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HEPATIC CANCER (N PARIKH, SECTION EDITOR)

Downstaging and Expanded Criteria Hepatocellular Carcinoma Liver Transplantation

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Abstract

Purpose of Review Liver transplantation (LT) has been utilized in the last two decades for the treatment of selected patients with hepatocellular carcinoma (HCC). Currently, in most jurisdictions worldwide, only tumor size and number determine transplant candidacy, which may not sufficiently predict tumor behavior. Both tumor downstaging and expanding transplant criteria play an important role in expanding access to LT for HCC patients.

Recent Findings New downstaging protocols are emerging that incorporate response to locoregional therapies (LRT) among those that initially present beyond the accepted Milan criteria. In parallel, new serologic, histologic, and radiographic tools are being identified that may better predict outcomes after LT for HCC, in so-called extended criteria. The efforts of different jurisdictions worldwide in creating new treatment protocols have made it possible to evaluate and compare outcomes of patients over time.

Summary Improvements of LRT and expansion of the criteria for LT for HCC will both play a role in optimizing outcomes for patients with HCC.

Keywords Liver transplantation · Hepatocellular carcinoma · Locoregional therapies · Downstaging · Transplant criteria

Introduction

Liver transplantation (LT) remains the best treatment option for selected patients with early-stage hepatocellular carcinoma (HCC) as it addresses both the malignancy, by maximizing surgical margins, as well as the underlying liver disease [1, 2]. However, the discrepancy between the number of patients with HCC waiting for LT and the number of available organs poses a clinical challenge [3]. Selection criteria for LT in patients with HCC have evolved since the Milan criteria (single tumor ≤ 5 cm or 3 tumors each ≤ 3 cm) were published by Mazzaferro et al. in 1996 [4]. While the Milan criteria are the most frequently utilized and well established, many centers have raised concerns that they may be too restrictive, as tumor size and number alone may be insufficient to predict actual tumor behavior [5–7]. It has therefore been proposed a need to incorporate additional criteria in the selection process. New technologies to improve predicting outcomes after LT for HCC, response to locoregional therapies (LRT) while on the wait-list, along with determining tumor behavior are being incorporated into criteria.

Thus, this review will explore tumor downstaging strategies and expansion of transplant criteria in the setting of treatment of HCC.

Tumor Downstaging

In HCC, downstaging aims to use LRT to decrease the tumor burden of patients initially beyond acceptable LT criteria [8] with the goal of meeting "acceptable" criteria (mostly based on tumor size and number). To be considered a candidate for downstaging, patients must have no extrahepatic disease or macrovascular invasion [9].

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Downstaging Target

The initial tumor burden for patient inclusion in downstaging protocols varies between studies but should in part be dictated by the available pool of donor livers in each jurisdiction. However, a realistic downstaging goal should likely need to be set, to avoid including into downstaging protocol patients with very advanced disease. Serologic markers have been incorporated in the patient selection process. A serum alpha-fetoprotein (AFP) > 1000 ng/mL has been considered as a contraindication to both transplant and downstaging due to poor outcomes [10]. Successful downstaging allows for identification of tumors with more favorable biology and offers the benefit of LT for patients who were initially outside the locally accepted LT criteria. The target of downstaging may differ among jurisdictions, but the most commonly applied is the Milan criteria [11, 12]. In terms of post-downstaging follow-up, the most widely accepted is a minimum period of 3 months without tumor progression prior to LT [8, 13]. Patients who do not achieve accepted LT criteria and those who progress after being successfully downstaged and listed for LT are considered to have failed, and according to downstaging protocols should not undergo LT [14].

Types of Locoregional Therapies

Pre-interventional liver function and tumor morphology and location should dictate the LRT modality of choice and must consider the risk of hepatic decompensation before enrolling a patient in a downstaging protocol [13]. Though there is no recommended first-line choice, the selection of a specific LRT in downstaging is largely based on available data for bridging therapies—those that maintain a patient's candidacy for transplant [15]. These include transarterial procedures such as chemoembolization (TACE) and radioembolization (TARE) with yttrium 90 (Y-90), percutaneous ablation (radiofrequency [RFA] and microwave [MWA]), and stereotactic body radiation therapy (SBRT). Despite a lack of randomized controlled studies comparing the different strategies, TACE has become the most commonly utilized first-line technique for downstaging [9, 16]. TACE involves catheterization of the hepatic artery supplying the tumor, and injection of a combination of chemotherapeutic agents. TACE alone was sufficient in downstaging 40–50% of cases in prospective studies, but adjunctive LRTs are often required to achieve successful downstaging [17, 18]. The use of ablative techniques is acceptable, and the modality of choice is dictated by the size and location of the target lesion [19].

More recently, SBRT has been demonstrated to be safe and effective as bridging to LT in patients who are not eligible for other LRT [20]. In a retrospective study of patients listed for transplant, SBRT following the failure of TACE was similar to RFA and TACE as a bridging therapy to LT [21]. Transarterial radioembolization with Y-90 has additionally been demonstrated to be safe prior to LT, though prospective comparative studies are still lacking [22]. One retrospective study has demonstrated improved survival in those downstaged to Milan criteria with Y-90 compared to TACE [23]. The addition of sorafenib to Y-90 has been considered but was associated with increased biliary complications following transplant [24].

Sorafenib was the first drug approved for the treatment of HCC and is the standard of care when other treatments are not possible. Many agents tested in phase 3 trials failed to improve or even parallel the efficacy of sorafenib. Insufficient antitumoral activity, toxicity in the context of cirrhosis, and inadequate patient selection has attributed to these failures. Sorafenib remained the sole systemic therapy until lenvatinib showed antitumoral activity in a noninferiority trial [25]. There is a recent trend in positive trials for the recent years with an increasing optimism towards systemic treatment improvements for HCC [25]. Induction therapy with these new drugs may be an alternative to test tumor responsiveness to treatment prior to LT. However, this needs to be investigated in prospective trials.

Downstaging Protocols and Outcomes After Downstaging

The University of California San Francisco's (UCSF) group first published their downstaging protocol in 2005 [26]. Of note, UCSF downstaging protocol has a size and number limit for inclusion: patients must have a single tumor < 8 cm, or up to 3 tumors each ≤ 5 cm with a total tumor diameter ≤ 8 cm, or four or five tumors each ≤ 3 cm with total tumor diameter ≤ 8 cm. Since 2010, the UNOS policy considered accepting patients within UCSF criteria that were downstaged to Milan-in criteria, although after multiple discussions, it was only nationally implemented in August 2016 [27, 28]. Yao et al. prospectively enrolled 30 patients with HCC beyond Milan (within the UCSF criteria) to this downstaging protocol. Successful downstaging was defined by tumor meeting Milan criteria after a minimum follow-up of 3 months after LRT. Twenty-one (70%) patients were successfully downstaged and 16 (53%) underwent LT. After a median post-transplant follow-up of 25 months, there was no tumor recurrence. The UCSF experience with downstaging was expanded by subsequent publications. In 2008, among 43 patients enrolled in the downstaging protocol, 35 (57%) underwent LT with an intention-to-treat 1- and 4-year overall survival of 87.5% and 69.3%, respectively [29]. Again, after a median follow-up of 25 months post-transplant, no recurrences were noted. In the same year, Ravaioli et al. showed a comparable intention-to-treat 3-year disease-free survival (71% vs 71%, p = ns) and overall survival (56.3% vs 62.8%, p = ns) for patients initially Milan-out downstaged to Milan-in in a cohort of 177 patients submitted to LT for HCC [17]. Their criteria to include

patients in the downstaging protocol was single HCC 5–6 cm or two HCCs ≤ 5 cm or less than six HCCs ≤ 4 cm and sum diameter ≤ 12 cm.

The first paper from UCSF comparing outcomes between downstaging and Milan criteria came in 2015 [13]. One hundred eighteen patients enrolled in the UCSF downstaging protocol were compared to 488 patients within Milan at listing. In the downstaging group, 64 (54%) patients underwent LT and, in the within Milan group, 332 (68%) were transplanted. The 1- and 5-year intention-to-treat overall survival was 86% and 56% in the downstaging group and 85% and 63% in the Milan group, respectively ($p = 0.29$). The median recurrence-free survival was 95% and 91% for the downstaging group and 96% and 88% in the Milan group ($p = 0.66$). Among the downstaged patients, serum AFP > 1000 ng/mL and Child-Pugh B and C were associated with a risk of dropout. Mehta et al., in a retrospective analysis of 3819 patients from the UNOS database, found a comparable 3-year recurrence probability between Milan-in and downstaging protocol patients within UCSF criteria, but worse survival for an "all comers" protocol for downstaging consideration [30]. In addition, in an intention-to-treat analysis of 207 HCC patients included in a downstaging protocol, the 5-year survival of "all comers" (no limitation in the size and number of tumors) was significantly lower than patients within UCSF (21.1% vs 56.0%, $p < 0.001$) [31]. Therefore, it seems that an upper level of tumor burden before including patients in a downstaging protocol is needed.

Only a few additional studies have compared LT plus downstaging therapies in patients beyond Milan versus LT alone in patients within the Milan criteria. Heckman et al. showed a 5-year recurrence-free survival of 82% in the subgroup of 12 patients who were successfully downstaged [32]. In the same study, the 5-year recurrence-free survival among patients within Milan who underwent LT was 71% ($p = 0.76$). A group from Taiwan showed that patients beyond the UCSF criteria successfully downstaged to Milan had similar 5-year recurrence-free survival than patients who were within Milan at the time of LT (90.1% vs. 86.0%, $p = 0.81$) [33]. Recently, a meta-analysis by Kulik et al. showed a 1-year (RR = 1.11 [95% CI 1.01, 1.23]) and 5-year (RR = 1.17 [95% CI 1.03, 1.32]) survival benefit for patients undergoing downstaging therapies compared to those beyond Milan treated with LT alone [15]. In this meta-analysis, there was no difference in the post-transplant HCC recurrence between the groups (RR = 1.44 [95% CI 0.09, 2.29]).

Expanded Criteria to LT for HCC

In the last decade, several centers have developed their own expanded criteria for LT with satisfactory results. Most of these have focused primarily around anatomic criteria, such as tumor size and total tumor volume, whereas others have incorporated tumor biology, tumor differentiation on biopsy, and serum biomarkers such as AFP and des-gamma-carboxy protein (DCP). Table 1 summarizes these expanded criteria. At the University of Toronto, patients will currently only get MELD exception points if they have a total tumor volume ≤ 145 cm^3 and AFP ≤ 1000 ng/mL, but they can be transplanted with a living donor if they are beyond this criteria but within the Extended Toronto Criteria (ETC) (no limitations in size and number of HCCs, absence of vascular invasion or extrahepatic disease, absence of cancer-related symptoms, and biopsy of the largest mass rules out poor differentiation). Patients within the ETC had a 5-year overall survival and disease-free survival compared to Milan-in patients [37]. Optimal selection criteria must balance the oncologic long-term benefit and potential for cure from HCC within the confines of organ shortage and allocation process.

Serum and Tissue Markers as Surrogates of Tumor Biology

Histologic tumor differentiation has been shown to correlate with tumor recurrence [41, 42]. DuBay et al. found that imaging did not accurately correlate with HCC outcomes over 294 LT patients, and that biopsy would be helpful to diagnose tumoral poor differentiation [43, 44]. This, along with cancer-related symptoms, subsequently became a cornerstone in the Extended Toronto Criteria. Biopsy, however, has been criticized given the risk of tumor seeding and tumor heterogeneity. To avoid this, serum markers have been pursued as additional surrogates of tumor biology. Kaido et al., from Kyoto University, found levels of serum DCP greater than 400 mAU/mL to be predictive of HCC recurrence. Therefore, they proposed extending selection guidelines for LT in HCC patients with DCP < 400 mAU/mL, to a maximum of 10 tumors, with each tumor less than or equal to 5 cm [38]. Similarly, elevated AFP greater than 1000 ng/mL has been identified as a predictor of recurrence in patients within Milan criteria, and AFP less than 100 ng/mL predicts low rates of recurrence in those presenting beyond Milan criteria [10, 45]. As a result, AFP has been incorporated into the total tumor volume (TTV) and 5-5-500 criteria, and its elevation may preclude transplantation at certain centers (see Table 1) [36, 46, 47].

Response to Locoregional Treatments as a Surrogate of Tumor Biology

Recently, new surrogates of tumor biology have been proposed as adjuncts in patient selection by predicting results after LT for HCC. Among these strategies, response to LRT as "bridge" to transplant has been investigated as a potential predictor. A recent study by DiNorcia et al. demonstrated that patients with complete pathological response (cPR) after

Table 1 Liver transplantation expanded criteria for patients with hepatocellular carcinoma

Criteria	Country	Eligibility	Outcomes beyond Milan but within criteria
UCSF criteria [34]	USA	- Single tumor ≤ 6.5 cm or - 3 tumors all ≤ 4.5 cm with TTD ≤ 8 cm	DFS 90.9% (5 y) OS 80.9% (5 y)
Up-to-7 criteria [35]	Italy	- The sum of the maximum tumor diameter and number < 7	OS 64.1% (5 y) PTS 71.2% (5 y)
Total tumor volume (TTV) [36]	Canada	- Total tumor volume ≤ 115 cm^3 - AFP ≤ 400 ng/mL	OS 68% (4 y) PTS 74.6% (4 y)
Extended Toronto Criteria (ETC) [37]	Canada	- No limit in size and number - No vascular invasion - No extrahepatic disease - No cancer-related symptoms - Biopsy of largest tumor not poorly differentiated	OS 55% (5 y) PTS 68% (5 y)
Kyoto Criteria [38]	Japan	- Number ≤ 10 tumors - Size ≤ 5 cm - DCP ≤ 400 mAU/mL	OS 30% (5 y) PTS 65% (5 y)
5-5-500 [39]	Japan	- Tumor size ≤ 5 cm - Tumor number ≤ 5 - AFP ≤ 500	OS 71.4% (5 y) PTS 74.8% (5 y)
Metroticket 2.0 [40]	Italy	For AFP < 200 ng/mL: - Sum of number and size ≤ 7 For AFP 200–400: - Sum of number and size ≤ 5 For AFP 400–1000: - Sum of number and size ≤ 4	OS: training set 87.4% (5 y) - Validation set 77.9% (5 y) PTS: training set 91.6% (5 y) - Validation set 82.0% (5 y)

AFP α-fetoprotein, *DCP* des-γ-carboxyprothrombin, *TTD* total tumor diameter, *UCSF* University of California at San Francisco, *DFS* disease-free survival, *OS* overall survival, *PTS* post-transplant survival, *y* years

bridging therapies achieved a 5-year recurrence rate of 5.2%, compared to 16.4% of patients without cPR ($p < 0.001$) [48•]. However, this study, using data from the United States Multicenter HCC Transplant Consortium, is limited by the fact that this cannot be applied preoperatively and by a lack of more specific pathological data, including the proportion of tumor necrosis. In addition, studies have shown significant survival benefits for patients who successfully responded to LRTs even if not downstaged to Milan-in before LT [30, 49, 50]. In a retrospective analysis of 772 patients listed for LT in two different centers, Lee et al. found that failure to respond to LRT was associated with increased risk for recurrence (OR = 3.00) more so than progression of disease (OR = 1.36). These results suggest that despite progression of disease, patients who eventually can respond to LRT may represent favorable candidates for LT [49]. Furthermore, in a European cohort of 174 HCC patients, Finkenstedt et al. showed that disease recurrence in patients responsive to neoadjuvant therapies was equal to patients with upfront early and very early-stage HCC [50]. Conversely, response to LRT as a predictor of outcomes may be supplemented by response of serum AFP. Halazun et al. found that among 1450 patients from three US centers, the serum AFP response to treatment during the wait-list could predict post-transplantation outcomes, and should be incorporated into HCC selection criteria to allow its expansion [51•].

Future Prospects

New, non-invasive technologies have been proposed to improve prediction of tumor behavior. Specific signatures on contrast-enhanced CT scans, termed "Radiomics," have been proposed by Zhou et al. to predict recurrence after partial hepatectomy [52]. Radiomics considers size, number, and the presence or absence of a capsule, necrosis, vascular thrombosis, arterial involvement, and cirrhosis. While not yet investigated in the transplant population, non-invasive techniques for identification of patients at high risk of recurrence may prove to be useful in selecting patients for LT. Similarly, ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}FDG-PETCT) has demonstrated promise in determining tumor activity. The level of FDG uptake in HCC has been found to correlate with pathological tumor characteristics including microvascular invasion, degree of differentiation, and disease recurrence [53, 54]. Functional imaging may eliminate the risk

of biopsy, while offering similar information on certain high-risk features.

In parallel, MacParland et al. found an intra-hepatic cellular immunologic heterogeneity using single-cell RNA that may point to understanding different tumor behavior among patients [55]. Additional non-invasive methods are in the process of development. Circulating tumor cells (CTC) and cell-free DNA, also known as liquid biopsy, may be the key to understanding HCC tumor behavior puzzle in the next few years [56, 57]. Currently, two methods for identifying CTCs have been approved by the FDA, though neither have been tested in the transplant population [57]. Cell-free DNA is appealing to identify microvascular invasion which would otherwise have been missed on a tissue biopsy, while additionally offering insight into the tumor's genetics [57].

Therefore, recent evidence suggests that for patients with tumors harboring specific histologic, serologic, and radiographic features, the indications for LT should be expanded beyond size and number. Accrual of clinical outcomes of LT using such expanded criteria have improved the understanding of the complex tumor biology of HCC. Due to heterogeneity in data, which is subject to selection bias and limitations inherent to retrospective studies, there is lacking consensus on which criteria provide the most optimal results.

LDLT for HCC

Less stringent selection criteria will theoretically increase risk of tumor recurrence and decrease survival after LT for HCC. A 5-year survival of a minimum of 50% was previously accepted as a cutoff to be listed for LT [58]. More recently, a 5-year survival of at least 61% after LT for HCC has been suggested to not outweigh harm to other patients on the wait list [59].

This issue of organ shortage may be circumvented by the use of living donor liver transplantation (LDLT). This concept has been well adopted in Eastern countries due to the large mismatch between organ donation and a high incidence of HCC [60]. The interest for LDLT has grown recently in the west. By bypassing the organ allocation process, selection criteria for LT in HCC may be naturally expanded. Hence, patients may be able to undergo LT sooner and limit the risk of tumor progression on the wait list.

Outcomes after LDLT versus DDLT has been extensively studied, with results showing similar outcomes between treatments [61, 62]. LDLT results are comparable to DDLT (both donation after circulatory death [DCD] and donation after brain death [DBD]), as published by Kollmann et al., demonstrating 5-year overall patient survival of 71.6% for DCD, 83% for DBD, 88.8% for LDLT, and graft survival of 69.2%, 79.9%, and 84.7%, respectively among 1054 patients from a single center ($p = 0.14$) [63]. Initially, some studies showed higher recurrence in patients transplanted with LD and investigators hypothesized that liver regeneration could be the reason for this finding [64]. However, these studies evaluated the outcomes after transplantation, without an intention-to-treat (ITT) analysis at the time of listing. Goldaracena et al. recently published the benefit in terms of overall survival (OS) and disease-free survival for patients with HCC who had a potential donor for LDLT in an ITT analysis, with a 5-year OS of 68% for LDLT vs. 57% for DDLT ($p = 0.02$), reflecting a reduction in the dropout rate from 27.5% for DDLT vs. 14.6% for LDLT ($p < 0.001$) [65••]. Similarly, Wong et al. described a survival benefit for LDLT in an ITT and propensity score-matched analysis of 375 patients, with a 5-year OS of 81.4% for LDLT vs. 40.8% for DDLT ($p < 0.001$) [66••].

By expanding the pool of possible donors, LDLT may offer an additional route to extend selection criteria in patients with HCC. LDLT for patients with HCC may additionally allow improved understanding of the disease process, as selection criteria may be more flexible compared to traditional strict selection criteria in deceased donor LT.

Preventing Recurrence Postoperatively

Expansion of the donor and recipient pools may offer more patient access to LT for HCC. Postoperative management of these patients should also be considered in the future. Mehta et al. have proposed the individualization of patient follow-up post-LT for HCC based on objective tumor characteristics on explant pathology defining the RETREAT score validated in 341 different patients with results that will be further disseminated in the upcoming years [67, 68]. Postoperative considerations should also include pursuit of antiviral therapy (where previous reports have shown an increase in HCC recurrence) [69–71], adjuvant therapy (although Sorafenib, an oral multikinase inhibitor, showed no benefit in the adjuvant setting post-resection or ablation) [72], and choice of immunosuppression (with inhibitors of mechanistic target of rapamycin [mTOR] such as sirolimus and everolimus having favorable effects on decreasing post-LT HCC recurrence in retrospective data) [73–76].

Conclusion

As LT is considered the best treatment option for HCC, there is a conscious effort to extend the number of patients eligible for LT beyond size criteria. For patients with HCC limited to the liver that is outside of the Milan criteria, downstaging protocols offer acceptable post-LT outcomes. Good response to downstaging may reflect favorable biology that offers long-term survival with LT comparable to those initially diagnosed within transplant criteria. Conversely, prediction models based on not only tumor size and number, but also radiographic findings, genetics, tumor biology, and patient-specific

factors may extend the accepted transplant criteria beyond Milan. Expanding the donor pool, particularly with the use of LDLT, and improving post-transplant management of HCC may allow further expansion of selection criteria.

Compliance with Ethical Standards

Conflict of Interest Phillipe Abreu, Andre Gorgen, Christopher Griffiths, Tommy Ivanics, and Gonzalo Sapisochin each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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