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TOPIC HIGHLIGHT

Dr. Shahid A Khan, *Series Editor*

Liver transplantation for hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is the commonest primary malignancy of the liver. It usually occurs in the setting of chronic liver disease and has a poor prognosis if untreated. Orthotopic liver transplantation (OLT) is a suitable therapeutic option for early, unresectable HCC particularly in the setting of chronic liver disease. Following on from disappointing initial results, the seminal study by Mazzaferro *et al* in 1996 established OLT as a viable treatment for HCC. In this study, the "Milan criteria" were applied achieving a 4-year survival rate similar to OLT for benign disease. Since then various groups have attempted to expand these criteria whilst maintaining long term survival rates. The technique of living donor liver transplantation has evolved over the past decade, particularly in Asia, and published outcome data is comparable to that of OLT. This article will review the evidence, indications, and the future direction of liver transplantation for liver cancer.

Key words: Hepatocellular carcinoma; Selection criteria; Liver transplantation; Living donors

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the third most common cause of cancer death and the fifth most prevalent cancer in the world[1]. Cirrhosis itself is the major risk factor for the development of HCC[2-6]. Overall, 80%-90% of HCC develop in the context of liver cirrhosis[7]. Hepatitis B infection (HBV) particularly, can cause HCC in the absence of cirrhosis as a result of its direct carcinogenic effect[8]. Hepatitis B is the commonest cause of chronic liver disease in the East, whereas hepatitis C (HCV) and alcohol predominate in the West[9]. This has resulted in widespread geographical variation in HCC prevalence. In particular, in Asia and sub-Saharan Africa the incidence is far higher than in North America and Europe. In our Unit in London, 70% of patients with HCC on the background of liver disease have underlying chronic viral hepatitis; 40% have HCV, 30% HBV and a minority have a combined etiology including viral, steatohepatitis and/or alcoholic chronic liver disease.

The incidence of HCC is increasing in many parts of the world[10]. In the United States, for example, the rate of HCC has increased by 80% over the past 20 years[11]. This may be partly due to the fact that screening for HCC in patients with cirrhosis has become established practice. However, in our Unit over the past 5 years, only 55% of patients with HCC had their cancer detected as part of a screening program. Another likely reason for rising HCC incidence is the increasing burden of chronic viral hepatitis. In addition to HBV and HCV, both fatty liver disease and alcohol-related liver disease continue to rise. As a result, it is predicted that HCC prevalence will increase further over the coming decades.

Without specific treatment the prognosis is poor with median survival of early and advanced HCC being 6-9 mo and 1-2 mo, respectively[12]. Tumor resection in the context of cirrhosis and portal hypertension

leaves a residual cirrhotic liver which remains at risk of developing new lesions and a liver which is at risk of decompensation. Recurrence rates of 50%-70% have been reported after resection of HCC[13]. Many patients have advanced cirrhosis at presentation and are not eligible for resection. In addition, HCC is often multifocal and thus resection is not feasible.

EVOLUTION

The initial liver transplants were performed by Starlz in 1963[14]. Four years elapsed before there was a long term survivor[15]. Over the subsequent decades advances in organ preservation and particularly prevention of organ rejection led to a steady rise in both transplant numbers and outcomes. With the widespread acceptance of OLT, transplantation for HCC was attempted. Unfortunately, the initial results of OLT for HCC showed disappointing short and long term survival rates and high levels of tumor recurrence[16].

Given the huge demand for organs, transplantation needed to be limited to those with a good prognosis, and liver transplantation continued to flourish as the definitive treatment of end stage liver disease. A change in thinking arose from the following two observations. Firstly, finding small unexpected HCC in explanted livers did not affect the outcome of OLT[17]. Secondly, there was no significant difference in terms of overall survival between liver transplantation and resection in cirrhotic patients with hepatocellular carcinoma[18]. Furthermore, in small tumors, < 3 cm, whether uni- or bi-nodular, transplantation resulted in better survival than resection. This culminated in the development of the "Milan criteria" which has cemented OLT as an effective treatment for HCC.

MILAN CRITERIA

The seminal study by Mazzaferro *et al*[19] in 1996 established OLT as a viable treatment for HCC. In this study in Milan, Italy, 48 patients with HCC and cirrhosis were followed and transplanted. Twenty eight patients had preoperative therapy, mainly transarterial chemoembolization (TACE). All patients fulfilled the following restrictive radiographic criteria: single lesion $\leqslant$ 5 cm, up to 3 separate lesions all less than 3 cm, no evidence of vascular invasion, no nodal or distant metastases. The aim of the criteria was to achieve a good prognosis in those who fulfilled them, avoiding a poor prognosis in those who exceeded them. The overall actuarial survival after 26 mo was 75% and recurrence-free survival was 83%. Patients who fulfilled these criteria on the basis of explant pathology had actuarial survival of 85% and recurrence-free survival of 92%. These rates are not dissimilar to the outcome of patients undergoing OLT without HCC. These criteria have become known as the "Milan criteria" and these results have been confirmed throughout the world.

EXPANDED CRITERIA

Since the acceptance of OLT for the treatment of HCC, excellent post-transplant survival has been reported in many centers. With increasing experience of OLT many centers have recognized that many explanted livers have had HCC beyond the size described in the "Milan criteria". These transplanted patients have been followed over time and many have had excellent 1- and 5-year survival. Also, advances in imaging have occurred in the past decade since these criteria were originally published. As a result several groups have attempted to broaden the restrictive limits. A group from the University of California at San Francisco (UCSF) have reported a 5-year survival of 75% using less restrictive criteria derived by retrospectively analyzing 2000 patients undergoing OLT[20]. This was achieved by using the following criteria: a maximum tumor size 6.5 cm or 2 lesions < 4.5 cm diameter with a total tumor diameter < 8 cm. The same group validated the 'San Francisco criteria' on 168 patients based on preoperative imaging assessments[21]. Various other groups have published expanded criteria with results not dissimilar to the original "Milan criteria"[22-28]. The same group in Milan has recently published retrospective data regarding outcome in 1112 patients exceeding the original Milan criteria[29]. In this study, a 71.2% 5-year overall survival could be achieved using the "up-to-7" criteria (HCC with 7 as the sum of the largest tumor (cm) and the number of tumors). It is clear that the larger the tumor size and number, the worse the outcome. Tumor understaging, by preoperative imaging of patients has been one of the major concerns for liberalizing the "Milan criteria"[30-32]. Also, there can be significant tumor progression during the waiting time to transplantation[33]. At the present time, the "Milan criteria" remains the only universally accepted and recurrently validated criteria.

COMPARISON OF OLT TO OTHER TREATMENT STRATEGIES

Various treatment options are available for HCC including the surgical options as outlined above, and local ablative techniques such as radiofrequency ablation (RFA), transarterial chemoembolization (TACE), and percutaneous ethanol injection (PEI). Systemic chemotherapy has been unsuccessful in the studies thus far[34]. The local ablative treatments themselves are used as a palliative procedure or as a bridge to resection or transplantation. The only curative treatments are that of hepatic resection or transplantation.

The published observational studies to date suggest survival following OLT is at least as good as following resection in patients with adequate hepatic reserve[18]. Liver resection can leave residual liver which is of insufficient size to provide adequate function and as stated before, has the possibility of developing further lesions. In patients with well-compensated cirrhosis (Child Pugh A) and HCC, the decision whether to resect or transplant remains controversial. However, in the current realm of organ shortage and long waiting times, the decision to resect in this group appears attractive.

If tumor recurrence were to recur than salvage transplantation can be performed. This strategy has been retrospectively analyzed by different groups with conflicting outcome data. One retrospective study has shown no difference in either outcome or disease-free survival when comparing primary OLT to resection and salvage OLT[35]. In contrast, an observational series has shown primary OLT to have lower operative mortality, recurrence rates and survival rates[36].

REQUIREMENTS FOR LISTING

The United Network for Organ Sharing (UNOS) administers the allocation of organs for transplantation in the United States. UNOS provides a set of specific requirements[37] for listing patients with HCC: (1) Rough evaluation of the number and size of tumors and to rule out extra-hepatic spread by ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI) plus CT of the chest; (2) Prelisting biopsy is not mandatory, however patients must have one of the following: (a) a biopsy confirming HCC; (b) a vascular blush corresponding to the area of suspected HCC; (c) an α fetoprotein (AFP) > 200 mg/mL; (d) an arteriogram confirming a tumor; (e) a history of local ablative therapy (TACE, RFA, PEI); (3) Patients with chronic liver disease and a rising AFP > 500 mg/dL can also be listed even in the absence of discrete tumor on imaging studies; (4) The patient must not be a resection candidate; (5) Reimaging by CT or MRI every 3 mo is required to ensure continued eligibility for OLT.

BRIDGING THERAPY

The "dropout" due to tumor progression whilst waiting for OLT is reported to be at least 20%[20]. This problem has furthered the use of local-regional adjuvant therapy (LAT) whilst awaiting transplantation such as TACE, RFA, and PEI. Unfortunately no randomized, controlled trials have been conducted to assess this approach[38]. As a result, there is no universal consensus as to the optimum bridging therapy prior to transplantation.

The ultimate aim of LAT is to provide complete tumor necrosis in an attempt to halt tumor progression. Analyses of explant specimens subjected to RFA and TACE have shown complete tumor necrosis rates of 47%-66% and 16%-27%, respectively[30,39,40]. A retrospective study looking at tumor necrosis in 61 patients did not find any particular modality of LAT to be superior[41].

Retrospective analyses have shown that multimodality local treatment is associated with a modest survival benefit[42,43]. As a result most units offer dual as well as single modality ablative treatments, in an attempt to reduce tumor progression and recurrence rates. Hepatic resection has also been used as a bridge to transplantation[44]. This is in contrast to the traditional view of resection and transplantation being opposing strategies. Unlike LAT which has been shown in studies to achieve only partial tumor necrosis, resection should achieve the best tumor control. Resection also allows a thorough intra-operative assessment of liver status and tumor burden. A detailed histological analysis can be made of the resected specimen and can give invaluable information about the natural history of the tumor and the presence of microvascular invasion. Resection, however, is associated with increased risk and, as stated earlier, should only be attempted in well-compensated cirrhotic patients.

PROGNOSTIC FACTORS

Conforming to the "Milan criteria", in terms of tumor size and tumor burden, gives rise to 3-4-year recurrence-free survival rates of up to 92%[45-47]. Multivariate analysis has shown these to be the only independent variables predicting patient survival and tumor recurrence. Other biological factors such as tumor grading, microvascular invasion and microsatellites appear to play a role, but within the constraints of the size and number burden. These biological factors can only be accurately assessed post-transplantation or post-resection. The histological grade of the tumor can be assessed by lesional biopsy and several authors have recommended this approach[48-50]. Lesional biopsy does however carry the risk of tumor seeding which has been estimated at approximately 2%[51]. Furthermore, significant histological heterogeneity has been described in large tumors, which limits the utility of needle biopsy[52].

A scoring system incorporating tumor differentiation in addition to tumor size and number has been validated in a 2007 French multicenter study[53]. In this study, tumor histology improved the Milan criteria in predicting post-transplant outcome. These results conflict with a more recent 100 patient study in which tumor differentiation did not predict HCC recurrence[54].

LIVING DONOR TRANSPLANTATION

Living donor liver transplantation (LDLT) has evolved over the past decade, mainly in response to the scarcity of donor livers. Deceased liver donation is particularly scarce in Asia, where organ donation rates are less than 5 donors per million population compared to 10-35 per million in Western countries[55]. This is also compounded by the fact that in most Asian countries HCC is the most common cancer and a frequent indication for OLT. LDLT, in particular right liver transplantation, has dramatically increased the number of potential donors. This can eliminate the problem of long waiting times and 'dropout' whilst waiting for an organ because of disease progression. Furthermore, as there is no direct 'competition' from other potential transplant recipients the restrictive criteria on tumor burden can be relaxed somewhat.

The results from LDLT appear to show good long term survival rates with retrospective studies showing comparable rates to OLT[56-58]. There are, however, published retrospective studies which show a higher rate of tumor recurrence than with conventional OLT[59-61].

The reason for this is not entirely evident. It has been postulated that many candidates are not transplanted because of tumor progression whilst waiting for OLT; these patients, with more aggressive tumor biology, are then removed from the outcome analysis. In LDLT there is no protracted waiting time and hence the patients with aggressive tumors are transplanted.

LDLT has been performed, in some centers, in patients who have a tumor load beyond the Milan criteria with the consent of both the donor and recipient[62]. In addition, LDLT carries a risk to the donor during hepatectomy with morbidity and mortality rates of 14%-21% and 0.25%-1%, respectively[63]. This highlights the need for a universal consensus on the use of LDLT.

Akin to the published "expanded criteria" in OLT, several groups have attempted to determine an "expanded criteria" in LDLT. Using a scoring system including the measurement of "protein induced by vitamin K absence or antagonist-Ⅱ" (PIVKA-Ⅱ), a Japanese group have achieved a 5-year recurrence rate of only 4.9%[24,64]. PIVKA-Ⅱ, also known as des-carboxyprothrombin, is an abnormal prothrombin protein found in the serum of patients with HCC and in patients with vitamin K deficiency or on warfarin therapy. It has been suggested as an alternative marker to AFP for the surveillance of HCC, but is not currently used as standard practice internationally. This study reported an 86.7% survival rate in patients with ≤ 10 tumors, all ≤ 5 cm (on pre-transplant imaging) and with PIVKA-Ⅱ values ≤ 400 mAU/mL. Without the application of PIVKA-Ⅱ, patients with ≤ 10 tumors, all ≤ 5 cm had similar 5-year recurrence rates as those conforming to the Milan criteria (7.3% *vs* 9.7%)[24,64].

CONCLUSION

Liver transplantation remains the definitive treatment for HCC complicating cirrhosis. Since the publication of the "Milan criteria", OLT has progressed into a universally accepted treatment for HCC. The results of OLT for HCC continue to improve with time. The retrospective studies to date suggest outcome for OLT for HCC is only marginally worse than for end stage liver disease itself. Over the past decade LDLT has evolved but at present needs more stringent universal guidance on its usage. However, the results of LDLT for HCC seem slightly worse than for OLT but this may be a result of selection bias. The use of single or combined local ablative therapy in the period prior to OLT appears to be accepted. As operative techniques have improved, resection as a bridge to transplantation now appears a viable option in compensated cirrhotic patients. Resection also offers the ability to gain invaluable information about the tumor.

Undoubtedly further work will be published on expanded criteria for transplantation. The various studies to date have shown that acceptable long term outcomes are possible with OLT for HCC outside the "Milan criteria". With time a new universal consensus will be required to standardize these 'expanded' criteria.

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