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Review Article

Hepatocellular Carcinoma and the Role of Liver Transplantation: A Review

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Abstract

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer deaths worldwide and liver transplantation (LT) is the only potentially curative treatment. Over the years, Milan criteria has been used for patient selection. There is ongoing research in this field with introduction of new biomarkers for HCC that can help guide future treatment. Furthermore, newer therapies for downstaging of the tumor are being implemented to prevent dropout from the transplant list. In addition, combination therapies for better outcome are under investigation. Interestingly, the concept of living-donor LT and possible use of hepatitis C virus-positive donors has been implemented as an attempt to expand the organ pool. However, there is a conflict of opinion between different centers regarding its efficacy and data is scarce. The aim of this review article is to outline the various selection criteria for LT, discuss the outcomes of LT in HCC patients, and explore future directions of LT for HCC. Therefore, a comprehensive PubMed/MEDLINE review was conducted. To expand our search, references of the retrieved articles were also screened for additional data. After selecting the studies, the authors independently reviewed them to identify the relevant studies. After careful evaluation 120 studies relevant to out topic are cited in the manuscript. Three tables and two figures are also included. In conclusion LT for HCC has evolved over the years. With the introduction of several expanded criteria beyond Milan, the introduction of bridging therapies, such as transcatheter arterial chemoembolization and radiofrequency ablation, and the approval of newer systemic therapies, it is evident that there will be more LT recipients in the future. It is promising to see ongoing trials and the continuous evolution of protocols. Prospective studies are needed to guide the development of a pre-LT criteria that can ensure low HCC recurrence risk and is not overly stringent, clarify the role of LDLT, and determine the optimal bridging therapies to LT.

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Introduction

Hepatocellular carcinoma (HCC) constitutes greater than 80% of all primary liver cancers worldwide.[1] It is the sixth most common cancer and the third leading cause of cancer-related deaths.[2] In the US, from 1999 to 2016, the age-adjusted death rate due to HCC has increased annually by 2.1% (1.9% to 2.3%, $p<0.001$), with increased incidence in all 50 states.[3] Liver transplant (LT) remains one of the most curative treatment options for HCC. According to the Scientific Registry of Transplant Recipients (commonly referred to as the SRTR), in 2019, HCC was the primary diagnosis for 10.6% of waitlist candidates.[4] The deceased-donor transplant rate for candidates with HCC exception points remained higher than those without HCC exception (94.3 vs. 58.3 per 100 waiting list-years). Also, compared with 2018, the deceased-donor transplant rate among patients without HCC exception increased from 50.5 to 58.3 (per 100 waiting list-years). Interestingly, deceased-donor liver transplant (DDLT) recipients with a primary diagnosis of HCC had 5-year survival rates comparable to other disease etiologies (75.2%) but living-donor liver transplant (LDLT) recipients with HCC demonstrated worse 5-year survival rates (61.8%).[4] The prognosis of HCC depends on the tumor burden as well as the underlying liver function. Therefore, LT is an attractive option, especially in patients with HCC and cirrhosis. With the availability of living donor LT, an additional benefit is potential reduction in transplant wait times.

Epidemiology

HCC is the fifth leading cause of death in the USA amongst men and the ninth amongst women.[5] Its incidence has in-

Keywords: Hepatocellular carcinoma; Liver transplantation; Model for end-stage liver disease; Trans-arterial radioembolization; Locoregional therapies.
Abbreviations: HCC, Hepatocellular Carcinoma; LT, Liver Transplantation; DAA, Direct acting antivirals; MT, Metro ticket; OS, Overall Survival.
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creased over the years, and as per the Surveillance Epidemiology and End Results (commonly referred to as the SEER) database, it is estimated that in 2020 it contributed to 2.4% of all cancers and 5% of all cancer deaths. Based on cases from 2013 to 2017, after age adjustment, the reported incidence of liver and intrahepatic bile duct cancer was 9/100,000 men and women each year, rising an average of 1.7% per year between 2008 and 2017. American Indian/Alaskan native men showed the highest incidence (21.6/100,000), followed by Hispanic males (20.3/100,000). Cancer was most frequently diagnosed (35.3%) in the 55–64 years age group, with the highest mortality (29.9%) occurring in the 65–74 age group. Age-adjusted death rates rose an average of 1.7% each year between 2009 and 2018.[6]

Distribution of HCC varies across the globe. Per the 2020's International Agency for Research on Cancer (commonly referred to as the IARC) report conducted by the World Health Organization (commonly referred to as the WHO) in 2020, the incidence (72.5%), mortality (73.3%), and 5-year prevalence (73.6%) of HCC is highest in Asia. This is likely due to hepatitis B virus (HBV) being endemic to Asia. Europe and Africa follow in second and third place.[7]

Risk Factors

Viral

Up to 90% of HCC cases can be attributed to hepatitis B and C.[8] Globally, approximately 240 million people have chronic HBV infection, and 130–150 million have chronic hepatitis C virus (HCV) infection. HBV has been projected to cause 20 million deaths between 2015 and 2030.[9] High viral DNA levels, high alanine aminotransferase levels, HBV genotype, older age, male sex, and active hepatitis are risk factors for HCC progression. Although 70–90% of the HCC cases arise from HBV cirrhosis, HBV can also cause HCC in the absence of cirrhosis.[10] Comparatively, HCV is associated with a 15- to-20-fold increased risk of HCC, with the 25- to 30-year risk of cirrhosis being 15% to 35%.[11] Interestingly, hepatitis D virus when coinfected with HBV results in severe hepatitis and is reported to have oncogenic properties leading to HCC.[12]

Direct acting antivirals (DAAs) for HCV have dramatically increased sustained virological response (SVR), that helps to change the course of the disease.[13] Surprisingly, there has been some concerns that DDAs may result in unexpected increase in HCC occurrence in patients with HCV.[14] However, recent studies have shown that DAA treatment is not associated with a higher risk of HCC in patients with cirrhosis and chronic HCV infection.[15] In fact, they have a protective effect.[16] Thus, supporting the argument that earlier studies might have been subject to selection bias by attributing high risk patients in the DAA group or there might be pre-existing microscopic undetectable tumors. Therefore, DAAs are a valuable prospect in patients with underlying HCV that might aid in preventing the progression towards HCC and ultimately lowering the transplant burden.

Host

Susceptibility to HCC is influenced by factors such as male sex, older age, diabetes, smoking, alcohol consumption, and genetics. Heavy alcohol intake (>50–70 g/day) has a synergistic effect with HCV and HBV[17] and presumably accelerates the progression to cirrhosis. Similarly, a meta-analysis by Chuang *et al*.[18] concluded that cigarette smoking appears to interact with both HBV and HCV and increases HCC risk, separate from its independent carcinogenic effect. Aflatoxin exposure is another risk factor, whereby highly hepatocarcinogenic metabolites are secreted by certain *Aspergillus* molds commonly present in staple cereals (such as those made from corn, peanuts, and soybeans) when stored in damp conditions. Aflatoxins exhibit tumorigenic properties via mutating the tumor suppressor gene p53. Exposure is prevalent in HBV endemic areas (Sub-Saharan Africa and Eastern Asia).

Nonalcoholic fatty-liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH)

Individuals with obesity and diabetes experience a higher incidence of HCC than those without these comorbidities. A meta-analysis conducted by Larsson *et al*.,[19] in Europe, the USA and Asia, concluded that overweight and obese individuals have an increased relative risk of developing HCC (1.07, 95% confidence interval [CI]: 1.01–1.15 and 1.85, 95% CI: 1.44–2.37, respectively). Similarly, another meta-analysis by El-Serag *et al*.[20] reported a significant association between HCC and diabetes, independent of alcohol use or viral hepatitis. The obesity epidemic and insulin resistance are closely associated with the rising prevalence and severity of NAFLD/NASH, which causes hepatic fibrosis and leads to end-stage liver disease. A meta-analysis comprising of 88 studies from 22 countries reported global prevalence of NAFLD is 25.24% with pooled regional incidence of NAFLD from the West to be estimated around 28 per 1,000 person-years (95% CI: 19.34–40.57).[21] The annual incidence of HCC in NAFLD patients was 0.44 per 1,000 person-years (95% CI: 0.29–0.66), whereas for NASH the annual HCC incident rate was 5.29 per 1,000 person-years (95% CI: 0.75–37.56).[21] Similarly, a population-based study in the USA has shown that metabolic syndrome is significantly associated with an increased risk of HCC (odds ratio: 2.13; 95% CI: 1.96–2.31, $p<0.0001$).[22] Furthermore, the cumulative incidence of HCC in patients with NASH cirrhosis ranges from 2.4% over 7 years to 12.8% over 3 years.[23] Moreover, some studies have demonstrated that HCC can occur in patients who have NASH without cirrhosis.[24]

Surveillance

The aim of screening is early detection of tumor so it may be treated while still having a good prognosis. Cirrhosis is the fundamental risk factor for HCC and is found in 85–95% of HCC.[25] Subsequently, approximately 2–4% of patients with cirrhosis develop HCC annually.[26] Several surveillance guidelines for HCC have been developed across the globe. The American Association for the Study of Liver Diseases (commonly known as AASLD) recommends screening of adults with cirrhosis, using ultrasound (US) with/or without alpha-fetoprotein (AFP) every 6 months.[27] Once a lesion is detected, either multiphasic computed tomography (CT) or multiphasic magnetic resonance imaging (MRI) is recommended. It is recommend against screening of patients with Child-Pugh class C cirrhosis, unless they are on the transplant waiting list and the routine biopsy reveals indeterminate nodules.[27] Though the European Association for the Study of the Liver (commonly known as EASL) guidelines are similar to those of the AASLD, except that they are more aggressive in their surveillance and recommend to start screening in patients with bridging fibrosis (Metavir F3) but without AFP.[28] In comparison, the Chinese guidelines recommend mandatory AFP testing and a diagnostic diameter threshold of 2 cm (compared to 1 cm by EASL and

Table 1. Outcome of trials for systemic therapy

Study	Drug	Control	OS in months	HR (95% CI)
SHARP[37]	Sorafenib (TKI)	Placebo	10.7 vs. 7.9	0.69 (0.55–0.87)
Asia-Pacific[38]	Sorafenib (TKI)	Placebo	6.5 vs. 4.2	0.68 (0.50–0.93)
REFLECT[40]	Lenvatinib (TKI)	Sorafenib	13.6 vs. 12.3	0.92 (0.79–1.06)
RESORCE[41]	Regorafenib (TKI)	Placebo	10.6 vs. 7.8	0.63 (0.50–0.79)
CELESTIA[42]	Cabozantinib (TKI)	Placebo	10.2 vs. 8.0	0.76 (0.63–0.92)
REACH-2[43]	Ramucirumab (VEGRFI)	Placebo	8.5 vs. 7.3	0.71 (0.53–0.95)
IMbrave150[44]	Atezolizumab (CPI) and bevacizumab (VEGRFI)	Sorafenib	At 12 months 67.2% vs. 54.6%	–

CPI, check point inhibitor; TKI, tyrosine kinase inhibitor; VEGRFI, vascular endothelial growth factor inhibitor.

AASLD).[29] This discrepancy in guidelines is likely due to the cost effectiveness in the population that is being screened.

Prevention

Primary prevention is defined as avoiding the initiation of the disease process. Global vaccination against HBV is an excellent example of primary prevention. In Taiwan, due to the vaccination program initiated in early 1980s, the changes in age and sex-adjusted rate ratios for individuals aged 5 to 29 years led to in decreased HCC incidence by more than 80% till the early 2000s.[30] In addition, to avoid HBV and HCV transmission by blood contamination, practices of disposable needles and syringes use, adequate sterilization of equipment, and wearing gloves to handle wounds and blood products have been implemented.[31] Furthermore, alcohol abstinence and smoking cessation should be encouraged. A recent liver cancer pooling project consisting of 14 USA-based prospective cohort studies determined that smoking at baseline is associated with an increased risk of HCC (hazard ratio [HR]: 1.86, 95% CI: 1.57–2.20). Also compared to non-drinkers, heavy alcohol consumption (>7 drinks/day) was associated with an 87% increased HCC risk (HR: 1.87, 95% CI: 1.41–2.47).[32] Lifestyle modification to mitigate the development of metabolic syndrome is another reasonable intervention since obesity and diabetes are also linked to HCC.[32] Though data is limited, medications such as statins and metformin have shown a protective effect against HCC.[33,34] Secondary prevention is early detection and prevention of worsening disease. It can be achieved with agents such as interferon and antivirals (for example in cases of HBV infection) that can prevent viral replication and help achieve sustained virological response.[35]

Treatment options

Table 1 shows the results of treatment trials and Figure 1 shows the systemic therapy treatment algorithm.

Barcelona Clinic Liver Cancer (commonly referred to as BCLC) staging has been adopted worldwide as the background of HCC treatment. Patients with early-stage HCC are effectively treated with LT, radiofrequency ablation (RFA), or surgical resection. Individuals with intermediate stage with intrahepatic multifocal HCC benefit from liver-directed treatments, such as transcatheter arterial chemoembolization (TACE). Many transplant centers now accept patients with HCC patients who have been successfully down-staged by liver-directed therapy.[36]

Systemic therapy is recommended for advanced-stage HCC. After the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (referred to as 'SHARP') trial in 2008, sorafenib became the first approved systemic therapy for HCC.[37] It is an oral multi-kinase inhibitor of tyrosine kinase receptors, including vascular endothelial growth factor

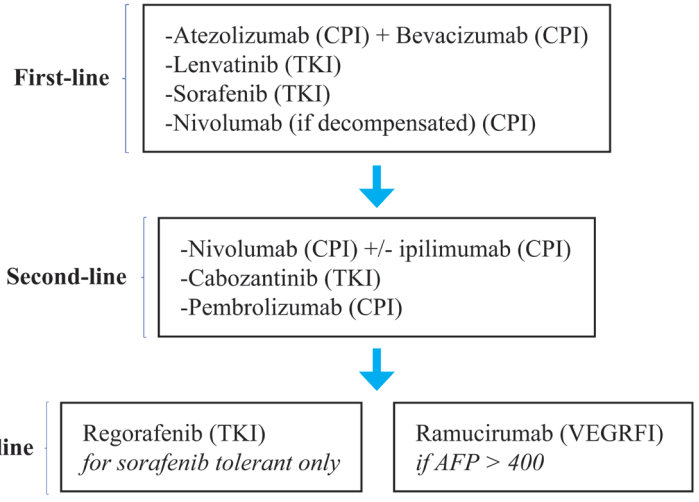

Fig. 1. Systemic therapy of HCC. CPI, check point inhibitor; HCC, Hepatocellular Carcinoma; TKI, tyrosine kinase inhibitor; VEGRFI, vascular endothelial growth factor inhibitor.

Table 2. Different criteria for liver transplantation

Criteria	Detail
MILAN[48]	1 lesion ≥2 cm and ≤5 cm OR up to three lesions, each ≥1 cm and ≤3 cm. No evidence of vascular invasion or extrahepatic metastases
UCSF[49]	Solitary tumor ≤ 6.5 cm or ≤ 3 tumors, with the largest ≤ 4.5 cm
Up-to-seven[51]	7 as total of the size of the largest lesion in cm and number of lesions. No vascular invasion
Toronto criteria[53]	No upper limit on size and number of lesions. No extrahepatic metastases, evidence of venous or biliary tumor thrombus cancer-related symptoms

receptors (commonly referred to as VEGFRs) and platelet-derived growth factor receptor (PDGFR)-β, which is associated with neovascularization and cell proliferation. Its benefit was confirmed by an Asia-Pacific study.[38] Analysis of these trials showed that sorafenib was of the greatest benefit to patients with HCV etiology, without extrahepatic spread and low neutrophil-to-lymphocyte ratio.[39] In 2018, lenvatinib, which is also a multi-kinase agent, proved to be non-inferior to sorafenib in the REFLECT trial for advanced HCC.[40] It did improve secondary endpoints, such as time to progression, progression-free survival and quality of life. It was effective in patients with AFP >200 ng/mL and less effective in patients with HCV etiology, in Western countries, and without extrahepatic spread. Currently, both are approved as first-line systemic agents. More recently, based on successful trials, three more multi-kinase inhibitors (regorafenib, cabozantinib and ramucirumab) were approved as second-line agents, after demonstrating success in trials.[41–43] Regorafenib is a multi-kinase inhibitor that was used in patients who tolerated sorafenib but showed radiological progression. Its use resulted in median survival of 10.6 months compared to 7.8 months with the placebo group (HR: 0.63, $p<0.0001$).[41] Unlike the trial for regorafenib, the drug cabozantinib was studied in patients who failed up to two previous systemic treatments, including prior immunotherapy. It produced favorable results in patients ≥65 years of age, with AFP ≥400 ng/mL, with extrahepatic spread, of non-Asian population, and with HBV etiology.[42] Although, median overall survival (OS) was only 1.2 months, ramucirumab showed benefit in patients with baseline AFP ≥400 ng/mL.[43] The IMbrave-150 trial, which included the combination of atezolizumab, a programmed death ligand 1 (commonly referred to as PD-L1) inhibitor, and bevacizumab, a monoclonal antibody targeting the vascular endothelial growth factor, demonstrated superiority over sorafenib[44] and the combination is now approved as first-line chemotherapy. This resulted in significantly longer OS and progression-free survival (OS at 12 months was 67.2% [95% CI: 61.3–73.1] with atezolizumab-bevacizumab and 54.6% [95% CI: 45.2–64.0] with sorafenib).[44] For patients without liver decompensations, these are now the preferred first-line agents for advanced HCC. Immunotherapy has further expanded treatment options for advanced hepatocellular carcinoma, and programmed cell death 1 (commonly referred to as PD-1) inhibitors nivolumab and pembrolizumab have received accelerated approval in USA.[45] With such advancement of systemic treatment options in recent years, several clinical trials are underway examining use of systemic treatments in intermediate stage disease. Two clinical trials involving a combination of immunotherapy and tyrosine kinase inhibitors are ongoing, specifically examining their potential as neoadjuvant treatments prior to LT and with a primary outcome of recurrence-free survival after LT.[46,47] In future years, such trials will likely significantly transform the treatment paradigm.

Selection criteria for LT

Selecting patients with HCC for LT and prioritizing them on the transplant waitlist has long been decided based on the Milan criteria (MC). This is defined as: (a) single tumor with a diameter ≤5 cm; OR (b) no more than three tumors, each ≤3 cm in size; and (c) no vascular invasion; and (d) no extrahepatic involvement. This is the earliest criteria that set standards for our current transplant protocol.[48] In patients transplanted using MC, the survival rate was 75% and the rate of recurrence-free survival was 83%.[48] As these results were comparable to individuals with benign disease, the MC was accepted worldwide. However, with concerns that the MC was too restrictive and excluded patients who might have benefited from LT, other criteria have been introduced. One of these is the University of San Francisco California (commonly known as the UCSF) criteria, which was introduced in 2001. This is defined as: a) solitary tumor ≤6.5 cm or ≤3 nodules with each lesion ≤4.5 cm; and b) total maximum diameter ≤8 cm. It showed comparable survival of 75.2% at 5 years.[49] A study published in 2007 on 467 transplants showed similar 5-year survival in patients meeting MC and UCSF criteria by preoperative imaging (79% vs. 64%; $p=0.061$) and explant pathology (86% vs. 71%; $p=0.057$).[50] However, survival beyond UCSF criteria was below 50%. Thus, with studies like this showing similar results, Mazzaferro *et al*.,[51] who introduced MC criteria, expanded it and proposed "up-to-7 criteria", defined as: the sum of the tumor number and the size of the largest tumor (in cm) not larger than 7. Patients without microvascular invasion, but who fell within the up-to-seven criteria, had a 5-year OS of 71.2%. In comparison, the survival rate was 48% in patients with microvascular invasion.[51] In addition to increased mortality, the presence of microvascular invasion is not assessable before transplantation. This limits the routine application of up-to-seven criteria.

Criterion by different countries, such as the extended Toronto criteria (no restrictions on tumor size or number), with 5-year survival of 68%, and the Kyoto criteria (tumor ≤10 nodules, all ≤5 cm and a serum des-gamma-carboxy prothrombin (commonly referred to as DCP) level ≤400 mAU/mL) with 5-year survival rate of 86.7% have been proposed.[52,53] However, the MC is still the gold standard for a successful LT and is used to assess the validity of other suggested criteria. Table 2 presents the different criteria.[48,49,51,53]

Metro ticket (MT) prognostic model

MT is a predictive model that was introduced in 2009 from a European cohort of patients.[51] It predicts 3-year and 5-year survival post-transplant using radiological data. The MT calculator only incorporates tumors >10 mm diameter, with a maximum of 10 nodules. Additionally, MT can also predict 5-year survival in patients who undergo transplant. This considers tumor size, number and the presence or absence of microvascular invasion and, therefore, can only be calculated from explant pathology. Raj *et al*.[54] validated this model in their study, where the predicted and observed out-

Table 3. Summary of some of the studies included in the manuscript

Reference	Country	Study Design	Samples, *n*	Median age	Median biological MELD score	Recurrence % at last follow-up, *n*/N	Survival % (1 or 5 year)	Follow-up in years
Mazzaferro *et al*. (1996)[48]	Italy	Prospective	48	52	Child-Pugh used	8.3 (4/48)	94% (1)	2.16
Yao *et al*. (2001)[49]	USA	Prospective	70	54	Child-Pugh used	11.4 (8/70)	73% (5)	5
Duffy *et al*. (2007)[50]	USA	Prospective	467	56.6	NA	21.2 (99/467)	82 (1), 52 (5)	6.6
Mazzaferro *et al*. (2009)[51]	Multi-national	Retrospective	1,556	55	NA	20.0 (311/1,556)	62 (4.4)	4.4
Ito *et al*. (2007)[52]	Japan	Retrospective	125	55	15	16 (20/125)	68.3 (5)	2.41
Sapisochin *et al*. (2016)[53]	Canada	Prospective	243	Within MC (57.9), exceeded MC (60.4)	Within MC (11), exceeded MC (10)	Within MC (16.1, *n*=20), exceeded MC (25.6, *n*=22)	Within MC 78 (5), exceeded MC 68 (5)	5

MELD, model for end-stage liver disease.

comes were within 95% CIs. In a larger single-center study comprised of 230 patients, MT accurately predicted patients with microvascular invasion and no invasion.[55] However, there was a high discrepancy in the 23 cases with macrovascular invasion, where the predicted 5-year survival rate was 43.5%, whereas the observed 5-year survival rate was only 8.7%.[55] This is one of the draw backs, as the MT calculator does not consider the difference in microvascular or macrovascular invasion and might need a revision. Recently, the MT calculator was revised and AFP was added.[56] Thus, with the additions of some more important parameters, accurate prediction could be made. As MT provides continuous survival probabilities, accurate prediction will be helpful for transplant centers to prioritize their transplant list.

LT Evolution and Outcomes

Table 3 summarizes some of the studies on this topic.

Introduction of MELD

Early studies of LT for HCC showed a 70% to 80% range for 5-year mortality rate.[57,58] This led to the introduction of strict allocation criteria such as the MC in 1996 and various other scoring systems. However, despite these advancements, patients with HCC remained on the waiting list longer than candidates without HCC, resulting in less than 5% LT for HCC in the USA from 1997–2002.[59] Thus, in 2002, the United Network for Organ Sharing (commonly referred to as the UNOS) adopted the model for end-stage liver disease (MELD) score for allocation. The MELD score is an objective predictor of 3-month mortality without LT and is calculated using serum bilirubin, creatinine, and international normalized ratio for prothrombin time (INR).[60] There have been several modifications to MELD based on different parameters and it is noteworthy to mention the MELD-sodium (Na) score. In cirrhotic patients, hyponatremia leads to portal hypertension, which is an independent predictor of survival at 3 and 12 months.[61] Thus, addition of Na to the MELD improves its predictive accuracy, especially for patients with lower range MELD scores, helping them to get prioritized on the transplant list. However, when the MELD score increases, serum Na contributes much less to increasing mortality prediction.[62] Furthermore, serum Na can change with the use of diuretics and intravenous hypotonic fluids. Thus, limiting the use of MELD-Na. Therefore, in order to promote equal allocation of donor organs between HCC and non-HCC patients on the waiting list, MELD exception points are given to HCC candidates. Initially, 24 points were assigned to stage 1 tumors (1 nodule <2 cm) and 29 points to stage 2 tumors (1 nodule 2–5 cm or 2 or 3 nodules each ≤3 cm). It was subsequently revised in 2005, when no points were assigned for stage 1 tumors and 22 points for stage 2 tumors (Table 4) with incremental increase in points over time.[63] This resulted in a rise from 5% to 26% LT for HCC from 2002–2007.[59] This criterion changes periodically and most recently in the UNOS regulation, with the candidate receiving a MELD score that is 3 points below the median MELD at transplant for liver recipients at least 18 years-old in the donation service area where the candidate is registered. However, If the candidate's exception score would be higher than 34 based on this calculation, the candidate's score will be capped at 34.[64]

Table 4. Changes in MELD score over time

Stage	Original MELD score	2005 MELD score	2018 MELD policy pointers
First stage: one tumor <2 cm	24	0	Upon initial registration candidate should be at least 18 years of age and will be assigned the calculated MELD
Second stage: one tumor 2–5 cm or two to three tumors not >3 cm	29	22	Initial exception request in 6 months for 3 points below the median MELD at transplant in donation service area, and subsequent requests every 3 months

MELD, model for end-stage liver disease.

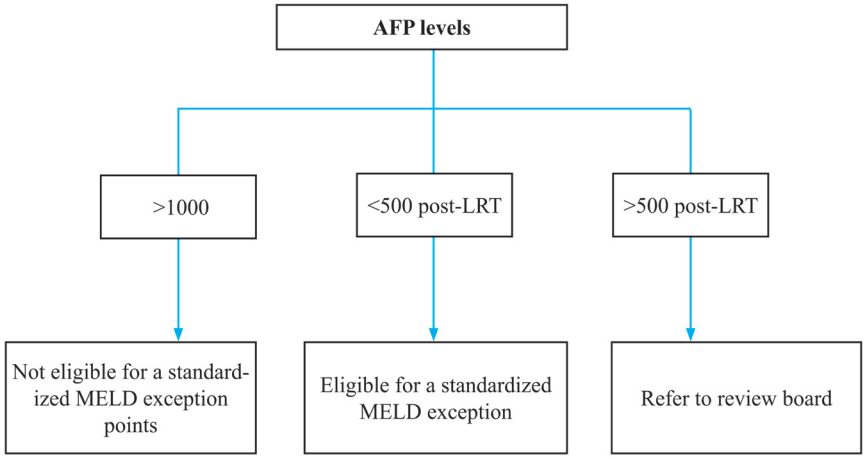

Fig. 2. Algorithm for selecting candidates for LT based on AFP levels. AFP, alpha-fetoprotein; LRT, locoregional therapy; MELD, model for end-stage liver disease.

Biomarkers and role of liver biopsy for HCC

Treatment of HCC is a moving target and there is ongoing research on predictive biomarkers that can set a standard for treatment. There are various prognostic markers, such as AFP, lens culinaris agglutinin-reactive fraction of α-fetoprotein (AFP-L3) and DCP that are being used for surveillance and diagnostic purposes. AFP has been commonly used in conjugation with US for HCC surveillance. Similarly, AFP-L3 predicts tumor recurrence and poor outcome. Cheng *et al* performed a meta-analysis and determined that high pre-treatment serum AFP-L3 suggested poor OS (HR: 1.65, 95% CI: 1.45–1.89, $p<0.00001$) and disease-free survival (DFS) (HR: 1.80, 95% CI: 1.49–2.17, $p<0.00001$) of HCC.[65] Furthermore, subgroup analysis revealed that pre-treatment AFP-L3 may have significant prognostic value in HCC patients, even with low AFP concentration. Interesting, DCP was once believed to be a useful predisposing clinical parameter for the development of portal vein thrombosis.[66] However, in addition, it is now thought to be a useful recurrence predictive factor, indicating 5-fold increased risk of HCC recurrence after LT.[67] Likewise, AFP >1,000 ng/mL among patients with HCC either within or beyond MC is associated with a very high risk of HCC recurrence and poor survival after LT.[68] A recent national policy has been recently implemented by UNOS, in which patients with HCC and AFP >1,000 ng/mL are deprived of HCC exception points. These patients are required to show a decrease in AFP to <500 ng/mL with locoregional therapy (LRT) before they can proceed with LT (Fig. 2).[69]

Biomarkers for HCC therapy, such as with sorafenib, have also been investigated. Sorafenib is an oral multikinase inhibitor that acts on VEGFR-2/3, PDGF-R, Flt3 and c-Kit, and the mitogen-activated protein kinases/extracellular signal-regulated kinase (commonly known as MAPK/ERK) pathway. Initially, it was thought that levels of phosphorylated-ERK may be a biomarker for the therapy.[70] However, this potential was not confirmed and there is still no validated prognostic or predictive markers of response to sorafenib.[71] More recently, there has been a lot of research on the potential use of microRNAs (commonly referred to as miRNAs), long non-coding RNAs (commonly referred to as lncRNAs), and circular RNAs (commonly referred to as circRNAs) as diagnostic and therapeutic biomarkers.[72] However, results are limited, warranting more prospective studies.

Liver biopsy for HCC can be challenging, as there is a risk of bleeding (3–4%) and chance of seeding (2.7%).[73,74] Although imaging alone is sufficient in cirrhotic patients, especially if the tumor is >1 cm. However, in non-cirrhotic patients, biopsy is strongly recommended by some international guidelines, such as that of the EASL.[28] Liver biopsy is not only helpful for correct diagnosis or proper staging; it can also be used for detection of therapeutic targets. However, as only small tissue samples can be obtained, there is a chance to miss tumor heterogeneity or dynamic tumor progression. Therefore, the non-invasive method known as liquid biopsy is becoming popular, where tumor components such as circulating tumor cells (also referred to as CTCs), circulating tumor DNA (commonly referred to as ctDNA) and miRNAs are analyzed from body fluids (blood, cerebral spinal fluid, etc.).[75]

Bridging therapies

The SRTR registry shows an increase in the number of new waitlist registrants (11,844 in 2018 vs. 11,514 in 2017 vs. 11,340 in 2016 and 10,636 in 2015) and a continued increase in the transplant rate (54.5 per 100 waitlist-years in 2018 vs. 51.5 per 100 waitlist-years in 2017) for patients with HCC.[76] While on the waiting list, candidates are prone to tumor growth, resulting in going beyond the transplant criteria and an eventual 12 month dropout probability of 25%.[77] Therefore, bridging therapies are offered to patients, which help in downstaging of the tumor. Amongst them, LRTs like the TACE, transarterial radioembolization (TARE), transarterial embolization (TAE) and RFA are most commonly used. Kulik *et al*.[78] carried out a meta-analysis of 63 studies on bridging therapies. The subgroup analysis compared TACE vs. RFA vs. multiple therapies and showed dropout from the waiting list to have a relative risk (95% CI) of 0.212 (0.027–1.650) vs. 1.434 (0.793–2.594) vs. 0.131 (0.038–0.449) and recurrence post-LT of 1.74 (0.49–6.15) vs. 0.745 (0.069–8.003) vs. 1.49 (0.826–2.7). Currently, there is heterogenicity amongst the studies and most of the data are from single centers. More multicenter randomized controlled trials (RCTs) are needed to further explore this branch of transplantation.

TAE

This technique uses particulate and liquid materials for embolization, which target hepatic vessels and thereby lead to cell necrosis via ischemia. It is commonly known as "bland"

embolization, as the particles do not have chemotherapeutic or radioactive functions. Cone-beam CT is used to make sure that only the target lesion is embolized.[79] A RCT comparing drug-eluting beads (DEBs)-TACE with TAE showed that DEB-TACE resulted in better local response, fewer recurrences, and a longer time to progression than TAE.[80] However, a meta-analysis comparing TAE to conventional-TACE (c-TACE) showed no significant difference in OS.[81] Thus, TAE is a promising option compared to conservative treatment and, as it is devoid of systemic toxicity (using no chemotherapeutic agent), it can be used more confidently in patients with borderline liver function.

TACE

This technique helps to cut blood supply to the neoplastic cells via embolization and chemotherapeutic drugs. Currently, it is the standard of treatment for intermediate (BCLC stage B) HCC. The most commonly used chemotherapy agent in TACE is doxorubicin.[82] A RCT showed a 2-year survival rate of 63% in patients with advanced HCC who received TACE compared to 27% survival among the conservative management group.[83] The c-TACE technique had a limitation of systemic toxicity. Therefore, the use of DEBs, which are non-absorbable embolic microspheres charged with cytotoxic agents, was introduced. Burrel *et al*.[84] reported a median survival of 48.6 months with the use of DEB-TACE. Currently, there is no clear evidence on the superiority of DEB-TACE over c-TACE. Lammer *et al*.[85] performed a RCT comparing the two therapies and reported that the DEB group had higher rates of complete response, objective response, and disease control compared with the c-TACE group (27% vs. 22%, 52% vs. 44%, and 63% vs. 52%, respectively). However, superiority was not established *(p*=0.11). Irrespective, DEB use was associated with improved tolerability, with a significant reduction in serious liver toxicity *(p*<0.001) and a significantly lower rate of doxorubicin-related side effects (*p*=0.0001).[85]

TARE

In this technique, the microspheres contain a radioactive element, yttrium-90 (Y-90), which undergoes beta decay and generates free radicles. This hinders the cell's repair mechanisms, leading to cell death.[79] This technique is particularly helpful in patients with portal vein thrombosis (PVT), who experience reduced embolic effect with other techniques. Following performance of a clinical trial using TARE, Salem *et al*.[86] reported OS of 17.2 months amongst Child-Pugh A cirrhotic patients with PVT, decreasing to 5.6 months among Child-Pugh B cirrhotic with PVT. In another study, regression of PVT was reported with the use of Y-90.[87] TARE has also shown to result in better quality of life scores compared to TACE.[88] However, when compared to sorafenib, trials have shown no difference in OS with TARE.[89,90] Nevertheless, as it does not have systemic effects like sorafenib, it is an attractive option in selected patients.

Ablation

Amongst the ablation techniques for HCC, RFA and microwave ablation (MWA) are the most commonly used. They are considered as valuable option in very early-stage disease (i.e. BCLC 0).[91] One study found that the 5-year survival rate in patients who had RFA pre-transplant was approximately 70%.[92] RFA is valuable in targeting smaller lesions but is prone to the heat-sink effect. Therefore, MWA can be used alternatively, as it targets multiple tumor sites with higher energy. Shibata *et al*.[93] reported equivalent therapeutic effects and complication rates for RFA and MWA. Similarly, a meta-analysis by Tan *et al*.[94] showed no significant difference between MWA and RFA regarding complete ablation, local recurrence, DFS, OS, and major complications. Thus, these ablation techniques can be used interchangeably based on center-specific experience, but there remains a need for more prospective studies. In conclusion, although data are scarce, patient survival (79% vs. 75%, *p*=0.03) and graft survival (76% vs. 71%, *p*=0.03) at 3 years post-LT indicates more benefit for HCC patients receiving ablative therapy vs. those not receiving locoregional treatment.[95]

Stereotactic body radiotherapy (SBRT)

This technique delivers high-dose radiation in small fractions and with great precision. The Asia-Pacific Primary Liver Cancer Expert meeting (referred to as APPLE), an association of liver cancer experts in the Asia-Pacific region, has recommended application of SBRT for early-stage or small-sized HCC.[96] Prospective data are limited, but studies have demonstrated 3-year OS up to 70% and 5-year OS up to 64% for tumors <5 cm.[97,98] Recently, a phase 2 multicenter trial found 3-year local control rate of 95%, progression-free survival of 36% and OS of 76%.[99] Furthermore, evaluation of gastroduodenal toxicity by esophagogastroduodenoscopy was performed before and 2 months after SBRT, and showed no significant difference.[99] Thus, this is considered a safe option. Sapisochin *et al*.[92] compared SBRT, TACE and RFA as a bridge to LT and reported no significant difference in dropout rate, OS from listing, or LT in any of the groups. Therefore, it is another option for patients with borderline liver function. However, more RTCs are needed to compare SBRT with other treatment modalities for HCC.

Combination therapy

Treating HCC can be challenging with monotherapy, and therefore the concept of combination therapy was introduced to increase OS. Although improved time to progression has been shown in studies combining systemic (sorafenib) with LRT (TACE), results on OS are contradictory.[100,101] Combination of LRTs, for example TACE and SBRT, have resulted in reduction in local recurrence and improved OS.[102] However, when TACE-RFA dual therapy was used, the response to TACE-RFA appeared to be similar to that of RFA but better than that of TACE monotherapy.[103] Similarly, combination therapy of PD-L1 inhibitor and a monoclonal antibody have shown longer OS.[44,47] Furthermore, there are ongoing trials involving combination of immunotherapy and tyrosine kinase inhibitors.[46,47] Thus, once we have more data, we will be more confident with the optimal treatment combinations for HCC.

LDLT

Currently, there is a growing demand for LT in HCC patients. In the USA, over 18,000 people await transplantation annually and only approximately 5,000 organs are available.[104] This has led to the suggestion of LDLT to meet the growing demand and reduce waitlist time. A meta-analysis carried out by Liang *et al*.[105] showed comparable results in terms of patient survival (5 years, OR: 0.64, 95% CI: 0.33–1.24), recurrence (5 years, OR: 1.21, 95% CI: 0.44–3.32), and recurrence-free survival rates (5 years, OR: 1.11, 95% CI:

0.70–1.77)) in patients undergoing LDLT vs. DDLT for HCC. In comparison, another meta-analyses comparing LDLT vs. DDLT showed overall hazard ratios for DFS as 1.59 (95% CI: 1.02–2.49, p=0.041) and the OS as 0.97 (95% CI: 0.73–1.27, p=0.81).[106] While this may suggest a worse DFS after LDLT, there may be a selection bias with limited assessment of tumor biology from the shorter waiting period of LDLT.

Likewise, a recent meta-analysis including 39 studies with 38,563 patients showed LDLT to be comparable in requirement for red blood cell transfusion, perioperative mortality, length of hospital stays, re-transplantation rate, HCV recurrence rate, and HCC recurrence rate with DDLT. Cold ischemia time was shorter, and duration of recipient operation was longer in LDLT. The postoperative intra-abdominal bleeding rate was lower in LDLT recipients (OR: 0.64, 95% CI: 0.46–0.88, p=0.006), but this did not decrease the perioperative mortality. LDLT was associated with significantly higher biliary (OR: 2.23, 95% CI: 1.59–3.13, p<0.00001) and vascular (OR: 2.00, 95% CI: 1.31–3.07, p=0.001) complication rates and better OS (1 year: OR: 1.32, 95% CI: 1.01–1.72, p=0.04; 3 years: OR: 1.39, 95% CI: 1.14–1.69, p=0.0010; and 5 years: OR: 1.33, 95% CI: 1.04–1.70, p=0.02).[107] Subsequent studies, including the Adult-to-Adult Living Donor Liver Transplantation Cohort Study (known as the A2ALL), did not find a significant difference in the 5-year post-transplant survival between LDLT and DDLT.[108] Therefore, with the current evidence, it is clear the survival of patients with HCC undergoing LDLT is not significantly impacted.

Eligibility criteria for LDLT currently used in the Johns Hopkins LT program

- Patients with HCC diagnosed by imaging according to the MC and biological MELD of ≤25. Bridging therapy may or may not be required.
- Patients beyond the MC, who have undergone downstaging should have MELD of ≤25, with no extrahepatic disease or vascular invasion, AFP of ≤500 or have well-differentiated lesion on biopsy. Bridging therapy may or may not be required.

Recurrence after transplant

Despite the strict criteria used for LT, tumor recurrence is expected in 15–20% of HCC patients who have undergone LT, with 75% of the recurrence occurring during the first 2 years after the LT.[109] A systemic review consisting of 61 studies showed recurrence rate of 16% at median time of 13 months post-transplant.[110] Early recurrence is thought to originate from micrometastasis. Also, patients beyond the MC prior to LT have higher rates of tumor recurrence. There is also a discrepancy between radiology and pathology results. A recent case series showed that approximately one-third of patients were within MC on explant pathology when they were all within MC according to imaging findings.[111] Other factors such as vascular invasion, degree of tumor differentiation, tumor stage and AFP levels also play an important role in recurrence. The OS after HCC recurrence is approximately 1 year. Surgical resection of localized HCC recurrence and systemic treatments for controlling extrahepatic spread of HCC recurrence have been shown to be associated with the higher survival rates.[110] Despite the advances in systemic treatments with immunotherapy, immunotherapy is not recommended in the post-transplant setting, due to graft failure and high mortality.[112] Recently, some serum markers such as AFP, neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio have been proposed in addition to morphological criteria to predict recurrence.[113] Furthermore, the Risk Estimation of Tumor Recurrence After Transplant (also known as the RETREAT) score, consisting of AFP levels, microvascular invasion and number/diameter of viable tumor, has been introduced.[114] However, data are limited and better biomarkers for prediction of HCC recurrence after LT are needed. Furthermore, the role of immunosuppressive therapy post-LT cannot be underestimated; although, calcineurin inhibitors (CNIs) are considered the main agents for use. These agents are used in combination with mammalian target of rapamycin inhibitors (commonly referred to as mTORi), such as sirolimus and everolimus, which represents an alternative immunosuppressive regimen. Unfortunately, a phase 1 RTC where everolimus was used in combination with sorafenib did not show improvement in OS.[115] This trial did not proceed to phase II, as they participants were unable to reach an antiproliferative dose of everolimus due to cirrhosis. Another phase II multicenter trial showed that everolimus resulted in severe adverse events without any added benefit of progression-free survival.[116] Its counterpart, sirolimus, has been associated with increased mortality rates.[117] A metanalysis comprising 42 studies showed that patients on everolimus had significantly lower recurrence rates of HCC, compared with those on sirolimus or CNIs (4.1% vs. 10.5% vs. 13.8%, respectively, p<0.05).[118] However, these results are biased, as everolimus-treated recipients had shorter follow-up period (13 vs. 30 vs. 43.2 months) and more frequently had been transplanted for HCC within MC (84% vs. 60.5% vs. 74%, respectively, p<0.05).[118] Nevertheless, studies have shown that everolimus used in combination with CNIs post-LT allows for decreased doses of CNIs and improvement in kidney function.[119,120] However, in light of the current limited evidence, everolimus is not used routinely as part of a treatment protocol and its use is center-specific.

Post-transplant Surveillance

Follow-up of transplant recipients is essential, as to ensure their health and identify potential complications. Per the SRTR report published in 2019, graft failure occurred in 6.6% of DDLT recipients at 6 months and 8.9% at 1 year for transplants performed in 2018. In addition, within 1 year, 12.3% of liver transplant recipients in 2017–2018 experienced at least one episode of acute rejection and 1% of adult liver recipients developed post-transplant lymphoproliferative disorder over 5 years.[76] Thus, timely follow-up is mandatory. Considering the poor outcome associated with HCC recurrence after LT, strict HCC surveillance after LT is recommended. Unfortunately, there is no standardized protocol worldwide regarding the type and frequency of post-LT cross-sectional imaging in surveillance of HCC LT recipients. At our center, postoperative HCC surveillance usually consists of contrasted cross-sectional imaging with CT or MRI with AFP measurement every 3 months for the first year and every 6 months for the second and third years.[111]

Conclusions

LT for HCC has evolved over the years. With the introduction of several expanded criteria beyond MC, the introduction of bridging therapies (such as TACE and RFA), and the approval of newer systemic therapies, it is evident that there will be more LT recipients in the future. It is promising to see ongoing trials and the continuous evolution of protocols. Prospective studies are needed to guide the development of a pre-LT criteria that can ensure low HCC recurrence risk and not be overly stringent, clarify the role of LDLT and de-

termine the optimal bridging therapies to LT.

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Conflict of interest

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Author contributions

Study concept and design (HM, AT, AG, RK), acquisition of data (HM, AT, AG, SYL), drafting of the manuscript (HM, AT, PST, MG, SAA, SYL), and critical revision of the manuscript for important intellectual content (AG, MG, SAA, PST, RK, AKK, CS).

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