Liver Transplantation and Hepatocellular Carcinoma

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Liver Transplantation and Hepatocellular Carcinoma

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I am honored to serve as the Editor in Chief of the first of a yearly monographic series that the transplant subsection of the **International College of Surgeons – United States Section** developed with the support of **Astellas Pharmaceuticals**. The College is proud to provide all its members, as well as all the transplant directors in the country, with a scientific tool that can be used for many purposes including teaching and updating knowledge in specific areas of transplant surgery. This project also has the objective of involving more transplant surgeons in the activities of the College. In fact, the main authors of each manuscript have been invited to be lecturers at the next meeting of the International College of Surgeons - US Section. Top-notch transplant surgeons in the country were asked to address a very hot topic in transplantation and have written the three papers enclosed in this monograph.

The first paper is entitled ***Role of Liver Transplantation in Management of Hepatocellular Carcinoma*** and it provides an overview of the importance of orthotopic liver transplantation (OLT) in the treatment of HCC patients. It is expected that in the next two decades the significance of this matter will increase, due to the current hepatitis C epidemic in which the number of patients that will develop HCC is likely to double. In this work, the proposed solution to limited numbers of transplantable livers is to increase live-donor liver transplantation.

The next part of our monograph is entitled ***Liver Transplantation for Hepatocellular Carcinoma Under MELD Score-Based Allocation System***. It summarizes the results of the introduction and the modification of the MELD system focusing on the importance given to HCC patients. Originally, the MELD system was implemented by UNOS in February 2002 to regulate organ allocation on the basis of medical emergencies. Priority was given to HCC patients by giving them extra points, since their liver functions are usually well maintained and the overall score for the HCC patient was lower and not proportionate to the risk of death from the tumor. An adjustment was needed to give a more appropriate score to these candidates. The results after the implementation of the modified system were optimistic and waiting list mortality decreased. Along with that, the national rate of transplantation for HCC patients increased significantly and concern that HCC patients were given excessive priority over the non-HCC patients arose. Consequently, a year later,

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the priority MELD score for HCC was decreased. The transplant community is very sensitive to this issue and the discussion is still open especially because the survival of patients with HCC after a transplant is higher than with the non-HCC patient's.

The title of the final paper is ***Immunosuppressive Strategy in Liver Transplantation with Hepatocellular Carcinoma*** and is based on the widespread concerns that in the last 15 years patients are overly immunosuppressed (IS). The paper illustrates the results, based on several studies, that standard IS treatment has on HCC patients. A thorough literature review was conducted on the topic of IS in post liver transplant patients with HCC. The result of the collection of experiences shows that it is highly unlikely that once HCC recurrence has taken place any changes or discontinuation of IS would reduce the recurrence of the disease. The best that can be expected is a delay in the progression of disease after recurrence. In summary, this part of the monograph suggests that even if there is no conclusive evidence, reduction in induction therapy and baseline maintenance of IS may be beneficial in the prevention and delay of HCC recurrence. In this work, the importance of the introduction of mTOR inhibitors is also recognized, but it is strongly recommended that large, multi-center studies be conducted to clarify the potential advantage of their use.

I hope you enjoy this publication and are able to garner some useful information that might be pertinent to your practice. On behalf of the Officers and Fellows of the United States Section of the International College of Surgeons I wish to convey my sincere gratitude for the opportunity to be involved in this project. I am proud to be associated with this noble group of surgeons and to have the opportunity to provide my colleagues with an educational tool that is sure to stimulate your consideration.

Editorial Policy

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Role Of Liver Transplantation In Management Of Hepatocellular Carcinoma

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver. It is well established that patients with underlying cirrhosis are more likely to develop HCC than non-cirrhotic patients. Hepatitis B virus accounts for the majority of cases of HCC in China and Africa. In the Western hemisphere, hepatitis C is the most common cause. Chronic alcohol abuse is a well-established risk factor for HCC and in the presence of either hepatitis B or C doubles the risk. Patients with hepatitis C have a 20 times greater risk of developing HCC compared to non-infected patients.

Given the current hepatitis C epidemic, the number of patients who will develop HCC is expected to double in the next two decades[1-3]. In fact, the annual risk of developing HCC is 5% for cirrhotic patients with hepatitis C and 0.5% for cirrhotic patients with hepatitis B[4]. To address this issue, the American Association for the Study of Liver Diseases (AASLD) has established a list of patients considered high risk for developing HCC for whom screening and surveillance are recommended. (Table 1)

Table 1: **AASLD Surveillance Recommendations**

Hepatitis B carriers
Asian Males >= 40 years
Asian Females >= 50 years
All cirrhotic hepatitis B carriers
Family history of HCC
Africans over age 20
For non-cirrhotic hepatitis B carriers not listed above the risk of HCC varies depending on the severity of the underlying liver disease, and current and past hepatic inflammatory activity. Patients with high HBV DNA concentrations and those with ongoing hepatic inflammatory activity remain at risk for HCC.

Non-hepatitis B cirrhosis
Hepatitis C
Alcoholic cirrhosis
Genetic hemochromatosis
Primary biliary cirrhosis
Although the following groups have an increased risk of HCC no recommendations for or against surveillance can be made because a lack of data precludes and assessment of whether surveillance would be beneficial.
Alpha1-antitrypsin deficiency
Non-alcohol steatohepatitis
Autoimmune hepatitis

Importance of Staging

As with other malignancies, treatment of HCC at an early stage yields the greatest chance for cure. Late-stage disease has a dismal prognosis. Unfortunately, most patients with HCC are diagnosed too late for effective intervention. (Table 2, page 7) illustrates the Barcelona Clinic Liver Cancer (BCLC) staging system. This system uses the degree of tumor burden, severity of cirrhosis, and the patient's performance status to determine the type of treatment required and ultimately the patient's life expectancy. Curative treatments such as resection, orthotopic liver transplantation (OLT), and local ablative therapies are reserved for patients with early-stage disease. OLT is reserved for early-stage patients who meet established criteria and who are not candidates for surgical resection or ablative therapy because of underlying cirrhosis. Hence, patient selection is paramount for the success of OLT in treating HCC.

Selection of Patients with HCC for OLT

Early failures of OLT for HCC in the 1990's led to a critical review of the selection of patients for transplantation. In 1996, Mazzaferro et al. published a set of selection criteria with improved recurrence-free survival.[5] The Milan Criteria have been adopted by the United Network for Organ Sharing (UNOS) in order to select patients who would benefit most from OLT. Patients who undergo OLT for HCC can now expect 5-year survival rates of 60-75%, a rate similar to that of patients undergoing OLT without HCC. Continuing success has prompted other groups 6,7 to call for further refinements to the Milan system (Table 3) in order to expand the number of patients who qualify for OLT.

Table 3 **The Milan Criteria**

	Single Tumor	Multiple Tumors		
	Maximal Diameter	Maximum Number	Largest Tumor	Total Tumor Size
Milan 1	≤5.0 cm	3	≤ 3.0 cm	Not Applicable
UCSF2	≤ 6.5 cm	3	≤ 4.5	≤ 8.0 cm

Results of Transplantation

Generally speaking, a patient with HCC who is properly selected with a good performance status can expect to have a 5-year survival of 75% after OLT. The recurrence of HCC in the transplanted liver is approximately 15-70%.

Organ Allocation

As the survival of patients with HCC treated by OLT has increased, several issues have arisen. The number of patients with HCC eligible to undergo transplantation is expected to increase. First of all, the number of patients who will be diagnosed with HCC is expected to double in the next two decades secondary to the hepatitis C epidemic. Secondly, if efforts to improve the screening and surveillance of cirrhotic patients are effective, then more patients will be diagnosed at an early stage and therefore more will be eligible for transplantation. Thirdly, improvements in selection criteria may illustrate that more patients would benefit from transplantation [7,8].

Currently, the number of organs available for transplantation is not sufficient. A significant number of patients will suffer progression of their disease while waiting for an organ and "drop out" of consideration for transplantation. Other patients will die while on the waiting list. Several clever strategies have been implemented in order to increase the organ supply: domino transplantation (taking the explanted liver from a patient with amyloidosis undergoing OLT and giving it to a patient with HCC), split-liver transplantation (splitting one organ into two lobes for two recipients), and expanded-criteria donors (hepatitis C infected or otherwise marginal donors). Unfortunately, these strategies are unable to meet the increasing demand for transplantation.

Of the possible strategies to increase the number of organs available for transplant, live-donor transplantation holds the most promise. Live-donor transplantation has the advantage of reducing the waiting time and allowing the surgery to be performed on an elective basis. Generally speaking, a live donor can be considered if the wait time for transplantation is expected to exceed the time required for the patient's disease to progress (in some centers approximately 7 months). As with all live-donor transplants, the morbidity and mortality of the donor must be given paramount importance. The success rate with live-donor transplants is similar to cadaveric transplants.

Summary

OLT is an effective treatment option for cirrhotic patients with HCC. Patient selection is the key to a successful outcome. While the goal of screening high-risk patients is to diagnose the disease early, the outcome may be a larger number of patients competing for a limited resource.

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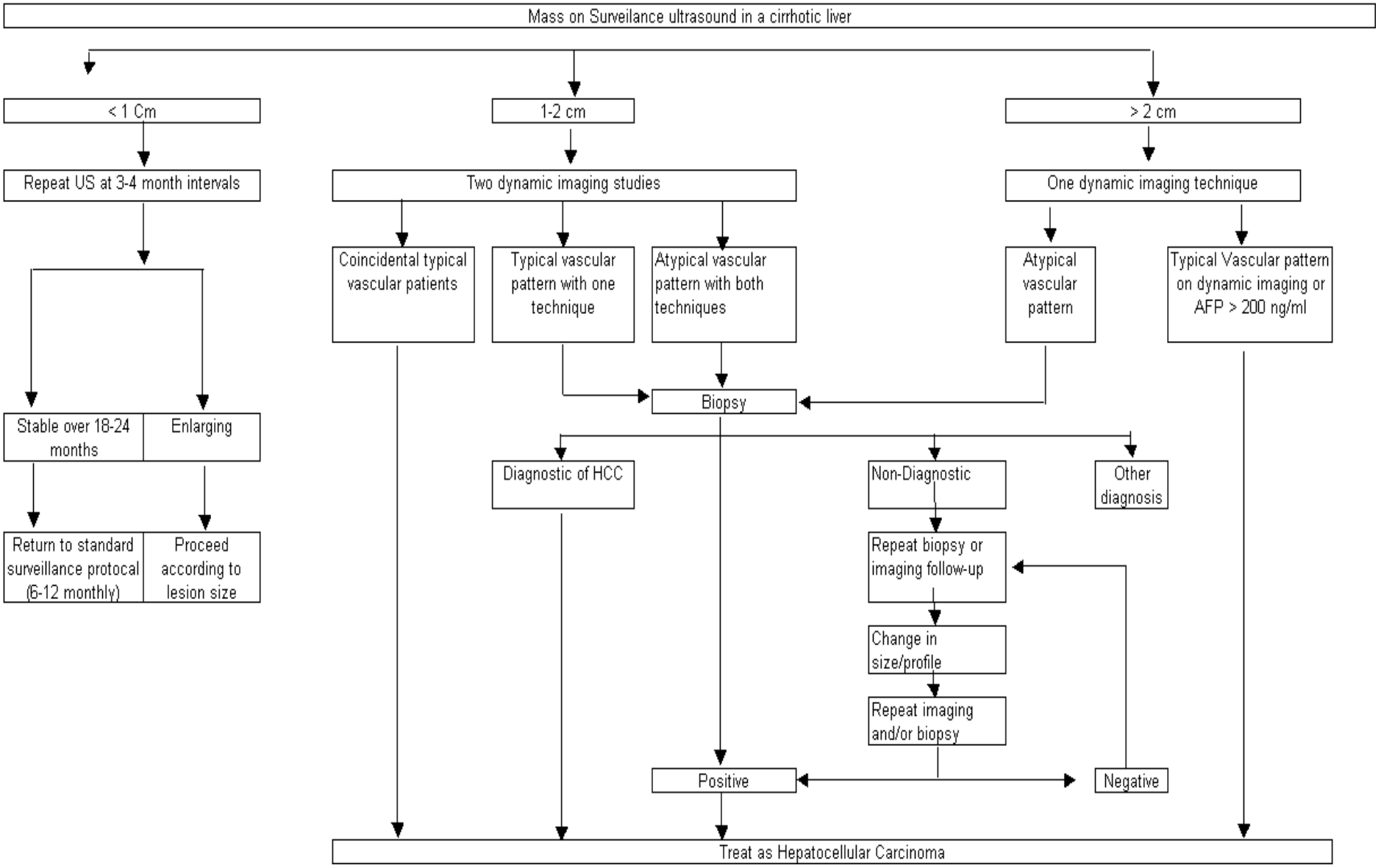
Table 2 **Barcelona Clinic Liver Cancer (BCLC) staging system**



Liver Transplantation for Hepatocellular Carcinoma Under MELD Score-Based Allocation System

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Liver transplantation is the acknowledged treatment of choice for patients with hepatocellular carcinoma (HCC). When using a restrictive set of criteria for tumor size and number, which limit the risk of tumor recurrence, transplantation offers the best chances for cure and long-term survival for patients. The reported 5-year survival rate after liver transplantation for patients with early-stage HCC has been reported to be consistently above 70%.[1-4] HCC in the early stage, but unresectable due to underlying cirrhosis, would be the best indication for liver transplantation. For proper selection of the patient for liver transplantation, careful imaging diagnosis to rule out extrahepatic metastasis and major vascular involvement in the liver is mandatory.

Introduction of a new organ allocation system based on medical urgency

Traditionally, organ allocation relied on the length of the recipient's waiting time. Due to unique characteristics of end-stage liver disease in patients who do not have any artificial means of maintaining life (such as dialysis for kidney failure or ventricular assist device for heart failure), the incidence of waiting list mortality has increased with an increased disparity between numbers of transplant candidates and available donor organs. Waiting list mortality due to the worsening shortage of organs has focused attention on an improved organ allocation system based on stratification of the medical urgency of transplant candidates rather than on a first come first served basis. The model for end-stage liver disease (MELD) score, which was originally developed to predict outcomes of the transjugular transhepatic portosystemic shunt procedure (TIPSS), has been shown to be useful in ranking transplant candidates according to their probability of death over a defined period. It also has been shown to be useful in predicting death independent of etiology and complications of portal hypertension.[5]

Based on the observed superiority of the MELD to the Child-Pugh-Turcotte score as a scale of disease severity and risk of mortality[6],the new MELD allocation policy was implemented by UNOS on February 27, 2002. In this model, patients are assigned a score that reflects their 3-month predicted mortality. In theory, the sickest patient with greatest risk of death on the waiting list would get the highest score.

In the previous system with a few tiers of UNOS status, priority status 2B had been given to candidates with early HCC. Despite this priority, the waiting time of these candidates was likely to be extended due to the system's poor discriminative capability, which favored the length of waiting time over medical urgency. Because of prolonged waiting time for livers for transplantation, these patients were at risk for tumor growth exceeding the acceptable criteria for transplantation. However, in the new MELD score-based system, the priority of HCC candidates was maintained by providing them with extra points in addition to their calculated points from the MELD algorithm. Due to the relatively preserved liver function in many HCC patients, their MELD scores were disproportionately low even with increased risk of death from the tumor. An adjustment was needed to take into account the greater risk of death due to HCC. When the MELD score-based system was implemented, candidates with T1 HCC (single lesion < 2 cm) were given a MELD score of 24, corresponding to 15% 3-month mortality. Those with T2 HCC (single lesion 2-5 cm, or two to three lesions all <3 cm) were assigned a MELD score of 29. Patients with HCC beyond a certain stage would not be given any extra priority than their calculated MELD score based on labs. A study of the first year after MELD implementation showed that the waiting time to liver transplantation became significantly shorter and the dropout rate from disease progression was reduced. Waiting list five-month survival was also increased.[7]

The size limit of the tumor for transplant candidacy has been questioned. Yao et al. have demonstrated nearly equal prognosis using their expanded criteria (UCSF criteria) for a single lesion <6.5 cm, three or fewer lesions, and a total tumor diameter smaller than 8 cm.[8] When using these expanded criteria, the dropout rate from the tumor growth can be reduced.

Where should we draw a line between too much or too little priority for HCC patients?

According to national data a year after implementation of MELD score-based allocation, the proportion of HCC candidates who had transplantation within 30 days was significantly increased (27% of stage I, 45% of stage II) and 87% of candidates received a transplantation within 3 months.[9] The national rate of transplantation for HCC post-MELD is 21.7% for the first year after implementation of MELD-score based allocation compared to 8.8% pre-MELD.[9] This observation raised concern that HCC candidates were being given excessive priority, which potentially confers an unfair advantage for these patients over other patients without HCC but with comparable MELD scores. The question whether the prioritization of HCC patients adversely affects sicker cirrhotic patients without HCC has not been completely answered. The issue was addressed in the UNOS/OPTN consensus meeting in January 2003, when the priority MELD score for HCC was decreased from 15% to 8% (equivalent to a MELD score of 20) for patients with T1 tumors and from 30% to 15% (equivalent to a MELD score of 24) for patients with T2 tumors. This modification took effect on February 27, 2003. According to the analysis of waiting list outcomes over the next year after implementation of modified MELD prioritization for HCC, which reduces extra MELD points to candidates with HCC, there was an increase in probability of waiting over 90 days and decrease in probability to receive transplantation, but there was no increase in the dropout rate due to progression of disease.[10]

The HCC-adjusted MELD scheme also raises concern due to the relatively high rate of misdiagnosis of HCC in the liver explant. All transplant programs have to submit the pathologic report of explant liver after transplantation for each patient who was granted extra priority due to HCC. There is still a significant portion of cases with false positive diagnosis of HCC on pretransplant imaging.[8]

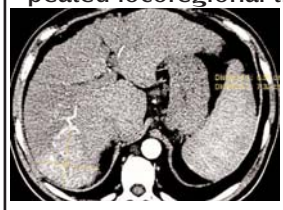
Role of locoregional treatment as a bridge to liver transplantation

Resection has been chosen as the first-line treatment for small HCCs in patients with no cirrhosis or Child A cirrhosis. Survival after resection has been comparable to transplantation and resection is a significantly less expensive treatment. However, in the case of tumor recurrence or progressive decompensation of hepatic function, salvage transplantation has to be considered.[11] A considerable proportion of resection patients may survive without recurrence for 5 years, and among those with recurrence the majority may be eligible for salvage transplantation.[12] On the other hand, it is easy to imagine that salvage transplantation after previous liver resection would be more difficult, associated with more complications, and possibly associated with additional recurrence.[13]

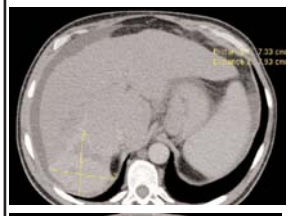
Chemoembolization has been proposed to play a role in tumor control before transplantation. The dropout rate has been reported as 15-25% for 6 months for patients within Milan/UNOS criteria. Even with chemoembolization, the dropout rate remains about 15%.[14] Regardless of bridge treatment before transplantation, the dropout rate significantly increases after 6 months in patients with a tumor larger than 3 cm or with multiple lesions.[14]

Radiofrequency ablation has also been widely used as a bridge treatment. However, it is very rare to achieve complete tumor necrosis with this modality, especially in larger tumors. (Figure 1)

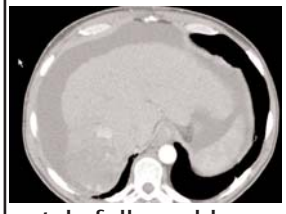
Figure 1. Incomplete necrosis of HCC after RFA, which still shows vascular enhancement. Histologic exam of explant liver still showed residual tumor cells even after repeated locoregional treatment prior to transplantation.



A: Initial CT scan of HCC with strong contrast enhancement in arterial phase.



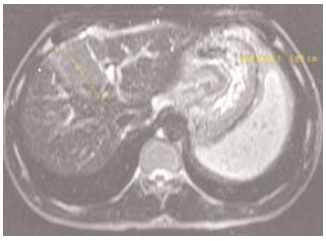
B: Follow-up CT scan of HCC 3 months after RFA, which still shows contrast enhancement with no reduction of size.



C: Follow up CT scan of HCC a month after transarterial chemoembolization immediately followed by second RFA, which still shows residual enhanced area. Increased ascites from multiple locoregional therapies can be noted.

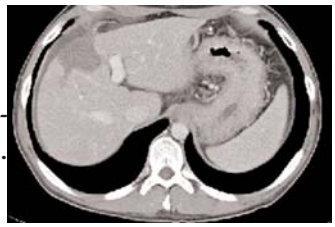
The value of these bridge treatments has been questioned in recent studies.[15,16] Survival benefit from either pretransplant chemoembolization or radiofrequency ablation is hard to determine. However, these bridge treatments have a role in down-staging tumor mass to within transplantable range. Cases with tumors beyond Milan/UNOS criteria can be submitted to the UNOS regional review board to get HCC points approved after size reduction by locoregional treatment (Figure 2). The serial measurement of the tumor before and after treatment has to be documented and forwarded for the review.

Figure 2. **A Successful Case of Radiofrequency Ablation of Hcc Prior to Transplantation.**



A: Initial size of HCC was 6.65 cm in long axis on MR

B: CT scan 5 months after RFA shows no contrast enhancement of tumor as well as reduction of size.

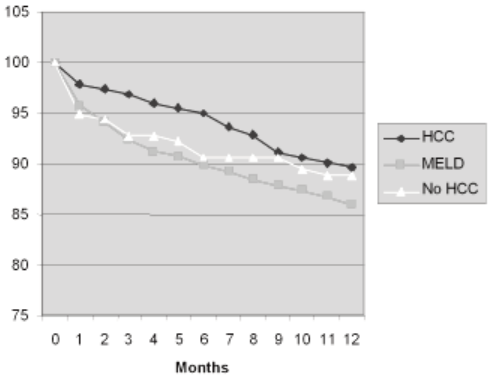


Conclusion

The MELD allocation model provides a useful, objective, and universal tool for clinicians to estimate risks for clinical decision models and to analyze the risk versus benefit. However, questions remain with respect to how much priority should be given HCC patients over non-HCC patients, the true limit of the anatomical stage of the tumor for transplantation, and the role of bridge treatment in reduction of dropout and increase of survival benefit after transplantation. It is possible to develop an additional allocation model combined with MELD in order to place marginal donor livers in HCC patients with relatively better underlying liver cirrhosis but still with high risk of dropout and death. This issue will continue to be discussed and debated especially since patients with HCC continue to enjoy excellent post-transplant survival as compared to patients without HCC (Figure 3).

Figure Three

One year Survival after Liver Transplant



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Immunosuppressive Strategy In Liver Transplantation With Hepatocellular Carcinoma

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With the increasing number of potent immunosuppressive agents available in the last 15 years, the rate of rejection is considerably low and graft loss from immunological reasons is rare after successful liver transplantation (LT).[1-3] However, there is a concern that patients may be overly immunosuppressed. Immunosuppressive agents reduce the host's natural surveillance mechanism creating a permissive environment for malignant cells to grow.

Increasing numbers of transplants are done in patients with hepatitis C viral (HCV) infection in which there is a higher incidence of hepatocellular carcinoma (HCC). Also, with the introduction of the Model for End Stage Liver Disease (MELD) system and additional points for HCC stage II tumors, more patients with HCC are receiving liver transplants.[4] Post LT management of these patients with adjuvant chemotherapy and/or modification in baseline immunosuppresive agents may have a role in preventing or delaying recurrence of HCC and may have an impact after recurrence of HCC.

In cases of post transplant lympho proliferative disorder (PTLD), withdrawal or reduction of immunosuppression (IS) has been shown to cause regression or slow down the progression of PTLD.[5] In the case of recurrence of HCC, it is unlikely that HCC will be eliminated or regress after reducing or even withdrawing IS. All one can expect is a reduction in the rate of progression of the disease. Withdrawal of IS is not without risk of inducing acute rejection, which may lead to hepatic dysfunction, chronic rejection, and graft failure. Withdrawal of IS must be done very carefully. One may negate the unproven advantage of delaying the progression of HCC while increasing the risk of graft loss and death. The general concern within clinician-based PTLD experience is that immunosuppressive agents provide a permissive environment for cancer cells to proliferate. Modification of IS may have a role in preventing cancer, but prospective, randomized, clinical trial data are not available. However, there are suggestions that IS with an anti-proliferative property (mTOR inhibitor, Rapamycin) and interleukin 2 (IL2) receptor-blocking agent may have an advantage over conventionally used calcineurin inhibitors (Cyclosporine, tacrolimus) and steroids.[6-7]

Literature Review

We conducted a literature review to investigate the issue of immunosuppressive strategy in post LT patients with HCC. The search revealed several anecdotal reports on heterogeneous populations from various centers.

In 1991, Yokohama et al. from the University of Pittsburgh reported an accelerated growth rate of HCC in cases of HCC recurrence after liver transplantation with IS compared to non-transplanted HCC patients who under went resection.[8] In 1992, contradictory reports were made by Steininger et al.[9] claiming that IS does not enhance tumor growth post liver transplantation. In 1996, Yokohama et al.[10] advocated the role of adjuvant chemotherapy to prevent recurrence of HCC.

In experimental in vitro settings, Freise et al.[11] and Hojo et al.[12] have independently shown the progression of hepatoma and cancer cells in the presence of Cyclosporine, whereas Schumacher et al.[13] showed that Rapamycin inhibits hepatoma cell growth and tacrolimus promotes the growth of these cells. Similar observations for other cancer cells have been reported by Eng CP et al.[14] and Hidalgo et al.[15] Inhibition of liver, kidney, and intestinal cancer cell regeneration was also shown by Francavilla et al.[16, 17] with use of Rapamycin.

Vivarelli et al.[18] of Italy reported 10 years of experience in 106 cases of liver transplants with HCC under a Cyclosporine - based IS regime. They found a benefit in cumulative, lower doses of cyclosporine in recurrence-free survival. In further detailed, retrospective multivariate analysis of 70 cases, 3 years later, they found that Cyclosporine exposure was the only independent predictive factor for tumor recurrence.[19]

Decaens et al.[20] examined 412 cases of HCC, which underwent liver transplantation in 14 centers in France. In a detailed analysis of five-year, tumor-free survival, the authors concluded that the use of ATG or OKT3 decreased tumor recurrence.

Kneteman et al.[21] of Canada reported on 40 LT cases with HCC (within and beyond Milan criteria). The cases within Milan criteria had a five-year, tumor-free survival rate of 81.1± 9.9% while the cases outside Milan criteria had a five-year, tumor-free survival rate of 76.8 ±10.5%. They felt that Rapamycin-based IS had a beneficial effect in the prevention of tumor recurrence. However, in the absence of control groups, they did not conclude that this protocol had a definite advantage.

Stadlbauer et al.[22] reported the feasibility of withdrawal of prednisone and reduction in IS in 11 cases of liver transplantation with HCC.

Liu et al.[23] reported the benefit of IL2-receptor antibody therapy with withdrawal of steroid and low dose tacrolimus for the prevention of hepatitis B virus (HBV) infection and HCC recurrence in 31 cases of liver transplants compared to 49 historic cases with standard IS.

In 2004, Guba et al. claimed that chronic IS promotes a tendency for HCC to recur and also promotes the development of various solid, hematological malignancies. They expressed hope that the cancers can be prevented with the use of mTOR inhibitors.[24,25]

Dalgic et al. (2005 Transplant Proc) reported on 10 cases of liver transplants with unresectable HCC treated with tacrolimus mono-therapy (n=8) or Rapamycin with early withdrawal of steroid (n=2) without any evidence of recurrence in 8 to 19 months of follow-up.[26]

Zhou J et al. examined retrospectively 36 heterogeneous cases of liver transplant patients with HCC who were converted to Rapamycin and felt that Rapamycin may inhibit the recurrence and metastasis of HCC and may also improve renal function.[27]

Stippel et al. published a case report of a liver transplant patient with HCC who had pelvic recurrence five months post liver transplantation. She underwent bilateral salpingooophorectomy, converted to Rapamycin, and remained recurrence-free for 14 months.[28]

Summary

When chemotherapy is used, baseline IS can be reduced drastically since chemotherapy has IS activity. Before the development of newer immunosuppressive agents, 6-marcaptopurine and Cyclophosphamide had been used as IS agents.

With the use of nonspecific, immunosuppressive agents to allow graft acceptance, the host immune system's natural surveillance to prevent growth of oncogenic cells is compromised. The increased risk of lymphoma and non-lymphoid lesions in the post kidney transplant population with IS was described in late 1960.[29,30] The reversibility of lymphoma was demonstrated in the early 1980s[5] by reconstituting the host's immune system using bone marrow transplants.

It is highly unlikely that once HCC has recurred that any change or even cessation of IS would be successful in reversing the course of the disease. The best one could expect is to delay the progression of disease after recurrence. Thus, prevention of HCC recurrence or delaying HCC recurrence would be the ideal goal. In either event, low maintenance of IS may have some advantage. Post LT introduction of mTOR inhibitors, which prevent the cellular proliferation from G1 to S phase, needs to be studied in randomized, prospective fashion for prevention of HCC, delaying the recurrence of HCC, and slowing pro-

gression of HCC after recurrence. At present the use of Rapamycin is prohibited by the FDA within first 30 days post LT because of increased incidence of thrombosis. There is an urgent need for the development of a strategy to carefully convert the patient to Rapamycin one-month post LT with careful adjustment of dosage and initial frequent monitoring of trough concentration.

Although there isn't conclusive evidence, reduction in induction and baseline maintenance of IS may to be beneficial in preventing or delaying the recurrence of HCC and also in slowing the progression of HCC after recurrence. Large, multicenter, prospective, randomized trials are required to confirm the advantage of the use of mTOR inhibitor to prevent or delay the recurrence of HCC and slow the progression after recurrence.

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