122–132.
[56] Levitsky J, Verna EC, O'Leary JG, Bzowej NH, Moonka DK, Hyland RH, et al. Perioperative ledipasvir-sofosbuvir for HCV in liver-transplant recipients. N Engl J Med 2016;375:2106–2108.
[57] Terrault NA, McCaughan GW, Curry MP, Gane E, Fagiuoli S, Fung JYY, et al. International Liver Transplantation Society consensus statement on hepatitis C management in liver transplant candidates. Transplantation 2017;101:945–955.
[58] Curry MP, Forns X, Chung RT, Terrault NA, Brown R Jr, Fenkel JM, et al. Sofosbuvir and ribavirin prevent recurrence of HCV infection after liver transplantation: an open-label study. Gastroenterology 2015;148:100–107 e1.
[59] Ueda Y, Ikegami T, Akamatsu N, Soyama A, Shinoda M, Goto R, et al. Treatment with sofosbuvir and ledipasvir without ribavirin for 12 weeks is highly effective for recurrent hepatitis C virus genotype 1b infection after living donor liver transplantation: a Japanese multicenter experience. J Gastroenterol 2017;52:986–991.
[60] Belli LS, Duvoux C, Berenguer M, Berg T, Coilly A, Colle I, et al. ELITA consensus statements on the use of DAAs in liver transplant candidates and recipients. J Hepatol 2017;67:585–602.
[61] Manns M, Samuel D, Gane EJ, Mutimer D, McCaughan G, Buti M, et al. Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicentre, open-label, randomised, phase 2 trial. Lancet Infect Dis 2016;16:685–697.
[62] Kwo PY, Mantry PS, Coakley E, Te HS, Vargas HE, Brown R Jr, et al. An interferon-free antiviral regimen for HCV after liver transplantation. N Engl J Med 2014;371:2375–2382.
[63] Chen K, Man K, Metselaar HJ, Janssen HL, Peppelenbosch MP, Pan Q. Rationale of personalized immunosuppressive medication for hepatocellular carcinoma patients after liver transplantation. Liver Transpl 2014;20:261–269.
[64] Wei Q, Gao F, Zhuang R, Ling Q, Ke Q, Wu J, et al. A national report from China liver transplant registry: steroid avoidance after liver transplantation for hepatocellular carcinoma. Chin J Cancer Res 2017;29:426–437.
[65] Yanik EL, Chinnakotla S, Gustafson SK, Snyder JJ, Israni AK, Segev DL, et al. Effects of maintenance immunosuppression with sirolimus after liver transplant for hepatocellular carcinoma. Liver Transpl 2016;22:627–634.
[66] Geissler EK, Schnitzbauer AA, Zülke C, Lamby PE, Proneth A, Duvoux C, et al. Sirolimus use in liver transplant recipients with hepatocellular Carcinoma: a randomized, multicenter, open-label phase 3 trial. Transplantation 2016;100:116–125.
[67] Menon KV, Hakeem AR, Heaton ND. Meta-analysis: recurrence and survival following the use of sirolimus in liver transplantation for hepatocellular carcinoma. Aliment Pharmacol Ther 2013;37:411–419.
[68] Foroncewicz B, Mucha K, Ryszkowska E, Ciszek M, Zióikowski J, Porowski D, et al. Safety and efficacy of steroid-free immunosuppression with tacrolimus and daclizumab in liver transplant recipients: 6-year follow-up in a single center. Transpl Proc 2009;41:3103–3106.
[69] Vivarelli M, Cucchetti A, La Barba G, Ravaioli M, Del Gaudio M, Lauro A, et al. Liver transplantation for hepatocellular carcinoma under calcineurin inhibitors: reassessment of risk factors for tumor recurrence. Ann Surg 2008;248:857–862.
[70] Nair S, Eason J, Loss G. Sirolimus monotherapy in nephrotoxicity due to calcineurin inhibitors in liver transplant recipients. Liver Transpl 2003;9:126–129.
[71] Cholongitas E, Mamou C, Rodríguez-Castro KI, Burra P. Mammalian target of rapamycin inhibitors are associated with lower rates of hepatocellular carcinoma recurrence after liver transplantation: a systematic review. Transpl Int 2014;27:1039–1049.

[72] Tarantino G, Magistri P, Ballarin R, Di Francia R, Berretta M, Di Benedetto F. Oncological impact of M-Tor inhibitor immunosuppressive therapy after liver transplantation for hepatocellular Carcinoma: review of the literature. Front Pharmacol 2016;7:387.
[73] Xu SL, Zhang YC, Wang GY, Yang Q, Liu B, Zhang J, et al. Survival analysis of sirolimus-based immunosuppression in liver transplantation in patients with hepatocellular carcinoma. Clin Res Hepatol Gastroenterol 2016;40:674–681.
[74] Sapisochin G, Bruix J. Liver transplantation for hepatocellular carcinoma: outcomes and novel surgical approaches. Nat Rev Gastroenterol Hepatol 2017;14:203–217.
[75] Bodzin AS, Lunsford KE, Markovic D, Harlander-Locke MP, Busuttil RW, Agopian VG. Predicting mortality in patients developing recurrent hepatocellular carcinoma after liver transplantation: impact of treatment modality and recurrence characteristics. Ann Surg 2017;266:118–125.
[76] Sapisochin G, Goldaracena N, Astete S, Laurence JM, Davidson D, Rafael E, et al. Benefit of treating hepatocellular carcinoma recurrence after liver transplantation and analysis of prognostic factors for survival in a large Euro-American series. Ann Surg Oncol 2015;22:2286–2294.
[77] Shetty K, Dash C, Laurin J. Use of adjuvant sorafenib in liver transplant recipients with high-risk hepatocellular carcinoma. J Transpl 2014;2014:913634.
[78] Huang L, Li GM, Zhu JY, Li Z, Li T, Leng XS. Efficacy of sorafenib after liver transplantation in patients with primary hepatic carcinoma exceeding the Milan criteria: a preliminary study. Onco Targets Ther 2012;5:457–462.
[79] Zhang Q, Chen H, Li Q, Zang Y, Chen X, Zou W, et al. Combination adjuvant chemotherapy with oxaliplatin, 5-fluorouracil and leucovorin after liver transplantation for hepatocellular carcinoma: a preliminary open-label study. Investig New Drugs 2011;29:1360–1369.
[80] Saab S, McTigue M, Finn RS, Busuttil RW. Sorafenib as adjuvant therapy for high-risk hepatocellular carcinoma in liver transplant recipients: feasibility and efficacy. Exp Clin Transplant 2010;8:307–313.
[81] Xu J, Shen ZY, Chen XG, Zhang Q, Bian HJ, Zhu P, et al. A randomized controlled trial of licartin for preventing hepatoma recurrence after liver transplantation. Hepatology 2007;45:269–276.
[82] Satapathy SK, Das K, Kocak M, Helmick RA, Eason JD, Nair SP, et al. No apparent benefit of preemptive sorafenib therapy in liver transplant recipients with advanced hepatocellular carcinoma on explant. Clin Transpl 2018;32:e13246.
[83] Qi HL, Zhuang BJ, Li CS, Liu QY. Peri-operative use of sorafenib in liver transplantation: a time-to-event meta-analysis. World J Gastroenterol 2015;21:1636–1640.
[84] de'Angelis N, Landi F, Nencioni M, Palen A, Lahat E, Salloum C, et al. Role of sorafenib in patients with recurrent hepatocellular carcinoma after liver transplantation. Prog Transplant 2016;26:348–355.
[85] Mancuso A, Mazzola A, Cabibbo G, Perricone G, Enea M, Galvano A, et al. Survival of patients treated with sorafenib for hepatocellular carcinoma recurrence after liver transplantation: a systematic review and meta-analysis. Dig Liver Dis 2015;47:324–330.
[86] Zhou B, Shan H, Zhu KS, Jiang ZB, Guan SH, Meng XC, et al. Chemoembolization with lobaplatin mixed with iodized oil for unresectable recurrent hepatocellular carcinoma after orthotopic liver transplantation. J Vasc Interv Radiol 2010;21:333–338.

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