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Liver Transplantation in Hepatocellular Carcinoma

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Abstract

Liver transplantation is the best curative treatment for patients with hepatocellular carcinoma and decompensated cirrhosis. The initial experience in liver transplantation has been disappointing, with a dismal outcome caused by aggressive tumor recurrence. The observations that an advanced tumoral stage before transplantation was directly related to a high rate of tumor recurrence, and that patients with minute or incidental hepatocellular carcinoma had the same outcome as patients without malignancy, provided the rationale for the establishment of restrictive inclusion criteria. The so-called Milan criteria have been widely used during the last 15 years as a selection guideline in many transplant centers. Therefore, the time spent on waiting lists, which increases year by year because of the shortage of donors and the rising number of candidates for liver transplantation for hepatocellular carcinoma, is a fundamental factor for the results of liver transplantation in an intent-to-treat model. Many studies suggested that the Milan criteria are too restrictive and tumor stage beyond the Milan criteria does not necessarily predict worse survival after liver transplantation. Recent studies defined an expanded set of criteria based on pathological data from explanted liver and reported a 60-70% five-year survival rate. The lack of robust and solid evidence-based data asserts the urgent need for a well designed study to address this issue. The increasing donor pool and the treatment while on the waiting list are the main relevant options to improve the results. **(Trends in Transplant. 2010;4:51-7)**

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Key words

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Introduction

Liver resection and liver transplantation are considered the first-line treatments for patients with hepatocellular carcinoma (HCC). In many countries, most HCC develops in livers with hepatic cirrhosis. Cirrhosis is the fundamental risk factor and the accumulated incidence ranges from 15-20% in these patients[1]. With this association, the prognosis of these patients at the time of diagnosis not only depends on the stage of the tumor, but also on the degree of deterioration in liver function[2]. Systematic follow-up of patients with a high risk of developing HCC allows diagnosis at an initial stage, leading to the implementation of effective treatment[3]. According to the conference on HCC in the European Association for the Study of the Liver (EASL), the absence of randomized, prospective, controlled studies on these two surgical options has not permitted the recommendation of one surgical option over the other[1]. Thus, each group must identify the best therapeutic choice based on their technical and human resources. Resection is contraindicated in patients with decompensated cirrhosis, so for them a transplant is the only option.

Improvement in surgical techniques, maintenance anesthesia, postoperative care, and the efficacy of immunosuppressive agents has led to good results with liver transplantation in cases of benign liver diseases. Initially, these results facilitated the wide use of liver transplantation in cases of HCC, with the assumption that the results would be similar to those obtained in cases of non-tumoral diseases. This strategy led to the inclusion of patients who were not candidates for resection because of the presence of large or multinodular tumors. The results soon proved to differ from the foreseen expectations. During the 1980s, disappointing survival rates were reported in different transplant programs[4-7]. In 1991, the data from the Cincinnati Tumor Registry described a five-year survival of only 18% in 365 patients with HCC treated with liver transplantation[8]. However, it should be pointed out that during the same time period, good expectations of survival were reported in transplanted patients with incidental HCC discovered on liver explantation[9,10]. Very low rates of recurrence were described in these cases, leading to the conclusion that the selection criteria of the patients was fundamental in the results obtained with transplantation. The data analyzed during the initial years of the transplantation era, when transplanted patients included from incidental tumors to multifocal or diffuse HCC, provided the background data to identify the optimal criteria to select the HCC patients who would benefit from this option. Large and multifocal disease, vascular invasion, and extrahepatic spread were recognized as the majors predictors for recurrence, and thus, thereafter most of the groups decided to restrict the indication for liver transplantation to those patients with solitary tumors < 5 cm or up to three nodules each < 3 cm. Applying this selection policy, the five-year survival exceeds 70% and the recurrence rate is less than 15%[11,12]. The Milan criteria are now considered as the gold standard for selection of the best candidates for liver transplantation after numerous external validations[13-15].

Selection criteria

The advantage of transplantation versus other types of treatment, and particularly with respect to resection, is not only the elimination of the tumor, but also its oncogenic potential cures the subjacent cirrhosis. Since the determination that patients with tumors who were not candidates for surgical resection because of the tumor size could not be transplanted, the strategy of considering that good results would only be achieved with transplantation in patients who could, hypothetically, be resected was implemented. As previously mentioned, the analysis of the first transplant series in patients with advanced

cirrhosis demonstrated that some patients had small tumors that had not been detected in the pretransplantation studies[9,10,16]. These tumors, which may at present be restricted to tumors of < 2 cm in diameter with modern radiologic techniques, were, at that time, of up to 5 cm in size[15,16]. Thereafter, good candidates were considered to be patients with single tumors of ≤ 5 cm in size. The observations that an advanced tumoral stage before transplantation was directly related to a high rate of tumor recurrence, and that patients with minute or incidental HCC had the same outcome as patients without malignancy[3], provided the rationale for the establishment of restrictive inclusion criteria. The seminal paper by Mazzaferro, et al. published in 1996[11] showed that patients with radiological evidence of a single tumor ≤ 5 cm or 2-3 tumors each ≤ 3 cm had a four-year cumulative and disease-free survival rate of 85 and 92%, respectively, a result comparable to the survival of patients transplanted for cirrhosis and without HCC. These so-called Milan criteria were subsequently validated by many other groups[13-15,19,20], reporting five-year survival rates of 70% or better, and widely used as selection guidelines in many transplant centers. In the USA, the United Network for Organ Sharing (UNOS) therefore incorporated the Milan criteria into T1 and T2 in a modified staging system for HCC to enlist patients[10,11], and T2 stage (single tumor 2-5 cm or 2-3 tumors each ≤ 3 cm) has recently become a condition of prioritization under the Model for End-stage Liver Disease (MELD)[23]. The main problem after resection is disease recurrence, which may exceed 70% at five years and might be predicted by pathological analysis such as differentiation degree, multinodular HCC, and the existence of satellites and microvascular invasion[13,24]. Since recurrence is not so frequent after transplantation even with the same pathological characteristics, we decided to offer the possibility of entering the waiting list for liver transplantation to those patients in whom we detected these major predictors of risk after surgical resection[25]. The preliminary analysis shows that all the patients that have shifted to transplantation have been shown to have residual disease in the explant at transplant, and thus, we feel that this is a policy that can be recommended in clinical practice.

As previously mentioned, in the case of HCC, the prognosis of patients does not only depend on tumor stage[3]. In fact, the current prognostic models should consider four fundamental aspects: tumor stage, degree of liver function, the general status of the patients, and treatment efficacy. Other classifications which only consider some of these factors (Child-Pugh, tumor node metastasis, performance status) are of little use at present. The tumor node metastasis classification, which has been widely used, is not adequate to evaluate the candidates since patients with two synchronic tumors < 2 cm in size located in the two lobes are classified as advanced patients, while small tumors with evident vascular involvement and an invasive pattern affecting a single lobe are classified as initial stage disease[19]. The Barcelona Clinic Liver Cancer (BCLC) staging classification is more adequate with the current situation. With this classification, four groups which select the best candidates for each treatment currently available are established[26]. Prognostic factors, such as the presence of portal hypertension, which has been demonstrated to be of greater importance at the time of selecting adequate surgical treatment, whether resection or transplantation, are taken into account with this classification[27].

Results

Therefore, the time spent in waiting lists, which increases year by year because of the shortage of donors and the rising number of candidates for liver transplantation for HCC, is a fundamental factor for the results of liver

transplantation in an intent-to-treat model[13]. The waiting list for transplantation in our center was initially two months, but in recent years this time has increased to up to six months in the best of cases. The analysis of the results demonstrated that during this waiting time, tumoral progression was produced, obliging exclusion of the patients. This exclusion had such a direct impact on the survival that analysis of the results of the first period showed a survival of 84 and 74% at one and five years, respectively, while survival analyzed according to intent-to-treat was 84 and 69% at one and three years, respectively. Dropout from the waiting list is the main limitation for success in liver transplantation for patients with HCC. The evidence of selection benefits shown by the Milan criteria created a debate on whether or not such criteria should be expanded, allowing liver transplantation also for those patients exceeding the Milan criteria because of larger tumors. Recent studies have proposed expanded criteria in such direction[28-31]. The UCSF criteria (single tumor ≤ 6.5 cm or 2-3 tumors each ≤ 4.5 cm with total tumor diameter ≤ 8 cm) were proposed in a retrospective study by Yao, et al. in 2001[32], these results have been further independently validated by other retrospective studies[29,33,34] and by a recent prospective study by Yao, et al.[35]. On the contrary, adoption of restrictive criteria has made transplantation a therapeutic option of extraordinary value, with a five-year survival of up to 70% in some series[11-13], similar to that obtained in cirrhotic patients without HCC[36], and recurrence rates of less than 15%[37]. These good results are valid for patients undergoing transplantation. The scarcity of donors does not allow all patients on the liver transplant waiting list to be transplanted[38]. The expansion of the waiting list, lengthening the waiting time for an organ, and the consequent deterioration of liver function and/or the progression of tumoral disease, in some cases lead to formal contraindications for transplantation, and in others to the death of the patient. The current dilemma in the HCC transplant community is whether some patients with tumors exceeding the standard criteria can be cured by transplantation, and how is it possible to recognize them by preoperative radiological means[39]. The lack of robust and solid evidence-based data argues for the urgent need for a well designed study to address this issue[40]. To further analyze the rationale of the proposals of extension of indications, at least two considerations should be taken into account: definitions of extension criteria at time 0 of waiting time and the impact of the extended criteria in dropout rates and intent-to-treat survival[41].

Two mechanisms may be effective to reduce this negative effect: increasing the donor pool and curbing tumoral progression while on the waiting list.

Increasing the donor pool

The options for increasing the donor pool include the use of so-called marginal organs, whether they are livers with steatosis or from elderly donors, livers from hepatitis C virus donors, or livers from deceased donors. On the other hand, it is possible to perform split-liver transplantation, which provides the possibility for the sharing of one organ by two patients, performing domino transplantation, in which the donor and the patient are carriers of a metabolic disease and, lastly, living-donor transplantation.

It is clear that the possibility of carrying out living-donor transplantation is of great importance for patients with HCC since, in many cases, this is the only solution for avoiding the long waiting lists. In a recent cost-effectiveness analysis it was shown that living-donor transplantation may be an excellent option when the waiting list exceeds seven months[42]. It may even be the solution to cases not fulfilling the strict selection criteria for cadaveric transplantation. The rational basis for these

cases rests in that up to 40% of patients have disease progression while on the waiting list, although this does not lead to exclusion since the progression does not involve vascular invasion or distant disease[11,13]. In these cases, transplantation may achieve a five-year survival of 50% with a rate of recurrence of around 20%. It is therefore considered that despite not being the best candidates, the survival and recurrence rates achieved are not unacceptable. This group of patients is comparable to the subgroup of optimum candidates used to analyze the natural history of the disease[43]. They present a three-year survival of 50% and thus, if considered for living transplantation, they are expected to achieve a relevant increase in life expectancy. Based on these facts, a pilot study is currently ongoing in our center, in which the criteria for being a living-donor liver transplantation candidate have been expanded[3]. It is evident that these patients with HCC do not have ethical problems derived from accepting receptors with objective data predicting failure due to tumoral recurrence within the first year posttransplantation. Although many groups understand that living-donor transplantation is a personal decision by both the donor and the receptor, the submission of a donor to a not insignificant surgical risk to achieve short-term survival should be carefully considered. In our study, a single nodule ≤ 7 cm in diameter, or three nodules ≤ 5 cm each, or five nodules of ≤ 3 cm each are accepted[3]. Nonetheless, an adequate follow-up period is necessary to draw conclusions.

Treatment while on the waiting list

The other possibility for impeding exclusion from the waiting list is to avoid tumor progression while awaiting transplantation. One of the possibilities is the use of adjuvant or neoadjuvant chemotherapy. Some older studies have reported promising survival rates with the use of doxorubicin[44-47] with the aim of eliminating the micrometastases which may disseminate during surgery[48]. However, these uncontrolled studies included small series with a short follow-up, in which patients with lymph node or macroscopic vascular involvement were deliberately excluded, making it difficult to guarantee the beneficial effect of chemotherapy[48]. In view of these results with systemic chemotherapy, a similar beneficial effect was studied with the use of pretransplant chemoembolization[11,36,49], with a five-year survival of greater than 70% being achieved in some cases. However, these were not randomized controlled trials and the results of Mazzaferro and Majno confirm the lack of differences in terms of survival[11,49]. It is therefore necessary to point out that similar results have been obtained in programs in which preoperative transarterial chemoembolization was not used, and thus its possible benefits in these cases remains to be confirmed[13]. The beneficial effect of chemoembolization in the treatment of HCC has recently been demonstrated for the first time in a randomized controlled study[50]. This study has led to the possibility of reproducing these results in potential transplant patients.

Other possibilities are the use of surgery or the injection of percutaneous ethanol (PEI) during the waiting period[3] or, more recently, the use of radiofrequency ablation (RFA)[51]. The injection of ethanol has been proven to be effective in HCC[3]. In our center, we recently analyzed the impact of carrying out treatment while awaiting transplantation on survival and cost-benefits[52]. With the use of the Markov model, the benefits of surgery were demonstrated in terms of increased survival and with an acceptable cost when the waiting list time was more than one year, while the cost-benefits were not accepable with short waiting lists or with a high incidence of dropouts. On the contrary, the use of PEI was effective both in terms of gaining years of survival and cost per year of life gained, regardless of the waiting time on the transplantation list.

There are clinical evidences that RFA is more effective than the other modalities of local ablative therapy, and that radiofrequency is a safe bridging therapy before liver transplantation. However, insufficient evidence exists to determine if RFA improves transplantation rates and posttransplantation outcomes[51].

In conclusion, the increase in the incidence of HCC may lead to a collapse in the transplantation waiting lists for these patients. Transplantation is the treatment of choice, but from a realistic view of the problem, the lack of donors for all transplantation candidates requires a search for all possible alternatives for further optimizing the results obtained.

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