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Living Donor Liver Transplantation in Hepatocellular Carcinoma: How Far Can We Go?

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1. Abstract

The expansion in Liver Transplantation (LT) selection criteria for Hepatocellular Carcinoma (HCC) has shown acceptable results in survival rate and tumor recurrence. Historical analysis of the results shows that the path taken so far is correct; however, there are still doubts about the limit of this expansion. The acquisition of new selection tools that measure the biological behavior of the tumor, instead of the historic and simple preoperative morphological analysis, has been gaining strength in this expansion. In this context, analyzing the ethical perspective in the use of grafts from living donors is essential in order to seek a risk vs. benefit balance for both donor and recipient.

2. Introduction

More than a quarter century after its description, the Milan Criteria (MC) [1] still represents the benchmark for indicating Liver Transplantation (LT) in cases of Hepatocellular Carcinoma (HCC). However, we have been held hostage by the good results of patients selectively transplanted under these criteria and have been afraid of the potential costs of expanding the limits established by the MC, as is well described in the "Metroticket paradigm" [2]. At the same time, expanding the MC, and consequently including more patients on the waiting list, would impact the allocation of already scarce grafts from deceased donors to patients with non-oncological indications, determining harm by delaying the LT for them. In Europe, HCCs represent up to 15% of all indications for LT [3]. In analyzing the expansion of the limits of indication for HCC in the context of Living Donor Liver Transplantation (LDLT), this study subtracts the conflicts of interest related to equity of opportunities with other indications for LT. The experience in Asia, where most HCC LT with expanded criteria are performed with living donors, pushes us towards new references for setting the limits of how far we can go [4]. The use of LDLT in HCC patients beyond the MC brings up relevant questions, such as the impact on recipient survival and recurrence rates; the establishment of predictive markers of the biological behavior of the tumor (in lieu of simple morphological analysis); as well as whether the LDLT offers safety for the donors and efficacy for the treatment of these patients. The aim of this article is to review the current literature related to the use of LDLT in HCC outside the Milan criteria.

3. Extended Criteria

3.1. The Search for the Right Measure – Patient Selection

As demonstrated in previous studies, it is possible to obtain an acceptable survival after LT, in patients with HCC selected beyond the MC [5,6]. The point of contention is in the choice of the selection tool, which has discriminatory power in differentiating patients with initial and intermediate stages, who are indicated for LT, from those with advanced disease, for whom the LT should be contraindicated.

3.2. How Much is the Ticket for a Long Trip? – Acceptable Survival and Recurrence Rates after LDLT

The main question is what is the minimum acceptable Overall Survival (OS) after LT for patients with HCC. In 2010, the Consensus Conference in LT for HCC recommended that LDLT would be an

ethical alternative for patients who presented a survival estimate comparable to that of patients on the waiting list for a deceased donor graft [7], although this may be questionable due to the diversity of results among transplant centers. Preliminary reports suggested that 50% in 5 years after LT would be the minimally acceptable OS for these patients [8]. However, Volk et al. demonstrated, through Markov's model, that the adverse effects of expanding the criteria could exceed the benefits if the patient survival was less than 61% in 5 years [9]. Therefore, more recently, a minimum 5-year survival expectation of at least 60% has been recommended.

3.3. Historical Evolution

In 2007 began the first publications correlating the selection of patients with HCC beyond MC and survival or recurrence rates after LDLT. Most of them were from Asia and presented different limits of oncological disease, more specifically to the size of the largest lesion and number of nodules (Table 1). A critical aspect to emphasize is that most of the publications were retrospective analyses based on the histological characteristics of the explanted liver, thus not presenting as a predictive value for selection before LT, characteristics pointed out one decade earlier in the precursor paper published by Mazzaferro et al [1]. This had already been the subject of discussion and criticism in 2001, with a publication by Yao et al 6, not showing adverse impact on survival from expanding tumor size limits; however, this was also based on pathologic tumor staging criteria from the explanted liver. The tumor stage is underestimated in 20-30% of patients undergoing LT [1,6,8] and this was cited as a concern in the adoption of those criteria. Six years later, the same author published a paper validating the criteria established in 2001, known as University of California San Francisco (UCSF) criteria, now based on preoperative images [10]. It's important to note that, also in 2007, Kyoto's group published a study [11] that includes the use of Des-Gamma-Carboxy Prothrombin (DCP) in addition to preoperative radiological analysis as a selection criteria for LDLT, demonstrating a 10% recurrence rate in 5 years.

More recently, other studies have been published that incorporate, in addition to morphological analysis, tumor aggressiveness biomarkers such as DCP and Alpha-Fetoprotein (AFP) [12-14], presenting acceptable rates of survival and recurrence, as show in TABLE. We must also point out the multicenter retrospective study of the Japanese Nationwide survey – the 5-5-500 rule – (features and results in the Table 1) [14]. From 1990 to 2005, 965 HCC patients who underwent LDLT were included, of which 301 (31%) were beyond MC and within the 5-5-500 rule. There was no difference in results in the analysis of the different historical series. The favorable results have determined the implementation of those criteria in Japan, covered by the Insurance System of the Japanese Ministry of Health, for LDLT and DDLT. One of the main limitations of this study was a failure to analyze the effect of Locoregional Therapies (LRT) for HCC before LT, since currently in Japan all patients diagnosed with HCC are promptly submitted to LRT, if liver function allows.

3.4. Checking the Tools – Navigation Chart

The evolution of the accuracy of imaging in the diagnosis of HCC is notorious; however, improvements are still needed to fill the gap. Analysis of the predictive factors of recurrence shows that part of the problem lies in the disagreement between the established selection criteria and the pathological stage of the explanted liver disease, which often shows disease beyond the selection criteria, probably due to an underestimation in the preoperative imaging examination, as we mentioned previously. This occurrence is higher for the detection of small nodules due to the low sensitivity and specificity of preoperative imaging studies [8,9,15]. Llovet et al. showed a recurrence rate in 5 years of 23.8% (Table 1) and, as expected, 6 out of 7 recurrences occurred in those patients with pathological staging beyond the selected criteria [15]. To mitigate this finding, additional imaging with 2 coincidental techniques is recommended if the size of the additional nodules is in the range of 1 to 2 cm. Satellite nodules − defined as up to 2 cm and distant up to 2 cm from the perimeter of the main node − should be designated, due to the progression in staging disease. Also, larger tumors deserve attention, since those > 5 cm in diameter are associated with a higher risk of vascular invasion, the most dangerous predictor of recurrence after LT [16, 17]. The remote suspicion of vascular invasion, after confronting 2 coincidental imaging techniques, should be ruled out by biopsy [15].

3.5. Markers of Tumor Biological Behavior – Adding a GPS to the Trip

Recently it has become evident that the selection of patients based only on morphological data (tumor size, number of nodules, and volume of oncological disease) doesn't add predictive value in the expansion of criteria, and many authors consider the inclusion of tumor biological behavior markers as mandatory in this selection [11-14]. AFP and DCP have been used as markers of recurrence risk and are currently included among different criteria for selecting HCC patients, as shown in Table.

3.6. AFP

AFP evolved from the simple role of HCC screening in high-risk patients, and was included as an instrument in managing LT for HCC. It was thus established as a tool to include, exclude or reinclude after DWS, patients waiting for LT. For example, the level of AFP was included in candidate selection criteria in France, in a multicentric study of patients within the Milan criteria [18], and in Canada, in a prospective study of patients with extended criteria [19]– in both studies, patients with values ≥ 1,000 ng/mL were excluded from the indication for LT.

Table 1: Expanded Criteria for LDLT in patients with HCC – Publication chronology.

Criteria [Ref.] Year	Features & Analysis	OS - 5 years	DFS - 5 years or REC - 5 years
5-5 rule [45] 2007	≤ 5 tumors, ≤ 5cm	• OS: 75%	• DFS: 90%
Kyoto [11] 2007	≤ 10 tumors, ≤ 5cm, DCP ≤ 400mAu/mL Radiological	• OS: 70%	• REC: 10%
Asan [46] 2008	≤ 6 tumors, ≤ 5cm Histological	• OS: 76.3%	• REC: 15%
*Up-to-Seven [2] 2009	Tumor number + size of the largest ≤ 7 wo MI Histological	• OS: 71.2% wo MI • OS: 48.1% wi MI	• DFS: 64% wo MI
Kyushu [12] 2011	Any number, ≤ 5 cm or DCP ≤ 300 mAu/mL Histological		• DFS: 80%
Samsung [13] 2014	≤ 7 tumors, ≤ 6cm, AFP ≤ 1000 ng/mL Histological		• DFS: 89.6%
BCLC [15] 2018	1 tumor ≤ 7cm, or 3 tumors ≤ 5cm, or 5 tumors ≤ 3cm + MC up to 6m after LRT / Radiological	• OS: 80.2%	• REC: 23.8%
5-5-500 rule [14] 2019	≤ 5, ≤ 5cm, AFP ≤ 500 ng/mL Histological Radiological	• OS: 76%	• DFS: 73.2% • REC: 7.3%

OS: Overall survival; DFS: Disease-free survival; REC: Recurrence; wi: with; wo: without; MI: Microvascular invasion; BCLC: Barcelona-Clinic Liver Cancer; MC: Milan criteria; DCP: Des-carboxy prothrombin; AFP: Alpha-fetoprotein; LRT: Locoregional therapies.
* Patients underwent LDLT or DDLT.

In the setting of LDLT, different cutoff values for AFP have been used for selecting patients, and again the Metroticket paradigm is observed: when this limit is more liberal, more patients are selected, and consequently the risk of recurrence increases, whereas when it is more restrictive, fewer patients are included as beneficiaries for LT. This is evidenced in the rationale for the value of 500 ng/mL included in the "5-5-500 rule," which was based on including the maximum number of patients, by taking into account the combination of tumor size (≤ 5 cm) and number of nodules (≤ 5) with a recurrence rate limit below 10% [14]. Different studies have tried to establish the right measure (Table 1).

3.7. DCP

Histological analysis of explanted livers points to a positive correlation between the presence of Microvascular Invasion (MI) and the expansion of the Milan criteria [20]. The presence of MI was associated with the significant worsening of recipient survival and tumor recurrence, as reported by Mazzaferro et al. in 2009 [2], when the "up-to-seven criteria" was established (features shown in Table 1). In that study, the presence of MI determined worse survival when compared to patients without MI: 48.1% vs 71.2% in 5 years, respectively. This suggests it is essential to add, in the workup of these patients, methods that can predict this finding.

DCP, also known as protein induced by vitamin K absence or antagonist II (PIVKA-II) was validated as a prognostic marker in HCC beyond MC for LDLT [21-23], and has been reported as the strongest predictor for MI, intra- and extra-hepatic spread [24-26]; however, it has received criticism due to unavailability in the West, as well as the frequent serum change due to the status of vitamin K and when administering warfarin [27].

3.8. Other Biomarkers

The neutrophil-to-lymphocyte ratio [28, 29] and fluorine-18-fluorodeoxyglucose Positron Emission Tomography (F-FDG PET) [30,31] are promising markers in predicting recurrence after LT in HCC with expanded criteria. F-FDG PET was reported as a good predictor of microvascular tumor invasion in LT recipients [31].

3.9. Locoregional Therapies (LRT), Downstaging (DWS) and Waiting Time (WT)

Tumor progression during the WT despite LRT has been reported as a predictor of tumor recurrence after LT.29 LRT with DWS and WT has been used as a tool for selecting patients for LT [32], especially those with HCC with expanded criteria, and has even been included in some expanded criteria, such as BCLC [15]. (features shown in TABLE) In 2018, the AASLD guidelines recommended that patients outside MC should undergo LRT for DWS, and that only those who achieved MC and remained within criteria for at least 3 to 6 months should be considered for LT [33,34]. In the context of LDLT there is controversy regarding moving forward with LT in expanded criteria or waiting for DWS after LRT and LT only in tumors within MC [35].

Another topic of discussion is WT. Comparative analysis of preliminary results of post-LT recurrence rates between LDLT and DDLT showed greater recurrence for patients transplanted with live donors [36,37]. The reason for the recurrence rate in this group is likely due to the fast-track approach and consequent lack-

ing knowledge of tumor biology. Perhaps this reduced WT did not allow for the exclusion of patients with more aggressive HCC, as the WT might work as a filter for such patients. Another explanation for these preliminary unfavorable results would be that LDLT was indicated for patients who had been delisted for disease progression while waiting for a deceased donor [37]. Currently, the recommendation is that patients undergo some type of LRT and wait at least 3 months from the last LRT to LDLT, a minimum period required to observe the stability of the disease [38,39]. Some Asian countries, such as Japan, a patient diagnosed with HCC will be submitted to LRT, if liver function allows, fulfilling the WT of 3 months prior to LDLT, a rule defined by government regulation [14]. Patients are only recommended for LRT if they have an adequate functional liver reserve, i.e., bilirubin up to 3 mg/dL, up to Child B, and Transarterial Chemoembolization (TACE) are proposed as the first line for DWS [38,39].

In short, different criteria can be combined to obtain a greater refinement in the selection for LDLT in patients with expanded criteria. Thus, a combination of different validated tools can be used, such as AFP, DCP, F-FDG PET, as well as an observed response to LRT [40].

4.0. LDLT in Expanded HCC: Ethical Outlook

The question of how far we can go in the use of living donors in candidates with expanded HCC should always be answered from an ethical perspective, weighing the real benefits against the risk of futility of what's being proposed. Therefore, it would be ethically justified "when the benefits to both – donor and recipient – outweigh the risks associated with the donation and transplantation." [41]. Donor safety is one of the main concerns in this matter, and we must establish a metric to identify the acceptable risk limit for the donor. In 2004, Dindo and Clavien et al [42]. published a paper with a score of complications that have been validated and are currently used for measuring risks related to surgical procedures in donors. A multicenter study of 5,202 living liver donors established acceptable rates for complications related to hepatectomy for donation: overall donor complication rates up to 27%, and of these less than 6% grade III and IV [43]. However, the current recommendation is that liver transplant centers should aim for right hepatectomy for donation with a perioperative mortality of zero, and an acceptable maximum risk of up to 20% for minor complications (grades I and II) and up to 5% for grades III and IV [40,44].

5. Conclusion

Expansion of the limits for LT in HCC candidates reveals acceptable survival and recurrence rates. This selection should be based not simply on the preoperative morphological analysis of the tumor, but also on the combination of validated tools to assess tumor biological behavior. The safety of the donor should be a constant and primary concern in the use of grafts from living donors for these candidates.

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