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REVIEW

Liver transplantation as a management of hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide and has a poor prognosis if untreated. It is ranked the third among the causes of cancer-related death. There are multiple etiologic factors that can lead to HCC. Screening for early HCC is challenging due to the lack of well specific biomarkers. However, early diagnosis through successful screening is very important to provide cure rate. Liver transplantation (LT) did not gain wide acceptance until the mid-1980s, after the effective immunosuppression with cyclosporine became available. Orthotopic LT is the best therapeutic option for early, unresectable HCC. It is limited by both, graft shortage and the need for appropriate patient selection. It provides both, the removal of tumor and the remaining cirrhotic liver. In Milan, a prospective cohort study defined restrictive selection criteria known as Milan criteria (MC) that led to superior survival for transplant patients in comparison with any other previous experience with transplantation or other options for HCC. When transplantation occurs within the established MC, the outcomes are similar to those for nonmalignant liver disease after transplantation. The shortage of organs from deceased donors has led to the problems of long waiting times and dropouts. This has led to the adoption of extended criteria by many centers. Several measures have been taken to solve these problems including prioritization of patients with HCC, use of pretransplant adjuvant treatment, and living donor LT.

Key words: Hepatocellular carcinoma; Management; Liver transplantation; Pretransplant adjuvant therapy; Milan criteria

Core tip: Hepatocellular carcinoma (HCC) has a poor prognosis if untreated. Screening is challenging due to the lack of specific biomarkers. Successful screening is very important as early diagnosis can provide curative opportunities. Orthotopic liver transplantation (LT) is the best therapeutic option for early, unresectable HCC. When transplantation occurs within the established Milan criteria, the outcomes are good. The shortage of organs from deceased donors led to the adoption of extended criteria. Several measures have been taken to solve these problems including prioritization of patients with HCC, use of pretransplant adjuvant treatment, and living donor LT.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a major health problem[1]. It is ranked as the third cause of cancer-related death worldwide[2]. Up 80%-90% of cases are associated with underlying cirrhosis[3]. Liver resection and local ablative procedures are regarded as potentially curative treatments, but their effect on the functional reserve of the liver restricts their application. Also, there is a high chance of recurrence in the liver remnant[4]. Liver transplantation (LT) is the ideal treatment for patients with HCC and cirrhosis. It has the ability to remove the tumor as well as the underlying liver cirrhosis. This gives the chance to restore the liver function and decrease the risk of development of new HCC[5]. Since the first LT done by Starzl *et al*[6] in 1963, the procedure did not gain wide acceptance until the mid-1980s, when immunosuppression with cyclosporine became available[7]. The goal of LT is to provide liver recipients with the maximum benefit possible in a fair, ethical, and cost-effective manner. Mazzaferro *et al*[8] in Milan established criteria for orthotopic LT (OLT) as a variable treatment for HCC in a study published in 1996. By adoption of these criteria, LT can achieve a good prognosis in the recipients who fulfilled them and avoid the poor prognosis in those who exceeded them.

SELECTION CRITERIA

Initial results of OLT in patients with HCC were poor[2,9,10]. In 1996, a study from Milan found that restrictive selection criteria (single tumor up to 5 cm or up to three tumors, each no larger than 3 cm, without macrovascular invasion or extrahepatic spread) led to similar outcomes when compared with OLT performed in patients without HCC[11]. These Milan criteria (MC) were used by the United Network for Organ Sharing (UNOS) to arrange the listing priority of patients presenting with HCC. The aim of these criteria was to achieve satisfactory results in patients who fulfilled the criteria and avoid poor outcomes in recipients who exceeded them. This study concluded that the 10-year overall survival was 70% in 300 liver transplants for HCC that fulfilled the MC. The same results have been confirmed worldwide[12,13]. Other groups have showed favorable outcomes in patients with early HCC[11,14-18].

The good outcome of OLT depending on the MC has encouraged putting more patients with HCC on the list of transplantation. Some studies found that the MC may be too restrictive and prevent some recipients from their chance in LT. Extending the selection criteria showed relatively good results. This extension was applied to both transplantation of patients with tumors outside the MC and the use of pre-LT treatment to downstage the tumor stage to fulfill the MC[19-21].

A multicenter study performed in multiple European centers to assess how to expand the MC. Data were collected from 466 patients who were transplanted for HCC with tumors exceeded the MC diagnosed by posttransplant pathologic assessment[13,21]. One of the proposed expanded criteria was the UCSF criteria which include single tumor nodule up to 6.5 cm; or three or fewer tumors, the largest of which is 4.5 cm with the sum of the tumor diameters 8 cm[20]. The 1 and 5-year survival rates in 60 patients included in the study who met these criteria were 90% and 75.2%, significantly higher than patients with HCC exceeded these limits (50% at 1 year, $P < 0.0005$) and comparable with the survival rates in the Milan study (75% at 4 years)[11]. Some groups have studied the expanded criteria and had results in favor of the Milan study[22-28]. A study performed by the same group in Milan. They gathered retrospective data regarding outcome in 1112 patients exceeding the original MC[29]. A 71.2% 5-year survival could be achieved using recipients with HCC up to 7 cm of the largest tumor and number of tumors up to 7. This is known as the "up-to-7" criteria. There is a direct association between the larger tumor size and increased number, with the worse outcome. Preoperative imaging understaging tumors has been one of the major concerns for expanding the MC[30]. This understaging occurs in 20% of patients[13]. Up till now, the MC remains the only universally accepted criteria. Currently, by increasing demand and organ shortage, multiple studies have suggested a 50% 5-year patient survival to be the minimum acceptable to approve the expansion of MC[13]. This point was studied by the UCSF group, who has applied expanded criteria to benefit an additional 10% of patients with HCC regarding posttransplant survival and tumor recurrence. In living donor LT (LDLT), the recipients with larger and/or multiple tumors with no vascular invasion, are not excluded from transplantation as the graft donation here not public but depends on the donor's intention[31].

Prioritization of liver transplant candidates on waiting list, decreasing dropout rates and shorting the waiting time for LT.

After the selection of patients with HCC for transplantation and putting them on a waiting list, the problem of the progression on waiting list arise. This progression will lead to exceeding the MC and dropout from the list. Dropout rates become an increasing problem with the prolonged waiting times. One study concluded that, with a short waiting time (mean 62 d) there are minimal or no dropouts resulting in 85% 2-year survival, while a longer waiting time (mean 162 d) lead to 23% dropout rate and less than 60% 2-year survival[32]. The available liver grafts have to be allocated to the sickest patients.

In February 2002, UNOS adopted a modified form of scoring system as the basis of its liver allocation

policy. This system aims to arrange the recipients on the waiting list for LT based on statistical formulas to predict who is most likely to die soon from liver disease. The model for end stage liver disease (MELD) is used for adult and the pediatric end stage liver disease model is used for pediatric patients[33-35]. The MELD scoring system was initially developed to detect the risk and mortality in patients undergoing transjugular intrahepatic portal systems shunt[36]. Wiesner *et al*[34] and Wiesner *et al*[35] used the MELD score to patients with end-stage liver disease not undergoing transplantation and proved its relevance in UNOS status 2A or 2B patients listed for transplant between November 1999 and December 2001[37]. MELD score is a numerical scale, ranging from 6 (less ill) to 40 (gravely ill). It gives each individual a "score" which denotes how urgently the patient needs a liver transplant within the next three months. MELD score can be calculated from three laboratory values: creatinine, total bilirubin, and international normalized ratio of the prothrombin time[35]. It's ability to predict 3-mo mortality was not affected by other complications of cirrhosis as ascites, encephalopathy, variceal bleeding, and spontaneous bacterial peritonitis[35]. The application of MELD scoring system is an important step in moving from a retrospectively derived allocation system to a prospective evidence-based approach[38]. By prioritization organ donation on the basis of mortality risk, the MELD scoring system had achieved improvements in waiting list mortality and fairness of access to LT[39,40].

Patients with early HCC usually have near normal synthetic liver function which gives them a low MELD score, and lower chance for liver transplant. Most of these patients have the risk of progression of their HCC leading to dropout form the waitlist rather than by deterioration of their liver disease. This problem was solved by the invention of MELD score specially for HCC patients attempting to reflect the risk of dropout, and consider the equivalent in outcome to death[37]. Patients with T1 lesions which mean a single tumor up to 2 cm, were given a MELD score of 24 points and patients with T2 lesions which are beyond T1 but within MC, were allocated a score of 29 points. By applying this MELD score for patients with HCC, there was an increase in the LT for HCC patients, relative to non-HCC patients. LT for HCC increased from 7% to 22% of all deceased donor transplants, with improvements in the waiting list times and dropout rates for HCC patients relative to the pre-MELD era[41]. Also, the outcomes for patients with HCC exceeded those of non-HCC patients with equivalent MELD scores[42]. Some investigators found that more than 33% of patients diagnosed preoperatively to have T1 lesions, found not to have HCC in the explant[43]. Since the start of use of HCC MELD score in 2002, three changes have occurred, aimed at addressing fairness between HCC and non-HCC patients. Under the current system, the native MELD score is used for patients with T1 lesions. For patients with T2 lesions, they receive an HCC score of 22 points and also receive point upgrades, for every three month period on the waiting list[41]. The update HCC MELD score now provides a fair way to access LT for HCC patients[44].

Bridging therapy and managing liver transplant candidates on the waiting list: It is very important to continuously evaluate the patients with HCC on the waiting lists to make sure that they are still within the inclusive criteria for LT. Multiple procedures have been developed to manage the patients whose HCC is at risk or shows signs of progression while on the waiting list for LT. There is no ideal imaging method nor proper specific timing to follow up these patients, although a 3-mo interval is common[45]. Some reports showed that an increase in α-fetoprotein level is associated with poorer outcome after LT and the use of locoregional therapy (LRT) is effective in the reduction of that risk. Periodic evaluation of the patients on the waiting list should be performed by imaging (dynamic computed tomography (CT), dynamic magnetic resonance imaging (MRI), or contrast-enhanced ultrasonography) and serum α-fetoprotein measurements[45]. Cancer progression in patients with HCC on waiting list is common and leads to dropout from the waiting list which is reported to be at least 20%[46].

Pre-transplant LRT are used on patients with HCC on the waiting list aiming at decrease the tumor progression and lowering the dropout rate[47]. They are not of benefit in patients with UNOS T1 tumors less than 2 cm[45]. Llovet *et al*[15] found good survival results of OLT in early HCC with no adjuvant therapy with waiting time 58.9 ± 45.1 d. There is no randomized control data to prove any benefit of pre-LT LRT for the prevention of dropout or reduction in post-LT recurrence[5,48]. Most data that showed benefits of pre-LT LRT came from small single centre, non-controlled studies. As a result, there is no universal consensus as to the optimum bridging therapy prior to transplantation[49]. The bridging strategies might be of benefit for patients with UNOS T2 tumors which means one nodule 2-5 cm or three or fewer nodules each ⩽ 3 cm, who may wait for 6 mo or more on the waiting list. High α-fetoprotein levels and large sized tumors seem to have a higher risk for dropout[50-52]. The most commonly used procedures include transarterial chemoembolization (TACE), radiofrequency ablation (RFA), multimodality therapy using combinations of TACE and RFA[48], Percutaneous ethanol injection (PEI) and combination of TACE with PEI[53,54]. Multiple studies showed no statistically significant survival improvement[11,17], but Harnois *et al*[16] showed that TACE was well tolerated and associated with promising results in selected HCC patients with some functional hepatic reserve with average waiting time of 167 d. In a retrospective study, it was found that pre-LT TACE can produce downstaging or total necrosis in tumors less than 3 cm[55]. Other retrospective studies have shown that multimodality local treatment is associated with an average survival benefit[56,57]. Explants of patients received pre-LT RFA and TACE were analyzed. The results showed complete tumor necrosis rates of 47%-66% and 16%-27%, respectively[52,58,59]. Other studies showed

that combination of TACE with PEI led to improved survival and complete tumour necrosis compared with no pre-LT treatment in small numbers HCC patients[53,54]. Some studies have proved[60] and emphasized[61] the role of TACE in the HCC patients on the waiting list for LT. Another study reported the survival results of arterial embolization or chemoembolization against symptomatic treatment in HCC not suitable for curative treatment and Child-Pugh class A or B and Okuda stage Ⅰ or Ⅱ[62]. This study showed 2-year survival probability 50% for embolization, 63% for chemoembolization and 27% for control (chemoembolization *vs* control $P < 0.009$). A retrospective study assessed tumor necrosis in 61 patients did not find any local ablation therapy (LAT) procedure to be superior[63].

A recent study by Lesurtel *et al*[64] did not show any benefit for pre-LT TACE regarding the dropout rate or post LT survival. Similarly, several small, single centre, uncontrolled studies reported the results of pre-LT RFA on dropout rates, without giving any conclusion[58,59]. Major complication and mortality rates for TACE as pre-LT LRT are amounted to 5% and 2.5%, respectively[65]. Regarding RFA as pre-LT LRT, major complications were observed in about 8% of cases[59]. One study showed an increased rate of post-LT tumor recurrence following incomplete tumor necrosis induced by LRT[66]. Other compilations of LRT include, needle track seeding and extra-hepatic metastases[67].

Other new pre-LT modalities are likely to show up aiming to improve post-LT results[68,69]. Recent randomized controlled trials showed the ability of the oral multikinase inhibitor sorafenib to delay HCC progression and improve survival. A randomized control trial examining the utility of this agent in combination with pre-LT TACE is already in progress[70]. External beam radiotherapy also showed promising results as a new pre-LT LRT[71].

Hepatic resection has been used as a bridge to LT[72]. Unlike LAT, resection should achieve the best tumor control. It gives the chance for intra-operative assessment of liver status and tumor burden. All the data needed about the nature of the tumor, natural history and microvascular invasion can be issued from the analysis of the surgical specimen. On the other side, resection, is associated with complications and should only be offered to well-compensated cirrhotic patients[49].

So currently, no recommendation can be made on bridging therapy in patients with UNOS T1 lesion (⩽ 2 cm). In patients with UNOS T2 lesions with one nodule 2-5 cm or three or fewer nodules each ⩽ 3 cm that fulfill MC and a likely waiting time > 6 mo, LRT may be appropriate. No superiority of one LRT to others. Patients who progressed on the waiting list and exceeded the criteria for listing should considered for understaging by LRT. Patients with progressive disease, in whom LRT intervention is not considered of benefit or effective should be dropout from the waiting list[45].

The role of LDLT in HCC: LDLT has evolved, mainly due to the scarcity of donor livers and in some cases, totally unavailable[73-75]. It is the main source of grafts for recipients on the list for LT in Japan and much of Asia because the lack of societal acceptance of organ retrieval from brain dead donors[76,77]. Moreover, in most Asian countries, HCC is the most common cancer and a common indication for OLT. Also, due to organ shortage, long waiting times associated with deaths on the waiting list, drop-out due to medical reasons, or progression of tumors beyond acceptable criteria, LDLT has been used in countries with well established programmes for organ donation from brain dead or non-heart-beating donors[45]. The main principle in LDLT is the safety of donor[78,79]. Although there are concerns of donor morbidity and mortality, LDLT has opened up the possibility of living donation to the adult patients with end-stage liver disease. Some studies compared deceased-donor LT (DDLT) and LDLT for HCC[80-85]. No significant difference in outcome could be identified between both types of grafts. The results from LDLT appear to show good long term survival rates with retrospective studies showing comparable rates to OLT[82,86,87]. Some other retrospective studies showed a higher rate of tumor recurrence with LDLT than with conventional OLT[81,83,84]. This may be due to the short waiting time for patients in LDLT and hence patients with aggressive tumors are transplanted without declaring themselves while with OLT these patients are not transplanted because of their tumor progression whilst on waiting list due to longer waiting time so they will be removed from the outcome analysis. To minimise donor risk and maximise recipient outcome, LDLT must be performed only in centers of excellence in liver surgery and LT[45]. Psychosocial considerations for both the donor and recipient are very important. Unlike deceased-donor donation, it is ethically acceptable for LDLT to be offered to patients with tumour exceeding the MC since, other listed patients will not by this process[88]. Deceased-donor grafts can be offered for failed grafts after LDLT, even if extended criteria were used. Other centers offer retransplantation to recipients who received a living graft, within the accepted criteria, however, it is not recommended for patients following LDLT for HCC outside the accepted regional criteria for DDLT[89]. Rates of retransplantation due of graft failure after LDLT are low and their outcomes are favorable.

Post LT management: The risk of tumour recurrence is the main concern after LT. It occurs in 8%-20% of recipients[90]. It is usually seen within the first 2 years after LT, and is associated with a median survival of less than 1 year from the time of diagnosis[91]. Early recurrence can be diagnosed by routine imaging and α-fetoprotein monitoring[92]. Post-LT monitoring may include 6-12-mo contrast-enhanced CT or MRI imaging for the first 3-5 years after LT and α-fetoprotein levels[45].

Surgery can be offered for resectable for resectable recurrent HCC lesions[45]. LRT as RFA, or TACE, has been successfully used in selected patients when

technically feasible and with limited disease[93]. Some studies showed that sirolimus, an mechanistic target of rapamycin (mTOR) inhibitor, was associated with lower tumour recurrence and improved survival after LT[94-96]. However, no recommendation can be made on the use of mTOR inhibitors to reduce the risk of HCC recurrence outside clinical trials[45]. A study showed that, sorafenib had an antitumour effect in patients with advanced HCC[68]. It is currently studied in phase 3 trial (STORM trial) as an adjuvant therapy after resection or ablation of HCC. It has been used with limited side effects after LT[97]. Licartin, a 131I-radiolabelled murine monoclonal antibody was shown to have a positive effect on prevention of tumour recurrence and on survival[98]. Retransplantation is not appropriate treatment for recurrent HCC, as most recurrences are associated with systemic tumour dissemination. Development of *de-novo* HCC in the transplanted graft should be treated as having new tumors and retransplantation might be considered[99].

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