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EDITORIAL

Liver transplantation or resection for early hepatocellular carcinoma: More questions than answers☆

Transplante hepático o resección para el hepatocarcinoma temprano: más preguntas que respuestas

Hepatocellular carcinoma (HCC) is one of the most frequent malignant tumors and is the third in mortality attributed to cancer, reflecting its high level of lethality.[1] In a recent analysis of the Surveillance Epidemiology and End Results (SEER) database on subjects in the United States, 5-year survival in patients with HCC was only between 4.7 and 11%; this is partially due to the fact that the majority of tumors are detected at stages in which the only option is palliative treatment.[2] The most widely accepted staging system is the Barcelona Clinic Liver Cancer (BCLC) staging and treatment strategy, which in addition to being a prognostic system, suggests the best therapeutic strategy for each stage. The curative treatment options, such as ablation, resection, and liver transplantation (LT), are limited to early stages.[3] The BCLC model favors resection over LT in the early stage for single tumors when there are no contraindications, and suggests LT for the rest of the early-stage tumors and for intermediate-stage tumors with successful downstaging.[3] Taking into account that nearly all HCC occurs in the presence of cirrhosis, LT is the best treatment that can be offered to patients because it cures not only the tumor, but also the underlying liver disease. However, it is a scarce resource. There has been controversy over the years, with respect to the type of treatment that should be offered to patients with early-stage tumors. Regarding both resection and transplantation, studies comparing the two strategies have produced controversial results.[4]

In this issue of the *Revista de Gastroenterología de México*, Magadan-Álvarez et al. present a retrospective study that compares the outcomes of 58 patients that underwent liver resection for HCC and 38 patients that were treated with LT.[5] Factors associated with recurrence and survival were also evaluated. The patients that underwent resection had better liver function and a higher tumor burden. The patients that underwent LT had better overall survival, less recurrence, greater recurrence-free survival, but did not have a lower HCC-associated mortality rate. The factors associated with overall mortality were liver resection, the neutrophil-to-lymphocyte ratio, and alpha-fetoprotein (AFP) levels. The presence of portal hypertension was a protective factor for mortality due to HCC. Upon analyzing the groups separately, Child-Pugh stages B and C were associated with mortality in the patients that underwent liver resection. With respect to recurrence risk, the associated factors were liver resection, diabetes mellitus, AFP, and tumor burden in the surgical specimen.

The study, albeit on a very limited number of patients, adds to the controversy of similar publications that have compared the two strategies, and documents the difficulty in retrospectively comparing the two groups of patients. Even though survival was higher in the LT group, there was no difference in HCC-associated death between the groups, suggesting that the higher mortality rate in the resection group was due to progression of the underlying liver disease (e.g., decompensation). This reasoning assumes that each of the strategies is effective for treating HCC and that the difference in mortality was because the patients that underwent liver resection did not undergo LT later, perhaps due to a contraindication. Supporting this idea, as can be seen in the Kaplan-Meier curves, was a minimal difference in mortality and specific mortality within the first 3 years, which is when the majority of cases of recurrence are expected. The only LTs in the resection group appear to be the 10 transplants performed *ab initio*; they were not rescue LTs (i.e., before HCC recurrence) or due to liver dysfunction, which is somewhat atypical, given that in the majority of case series,

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between 30 and 60% of the patients that undergo resection had *a priori* contraindications for LT.[6,7] This led the multidisciplinary committee to recommend resection over LT in some patients, introducing a confounding by indication bias when analyzing the results. In this same line of thought, the patients that underwent liver resection were significantly older (some of whom most likely were above the age considered acceptable for LT at that center) and had a higher tumor burden (some of which very possibly had dimensions outside of the Milan criteria). A fairer comparison, so to speak, would include only patients within the Milan criteria in the resection group, and ideally, with single lesions. In brief, if resection was opted for in some cases because the patients were not eligible for LT, that implies that those patients were not offered LT as rescue therapy, which is relevant, given that studies have reported no differences in survival when patients that initially underwent LT were compared with those that first underwent resection and then had rescue LT.[7]

The present work is novel in two aspects. First, it included the Tumor Burden Score in the analysis. It was originally developed for patients with liver metastases from colorectal cancer, (TBS), but has now been studied in patients with HCC, enabling the definition of different prognostic groups within the different stages of the BCLC model.[8] In this case, only the histologic TBS was important, given that, unlike the radiologic TBS, it was associated with recurrence risk, implying that the score could not choose whether a patient should initially undergo resection or LT, but it couldutilized to aid in determining which patient should have adjuvant therapy or should undergo be ab initioLT. In addition, the center where the present study was conducted, utilizes theab initioLT strategy[9] which despite being recommended by the BCLC[3] is not routinely performed. The authors stated that the,[10] patients that underwent LT after resection, did so before presenting with recurrence, due to the presence of poor outcome factors in the resected specimen.

Some of the association results contained in the present study differ from those described by other authors, which in part, may be due to the fact that the authors analyzed the two groups together, instead of separately. Because they are different strategies and are applied to patients with different baseline characteristics, the factors associated with the outcomes of interest (e.g., recurrence and mortality) are likely to be different between the two groups. Consequently, poor prognosis factors, such as portal hypertension and the number of lesions, were associated with better survival, reflecting the fact that these variables are utilized for favoring LT over resection. Factors that often have been associated with recurrence in patients that undergo resection, such as the presence of microvascular invasion or satellite lesions,[10] were not associated with recurrence, which could be because the patients presenting with those factors, at least in the resection group, underwent *ab initio* LT, before presenting with recurrence. One limitation is that surgical margin distance was not analyzed, given that the smaller the margin, the greater the risk for recurrence, mainly in patients with a high TBS.[11,12] Regarding survival, of the factors that have been described in patients undergoing resection (e.g., MELD, AFP, number and size of lesions, cirrhosis, aspartate aminotransferase levels),[13] only liver function, defined by the Child-Pugh scale, was associated with mortality in this study.

This research provides salient information, but also omitted valuable information from the results. Of the patients that had recurrence after resection, whether their recurrence fell within or outside of the Milan criteria was not described, which would have enabled the number of patients that could potentially have been rescued with LT to be calculated. For example, in the studies by De Haas et al.[14] and Cherqui et al.,[6] 75% of recurrences were within the Milan criteria. The results of the 10 patients with *ab initio* LT were not presented either, making it impossible to know if there was recurrence after LT and to evaluate the efficacy of this strategy. Also missing was a more in-depth description of some of the cases, by which the reason why resection or LT was opted for, outside of the usual recommendations, could be understood. For example, there were patients with very early-stage HCC that underwent LT and patients with decompensated cirrhosis (Child B and C) that underwent liver resection. Similarly, some patients with signs of macrovascular invasion in the diagnostic imaging study (BCLC stage C) underwent either LT or resection. Lastly, although the sample size was limited, early recurrence has been associated with a lower survival rate in patients that undergo resection, but that was not evaluated in the present study.[15,16] Another analysis of interest would have been the evaluation of patients with a single lesion that underwent resection, given that the resection of multinodular tumors is associated with a higher risk for recurrence.[17]

Regarding the methodology, there are certain elements that make it difficult to interpret the results. For example, follow-up ''time zero'' for the patients that received LT is not clear in the manuscript; in an intention-to-treat analysis, time zero should be the moment at which patients are referred to the transplant program or the moment at which they are enrolled, to consider the patients that are not transplanted, due to a contraindication or HCC progression, in the analysis. The absence of information about the dropout rate, which has been reported at 15–30% in some studies,[18,19] suggests that the authors considered the moment of the LT to be time zero, thus introducing bias and favoring the LT group.

The results of the present study, even with the points described above, are concordant with other studies, with respect to there being better survival in patients that undergo LT, compared with resection. Considering that to be the case, due to the scarcity of organs, performing LT in all patients with very early or early HCC would not be feasible at the majority of centers that carry out LT. In addition, the fact that resection offers advantages must be taken into account, and the following benefits stand out: (a) 20–46% of patients will not experience recurrence of HCC and will not require a LT in the short term or medium term,[6] which on the one hand, increases the supply of organs for patients with decompensated cirrhosis, and on the other hand, avoids the morbidity and mortality associated with LT in the patient that does not need it; (b) unlike LT, resection is a treatment that is not subject to a waiting list, eliminating the risk of progression while waiting for an organ/treatment; (c) resection does not contraindicate a LT, to the contrary, it provides relevant histopathologic information for decid-

ing on an ulterior therapy: *ab initio* LT, adjuvant therapy, or active surveillance; and (d) it can function as a test for knowing the biology of the tumor, avoiding a futile LT, given that early recurrence after resection and outside of the LT criteria would indicate aggressive tumor biology, suggesting those patients would have developed an early recurrence after LT. In fact, even those in favor of the *ab initio* strategy suggest waiting 6 months after resection before activating patients on the waiting list, in order to evaluate the behavior of the tumor.[9]

In conclusion, although LT appears to offer better survival, compared with resection, there are notable limitations and vast heterogeneity in the majority of observational studies comparing the two strategies, limiting the interpretation of the results. In addition, given the scarcity of organs, it would not be very feasible to offer LT to all patients with early/very early HCC, making the promotion of research to identify the ideal candidates for each of the strategies imperative: resection, resection followed by *ab initio* LT, and LT as the initial treatment. Finally, given that the study evaluating atezolizumab/bevacizumab as adjuvant therapy after resection was positive,[20] the conclusions of studies comparing resection and LT, including this one, will have to be reconsidered, if adjuvant therapy becomes a standard in the near future.

Ethical considerations

The present article is a commentary reflecting the opinion of the author and does not require authorization by an ethics committee.

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Conflict of interest

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