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Review Article

Hepatocellular Carcinoma: Downstaging to Liver Transplantation as Curative Therapy

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Abstract

Hepatocellular carcinoma (HCC) ranks among the leading cancer-related causes of morbidity and mortality worldwide. Downstaging of HCC has prevailed as a key method to curative therapy for patients who present with unresectable HCC outside of the listing criteria for liver transplantation (LT). Even though LT paves the way to lifesaving curative therapy for HCC, perpetually severe organ shortage limits its broader application. Debate over the optimal protocol and assessment of response to downstaging treatment has fueled immense research activity and is pushing the boundaries of LT candidate selection criteria. The implicit obligation of refining downstaging protocol is to ensure the maximization of the transplant survival benefit by taking into account the waitlist life expectancy. In the following review, we critically discuss strategies to best optimize downstaging HCC to LT on the basis of existing literature.

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Introduction

Hepatocellular carcinoma (HCC) is the most prevalent primary liver malignancy. It is the sixth most common neoplasm and fourth cause of cancer-related mortality globally.[1,2] As the incidence of HCC is projected to increase in the USA as nonalcoholic fatty liver disease continues to increase exponentially and alcohol and hepatitis C remain public health issues, HCC has emerged as a leading indication for liver transplantation (LT).[3–5]

LT offers a successful therapy for early-stage HCC patients because it simultaneously removes the lesion(s) and the preneoplastic liver.[6] Early records of post-LT outcome delineated high recurrence rates and were plagued with dismal patient survival.[7,8] Apart from tumor measurements, factors influencing recurrence include vascular invasion, histologic differentiation, previous response to local-regional therapy (LRT) and serum marker levels.[9–12]

The primary aims of establishing criteria for LT are to select candidates with good post-LT prognoses and to exclude patients whose disease conditions are suitable for other therapies, such as resection or systemic therapy. The Milan criteria (MC) (a single nodule ≤5 cm, 2–3 nodules ≤3 cm), proposed in 1996, emerged as an international benchmark to select patients with HCC for LT. According to MC, post-LT 5-year survival in HCC is >70% with a recurrence rate <10–15%.[13–15] The American Association for the Study of Liver Disease (commonly known as AASLD) and Guidelines of the European Association for the Study of the Liver (commonly known as EASL) recommend LT for HCC patients within MC but unsuitable for resection.[16,17]

However, debate in the past two decades has revolved around the dichotomous nature of MC. The stringent MC precludes access to LT for patients with larger or more numerous tumors who potentially have acceptable post-LT outcomes but who otherwise are not candidates for curative therapy. A plethora of studies have evaluated the liberalization from conventional criteria for HCC LT.[18–24] An alternative form of expansion relates to LT of candidates whose tumor burden exceeds MC without utilizing pre-LT treatment, while another form is linked to using treatment to successfully "downstage" tumor burden to within standard LT listing criteria based on radiographic assessment and markers of tumor biology. The current article reviews the framework for the downstaging of HCC and sheds light on recent updates in the field of prognosticators of post-LT outcomes.

Expanded selection criteria

Several expanded criteria for HCC beyond MC have been proposed (Table 1).[13–15,19–24] It is important to preface that most of the earlier studies predominantly relied on tumor morphological characteristics, which undermined their power in establishing ideal cutoffs. Additionally, prospective study design constructs a stronger evidential foundation for expanded criteria than does retrospective study proposals,

Keywords: Downstaging; Milan criteria; Hepatocellular carcinoma; Liver transplantation.

Abbreviations: 18F-FDG, 18F-fluorodeoxyglucose; AASLD, American Association for the Study of Liver Disease; AFP, alpha-fetoprotein; AFP-L3, lens culinaris agglutinin-reactive alpha-fetoprotein; CT, computed tomography; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; DCP, des-γ-carboxy prothrombin; EASL, European Association for the Study of the Liver; ETC, extended Toronto criteria; HCC, hepatocellular carcinoma; LT, liver transplantation; LRT, local-regional therapy; MC, Milan criteria; mRECIST, modified response evaluation criteria in solid tumors; MWA, microwave ablation; OLT, orthotopic liver transplantation; OPTN, Organ Procurement and Transplantation Network; PD-1/PDL-1, programmed cell death protein 1/programmed death ligand 1; PET, positron emission tomography; RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy; TACE, transarterial chemoembolization; UCSF, University of California in San Francisco; UNOS, United Network for Organ Sharing; VEGF, vascular endothelial growth factor; Y-90, Yttrium-90.

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Table 1. Details of different criteria for LT in HCC

Selection system	Assessment	Criteria	Years of follow-up	Survival, %	Recurrence rate, %
MC[13–15]	Radiology	Tumor size of ≤5 cm; up to three separate lesions, none larger than 3 cm; no evidence of gross vascular invasion; and no regional nodal or distant metastases	4	>70 (OS)	<10–15
UCSF criteria[19]	Radiology	Single tumor ≤6.5 cm or two to three lesions, none exceeding 4.5 cm with total tumor diameter ≤8 cm	5	80.9 (RFS)	9.1
Total tumor volume and AFP criteria[21]	Radiology	Total tumor volume ≤115 cm^3 and AFP ≤400 ng/mL, without macrovascular invasion	4	74.6 (OS)	9.4
Up-to-seven criteria[20]	Pathology	Size of largest HCC plus number of HCCs ≤7	5	71.2 (OS)	9.1
ETC[24]	Radiology	Any size or number of tumors, provided no extrahepatic spread, vascular invasion, or poor differentiation on pre-LT biopsy	5	68 (OS)	25.6
Hangzhou criteria[22]	Pathology	Total tumor diameter ≤8 cm or a total tumor diameter >8 cm, with a histopathologic grade I or II and a preoperative AFP ≤400 ng/mL	5	70.7 (OS)	N/A
Kyoto criteria[23]	Radiology	Tumor number ≤10; all ≤5 cm; and serum DCP ≤400 mAU /mL	5	65 (OS)	30

OS, overall survival; RFS, recurrence-free survival.

by eliminating confounding variables and carefully selecting participants.[25,26]

In 2001, Yao *et al*.[18] retrospectively analyzed LT recipients and propounded a modestly expanded criteria for orthotopic liver transplantation (referred to herein as OLT) on the grounds of explant histological characteristics. The exploratory study set forth the University of California in San Francisco (UCSF) criteria: (1) single lesion ≤6.5 cm; or (2) ≤3 lesions, with the largest ≤4.5 cm and total sum of diameters ≤8 cm. In a follow-up study, Yao *et al*.[19] prospectively validated the UCSF criteria for OLT based on pretransplant imaging and outlined post-OLT tumor recurrence and survival. The 5-year patient survival without recurrence was 81% and the recurrence-free probability exceeded 90% for patients meeting the UCSF criteria, which were similar to the patients fulfilling the MC.

Mazzaferro *et al*.[20] examined the feasibility of "up-to-seven criteria" (the sum of the size of the largest nodule and the number of nodules ≤7 without microvascular invasion) derived from explant pathology collected from 36 centers worldwide. Notably, the 71.2% 5-year OS rate achieved among patients beyond MC but within the "up-to-seven" criteria was associated with the absence of microvascular invasion, a variable difficult to ascertain pre-LT. It is noteworthy that upper tumor size and number limits beyond MC may increase the likelihood of microvascular invasion.[27]

In a prospective validation attempt to extend MC, Toso *et al*.[21] presented data in which LT candidate selection depended on a composite of the total tumor volume (≤115 cm^3) and alpha-fetoprotein (AFP) ≤400 ng/mL without macrovascular invasion or extrahepatic disease. Even though post-LT survival and recurrence were comparable to patients meeting MC, the waitlist drop-out rates posed a disadvantage. In China, the Hangzhou criteria also accounted for AFP levels in their protocol for selecting HCC patients for LT. Specifically, the Hangzhou criteria integrated total tumor diameter ≤8 cm or a total tumor diameter >8 cm, with a histopathologic grade I or II and preoperative AFP ≤400 ng/mL.[22]

A research group from Kyoto University proposed the Kyoto criteria that involved HCC tumor number ≤10, each tumor diameter no larger than 5 cm, and serum des-γ-carboxy prothrombin (referred to herein as DCP) ≤400 mAU /mL. The group's recent intention to treat analysis resulted in a 5-year OS rate and recurrence rate of 82% and 7%, respectively.[23]

Researchers at the University of Toronto endeavored to validate their extended Toronto criteria (commonly known as ETC), which relied on poor tumor differentiation, elevated AFP and cancer-related symptoms to select HCC candidates for LT, rather than the conventional measurements of tumor size and number at presentation. Although the 5-year OS of 68% for patients transplanted according to ETC was not statistically inferior to patients within MC amongst the prospective cohort of patients followed, tumor recurrence post-LT was higher for patients who exceeded MC but satisfied the ETC.[24]

Nonetheless, MC remains the gold standard for HCC patient selection and prognostic evaluation in LT.[28] The adoption of extended selection criteria generates the dilemma of a sharp rise in HCC patients on the LT waitlist with unknown regional repercussions on non-HCC patients waiting for LT, while persistent shortages of donor organs highlight the fundamental challenge of maintaining equity in liver transplant allocation.

Dynamism of serum markers

The multifactorial nature of HCC necessitates the integration of prognostic markers to assess tumor biological features and vascular invasion during the transplant evaluation process. No longer a contentious tool in candidate selection, AFP is widely used to distinguish the subset of LT candidates with a reasonable life expectancy after LT.[29–32] Many liver transplant centers globally incorporate AFP into their listing criteria, with differences in cutoffs. Therefore, the optimal serum AFP level cutoff as an exclusion criterion for LT in pretransplant HCC patients has garnered conspicuous research focus. In a detailed analysis of national United Network for Organ Sharing (UNOS) data, the subset of patients outside

the MC with low serum AFP levels (0–15 ng/mL) displayed improved post-LT survival.[30] The high end of AFP level cut-off ranges from 400 ng/mL to 1,000 ng/mL.[33–35] Mounting evidence reveals that AFP >1,000 ng/mL manifested in HCC patients either within or outside MC portends reduced post-LT survival and considerable risk for HCC recurrence.[34,36,37]

There is a paucity of data on the predictive value of other serum markers for post-transplant mortality and HCC recurrence. In the absence of a universal AFP cutoff point, some members of the liver transplant community have investigated DCP, lens culinaris agglutinin-reactive alpha-fetoprotein (AFP-L3) and/or the ratio of AFP-L3 to total AFP (AFP-L3%) as adjuncts within patient selection algorithms.[38–40] Moreover, the elevated neutrophil-lymphocyte ratio, an index of systemic inflammation, has been pursued as a maker of propensity to recurrence and unfavorable prognosis in parallel with AFP.[41] External validation is needed prior to amending organ allocation strategies to embrace these promising serum markers.

LRT: Bridging and downstaging

LRT plays a pivotal role in the therapeutic management of HCC patients. Forms of LRT encompass a wide range of modalities that include transarterial chemoembolization (TACE), radiofrequency ablation (RFA), microwave ablation (commonly known as MWA), radioembolization, stereotactic body radiotherapy (commonly known as SBRT) and/or hepatic resection.[42,43]

LRT is frequently employed as a bridge to transplant in patients listed for LT within the Organ Procurement and Transplantation Network (commonly known as OPTN) T2 (Milan) criteria to prevent dropout from the waiting list by inducing tumor necrosis and deterring tumor progression.[44,45] The rationale for bridging therapy lies in noncomparative studies reporting waitlist dropout rates as low as 8.7% at 6 months and between 22.9% at 12 months. By comparison, reported waitlist dropout rates are as high as 25% at 6 months and 38% at 12 months without the use of LRT.[44,46–48] The possible beneficial effect of bridging therapy for HCC patients' waitlist times of <6 months remains poorly characterized.[28] Despite the liability for selection bias and lack of randomized control trials, European guidelines recommend LRT to reduce the risk of pre-LT drop-out in regions of anticipated wait times longer than 6 months.[17] It is imperative to consider the risk of hepatic decompensation in advance of undergoing LRT. Furthermore, the variability in organ availability and hence vastly differing median waiting times across geographic regions culminate in a conditional recommendation for bridging therapy. Consequently, studies exploring LT waitlist dropout and post-LT outcomes founded on pre-transplantation treatment response radiologically evaluated by modified Response Evaluation Criteria in Solid Tumors (commonly known as mRECIST) are more logistically plausible to conduct than randomized controlled trials to elucidate the net effects of bridging LRT.[49,50] Such future studies will also lend insight into how the development of new lesion(s) notwithstanding partial or complete response of the target lesion(s) affects outcomes. With the changes in UNOS model for end-stage liver disease score exception criteria now mandating a 6-month delay before exception points can be obtained, LRT has become standard of care in patients with HCC awaiting liver transplant. These changes inevitably cause a prolonged wait time that reinforces the usefulness of LRT. In a multivariate analysis of the UNOS database, Halazun *et al*.[5] demonstrated that a waiting time of less than 4 to 6 months adversely impacts post-LT survival. Transplantation of patients with aggressive tumors in areas without a mandatory observational period can theoretically occur prematurely before tumor biologic behavior is assessed, thereby causing poor outcomes with aggressive recurrence. Accordingly, a minimal observation period aids in better candidate selection and possibly leads to lower risks of post-LT HCC recurrence.[51,52]

Tumor "downstaging" is a process that applies LRT to decrease tumor size and number in patients first deemed outside of the locally predefined criteria, commonly MC, for LT.[53] First recommended in 1997, tumor downstaging provides a viable alternative approach to expanding MC limits to select a subgroup of patients whose LT candidacy would otherwise be disregarded.[54–56] Sustained response to LRT can function as a measure of favorable tumor biology, whereas unresponsive and proliferative tumor burden after LRT yields worse post-LT outcomes.[45,57–60] The latest AASLD guidelines suggest that patients beyond the MC (T3) should be considered for LT after successful downstaging to MC.[16] Due to non-standardized downstaging protocol with precisely defined upper tumor limits across geographic regions, UNOS adopted the UCSF inclusion criteria for downstaging (single nodule ≤8 cm, 2–3 nodules each ≤5 cm, or 4–5 nodules each ≤3 cm with sum of the maximal tumor diameters ≤8 cm) as USA policy in 2017.[58,61] The notion of placing restrictions to enter downstaging is predicated on concerns over fairness and appropriate prioritization in liver allocation for all indications.

The first analysis of the UNOS database of 3,276 patients within MC and 422 patients within UNOS downstaging criteria, who underwent LT from 2012 to 2015, confirmed the validity of UNOS downstaging criteria by showing similar 3-year post-LT survival between HCC patients always meeting MC and patients whose initial tumor burden met the UNOS downstaging criteria and were then downstaged to LT.[62] Given the study's dependence on pre-LT data submitted to UNOS by LT centers, reporting biases pertaining to radiographic response to LRT are plausible. For example, underestimation of tumor size, whether intentional or unintentional, can inflate the proportion of patients in the downstaging group with explant tumor burden beyond MC.[63] Nevertheless, the findings that AFP ≥100 ng/mL at LT and short wait regions (median wait time of 2.6 months) or mid wait regions (median wait time of 6.5 months) were predictors for impaired post-LT survival in the downstaging groups support the need to incorporate AFP and expected wait times into tumor downstaging models.[62]

Efficacy of downstaging modalities

Currently, there are sparse data to draw conclusions on the optimal form of LRT for downstaging. Reported efficacies of common downstaging techniques defined as the successful anatomical reduction of tumor burden to within MC are highly variable.[64–67] A systematic review by Parikh *et al*.[65] revealed an overall downstaging success rate of 48%, with a post-LT HCC recurrence rate of 16%. The discrepancies in success of downstaging are attributed to various factors, such as initial tumor burden, choice of LRT utilized, LT program's downstaging procedures, and lack of a standardized time interval to determine radiographic response to LRT. The type of LRT performed for each patient is contingent upon the location of tumor, underlying liver function, performance status of patient, as well as local expertise in each treatment modality. In this systematic review, there was no significant difference comparing TACE and transarterial radioembolization, but the highest success rates were in patients that underwent multimodal therapy. There was not a significant difference in downstaging success rates in patients with more or less advanced liver disease, although other studies have reported lower success in patients with

Child's C cirrhosis.[65] Overall, the studies are variable in terms of success of downstaging, but overall it can be expected that approximately half of patients that are attempted to be downstaged will actually undergo LT.

Hepatic resection is the preferred curative treatment for patients with small localized tumors and well compensated liver disease and is an option for downstaging.[68] Comprehensive pathological examination of resected specimens may facilitate the identification of patients with histological features of poor prognosis, for instance macrovascular invasion gone unobserved.[69] This significantly influences subsequent treatment choices during postoperative surveillance of tumor recurrence patterns. Although large lesion size is not an absolute contraindication to hepatic resection, portal hypertension and end-stage liver disease are major risk factors for postsurgical complications and death.[70] There is a subset of patients who require resection in conjunction with LRT to complete downstaging. However, surgical resection has been reported in a minority of studies as a downstaging modality so no statement can be made about its efficacy.

TACE is the most frequently used palliative treatment technique in downstaging protocols, particularly for multifocal HCC.[43] The reported downstaging success rates with TACE (23.7–90%) are inconsistent and should be interpreted with caution.[64] Since the TACE mechanism of action targets the hepatic arterial supply, its efficacy depends on responsive HCCs with good blood supply and uptake. While TACE is not advised to be performed in the presence of portal vein thrombosis, transarterial radioembolization with Yttrium-90 (Y-90) beads is a safe alternative downstaging therapy.[71,72] Per available data there is no statistically significant difference between success rates of TACE and radioembolization for downstaging.[65] It is important to note the risk of inaccurate staging when relying on imaging results to gauge radiological response to TACE or radioembolization in terms of tumor size and viability. For example, tumor response to Y-90 typically evolves gradually and may require 3–6 months to exhibit an adequate response on triphasic computed tomography (commonly known as CT) or magnetic resonance imaging.[73] Therefore, timely intervals between treatment sessions and imaging are crucial to reduce confounding by image interpretation.

RFA confers its curative effects through thermal energy to achieve complete necrosis at a success rate of up to 90% in tumors of ≤3.0 cm in diameter.[74] The rare complication of tumor seeding and risk of bleed with superficially located tumors are a few limitations within RFA's safety profile.[42] RFA is contraindicated near large vessels because of the heat sink effect, whereas MWA is a safe therapeutic option.[70,75] SBRT, an extracorporeal technique, administers high doses of radiation to the target tumor. Published data investigating SBRT for downstaging are scant, but it appears to be a safe LRT for patients with decompensated liver function, especially in tumors near the major bile ducts.[76,77]

No evidence appears to render the superiority of one downstaging modality over another. The heterogeneity in the quality of data on the downstaging effectiveness of LRTs warrants large, multicenter, prospective cohort studies enriched with multidisciplinary tumor board referrals and standardized data reporting criteria in regions of differing waitlist times.

Systemic therapy and immunotherapy in advanced HCC

The goal of treatment is to maximize survival while prolonging the highest quality of life. Hence, it is paramount to assess the strength of scientific data for the selection of an appropriate treatment approach in HCC patients with advanced disease. When liver-directed therapy fails to successfully downstage patients into MC, HCC patients often transition into systemic therapy. Sorafenib is an oral tyrosine kinase inhibitor, whose anti-vascular endothelial growth factor (i.e. VEGF) receptor properties are proven to improve survival in advanced HCC patients, with a median survival of 10.7 months compared to a median survival of 7.9 months in placebo controls.[78,79] In the scenario of sorafenib's failure as a first-line systemic therapy, regorafenib, followed by cabozantinib, demonstrates a comparable survival benefit as second-line systemic therapy.[80,81] Recently, in an open-label, phase III, multicenter, non-inferiority trial, lenvatinib, another oral multikinase inhibitor, displayed clinically meaningful improvement in objective response rate, progression-free survival, and time to progression compared to sorafenib in unresectable and treatment-naive HCC. However, the median survival was not statistically significantly between 13.6 months for lenvatinib and 12.3 months for sorafenib, (hazard ratio of 0.92, 95% confidence interval of 0.79–1.06).[82] Newly, the REACH-2 phase III trial established the efficacy of ramucirumab, a monoclonal antibody that antagonizes VEGF receptor 2, in sorafenib-refractory patients with high AFP (of at least 400 ng/mL).[83] Notwithstanding the emergence of systemic therapies, it is pertinent to mention that the role of the systemic therapies remains under study in the tumor downstaging to transplant setting. In a pilot, single-center, randomized controlled trial, the safety and adverse event profile of sorafenib plus Y-90 was compared to Y-90 alone in HCC patients as a bridge to LT. Data from the study's limited sample size suggests the combination of sorafenib plus Y-90 in patients awaiting LT was linked with more peri-transplant biliary complications and a trend of higher acute cellular rejection rates.[84] Given the lack of robust data, further studies are required to investigate and elucidate the utility of tyrosine kinase inhibitors or other systemic therapies in the pre-LT patient population, with regards to both efficacy and safety in the transplant setting. Tyrosine kinase inhibitors are known to inhibit wound healing, and patients who undergo liver transplant while being treated with tyrosine kinase inhibitors may be at risk for higher complications.

In cases of unresponsiveness or unfitness to receive tyrosine kinase inhibitors, negative regulators of T cell immune function, such as programmed cell death protein 1/programmed death ligand 1 (i.e. PD-1/PDL-1) or cytotoxic T-lymphocyte-associated antigen 4 (i.e. CTLA-4), have been identified as potential therapeutic targets.[85] Two PD-1 checkpoint inhibitors, nivolumab and pembrolizumab, are promising immunotherapies for advanced HCC as second-line therapies.[86,87] These two immunotherapies remain under Food and Drug Administration conditional approval, based on phase II data. There is also a recent approval of atezolizumab in combination with bevacizumab for treatment of advanced HCC, as well as the combination of PD-1 with CTLA-4 immunotherapy (nivolumab and ipilimumab). The lack of safety data with immunotherapy prior to transplant warrants further investigation. There is little to no data in the literature on the effects of immunotherapy in the liver transplant setting, with regards to the possibility of hyperacute or acute rejection after treatment.

AFP response to LRT

In the context of downstaging, the degree of a decrease in AFP in response to LRT is a valuable indicator of tumor biological aggressiveness. Policy implemented in the USA requires patients with AFP >1,000 ng/mL to exhibit a reduction in AFP to <500 ng/mL with LRT before proceeding with LT, in an effort to preserve comparable 5-year survival rates

between HCC and non-HCC LT recipients.[61,88] Recently, Mehta *et al*.[89] endeavored to retrospectively validate the effects of this USA national policy using the UNOS database. In a multivariable analysis, a reduction in AFP from >1,000 ng/mL to 101–499 ng/mL was correlated with a greater than 2-fold reduction in post-LT death and close to a 3-fold reduction in HCC recurrence. The French AFP model identified a stricter AFP cutoff of ≤100 ng/mL for the subgroup of patients outside the MC as a predictor of nearly 70% 5-year overall survival rates and a low risk of recurrence.[36] Interestingly, increasing AFP slope as low as 7.5 ng/mL/month and as high as 15 ng/mL/month in spite of LRT is associated with unfortunate outcomes in patients awaiting LT.[90] While the implications of an AFP slope may seem irrelevant in world regions without a minimum 6 months waiting time, an observation period is essential for the "ablate and wait" strategy.[91] Thus, the lack of durable response to LRT measured by AFP captures a supplementary exclusion criterion for LT.

18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)

Another potential diagnostic tool for patients being downstaged is 18F-FDG-PET imaging. Increased 18F-FDG accumulation of HCC consistently reflects tumor aggressiveness and is connected to undesirable post-LT survival.[92,93] Poorly differentiated HCC expresses high 18F-FDG metabolism with a lesion-to-liver uptake ratio of more than 2.[94] Despite its high sensitivity for detecting extrahepatic metastases, 18F-FDG-PET is not a widespread routine imaging modality due to the absence of cost-effectiveness analyses and prospective validation studies in regions with scarce donor resources.[95] Ultimately, 18F-FDG-PET scans can help determine appropriate treatment options for 18F-FDG-PET-positive patients beyond MC by clarifying aggressiveness of disease.

Conclusions

In light of growing societal demands for LT, tumor downstaging surfaces at the heart of efforts to optimize the LT selection scheme. The premise of downstaging is to allow the opportunity of LT to a larger portion of HCC patients without affecting the transplant survival benefit. A multitude of robust data emphasize that the sole reliance on radiologic tumor size and number is a relatively crude method to gauge the complexity of HCC cases. Meanwhile, limited organ supply and waitlist life expectancy stress the value of surrogates for refined patient selection. AFP and novel biomarkers, LRT approaches, radiographic and AFP response to LRT, in combination with 18F-FDG-PET scans could be utilized as predictors of post-LT outcomes in a multifaceted LT evaluation process. Forthcoming longitudinal multicenter, well-designed studies are necessary to identify and prospectively validate reliable selection parameters. Overall, regional disparities in LT wait times and program-specific practices, like live donor LT, dictate patient eligibility for downstaging and individualized treatment decisions per recommendation and thorough follow-up by the program's multidisciplinary team involving, but not exclusively, radiologists, hepatologists, surgeons, pathologists, and oncologists. Given the complexity of this disease, it is difficult to determine one particular downstaging method that is most successful, as each patient needs to be evaluated on an individual basis for which pre-LT treatment they can tolerate and will best downstage them to within transplant criteria. In general, careful patient selection combined with aggressive locoregional therapy appears to have the best outcomes in long-term.

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Conflict of interest

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Author contributions

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Data sharing statement

All data are available upon request.

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