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REVIEW

Liver transplantation in hepatocellular carcinoma

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Summary

Liver transplantation is one option of surgical treatment for cirrhotic patients with hepatocellular carcinoma, it not only treats the malignancy but also the underlying disease. After an initial period of disappointing results, mainly due to lack of adequate selection, survival nowadays is similar to that obtained by cirrhotic patients without tumor. Currently the scarcity of donors is the main limitation in the treatment of this type of patients. Increased time on the waiting list does compromise the results if they are analyzed in an intention-to-treat basis. Adjuvant therapy on the waiting list (ethanol injection, chemoembolization, surgery, etc.) or the use of marginal grafts in order to increase the donor pool may be some alternatives to overcome this deficit. The development of adult living donor liver transplantation has proved to be a good alternative in this type of patients even if they do not fulfill the conventional criteria.

Introduction

In many countries, most hepatocellular carcinomas (HCCs) develop in livers with hepatic cirrhosis. Cirrhosis is the fundamental risk factor and the accumulated incidence ranges from 15% to 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 in an initial stage, leading to the application of effective treatment [3]. Most groups consider surgical resection or transplantation as the therapeutic option. Transplantation is the first surgical option in cases with decompensated cirrhosis. 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 does not permit the recommendation of a preference [1]. Thus, each group must identify the best therapeutic choice based on their technical and human resources.

Prior to establishing the surgical technique to be performed, the natural history of this type of patient must first be taken into account. Our group recently analyzed the survival of a group of patients in an intermediate tumor stage to whom treatment was not administered [4]. These patients did not undergo treatment having been randomized into a 'no treatment' group in two controlled studies. The global probability of survival in this group of patients was 54%, 40% and 28% at 1, 2 and 3 years after diagnosis, respectively. These reports are not only important to establish the prognosis of patients with HCC but also to evaluate the efficacy of treatments to cure or palliate. The treatment administered to these patients should, therefore, achieve greater survival than that reported, otherwise the selection of the patients would be qualified as inadequate.

Improvement in surgical technique, maintenance anesthesia, postoperative care and the efficacy of immunosuppressive agents led to good results with liver transplantation in patients with end stage of chronic liver disease. 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 nontumoral 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 [5–8]. In 1991, the data from the Cincinnati Tumor Registry described a 5-year survival of only 18% in 365 patients with HCC treated with liver transplantation [9]. Very rapid recurrence of the tumor was occurred in the new organ with subsequent mortality. 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 explant [10,11]. 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.

Selection criteria

The advantage of transplantation versus other types of treatment and, in particular, 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 tumors which were not candidates for surgical resection because of their advanced stage could not be transplanted, the strategy 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, which had not been detected in the pretransplantation studies [10–12]. These tumors, which may at present be restricted to tumors of <2 cm in diameter with modern radiologic techniques, at that time were up to 5 cm in diameter [13,14]. Thereafter, prospective candidates were considered to be patients with single tumor of not more than 5 cm in diameter. Similarly patients in whom rapid recurrence occurred, due to the presence of macroscopic vascular invasion or extrahepatic growth were discarded. In autopsic series it has been demonstrated that hematogenous dissemination is largely dependent on tumor size and the presence of multinodularity and thus, these factors supported the idea of early recurrence of these tumors in the new liver [15]. There is, however, new data to add to the previous data. The study of explanted livers demonstrated the previously undiagnosed presence of distant carcinomatous foci in a marked percentage (25–50%) of cases [16,17]. In transplanted patients, with more than one nodule <3 cm in diameter, disease-free survival was found to be greater than that achieved after resection. The greater percentage of recurrence after resection should be attributed to these preoperatively undetected carcinomatous foci, which transplantation was able to eliminate [16]. Given these data, most groups restrict transplant indications in patients with single tumors of a diameter of ≤5 cm or to a maximum of three nodules, none of which is >3 cm in diameter, and in patients without portal vascular involvement or distant disease. These indications are currently maintained as adequate selection criteria to achieve the best results in liver transplantation [17–20].

The main problem after resection is disease recurrence that may exceed 70% at 5 years and might be predicted by pathological analysis such as differentiation degree, multinodular HCC and the existence of satellites and microvascular invasion [21,22]. As recurrence is not so frequent after transplant, 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 resection. The preliminary analysis shows that all patients had residual disease in the explant at transplant. Thus, we feel that this can be recommended in clinical practice.

As previously mentioned, in the case of HCC, the prognosis of patients does not depend on tumor stage alone. In fact, the current prognostic models should contemplate four fundamental aspects: tumor stage, degree of liver function, the general status of the patients and treatment efficacy [23]. Other classifications, which only consider some of these factors (Child-Pugh, TNM, Performance Status) are of little use at present [23]. The TNM^{-21} classification which has been widely used is not adequate to evaluate the candidates, as patients with two synchronic tumors of <2 cm in diameter 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 [19,20]. A new classification, namely, Barcelona-Clinic Liver Cancer (BCLC) staging classification has recently been proposed by our Liver Transplant Unit, which is more adequate in the current situation. With this classification four groups, which select the best candidates for each treatment currently available are established [23]. 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, with this classification are taken into account [21,24].

Results

Many studies have been carried out in the last decade on the two surgical options, resection and transplantation. The analysis of the series of resected patients showed a low percentage of 5-year survival associated with a high percentage of disease recurrence [16,22,25–30]. Competitive results with transplantation are only achieved in

optimum candidates [21]. However, adoption of restrictive criteria has made transplantation a therapeutic option of extraordinary value [17,31] with a 5-year survival of up to 70% in some series [18,19,21], similar to that obtained in cirrhotic patients without HCC [31] and recurrence rates of around 15% [32]. 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 receive a transplant [33]. The expansion of the waiting list, lengthening of waiting time for an organ, and the consequent deterioration of liver function and/or the progression of tumoral disease in some cases led to formal contraindications for transplantation, and in others, to the death of the patient. The time required for the tumor to double its size varies, but waiting lists of more than 6 months may produce the conditions necessary to develop these contraindications. The results of transplantation based on intention to treat have recently been studied in our center [21]. The waiting list for transplantation in our center was initially of 2 months but, in recent years, this time has increased to up to 6 months in the best of cases. The analysis of the results demonstrated that during this waiting time, tumoral progression was occurred, thus obliging the 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 1 and 5 years, respectively, while survival analyzed according to intention to treat was of 84% and 69% at 1 and 3 years, respectively. Dropout from the waiting list is the main limitation for success in liver transplantation for patients with HCC. 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 could be livers with steatosis or elderly donors, livers from hepatitis C virus donors [34] or livers from not beating donors. On the other hand, it is possible to perform split liver transplantation which provides the possibility of two patients sharing one organ, perform domino transplantation, in which the donor and the patient are carriers of a metabolic disease and lastly, living donor transplantation [35–37].

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 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 7 months [38]. It may even be the solution for cases not fulfilling strict selection criteria for cadaveric transplantation. The rational basis for these cases lays in that up to 40% of patients have disease progression while on the waiting list, although this does not lead to exclusion as the progression does not involve vascular invasion or distant disease [18,21]. In these cases, transplantation may achieve a 5-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 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 [4]. They present a 3-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 because of tumoral recurrence within the first year post-transplantation. Although many groups understand that living donor transplantation is a personal decision by both the donor and the recipient, the submission of a donor to a significant surgical risk to achieve short-term survival should be carefully considered. In our study, a single nodule of not >7 cm in diameter, or three nodules of up to 5 cm each or 5 nodules of not >3 cm each are accepted [3]. Nonetheless, an adequate follow-up period is necessary to make conclusions. Recently the results of liver transplantation in patients with HCC exceeding conventional selection criteria have been communicated [39,40]. It is, therefore, necessary to point out that the Yao paper from San Francisco [40] is based on pathology and not on imaging. Thus their proposed expansion criteria should not be applied as the dropout rate would sharply increase and the results deteriorate if there is a significant waiting time.

Curbing progression on 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 [20]. Some studies have reported promising survival rates with the use of doxorubicin [41–44] with the aim of eliminating the micrometastasis, which may disseminate during surgery [20]. 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 [20]. In view of these results

with systemic chemotherapy, a similar beneficial effect was studied with the use of pretransplant chemoembolization [18,31,45] with a 5-year survival of >70% being achieved in some cases. However, these were not RCT studies and the results of Mazzaferro *et al.* [18] and Majno *et al.* [45] confirm the lack of differences in terms of survival. It is, therefore, necessary to point out that similar results have been obtained in programs in which preoperative TACE was not used, and thus, its possible benefits in these cases remain to be confirmed [19,21]. The beneficial effect of chemoembolization in the treatment of HCC has recently been demonstrated for the first time in a randomized, controlled study [46]. 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. The injection of ethanol has been proven to be effective in HCC [17,47,48]. In our center, we recently analyzed the impact of carrying out treatment while awaiting transplantation on survival and cost-benefits [49]. With the use of the Markov model the benefits of surgery were demonstrated, in terms of increased survival and with an assumable cost, when the waiting list was of more than 1 year, while the cost-benefits were not assumable with short waiting lists or with a high incidence of dropouts. To the contrary, the use of PEI was effective in both terms of gaining years of survival and cost per year of life gained regardless of the waiting time on the transplantation list.

In conclusion, the increase in the incidence of HCC may lead to a collapse in the transplantation waiting lists for these patients. Transplantation is one option of surgical treatment but from a realistic view of the problem the lack of donors for all transplantation candidates requires searching of all possible alternatives to further optimize the obtained results [50].

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