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New horizons in liver transplantation for hepatocellular carcinoma

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Primary liver cancer was the third most common cause of death due to cancer worldwide in 2020. As the predominant type, hepatocellular carcinoma (HCC) represents the overwhelming majority of newly diagnosed primary liver tumours. Liver transplantation remains the treatment of choice for a cure in otherwise unresectable HCC. For nearly thirty years, the Milan and Barcelona Clinic Liver Cancer (BCLC) criteria have guided physicians' clinical decision-making for selection of liver transplant candidates in the treatment of HCC. More recently, studies have demonstrated survival benefit for patients transplanted beyond Milan criteria. This remains an area of active research and includes advancements in local-regional therapies and their role in downstaging tumours to within transplant criteria as a bridge to transplant. Other advancements on the horizon include the identification of tumour biomarkers that may lead to earlier diagnosis and more accurate prediction of prognosis and risk of recurrence, as well as new neoadjuvant therapies and post-transplant immunosuppression regimens that may allow for further expansion of transplant eligibility criteria. Additionally, several recent studies have investigated the potential survival benefit of combination therapy using local-regional intervention with systemic immunotherapy to downstage otherwise unresectable disease that is beyond Milan criteria. Liver transplantation will continue to play an important role in the treatment of HCC for the foreseeable future and based on currently available evidence, both local-regional therapies and immunomodulation in combination are poised to change the landscape of liver transplantation for HCC as we currently know it.
Keywords: liver transplantation, hepatocellular carcinoma, local-regional therapy, locoregional therapy, Milan criteria

Introduction

As the third most common cause of death due to cancer worldwide in 2020, primary liver cancer continues to be a major contributor to mortality across the globe.[1] It has been estimated that by the year 2025, more than 1 million people will develop liver cancer annually.[1] As the predominant type, hepatocellular carcinoma (HCC) accounts for up to 90% of all liver cancers.[1,2] The aetiology and incidence of HCC vary widely across geographic regions. Viral aetiologies predominate, specifically the Hepatitis B virus (HBV) across most of Asia, Africa and South America, and the Hepatitis C virus (HCV) across North America, Western Europe and Japan.[1] Alcohol intake remains the main contributor in Central and Eastern Europe.[1] It is important to note that the incidence of non-alcoholic steatohepatitis (NASH) is on the rise and is predicted to soon become the leading cause of HCC, particularly in high-income regions.[1]

Despite many advancements in systemic and local-regional therapies, surgical resection and liver transplantation continue to be the mainstay of curative treatment for HCC. Several early observational studies demonstrated the benefit of local resections over major hepatectomy for small HCCs. However, many patients with HCC have background liver cirrhosis, which substantially increases the associated risks of surgical resection. Additionally, surgical resection leaves behind diseased liver parenchyma that is at risk of developing new HCCs in the future. There is a reported estimated risk of recurrence of HCC in patients undergoing surgical resection of 35% at 1 year, 40–50% at 3 years, and up to 70% risk of recurrence at 5 years following resection.[3-6] Therefore, in patients who meet eligibility criteria, liver transplantation as a cure for HCC is considered the gold standard treatment.

This article aims to present the current evidence-based practices for the role of transplantation in the treatment of HCC. This includes more recent evidence supporting expansion of eligibility criteria for transplantation and the concept of downstaging HCC tumours as a bridge to transplant, as well as advances in local-regional therapy, the use of neoadjuvant systemic therapies and new post-transplant immunosuppression regimens, all of which represent new horizons in transplantation for HCC.

Barcelona Clinic Liver Cancer criteria

The Barcelona Clinic Liver Cancer (BCLC) criteria for the management of HCC were first proposed more than 20 years ago and represent a classification system that not only allows for categorisation of tumour by stage and prognosis, but also provides evidence-based treatment guidelines for each tumour stage.[2,7] The guidelines are updated regularly, most recently in 2022.[8] Patient factors such as evidence of portal hypertension, bilirubin level, tumour size and number are all included to stratify patients into categories based on prognosis with corresponding treatment schedules recommended for each stage of disease. According to these criteria, patients in whom transplantation for HCC should be considered include BCLC-0 (very early stage, single lesion

less than or equal to 2 cm with preserved liver function), BCLC-A (early stage, single lesion irrespective of size or up to 3 lesions each less than or equal to 3 cm with preserved liver function), BCLC-B (intermediate stage, multinodular HCC with preserved liver function), and in some cases BCLC-D (terminal stage, any tumour burden with end stage liver function).[8] Particularly for stage BCLC-B HCC, extended criteria for liver transplantation with local-regional therapy to downstage the HCC tumour burden are required, as patients with large single lesions or multinodular HCC fall outside of most traditional liver transplant criteria. In addition, BCLC-D patients who meet liver transplant criteria for other reasons and who also happen to have HCC within transplant criteria may potentially remain eligible for transplant.

Eligibility criteria for transplantation for HCC

First published in 1996 by Mazzaferro and colleagues from the University of Milan, criteria for liver transplantation as treatment for HCC included a single tumour less than 5 cm or no more than 3 tumours in total, each less than or equal to 3 cm in size.[9] In that initial prospective, observational study, the authors included a total of 48 patients with cirrhosis and otherwise unresectable HCC who underwent liver transplant.[9] After a median of 26 months post-transplant follow-up, the authors reported an actuarial survival rate of 75% and a recurrence-free survival of 83% at four years, compared to a 25% three-year survival of untreated HCC.[9,10] This landmark study clearly demonstrated the survival benefit of transplant as a cure for HCC when patients were transplanted within what have become known as the Milan criteria.

Nearly thirty years later, the Milan criteria for liver transplantation remain the benchmark for determining eligibility of patients for liver transplantation in the treatment of HCC.[11] However, as multiple observational studies have demonstrated, consideration of tumour size and number alone at the time of presentation does not fully allow for selection of patients who may gain a survival benefit from liver transplantation.[12-17] Other important factors that correlate with tumour biology, such as the tumour marker alpha fetoprotein (AFP) as well as response to local-regional therapy, have improved our ability to predict recurrence and mortality post-transplant. The use of local-regional therapy as a bridge to transplant is sometimes referred to as the "ablate and wait" strategy, where a waiting period of at least 3 months, but more often 6 months in practice, is used to assess for early progression of disease prior to transplant.[18]

A working group from the International Liver Transplant Society (ILTS) Transplant Oncology Consensus Conference recently published guidelines on liver transplantation for HCC.[19] The group found that consideration of tumour biology, including AFP levels, tumour size and number, probability of survival, transplant benefit, organ availability, waitlist composition and allocation priorities were all important selection factors for patients with HCC. They also concluded that consensus on expanded criteria for liver transplantation in HCC has not yet been reached. The group did propose that composite criteria which take into consideration surrogates of tumour biology and response to neoadjuvant treatment will likely replace conventional morphological criteria for defining transplant eligibility in the future. The working group suggested that eligibility criteria for downstaging should be defined upfront and if there is evidence of treatment response, a no-treatment period to assess end-treatment sustainability was recommended.

Several criteria which incorporate factors associated with tumour biology, allowing for the expansion of transplant eligibility criteria while maintaining acceptable outcomes after transplant exist and are summarised in Table I. The University of California San Francisco (UCSF) and Up-to-Seven Rule criteria are among the most commonly used.[12,13] Others, including the French AFP Model, have routinely been used for liver transplant allocation in France since 2013, and the Extended Toronto Criteria (ETC) are currently being used in Canada.[15,16] National guidelines for liver transplantation for patients with HCC outside of Milan criteria in the United States include a tumour burden at time of diagnosis that falls within the UCSF criteria, a sustained response to local-regional therapy if successfully down-staged to within Milan criteria and AFP levels less than 500 ng/mL after local-regional therapy if AFP was greater than 1000 ng/mL at the time of diagnosis.[20] These criteria have been shown to result in an 80% overall survival at 5 years post-liver transplant, which is comparable to overall survival following liver transplant for non-malignant indications.[11]

Table I: Summary of proposed criteria for liver transplantation for hepatocellular carcinoma

Reference	Classification system	Criteria	Overall survival (%)
Mazzaferro V, et al. 1996.[9]	Milan Criteria	Single nodule < 5 cm or 3 nodules each < 3 cm	80%
Yao FY, et al. 2001.[12]	UCSF Criteria	Solitary tumour < 6.5 cm, or < 3 nodules with the largest lesion < 4.5 cm and total tumour diameter < 8 cm	77.8%
Mazzaferro V, et al. 2009.[13]	Up-to-seven Criteria	Seven as the sum of the size of the largest tumour in cm and the number of tumours (ex: 2 tumours up to 5 cm in size, 3 up to 4 cm, 4 up to 3 cm, 5 up to 2 cm).	71.2%
Shimamura T, et al. 2019.[14]	5-5-500	Up to 5 nodules with a maximum diameter of 5 cm and AFP < 500	75.5%
DuBay D, et al. 2011.[15]	Extended Toronto Criteria	Any size or number of tumours, no systemic cancer-related symptoms, extrahepatic disease, vascular invasion, or poorly differentiated tumours	70%
Duvoux C, et al. 2012.[16]	French AFP Model	Scoring system including tumour diameter (3, 3-6, > 6 cm), number of nodules (1-3, 4) and AFP level (100, 100-1000, > 1000). A score of 2 is considered low risk	67.8%
Toso C, et al. 2009.[17]	TTV-AFP Model	Composite score of total tumour volume < 115 cm and AFP < 400 ng/mL	60%

Tumour downstaging using local-regional therapies

There are multiple forms of local-regional therapies available including transarterial chemoembolisation (TACE), transarterial radioembolisation (TARE) most often with Yttrium-90 (Y-90), radiofrequency ablation (RFA) and microwave ablation (MWA) techniques, as well as percutaneous ethanol injection (PEI). The recommended first line treatment modality for treatment of HCC as a bridge to transplant is TACE.[21,22] TACE was the first modality to have level one evidence supporting its use and has since become the gold standard reference for comparison in studies investigating other local-regional therapies.[8,21,22] However, encouraging results after TARE have also been published, including the potential immunomodulatory effects that occur after treatment that then aid in tumour suppression.[23] The data are not currently as robust for TARE and as such it has not yet been widely adopted into downstaging algorithms.

Transarterial embolisation

Transarterial embolisation (TAE) represents a broad category of embolisation techniques including bland embolisation, chemoembolisation (TACE) and embolisation with drug-eluting beads (DEB-TACE). Bland embolisation involves injection of particles to selectively occlude the arterial supply to the tumour, resulting in hypoxia, cell death and subsequent tumour necrosis.[24] In TACE, the tumour arterial blood supply is similarly selectively occluded, and an emulsion of chemotherapy drug with an oil-based contrast agent is administered directly into the tumour. This is usually followed with injection of gel foam, which both minimises systemic circulation of the chemotherapeutic agent and occludes the arterial blood supply to the tumour.[25] The DEB-TACE technique is similar and involves injection of microspheres, typically coated with doxorubicin, which results in sustained release of chemotherapy and occlusion of the tumour arterial blood supply.[26] When TACE and DEB-TACE were compared in randomised controlled trials, there was no statistically significant difference in tumour response rates between the two modalities, therefore use should be guided by local practice preference.[27]

Transarterial radioembolisation

Transarterial radioembolisation (TARE), sometimes referred to as selective internal radiation therapy (SIRT), typically involves delivery of the Y-90 radionuclide bound either to glass or resin microspheres directly to the tumour.[28] The benefit of this technique is that it limits the dose of radiation to the liver parenchyma and results in a low incidence of post-radioembolisation complications. Several recent studies have compared the efficacy of TARE vs TACE in downstaging HCC prior to liver transplant.[23,29,30] In a study comparing time to progression for TARE vs TACE, patients who received TARE had a significantly longer time to progression (26 vs 8.6 months, $p < 0.01$).[29] Similarly, Sarwar and colleagues investigated the presence of complete pathologic necrosis on explanted livers following TACE, TARE and thermal ablation.[30] The authors found that patients who underwent TARE or thermal ablation were more likely to have complete pathologic necrosis of the tumour (TARE - OR 1.92; 95% CI 1.57–2.36; $p < 0.001$ and thermal ablation - OR 2.19; 95% CI 1.86-2.57; $p < 0.001$). Both increased time to progression and complete tumour necrosis may have significant implications for patients on waiting lists for liver transplantation.

Radiofrequency ablation and microwave ablation

Both radiofrequency ablation (RFA) and microwave ablation (MWA) techniques rely on image-guided placement of probes into the targeted tumour. They can be performed via laparotomy, laparoscopy or percutaneously. RFA results in cell death due to frictional heating which occurs after application of a high frequency (375–480 kHz) alternating current through the probe(s) placed within the targeted tumour.[31] MWA results in cell death through excitation of water molecules after application of energy via antenna(e) inserted into the tumour at a frequency of 900–2450 MHz.[31] Both treatment techniques are limited by the risk of thermal injury to nearby critical structures. RFA in particular is susceptible to the heat-sink effect, which becomes relevant for tumours located near large blood vessels, as the continuous flow of blood results in a cooling effect and decreases the efficacy of the ablative therapy. Additionally, thermal ablation is relatively contraindicated for tumours near major biliary structures, the diaphragm and bowel all due to the risk of thermal injury or incomplete treatment.

Several studies have investigated the efficacy of ablation strategies compared to TACE and TARE techniques in patients undergoing local-regional therapy as a bridge to transplant.[26,32,33] In a study by Kolarich and colleagues, waitlist mortality and dropout among liver transplant candidates with HCC was investigated using 10 years of data from the scientific registry of transplant recipients.[26] RFA and TACE as a bridge to transplant were compared and the authors found no difference in either waitlist mortality or dropout between the two treatment groups (HR 0.91, 95% CI 0.79–1.03). Wu and colleagues investigated the cost-effectiveness of ablation, TACE, and TARE liver-directed therapies for downstaging patients with HCC prior to liver transplantation.[32] The authors found that for patients with single, small (< 3 cm) HCCs, ablation was the most cost-effective treatment modality. However, in a prospective, observational study that compared RFA to observation alone in patients awaiting transplant for HCC, no survival benefit for the RFA group over observation alone was identified.[33] Without conclusive evidence to support improved outcomes for patients awaiting liver transplantation who undergo ablation, TACE remains the local-regional treatment modality of choice.

Percutaneous ethanol injection

Percutaneous ethanol injection (PEI) is one of the first percutaneous ablative techniques performed for liver tumours.[30] It requires injection of 95% ethanol into liver tumours which induces coagulative necrosis, microvascular thrombosis and ischaemia.[30] Results from several studies suggest higher rates of recurrence and lower overall survival with PEI compared to other available therapeutic interventions, which has resulted in limited use of PEI in the management of patients with HCC.[34] Lazzarotta-da-Silva and colleagues recently compared PEI alone, TACE alone and PEI combined with TACE as a bridge to transplantation.[34] The authors investigated waitlist dropout rates and post-transplant recurrence free survival for the three groups and found similar dropout rates with no statistically significant

difference in five-year recurrence free survival among the three groups (PEI alone 55.6%, TACE alone 55.1%, combined PEI and TACE 71.4%, p = 0.42). This study supports PEI and/or PEI with TACE as an alternative local-regional therapy when other modalities may be otherwise technically difficult or contraindicated.

Recent evidence supporting bridge to transplant protocols

The success of the use of local-regional therapy in downstaging or bridge to transplantation protocols for patients who initially present with HCC outside of Milan criteria rests on its ability to test tumour biology. The mandatory 3–6 month waiting period after therapy but before transplantation is a window of opportunity to measure tumour response. For patients who progress after therapy, there is data to suggest those patients would have a worse outcome post-liver transplant.[35] Additionally, the use of local-regional therapy allows for control of tumour growth while on the waiting list, which reduces the risk of dropout prior to transplantation. Recently published data demonstrate the benefits of local-regional therapy in downstaging HCC prior to transplantation.[36-39]

In a randomised controlled trial performed across nine Italian tertiary care and transplant centres, investigators evaluated the survival benefit for patients transplanted after successful downstaging to within Milan criteria.[36] The study was an open label, multi-centre, phase 2b/3 trial that compared liver transplantation to best available tumour-directed therapy. The primary aim of phase 2b was to assess the 5-year tumour event-free survival in patients successfully downstaged and transplanted. The primary aim of phase 3 was to measure 5-year overall survival after transplant. A total of 74 patients were enrolled from 2011 through 2015 with a 5-year tumour event-free survival of 76.8% in the transplant group versus 18.3% in the best available tumour directed therapy group (HR 0.20, 95% CI 0.07–0.57, p = 0.003). Similarly, the overall 5-year survival was significantly longer in the transplant group (77.5% vs 31.2%, HR 0.32, 95% CI 0.11–0.09, p = 0.035). Unfortunately, the study was terminated early due to changes in liver allocation policy and HCC priorities after the study began. Despite this limitation, the reported data are encouraging and add to the existing body of observational data supporting liver transplantation after downstaging of HCC to within Milan criteria as a viable treatment pathway for patients that results in improved survival.[37,38]

In a study published in JAMA Surgery in 2022, Tabrizian and colleagues reported 10-year outcomes after liver transplantation for patients with HCC.[39] A total of 2645 patients who underwent liver transplant for HCC across 5 US centres between 2001 and 2015 were included. The investigators reported 10-year outcomes between three distinct patient groups: (1) patients whose disease was downstaged to within Milan criteria (n = 341), (2) patients whose disease was always within Milan criteria (n = 2122), and (3) patients whose disease was not successfully downstaged (n = 182). The 10-year post-liver transplant overall survival and recurrence rates for patients successfully downstaged to within Milan criteria was 52.1% and 20.6%, respectively, compared to 61.5% and 13.3% among patients transplanted after always being within Milan criteria. For those patients transplanted beyond Milan criteria, 10-year post-transplant survival and recurrence rates were 43.3% and 41.1%, respectively (all $p < 0.001$). An important finding from this large patient cohort was the observation that for patients who developed recurrence after transplant and were treated with surgical resection, they had significantly improved survival over those treated with local-regional or systemic therapies. Overall, the results of this study strongly supported downstaging protocols for liver transplantation with excellent 10-year post-liver transplant outcomes.

New horizons

As is common in many areas of oncology, tumour biology appears to be the main determinant of recurrence-free and overall survival in patients with HCC. There are many areas of active research that may result in further expansion of transplant eligibility criteria including improved biomarkers for HCC, new systemic neoadjuvant therapies, and improved post transplantation immunosuppression regimens.

Biomarkers

AFP is currently the only widely used biomarker for assessing HCC tumour biology. While there are other biomarkers which have shown promise in early detection of HCC including AFP-L3 and des-γ-carboxyprothrombin, they have not yet been validated for clinical use.[40,41] The pre-transplant neutrophil to lymphocyte ratio has also been suggested as a potential marker of prognosis and risk of recurrence after liver transplantation. Similarly, liquid biopsy for circulating tumour cells (CTC), cell-free DNA (cfDNA) and extracellular vesicles are also currently under investigation.[42,43] The use of CTCs and cfDNA includes the potential for gene sequencing of individual tumours to identify favourable or unfavourable mutations that can aid in determining prognosis. Extracellular vesicles, formed by budding lysosomes, cell membranes or apoptosis and subsequently released into circulation, can be used both as targets for therapy as well as for assessment of tumour biology.[44] Lastly, it has been shown the FDG-PET avidity combined with AFP levels is a better predictor of HCC recurrence after transplantation compared to the Milan criteria alone.[45]

Neoadjuvant systemic therapies

While there are multiple FDA-approved immunomodulatory agents for systemic treatment of advanced HCC, there is currently only limited, but optimistic data to support the use of neoadjuvant systemic therapies prior to liver transplantation for HCC.[46,47] Previously, immunomodulatory therapies have been avoided in the pre-transplant management of HCC due to reports of severe rejection and graft loss.[48,49] Sorafenib, a tyrosine kinase inhibitor, was the first immunomodulatory systemic therapy to be approved by the FDA for the treatment of advanced staged HCC. While it has remained an effective treatment option, its use in neoadjuvant therapy prior to transplant has resulted in conflicting outcomes in small retrospective studies.[50,51] Other tyrosine kinase inhibitors have since been approved including lenvatinib and regorafenib, however, very little data exist regarding use of these agents in the neoadjuvant setting.

Immune checkpoint inhibitors (ICI) have gained increasing traction after demonstrating improved efficacy in the management of advanced HCC over tyrosine kinase inhibitors alone. So much so that the combination of the

programmed death-ligand 1 (PD-L1) inhibitor atezolizumab with bevacizumab (monoclonal antibody targeting VEGF) is now considered first-line therapy over sorafenib. A recent series of nine patients with HCC who underwent neoadjuvant treatment with the PD-1 inhibitor nivolumab was published by the Mount Sinai group with encouraging results. There were no reported instances of severe graft rejection, graft loss, tumour recurrences or deaths at a median follow-up of 16 months, and near complete tumour necrosis was observed in one third of explanted livers.[46] Conversely, in another retrospective small case series from the University of California San Diego, of five patients who had received neoadjuvant treatment with nivolumab, two developed severe hepatic necrosis and biopsy-proven cellular rejection.[52] In a third study from China, 16 patients who received a PD-L1 inhibitor as neoadjuvant therapy underwent transplant. Of note, 14 of the 16 patients underwent combination therapy with lenvatinib or sorafenib. Nine patients were diagnosed with rejection in the early postoperative period but were all successfully managed with immunosuppression modification and no graft losses were reported.[53] Importantly, a significantly shorter time interval was identified in the rejection group between neoadjuvant ICI therapy and liver transplant (21 vs 60 days, $p < 0.01$), a finding similarly reported in the University of California San Diego case series.

There are currently two ongoing trials, PLENTY202001 (NCT04425226) and Dulect2020-1 (NCT0443322), both of which aim to assess the role of combination systemic therapy in the neoadjuvant setting prior to liver transplant. As experience with multimodal immunomodulatory therapy in the pre-transplant setting continues to grow, it will be essential to further delineate treatment protocols and to identify which patients would be most appropriate, giving consideration to individual tolerance of treatment and to risk of post-transplant rejection.

Combined local-regional and systemic therapy regimens

While several studies have demonstrated improved disease control, overall survival, and time to progression with a combined treatment approach using local-regional therapies (most commonly TACE) and systemic immunomodulatory agents,[54,55] multiple randomised controlled trials have failed to show a significant difference.[56,57] There is an ongoing trial by the Methodist group (NCT05171335) that is investigating the efficacy of lenvatinib with TACE inducing tumour necrosis in the liver explant at the time of transplantation.[58] The trial was launched after preliminary retrospective data from the same institution demonstrated a significant improvement in 5-year disease-free survival for patients who received sorafenib plus TACE compared to TACE alone prior to transplant (100% TACE+sorafenib vs. 67.2% TACE alone, $p = 0.07$). However, there was no difference in overall 5-year survival between the two groups (77.8% vs 61.5%, $p = 0.51$).[59]

Post-transplant immunosuppression regimens

Patients who have undergone transplant remain at increased risk of malignancy due to life-long immunosuppression. In patients transplanted for HCC, modification of post-transplant immunosuppression regimens that balance keeping organ rejection at bay while minimising the risk of cancer recurrence is preferred. The mammalian target of rapamycin (mTOR) receptor plays a critical role in cell proliferation as well as cell growth and metabolism, and has been implicated in the pathogenesis of the development of HCC.[60] There is data to suggest that the use of the mTOR inhibitors like everolimus for post-transplant immunosuppression may decrease the rate of HCC recurrence and improve overall survival in patients transplanted for HCC when compared to the classic calcineurin inhibitor regimens.[61,62]

Conclusions

Primary liver cancer, of which HCC represents the majority, continues to be a major cause of mortality worldwide, and the annual incidence continues to increase. Liver transplantation remains the treatment of choice for a cure in patients with otherwise unresectable disease who meet transplant eligibility criteria. Recent evidence has allowed for expansion of the Milan criteria to include more advanced stages of disease downstaged using local-regional therapies. There are several areas of ongoing research including efforts to improve available local-regional therapies and identification of tumour biomarkers that will result not only in earlier diagnosis, but also allow for determining prognosis in patients with HCC. Several clinical trials are currently underway to investigate the efficacy of systemic neoadjuvant therapies alone and in combination with local-regional therapies on downstaging patients with otherwise unresectable HCC. Further work is being done on modification of post-transplant immunosuppression regimens to minimise the risk of recurrence. Based on available evidence, it seems both local-regional therapies and immunomodulation in combination are poised to change the landscape of liver transplantation for HCC as we currently know it.

Conflict of interest

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