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Review Article

Hepatocellular Carcinoma and the Role of Liver Transplantation: An Update and Review

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Abstract

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related death worldwide. Multiple treatment modalities are available for the management of HCC, depending on its stage as determined by the Barcelona Clinic Liver Cancer staging system. Because liver transplantation (LT) theoretically removes the cancer and replaces the organ at risk for future malignancy, LT is often considered the most definitive and one of the most efficacious treatment options for HCC. Nevertheless, the success and efficacy of liver transplantation depend on various tumor characteristics. As a result, multiple criteria have been developed to assess the appropriateness of a case of HCC for LT, with the pioneering Milan Criteria established in 1996. Over the past 20 to 30 years, these criteria have been critically evaluated, expanded, and often liberalized to make LT for patients with HCC a more universally applicable option. Furthermore, the development of other treatment modalities has enabled downstaging and bridging strategies for HCC prior to LT. In this narrative and comprehensive review, we provided an update on recent trends in the epidemiology of HCC, selection criteria for LT, implementation of LT across different regions, treatment modalities available as bridges, downstaging strategies, alternatives to LT, and, finally, post-LT surveillance.

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Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, representing 85 to 95% of all cases.[1] It contributes significantly to the global disease and mortality burden. In fact, primary liver cancer is the fourth leading cause of cancer-related death worldwide, and in 2018, there were 841,080 new cases of liver cancer. Given the existing high incidence of HCC and the projected rise in cases in the coming years, the role of liver transplantation (LT) becomes an important topic of discussion.

Though more nuanced in practice, the definitive management of HCC is LT. However, it is not universally performed due to strict eligibility criteria that preclude some patients from undergoing transplantation, as well as the limited availability of donor organs.[2] Nevertheless, LT is particularly advantageous for patients with HCC, as it not only serves as a curative treatment for HCC but also eliminates the cirrhotic liver, which contributes to the patient's risk of HCC recurrence. Since the pathway to LT for patients with HCC is nuanced, other treatment modalities are implemented as alternatives to LT, as bridges to LT, or as mechanisms to downstage the disease before LT.[3]

In this review, we will discuss recent developments in HCC, including trends in epidemiology, surveillance and staging, and, most importantly, the available treatment modalities for this disease. Specifically, we will focus on various treatment options in comparison to or as a bridge to liver transplant.

Epidemiology

The most significant risk factors for HCC are underlying cirrhosis or chronic liver disease of any etiology. However, chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) are the predominant risk factors worldwide.[4] Recent estimates attribute 21% to 55% of global HCC cases to HBV and HCV.[5] Fortunately, these infectious diseases have decreased in both incidence due to vaccination efforts and in their propensity to cause chronic liver disease due to more targeted and effective antiviral therapies.

In contrast, alcohol-related liver disease and metabolic-associated steatohepatitis (MASH), also known as metabolic-dysfunction associated steatotic liver disease (MASLD), are both rising in incidence and in their contribution to HCC.

Table 1. Barcelona clinic liver cancer stages of HCC[14]

BCLC stage	Definition
Very early stage (Stage 0)	Single HCC ≤ 2 cm Preserved liver function PS* 0
Early stage (Stage A)	Single, or ≤3 nodules each ≤ 3 cm Preserved liver function PS 0
Intermediate stage (Stage B)	Multinodular Preserved liver function PS 0
Advanced stage (Stage C)	Vascular invasion and/or extrahepatic spread Preserved liver function PS 1-2
Terminal stage (Stage D)	Any tumor burden End-stage liver function PS 3-4

*Performance status indicates cancer-related symptoms: PS 0, absence of cancer-related symptoms, fully active and able to perform normal daily activities; PS 1, able to do most activities but unable to do heavy work; PS2, up and about most of the day, able to self-care, but unable to work; PS 3, requires significant rest, needs help with self-care; PS 4, bedridden, requires complete care; HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer classification.

MASH/MASLD is the fastest-growing etiology of HCC, with projected increases in HCC incidence of 47% in Japan, 82% in China, 88% in the United Kingdom, 117% in France, and a notable 130% in the United States.[6–8]

HCC disproportionately affects males, who have a substantially higher incidence and mortality burden from HCC compared to females.[9] Geographically, HCC has a higher incidence in Eastern Asia, though its incidence has stabilized or decreased in this region due to improved vaccination efforts.[5] On the other hand, HCC rates have stabilized or increased in areas historically considered lower risk, including Europe, North America, Australia/New Zealand, and South America. This is attributed to the increasing prevalence of metabolic risk factors, obesity, and alcohol consumption.

Surveillance

HCC is a high-morbidity disease, in part due to its frequent discovery in later stages, leading to worse prognosis. Early-stage HCC, which is typically asymptomatic and often undetected without dedicated screening programs, has a five-year survival rate exceeding 70%. In contrast, the median survival for symptomatic, advanced-stage HCC is much poorer, at only approximately 1–1.5 years. Given the characteristically asymptomatic nature of HCC until late in the disease course, it is important to screen high-risk individuals who may not yet exhibit overt symptoms or indicators of HCC. High-risk individuals typically include those with cirrhosis, certain individuals with hepatitis B, and other cases on a case-by-case basis where the patient may be at elevated risk for developing HCC.[10]

High-risk individuals are recommended to undergo screening ultrasonography every six months. A notable limitation of abdominal ultrasonography is its operator dependence and its reduced sensitivity in patients with obesity or MAFLD/MASH.[11] Previous research has suggested that the sensitivity of abdominal ultrasonography can be improved with concomitant alpha-fetoprotein (AFP) testing, although AFP is less specific and may lead to more false positive results.[12] Nevertheless, if either of these diagnostic parameters raises suspicion for HCC, further evaluation with magnetic resonance imaging (MRI) or triple-phase computed tomography (CT) scans can provide a more definitive answer regarding the presence or absence of HCC.

Staging HCC

HCC staging helps determine the most appropriate first-line treatment. As recommended by the American Association for the Study of Liver Disease (AASLD), all patients with HCC should first undergo a high-quality multiphase CT or contrast-enhanced MRI scan to assess tumor extent, as well as a non-contrast CT of the chest to evaluate for pulmonary metastases.[13] Although many staging systems for HCC exist, the most commonly used and recommended by the AASLD is the Barcelona Clinic Liver Cancer (BCLC) staging system.[14] The BCLC staging system utilizes factors such as the number of nodules, size of nodules, liver function, portal invasion, and extrahepatic spread to determine the stage of a patient's HCC. The stages range from stage 0 (very early stage), followed by stage A-D, with later letters corresponding to more severe disease. This system also links disease stages to the most appropriate treatment regimens. The most recent BCLC update was in 2022, and its staging system is summarized in Table 1.[14] The BCLC staging system is widely accepted as it integrates tumor stage, liver function, and performance status for a patient-centered approach in prognostication. However, as will be discussed throughout this review, it provides limited flexibility, particularly for those with intermediate or advanced-stage HCC.[15] This staging system may need to be reconsidered in the future, as rapidly advancing HCC therapies may make patients with higher-stage disease increasingly eligible for definitive treatments.

When LT is considered the most appropriate treatment, the Model for End-Stage Liver Disease (MELD) score is used to prioritize patients with more severe liver disease for transplant. The MELD score incorporates patients' serum bilirubin, creatinine, international normalized ratio, albumin, and biological sex to predict their three-month survival, with a higher score indicating worse predicted survival.[16] Since MELD scoring does not take HCC into account, and HCC worsens mortality, patients with HCC may be eligible for a "MELD exception".[17] HCC lesions eligible for MELD exception points include: (1) UNOS T2 HCC, which can be a single lesion up to 5 cm or up to three synchronous lesions, each individually

up to 3 cm in size; and (2) patients whose AFP levels are less than 1,000 ng/mL.[18,19] These lesions require patients to have a transplant list waiting time of at least six months to be eligible for exception points.

Surgical resection for HCC

Surgical resection is generally recommended for patients with a solitary HCC and preserved hepatic function (i.e., without cirrhosis). It can also be considered for patients with localized HCC and cirrhosis, provided they meet various criteria for preserved liver function and tumor characteristics that favor good outcomes post-surgery (e.g., fewer nodules, appropriate anatomic location, absence of vascular invasion, etc.).[4] Unfortunately, surgical resection tends to have worse survival outcomes than liver transplant, despite the lower risk in these patients. This may be related to the retention of the diseased liver, which remains at risk for HCC recurrence. An exception to this poorer survival post-resection versus liver transplant occurs when patients undergo enhanced surveillance after surgery, which requires patient motivation and resources for appropriate adherence.[20]

Selection criteria for liver transplant

The information presented thus far may suggest that liver transplant is an ideal treatment modality for HCC and raise the question of why it is not universally implemented for both low- and high-grade disease. Unfortunately, the limited availability of donor organs makes it necessary to establish criteria to appropriately and equitably allocate these organs. Additionally, it has been established that the five-year survival rate after LT for HCC progressively declines with increasing nodule size and number.[21] Therefore, numerous criteria have been set to determine patient eligibility for LT when HCC is present.

Milan criteria

Mazzaferro *et al*. developed the Milan Criteria in 1996: (1) for patients with a single HCC, the tumor should not exceed 5 cm in diameter; (2) for patients with multiple tumors, there should be no more than three tumors, and none should exceed 3 cm in diameter; and (3) patients' tumors should not invade blood vessels or lymph nodes.

These landmark "Milan Criteria" have historically been used to guide HCC patients' eligibility for LT and are associated with a four-year survival rate of 75%.[21,22] This survival rate is particularly notable as it is similar to that of patients undergoing LT in the absence of HCC.[22] Furthermore, the post-transplant recurrence rate for HCC is modest, at only 8%.[21,23]

Since the development of the Milan Criteria, several other criteria have been introduced and are discussed below. The Milan Criteria are often considered the most restrictive of these criteria. While its restrictive nature is likely a key factor in its excellent survival rate and low recurrence rate, subsequent studies on more liberal criteria have shown similar survival and recurrence rates following LT.

Other criteria

In 2001, the University of California, San Francisco (hereinafter referred to as UCSF) proposed new extended criteria for HCC, which included: (1) a solitary tumor less than or equal to 6.5 cm, OR (2) less than or equal to three nodules with the largest lesion at or below 4.5 cm, AND (3) a total tumor diameter less than or equal to 8 cm, making patients eligible for LT. These criteria were associated with an impressive survival of 90% at one and 75.2% at five years, similar to the survival noted with the more stringent Milan Criteria.[24] The two-year recurrence rate in the original study setting forth the UCSF Criteria was 11.4%.

Following this, Mazzaferro *et al*. proposed the "up-to-seven" criteria[25] in 2009. This allowed for LT eligibility if the sum of the number of nodules and the tumor diameters (in centimeters) did not exceed seven. The five-year overall survival and HCC recurrence rates were similar to previously studied criteria, at 71.2% and 9.1%, respectively. The Toronto Criteria proposed no upper limit on the size or number of lesions but did implement the following: (1) patients must have no extrahepatic metastases or evidence of venous or biliary tumor thrombus.[26] The five-year survival for patients using the Toronto Criteria was 69% for those whose tumors exceeded the Milan Criteria and 78% for those whose tumors met the Milan Criteria. The recurrence rate was notably higher than the other criteria, at 21.1% at two years.

The Kyoto Criteria served as one of the pioneers in including serum biomarkers within HCC scoring criteria for LT. The Kyoto Criteria stipulate that patients' HCC must involve no more than 10 nodules, each less than or equal to 5 cm, and that serum des-gamma-carboxy prothrombin levels must be less than 400 mAu/mL.[26–28] The five-year overall survival for patients within the Kyoto Criteria was 82%, with a recurrence rate of 4.4%. Subsequent scoring systems have more frequently included serum biomarkers in their models to guide patient eligibility for LT. For example, the Metroticket 2.0 model uses serum AFP levels, tumor size, and tumor number to predict death from HCC-related factors post-LT. Finally, Toso *et al*. proposed criteria that accounted for total tumor volume and serum AFP. For patients who met the criteria of a total tumor volume ≤ 115 cm AND serum AFP ≤ 400 ng/mL, the overall survival rate was 65% at five years, with a recurrence rate of 5.4% at 2.5 years.

The Malatya Criteria, developed in Turkey, require that a patient's HCC meet the Milan Criteria, or for HCC beyond the Milan Criteria, it must meet the following: AFP ≤ 200 ng/mL, gamma-glutamyl transferase ≤ 104 IU/L, differentiation grade well/moderate, and maximum tumor diameter ≤ 6 cm. This criteria was associated with an estimated five-year post-transplant survival rate of 79.7% and a recurrence rate of 5.4% at 2.5 years.[29]

In China, where HCC is highly prevalent, there are three predominant criteria: the Hangzhou, Chengdu, and Shanghai Criteria. However, the Hangzhou Criteria are the most widely accepted.[30] The Hangzhou Criteria require that the total tumor diameter be ≤8 cm, or that it exceed 8 cm but with an AFP level ≤ 400 ng/mL and a well-differentiated tumor histology.[31]

A comparison of the selection criteria

While the Milan Criteria are often lauded for their excellent outcomes, they have recently been criticized for being overly restrictive. With the advent of new treatment modalities and increased comfort with both LT and surgical resection, transplanting patients with higher-stage HCC should be actively considered. For example, the extended Toronto Criteria allowed for transplantation of patients with higher-stage HCC.[26] This yielded a predictably higher HCC recurrence rate but relatively similar mortality, as the patients who experienced recurrence generally had lower-stage recurrent disease that was amenable to aggressive surgical management.[32] The study that proposed the Kyoto Criteria had similar findings. Although patients who exceeded the Milan Criteria but met the Kyoto Criteria had higher rates of HCC

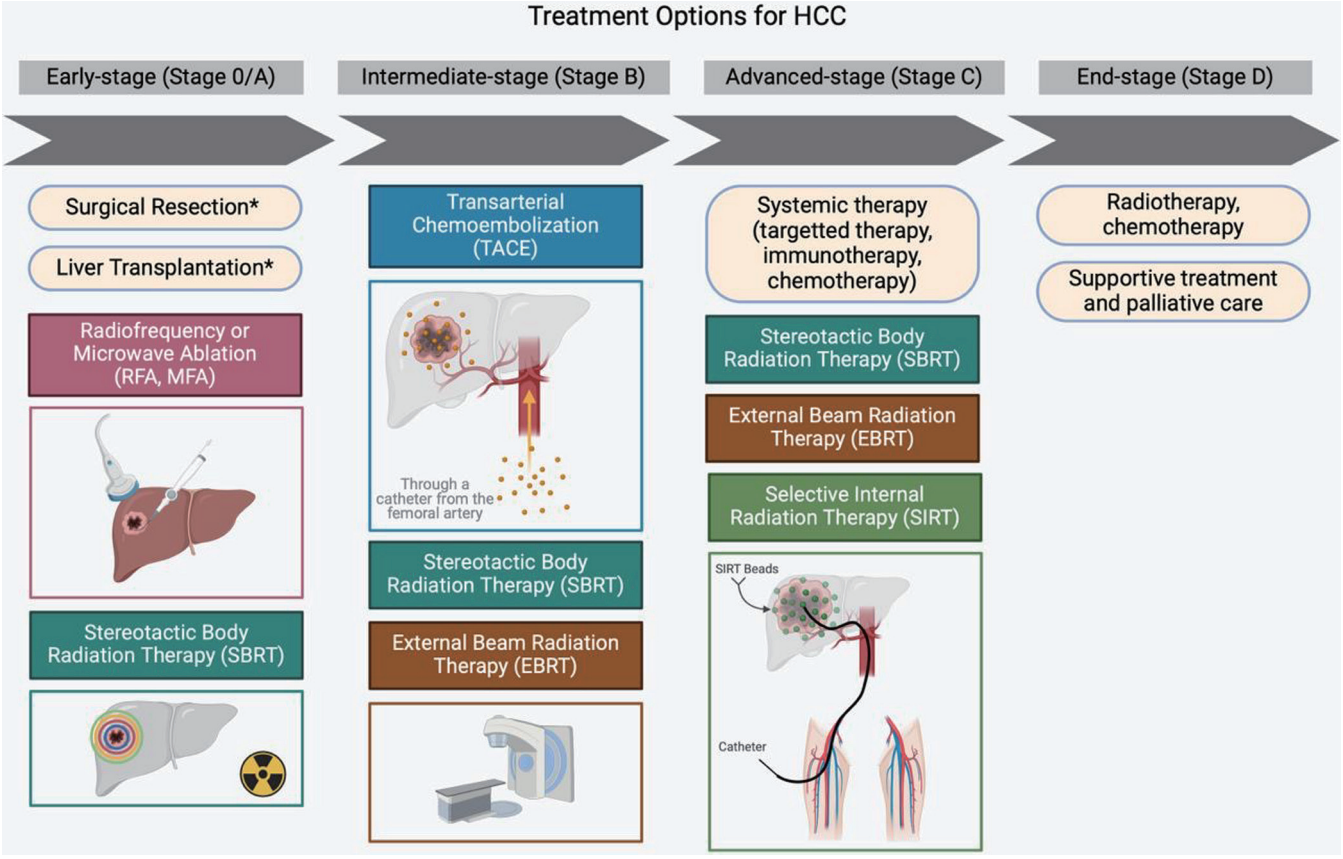

Fig. 1. Representation of treatment options for HCC. *If eligible for surgical resection or liver transplantation according to the guidelines. HCC, Hepatocellular carcinoma.

recurrence compared to individuals who met both criteria, the overall mortality was similar between the two groups.[28] This is likely due to lower-stage recurrent disease that may be increasingly amenable to surgical resection and medical management, the latter of which is a rapidly developing field.

The rising relevance of biomarkers

Another extremely important consideration is the inclusion of serum biomarkers in determining patient eligibility for LT, which we propose should be more frequently considered. Multiple prior studies have stratified patient survival by their pre-LT serum AFP levels; generally, increased pre-LT AFP is associated with worsened mortality.[33] Furthermore, the inclusion of biomarkers may reduce the inaccuracies incurred by solely utilizing radiographic evidence of HCC, which is operator-dependent and can be influenced by patient factors (such as the presence of ascites, patient movement, etc.).[34,35] A downside to the inclusion of serum biomarkers in selection criteria is that these biomarkers, particularly AFP, are notoriously influenced by factors unrelated to the severity of a patient's liver disease.[36,37]

While the absolute value of biomarkers has already been implemented in multiple risk-stratifying scores, more recent research has explored the utility of biomarker trends and dynamics in post-LT outcomes. Specifically, a 2018 study of 366 patients with multiple available pre-LT AFP levels plotted patients' pre-LT AFP levels over time. This analysis revealed that an AFP slope increasing greater than 7.5 ng/mL per month, despite locoregional therapy, was associated with worse overall survival (OS) and disease-free survival (DFS) and could even potentially serve as a predictor for microvascular invasion.[38] Another study similarly found that the rate of AFP increase pre-LT—specifically noting an AFP increase greater than 15 μg/L per month pre-LT—was one of the most relevant preoperative prognostic factors for low OS and DFS post-LT.[39]

The notion that a patient's absolute pre-LT serum AFP value is predictive of post-LT outcomes, including OS, DFS, and microvascular invasion, is certainly not a new one.[40,41] Nevertheless, the aforementioned studies regarding AFP dynamics—being even more useful than its absolute value at a single point in time—may support the monitoring of serum AFP levels on a more frequent basis for LT waiting list patients.

Bridging and downstaging therapies for HCC to LT

Patients who are not eligible for surgical resection may or may not be eligible for liver transplant, depending on the extent of their disease, as outlined by the Milan and other criteria above. Some patients who are eligible for liver transplant may experience long wait times, necessitating bridging therapies to prevent disease progression while awaiting LT.[2] Guidelines support the use of bridging therapy for UNOS Stage T2 lesions if the wait time is expected to be six months or longer.[42] Figure 1 summarizes the main treatment strategies for HCC.

For patients with HCC that is too advanced for LT, they

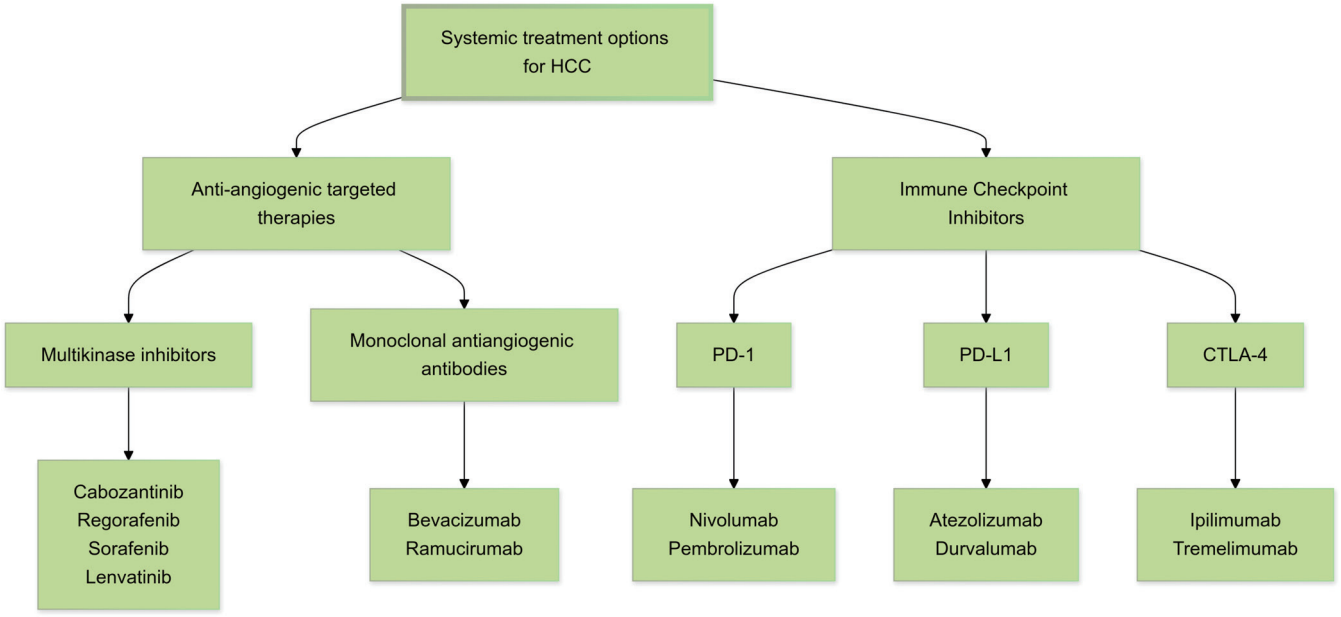

Fig. 2. Systemic treatment options for HCC. HCC, hepatocellular carcinoma; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T-lymphocyte associated protein 4.

may be eligible for downstaging treatment to achieve LT eligibility. UNOS has developed downstaging criteria (UNOS-DS criteria) that guide which patients are eligible for downstaging (single lesion ≤ 8 cm, or two to three lesions < 5cm with total tumor diameter < 8 cm, or four to five nodules all < 8 cm).[18,43,44] These criteria also require that patients be monitored for disease stability for six months after successful downstaging and prior to LT. The UNOS-DS guidelines have yielded excellent post-LT survival outcomes; conversely, much worse outcomes have been demonstrated when they are not followed.[45,46]

Bridging and downstaging therapies are nonsurgical techniques that include locoregional therapy and systemic therapies. We will focus on their utility prior to liver transplant and discuss their outcomes both as bridging and downstaging techniques.

Locoregional treatment

The most commonly implemented types of locoregional treatment (LRT) include radiofrequency ablation (RFA) and microwave ablation, transarterial chemoembolization (TACE), and transarterial radioembolization (TARE).

Radiofrequency and microwave ablation

RFA and MWA are two of the most common types of thermal ablation, generally used in low-stage HCC with no worse than Child-Pugh class A cirrhosis (low-severity liver disease as per the Child-Pugh score, which grades liver disease severity based on bilirubin, prothrombin time, albumin, and the presence of ascites and encephalopathy).[13] RFA is utilized when tumors are solitary and less than 2 cm, and it can be used as an alternative to surgical resection for single tumors 3–4 cm in size and —two to three tumors less than 3 cm.

Previous research has supported RFA as a monotherapy for bridging small HCC lesions, as well as an adjunct in combination therapy for larger HCC lesions.[47–51] MWA has also been studied in both bridging and downstaging contexts, but usually in conjunction with other LRT, primarily TACE.[50]

TACE

TACE is the standard of care for patients with intermediate-stage HCC that does not meet the Milan Criteria.[52] It involves delivering chemotherapy directly to the affected lobe of the liver, as well as embolizing the blood supply to that area. It is often employed with or without concomitant radiation therapy or chemotherapy. As a bridging-to-LT strategy, TACE has been shown to be quite effective, with a five-year survival rate as high as 93%.[53]

Conversely, TACE has shown variable success rates in downstaging HCC to achieve LT eligibility. However, for patients successfully downstaged to the Milan Criteria with TACE, survival rates post-transplant are generally quite similar to those who met the criteria without downstaging TACE.[54]

TARE

TARE delivers microspheres containing the radioisotope yttrium-90 through the hepatic artery to a targeted tumor.[55] TACE is traditionally the preferred choice for downstaging and bridging HCC to LT and is recommended by the BCLC guidelines for patients with intermediate-stage disease. Nevertheless, when compared to TACE, some studies have shown that TARE has similar survival rates and may actually be better tolerated, associated with fewer hospitalizations and treatment sessions, despite more advanced disease in TARE recipients.[55–57] Furthermore, TARE has shown similar or even better outcomes in downstaging HCC to become amenable to LT compared to TACE.[45,58–60] Finally, TARE may be particularly useful for HCC with portal vein thrombosis, though evidence supporting this is not definitive.[55,61,62]

Systemic therapies

The different types of systemic therapies for HCC are summarized in Figure 2. These therapies can be broadly categorized into anti-angiogenic targeted therapies and immune checkpoint inhibitors. Within anti-angiogenic targeted therapies, there are multikinase inhibitors (cabozantinib, re-

Table 2. Outcomes of trials for systemic therapy

Study	Drug	Route of administration	Control	OS in months	HR (95% CI)
SHARP[67]	Sorafenib (TKI)	Oral	Placebo	10.7 vs. 7.9	0.69 (0.55–0.87)
Asia-Pacific[68]	Sorafinib (TKI)	Oral	Placebo	6.5 vs. 4.2	0.68 (0.5–0.93)
RESOURCE[69]	Regorafenib (TKI)	Oral	Placebo	10.6 vs.. 7.8	0.63 (0.50–0.79)
REFLECT[70]	Lenvatinib (TKI)	Oral	Sorafenib (TKI)	13.6 vs. 12.3	0.92 (0.79–1.06)
CELESTIAL[71]	Cabozantinib. (TKI)	Oral	Placebo	10.2 vs. 8.0	0.76 (0.63–0.92)
REACH–2[72]	Ramucirumab (VEGRF1)	Intravenous	Placebo	8.5 vs. 7.3	0.71 (0.53–0.95
IMBRAVE-150[64]	Atezolizumab (PD-L1), AND Bevacizumab (VEGF)	Intravenous (both)	Sorafenib	At 12 months, 67.2% vs. 54.6%	0.66 (0.52–0.85)
CHECKMATE 040[73]	Nivolumab (PD-1 inhibitor), AND Ipilimumab (CTLA4)	Intravenous (both)	N/A (Phase II trial)	22.8	N/A
HIMALAYA[66]	Durvalumab (PD-L1), AND Tremelimumab (CTLA4)	Intravenous (both)	Sorafenib (PD-L1)	16.4 vs. 13.7	0.78 (0.65–0.92)
KEYNOTE 394[74]	Pembrolizumab (PD-1 inhibitor)	Intravenous	Placebo	14.6 vs. 13.0	0.79 (0.63–0.99)

OS, overall survival; HR, hazard ratio; CI, confidence interval; TKI, tyrosine kinase inhibitors; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T-lymphocyte associated protein 4.

gorafenib, sorafenib, and lenvatinib) and monoclonal antiangiogenic antibodies (bevacizumab, ramucirumab). Within immune checkpoint inhibitors, there are programmed death 1 inhibitors (nivolumab, pembrolizumab), programmed death ligand 1 (PD-L1) inhibitors (atezolizumab, durvalumab), and cytotoxic T lymphocyte-associated protein 4 inhibitors (ipilimumab, tremelimumab).

TKIs have shown efficacy in bridging patients to LT, both with and without concomitant LRT.[63] ICIs have been evaluated in a growing field of research and have demonstrated overall efficacy in pre-transplant bridging and downstaging when utilized with an appropriate washout period prior to LT.[2]

Though the use of systemic therapies as a bridge-to-transplant strategy is an area of active research, generally, systemic therapies are employed when patients have a higher tumor burden in the intermediate stage of HCC (BCLC B, multinodular) or, more rarely, in advanced-stage HCC (BCLC C) (see Table 1). We will outline the general treatment approach for HCC presentations that are not amenable to transplant, as per the recommendations from the AASLD guidelines.[4] Currently, there are three first-line therapies, two of which involve immunotherapy and are commonly used as the initial regimen. Bevacizumab and atezolizumab were evaluated for their efficacy as a combined therapy in the IMbrave150 trial in 2020.[64] Bevacizumab (a monoclonal antibody targeting vascular endothelial growth factor, or) plus atezolizumab (an immunotherapy targeting PD-L1) is often preferred for patients with advanced HCC. The OS was 19.2 months, compared to 13.4 months for patients treated with sorafenib. The hazard ratio, using sorafenib as the comparator, was 0.66 (95% confidence interval: 0.52–0.85). Patients in the bevacizumab plus atezolizumab group did have a higher risk of gastrointestinal bleeding compared to the control group, likely due to bevacizumab. Hence, patients are recommended to undergo screening EGD and address any stigmata of high risk for bleeding prior to initiation.

Another first-line therapy includes tremelimumab (a cytotoxic T lymphocyte-associated protein 4 inhibitor) and durvalumab (a PD-L1 inhibitor),[65] which was established in the HIMALAYA trial. The OS for this regimen was 16.4 months, compared to 13.8 months with sorafenib.[66] Again, using sorafenib as the comparator, the hazard ratio for tremelimumab plus durvalumab was 0.78 (95% confidence interval: 0.65–1.02). Alternatives to this regimen include sorafenib alone or lenvatinib alone as options for first-line therapy, especially for patients who have contraindications to immunotherapy.

After first-line therapies, other options include regorafenib, cabozantinib, and ramucirumab (for patients with AFP ≥ 400 ng/mL). Some research suggests that ipilimumab plus nivolumab may also be used.

Table 2 summarizes the cornerstone trials that evaluated the efficacy of various systemic treatments for HCC, and Figure 3 summarizes the recommended treatment approach for utilizing systemic therapies.[64,66,67–74]

Types of liver transplant

There are two main types of liver transplant: deceased donor liver transplant (DDLT) and living donor liver transplant (LDLT). DDLT involves waiting for a liver from a deceased donor, while LDLT involves a donor hepatectomy followed by transplantation into the recipient.

The Adult-to-Adult Donor Liver Transplant Cohort Study (A2ALL) is a cohort of patients who received either LDLT or DDLT and were followed longitudinally to compare outcomes between the different transplant procedures. Multiple analyses of these patients have been conducted over the years to compare LDLT and DDLT. LDLT has the notable advantage of a significantly shorter wait time from listing to transplant compared to DDLT, with one study reporting a wait time of 2.6 months for LDLT versus 7.9 months for DDLT).[30,31] Furthermore, when LDLT is compared to DDLT for any indication (including, but not limited to, HCC), some studies (even outside of the A2ALL cohort) suggest that LDLT actually offers improved survival, reduced hospital stays, and better immediate post-LT outcomes.[75] Unfortunately, some studies from the A2ALL cohort suggest that LDLT may not be as beneficial for transplant recipients with HCC due to higher rates of HCC recurrence post-LDLT (compared to DDLT), although overall

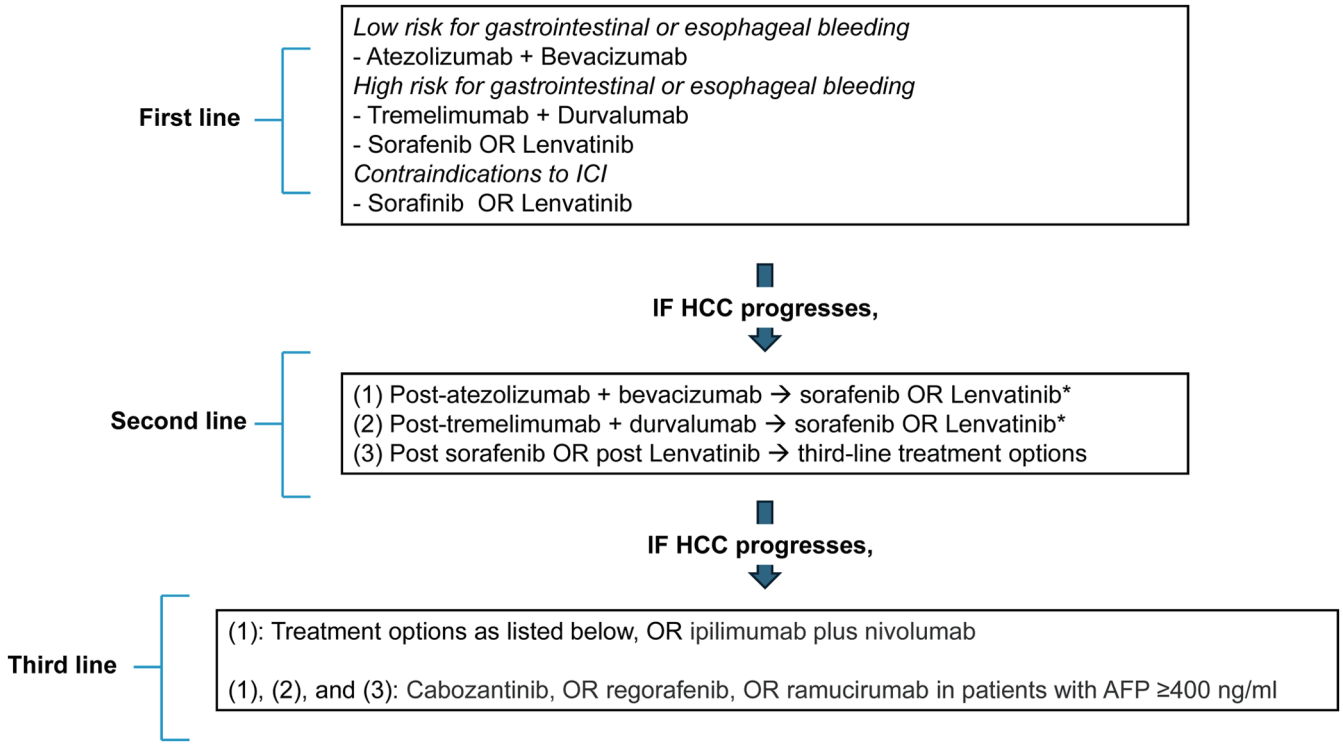

Fig. 3. Schematic of treatment recommendations for HCC not eligible for LT. *If patients not eligible for clinical trial. ICI, immunotherapy; AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; LT, liver transplant.

survival rates remain relatively similar. Specifically, in 2004, Fisher *et al*. found that HCC recurrence was significantly higher in LDLT recipients compared to DDLT recipients within three years of LT (HCC recurrence was 29% in LDLT recipients vs. 0% in DDLT recipients, $p = 0.002$).[76] Despite this higher recurrence rate, overall mortality and three-year recurrence-free survival rates were similar between DDLT and LDLT patients. In 2012, Kulik *et al*. found that unadjusted five-year HCC recurrence was significantly higher after LDLT compared to DDLT (38% for LDLT vs. 11% for DDLT, $p = 0.0004$), but noted that for patients transplanted after MELD prioritization, five-year post-transplant survival was not significantly different.[77] Of note, some have postulated that the higher HCC recurrence rates post-LDLT, compared to DDLT, could be due to longer wait times for DDLT. This results in patients with more significant disease losing their transplant eligibility, subsequently excluding patients with more severe disease from the DDLT outcome analysis.[78,79]

Two final challenges to the more widespread implementation of LDLT, especially given its obvious benefits of shorter wait times and greater availability, include ethical considerations and the proposed "learning curve" associated with its initial implementation. From an ethical perspective, the donor hepatectomy preceding the LDLT procedure is not without its risks.[75,80–82] From a hospital resource perspective, the A2ALL cohort noted significantly higher rates of mortality post-LDLT in the first few years after its implementation, suggesting a possible "learning curve" for physicians and surgeons adapting to this newer procedure.[83] It is possible that this learning curve would apply to its implementation at newer sites, potentially resulting in worsened outcomes for the first patients undergoing LDLT.

A final type of liver transplant is simultaneous liver-kidney transplantation (SLKT). Although there is data supporting the use of SLKT in patients with cirrhosis and end-stage renal disease, and some with chronic kidney disease, there is limited research supporting its use in patients whose indication for LT is in the setting of HCC. Singal *et al*. evaluated SLKT performed for various etiologies of liver disease (including HCC, primary biliary cirrhosis, primary sclerosing cholangitis, HCV, HBV, alcohol-related liver disease, cryptogenic cirrhosis, and MASH/MASLD). Among these etiologies, they found the three with the worst five-year outcomes were concomitant HCC, MASH/MASLD, and HCV.[84] Nevertheless, the liver graft, kidney graft, and patient survival rates five years after SLKT for HCC were reasonable at 72%, 71%, and 69%, respectively, for a sample size of 249 patients with HCC. Rich *et al*. followed up this investigation in 2017 with a retrospective analysis of the UNOS database of LT patients.[85] They found no significant difference in overall survival or in immediate post-transplant complications for patients undergoing SLKT for HCC compared to those undergoing SLKT for other etiologies.

Regional variation in transplant status

The United States

The United States has had the highest number of LTs in the past 20 years, with 223,571 candidates listed for LT between 1998 and 2019. Of these, 57.5% (128,664) received a transplant. Only 4.2% (5,399) underwent LDLTs, while the rest received DDLTs.[86] Among the DDLTs, 21% were due to HCC. For LDLT recipients, the proportion of HCC-related indications increased after 2006, reaching its highest point at 24% in 2016.

Notably, the etiology trends for HCC in the United States

have shifted in recent years, following the introduction of direct-acting antivirals. In 2013, HCV was the leading etiology for HCC, accounting for more than 60% of cases. By 2022, this proportion had decreased to around 27%.[86,87] Nonalcoholic steatohepatitis MASH/MASLD now leads among HCC etiologies, increasing from 10% to 31% over the past decade, followed by alcoholic liver disease, which rose from 9% to 24%.[87]

Eurotransplant

This translational mediator involves coordination between donor hospitals and transplant centers in eight countries: Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, the Netherlands, and Slovenia.[88] In Europe, two other associations also conduct liver transplants in the region: Scandiatransplant and the South Alliance for Transplantation.

From 2014 to 2023, a total of 16,933 liver transplants were performed in the Eurotransplant region.[88] Of these, 1,097 were living donor liver transplants, and 15,836 were deceased donor liver transplants.[88,89] This corresponds to around 1,600 liver transplants performed annually across 38 liver transplant centers in seven countries (Luxembourg refers its patients to Belgium or France).[88] Currently, the rate of transplantation for HCC is 21% of the total number of liver transplants.[88,90]

Turkey

A recent study analyzing data from 11 tertiary centers in Turkey from 2010 to 2020 showed that out of 5,080 liver transplant recipients, a significant majority (79.7%) underwent LDLT, while the remaining 20.3% received DDLT. The incidence of HCC-related liver transplants was 16.5% from 2010 to 2015 and increased significantly to 19.5% from 2015 to 2020.[91]

Japan

To date, data from the 69 largest liver transplant centers in Japan show that a total of 1,894 HCC-related liver transplants have been performed, 92.1% of which were LDLT. Among these, HCV was the leading cause, accounting for 1,007 cases, followed by HBV with 461 cases.[92] In contrast, there have been 147 DDLTs for HCC, with HCV accounting for 43 cases and HBV for 26 cases. In the 21st Nationwide Follow-Up Survey of Primary Liver Cancer in Japan, HCC was the most common diagnosis, affecting 91.4% of patients. The most frequent initial treatment was hepatic resection or liver transplantation, used in 38.8% of patients, followed by local ablation therapy (22.8%) and TACE.[92]

India

Among the centers, 17 out of 23 reported that HCC was present in 5–15% of LT recipients.[89] Regarding treatments, more than 90% of the centers considered the downstaging of HCC either as a bridge to transplantation or to meet the respective listing criteria for LDLT. TACE and TARE were the most commonly used treatment options.[93]

China

LT cases in China account for more than one-third of LT cases worldwide, with HCC being the main indication for LT. As of 2015, a total of 29,360 LT cases had been performed in China, with about 50% of these performed to treat HCC.[94]

Post-LT HCC monitoring and recurrence

Monitoring for HCC recurrence post-LT is generally performed with CT scans, MRI scans, and AFP monitoring. The National Comprehensive Cancer Network recommends screening with (1) AFP AND (2) a multiphasic, high-quality, cross-sectional CT OR MRI of the chest, abdomen, and pelvis, every three to six months for two years, and then every six months thereafter.[95] Unfortunately, post-LT HCC recurrence prognosis is generally poor, but aggressive management of recurrence can often improve outcomes.[21,23,96,97]

Despite the implementation of the aforementioned criteria for monitoring HCC recurrence post-LT, a non-negligible proportion of patients still experience recurrence after LT, as shown in Table 3.[21,25,26,28–30,98–100] Therapeutic strategies for HCC, other than LT, including surgical resection, LRT, and systemic therapies, have been increasingly studied in the post-LT recurrent HCC setting. In some cases, these strategies have been shown to improve outcomes.[96,101,102] Regarding systemic therapies, sorafenib has been most frequently evaluated and has been shown to improve outcomes in post-transplant HCC recurrence patients.[103] However, the use of immunotherapy post-transplant remains controversial due to the risk of transplant rejection.

Conclusions

In this review, we have discussed the global burden and epidemiology of HCC, the appropriate surveillance and staging methods for HCC, and how these relate to patients' eligibility for LT, as well as downstaging and bridging techniques prior to LT. We also covered different types of LT for HCC, the data supporting the use of LT for HCC, and post-LT care for patients with HCC.

Overall, LT remains a very powerful method for treating HCC. A key theme throughout this review is that while LT is efficacious for treating HCC, it must be employed in the correct settings. This "correct setting" was initially determined by criteria proposed as early as 1996. However, as available therapies for HCC bridging, downstaging, and post-LT recurrence continue to evolve and improve, it is essential that we critically re-evaluate these criteria to avoid unfairly excluding patients with more advanced disease who may be more appropriate for LT both now and in the future.

Nonetheless, for HCC to meet any criteria for LT, it is essential that it is discovered early enough in the disease course. This makes universally implemented screening programs critically important. This is an area we have identified as needing further research, given (1) concerns about the sensitivity of the widely implemented abdominal ultrasound for patients with significant abdominal adiposity and obesity, as abdominal ultrasonography is widely used as a screening tool in Western countries, where the rate of HCC from MASH/MASLD is projected to rise, and (2) the lack of nationwide implementation of screening in lower-resource countries.[4] For this reason, we propose that the more universal implementation of biomarkers, such as AFP, and possibly others like serum des-gamma-carboxy prothrombin, as shown to be useful with the Kyoto Criteria,[28] will be imperative in the coming years. Furthermore, we suggest considering more frequent biomarker monitoring for LT waiting list patients, as trends in biomarkers and their dynamics have shown greater utility than the absolute value of biomarkers at a single point in time.[38,39] The optimal frequency for measuring these biomarkers to predict post-LT outcomes warrants further investigation.

Another area of further research we have identified is in SLKT for HCC patients with concomitant renal dysfunction requiring transplant. Though preliminary analyses have confirmed the utility of SLKT, more research is needed to evalu-

Table 3. Different criteria for liver transplantation

Criteria	Detail	Survival rate	HCC recurrence rate
Milan Criteria[21]	(1) single nodule that should not exceed 5 cm in diameter, (2) if multiple nodules, should be no more than three tumors and none should exceed 3 cm in diameter, and (3) patients' tumors should not invade blood vessels or lymph nodes	75% at four years	8% at four years
UCSF[98]	(1) a solitary tumor less than or equal to 6.5 cm, or (2) less than or equal to three nodules with the largest lesion at or below 4.5 cm, and (3) a total tumor diameter less than or equal to 8 cm	81% five-year survival	11.4% at two years
Up-to-seven[25]	The sum of the number of nodules and the diameter (in centimeters) did not exceed seven	71.2% at five years	9.1% at five years
Extended Toronto[26]	No upper limit on the size and number of lesions, but no extrahepatic metastases, evidence of venous or biliary tumor thrombus cancer-related syndromes	69% at five years (for patients whose tumors exceeded Milan Criteria). 78% at five years (for patients whose tumors met Milan Criteria)	21.1% at two years
Kyoto[28]	HCC must be than or equal to 10 nodules, each less than or equal to 5 cm, and have a serum des-gamma-carboxy prothrombin level less than 400 mAu/mL	65% at five years	19% at five years
Total tumor volume < 115 cm[99]	Sum of volume for each tumor ≤ 115 cm^3 AND serum alpha-fetoprotein ≤ 400 ng/mL	75% at four years	5.4% at 2.5 years
Malatya[29]	HCC must meet the Milan Criteria OR patients beyond the Milan Criteria must meet the following criteria: AFP ≤ 200 ng/mL, gamma glutamyl transferase ≤ 104 IU/L, differentiation grade well/moderate, and maximum tumor diameter ≤ 6 cm	79.7% at five years	4.7% at five years
Hangzhou[30]	HCC must have a total tumor diameter of ≤8 cm, OR a total tumor diameter > 8 cm but with an AFP level of ≤400 ng/mL and a well-differentiated tumor histology	73.8% at five years	20% at five years[100]

AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma.

ate posttransplant outcomes and provide additional evidence to guide posttransplant care.

HCC treatment is a rapidly developing field, but LT is still regarded as the most definitive treatment for eligible patients. As we continue to learn more about HCC and its treatment modalities, the criteria for considering and downstaging HCC patients for LT should be critically reexamined to ensure that patients who could benefit from this potentially life-saving treatment are not excluded.

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Conflict of interest

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