Chapter 15

Transplantation for Hepatocellular Carcinoma

Ahmad Madkhali, Murad Aljiffry and
Mazen Hassanain

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1. Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer mortality worldwide, accounting for more than 500,000 deaths annually. Major risk factors include chronic liver disease and liver cirrhosis due to hepatitis B and C viral infections, alcoholic liver disease and non-alcoholic steatohepatitis (NASH). Surgical resection and liver transplantation are the only potentially curable options for patients with HCC. While surgical resection is the treatment of choice in patients with good hepatic function, it is contraindicated in those with moderate to severe cirrhosis (Child class B or C), leaving these patients with liver transplantation as the only option. Moreover, transplantation is the optimal treatment even for small, otherwise resectable disease. This is a reflection of a number of factors. Liver transplantation will most likely result in a microscopically negative resection, which is the most effective oncologic treatment. Most HCCs are multifocal especially in the background of cirrhosis, though pre-neoplastic lesions may not be visible on perioperative evaluation; they are likely to continue to evolve into new primary HCCs. Furthermore, transplantation eliminates cirrhosis and restores normal hepatic function. However, limited organ availability mandates the restriction of liver transplantation to patients with early stage tumors who are not candidates for resection.

2. Organ allocation

In an effort to prioritize liver transplant candidates according to the highest short-term risk of mortality from end stage cirrhosis, the model for end-stage liver disease (MELD) scoring system was implemented in 2002 (table 1). To impart more urgent access to liver transplantation for patients with small HCCs, additional points within the scoring system were

allotted to these patients. This is done to equilibrate their risk of death in comparison with the mortality of end-stage cirrhosis. The original scoring exception included lesions smaller than 2 cm, which resulted in an over distribution of donor livers to patients with HCC (with many expected small tumors turning out not to be HCC on explanted pathology). Therefore, the scoring exception was modified later by reducing the upgrade for Stage II tumors and eliminating it for Stage I tumors. Using the American Liver Tumor Study Group Modified TNM staging system, current UNOS guidelines do not allow upgrading of candidates with Stage I disease, irrespective of biopsy confirmation; only candidates with Stage II HCC disease are upgraded on the waiting list to a MELD score of 22 (equivalent to a 15% probability of candidate death within 3 months) with the intent to shorten their waiting time. From 2002-2007 in UNOS database, patients with an "HCC MELD-exception" had similar survival to patients without HCC.

MELD score component, calculation and mortality prediction	
Serum bilirubin (mg/dL)	
Serum creatinine (mg/dL)	
INR	
MELD = 3.8[Ln serum bilirubin (mg/dL)] + 11.2[Ln INR] + 9.6[Ln serum creatinine (mg/dL)] + 6.4	
* If a patient has had 2 or more hemodialysis treatments or 24 hours of CVVHD in the week prior to the time of the scoring, Creatinine will be set to 4 mg/dL	
MELD score	Mortality in 3 months
- <9	1.9 %
- 10–19	6.0 %
- 20–29	19.6 %
- 30–39	52.6 %
- >40	71.3%

Table 1. MELD score component, calculation and mortality prediction

3. Criteria for transplantation

Retrospective study by *Mazzaferro* and colleagues established that favorable results could be achieved in patients with cirrhosis with either a solitary HCC ≤5 cm or with up to 3 nodules ≤3 cm, criteria that came to be called ''the Milan criteria (Table3).'' The 5-year survival of these early-stage patients exceeded 70%. Recipient age, gender, type of viral infection, or Child-Pugh score (table 2) did not affect survival after transplantation. In a multivariate analysis by *Marsh JW* and colleagues, found that independent predictors of tumor-free survival included lymph node status, depth of vascular invasion, greatest tumor dimension, lobar distribution, and tumor number.

The strict application of the Milan criteria by UNOS for MELD upgrades allocation disadvantages patients with HCC with tumor profiles exceeding the criteria's maximal size or multifocal

CHILD – PUGH SCORE			
Clinical and laboratory parameter	**Scores**		
	1	2	3
Encephalopathy (grade)	None	1-2	3-4
Ascites	None	Slight	Moderate
Albumin (g/dL)	> 3.5	2.8-3.5	< 2.8
Prothrombin time prolonged (sec)	1-4	4-6	6
Bilirubin (mg/dL) · For primary biliary cirrhosis	< 2 < 4	2-3 4-10	> 3 > 10
Class A = 5–6 points; Class B = 7–9 points; Class C = 10–15 points. Class A: Good operative risk Class B: Moderate operative risk Class C: Poor operative risk			

Table 2. Child Pugh score

parameters but in whom favorable outcomes after liver transplantation have been demonstrated. There is an ongoing debate within the liver transplantation community regarding whether to expand indications for liver transplantation as primary therapy for HCC. For patients with HCC disease beyond Milan criteria in whom there is no macroscopic evidence of vascular invasion or extrahepatic spread, the survival rates after liver transplantation are generally comparable with patients transplanted for disease within the criteria. Most groups report a 5-year survival of more than 50% in patients transplanted for HCC beyond Milan, which many investigators have argued is the minimum acceptable survival rate. In 2001*Yao* and colleagues at the University of California, San Francisco (UCSF) defined an expanded set of HCC criteria (solitary tumor ≤ 6.5 cm, or ≤ 3 nodules with the largest tumor ≤ 4.5 cm and total tumor diameter ≤ 8 cm)(table3) for which 1 and 5-year survival rates after LT were 90% and 75%, respectively. Retrospectively evaluating post- liver transplantation survival for patients with tumors beyond Milan criteria but within ''UCSF'' expanded criteria by pre-transplantation imaging and explant pathology, the group at the University of California, Los Angeles (UCLA) confirmed acceptable 1,3-, and 5-year survival rates of 82%, 65%, and 52%, respectively. Moreover, the difference in 5-year recurrence-free survival after liver transplantation for HCC in the UCLA study did not reach statistical significance between Milan criteria and UCSF expanded criteria tumor groups (74% vs 65%, P =.09). Liver transplantation in such candidates is controversial and widely adopted. The short-term outcomes are similar to those who are transplanted within the Milan criteria.

Group from Edmonton have study Total Tumor Volume (TTV) in patients with HCC who had liver transplant based on Milan or UCSF criteria in 3 centers and they found TTV < 115 cm^3 has lower recurrence rate than TTV > 115 cm^3. In same study they also found that patients beyond Milan but within TTV < 115 cm^3 had survivals similar to those of patients within Milan. On the contrary, patients with TTV >115 cm^3 demonstrated lower survival than those within TTV <115 cm^3 when pathology (5-year: 47% versus 79%, P < 0.001) and radiology staging (5-year: 53% versus 76%, P < 0.1) was used.

Milan criteria: - Single lesion ≤ 5 cm or - ≤3 nodules each ≤ 3 cm Without vascular invasion.
"UCSF'' expanded criteria: - Single lesion ≤ 6.5 cm or - ≤ 3 nodules with the largest tumor ≤ 4.5 cm and total tumor diameter ≤ 8 cm Without vascular invasion.

Table 3. Criteria for liver transplantation

4. Pre-transplant treatment for HCC

The major limitation for liver transplantation as therapy for early-stage HCC is the insufficient number of donor livers. There is always a waiting period between candidate listing and transplantation. If the waiting period extends over a sufficient length of time, the tumor will grow and eventually hinders transplantation. In a study by *Yao* and colleagues of patients with HCC on the waiting list, a 6-month waiting period for liver transplantation was associated with a 7.2% cumulative dropout probability, increasing to 37.8% and 55.1% at 12 and 18 months, respectively. In this setting the treatment of HCC prior to liver transplantation has three potential goals: (a) controlling tumor growth and vascular invasion during the waiting time and therefore decrease dropouts from the waiting list; (b) carrying out neoadjuvant therapy to improve the post-transplant outcome by reducing the risk of postoperative recurrence, and (c) downstaging the HCC burden to make a patient eligible for transplantation.

Followups for patients on waiting list are required every three months by CT or MRI to ensure continued eligibility for liver transplantation.

5. Percutaneous ablation therapy

5.1. Bridging therapy

Bridge therapy is used to decrease tumor progression and the dropout rate from the liver transplantation waiting list. It is considered for patients who meet the transplant criteria. A

number of studies have investigated the role of locoregional treatment as a bridge to liver transplantation in patients on a waiting list. These studies included radiofrequency ablation (RFA), transarterial chemoembolization (TACE), surgical resection, conformal radiation therapy, and sorafenib as "bridge" therapies.

5.1.1. TACE

The rationale for using TACE as a bridge therapy prior to OLT is to control tumor growth while the patient awaits an organ. In addition, TACE could cause significant tumor necrosis, which may reduce tumor dissemination, making it a potential neoadjuvant therapy. TACE can also be used to learn more about the natural history and behavior of a particular tumor prior to liver transplantation. *Decaens et al.* failed to demonstrate survival benefit in a retrospective case-control study comparing 100 patients who underwent TACE prior to liver transplantation (median 1 session/patient) versus 100 matched controls without prior treatment. Mean waiting time was 4.2 months, and 5-year post-LT survival rates were 69% versus 63% (p = ns); dropout was not analyzed. *Yao et al.* retrospectively studied 168 HCC patients who underwent liver transplantation, 88 of whom received TACE (in most cases immediately prior to LT). For patients with HCC within the Milan criteria, 5-year recurrence-free survival was 96% for the TACE group versus 87% for controls (p = 0.12), but for HCC beyond the Milan criteria the difference was statistically significant (86% vs. 51%, p = 0.05). *Roayaie et al.* reported a 46% dropout rate, but only advanced HCC (>5 cm) were included in this study. *Graziadei et al.* found no dropout from the waiting list in patients treated wit TACE meeting Milan criteria and the mean waiting time was only 178 days. Furthermore, the monitoring protocol of repeat staging and the criteria for dropout was not specified. In view of this study and others, the dropout rate ranged from 15 to 46%. The rate of dropout was related to the tumor state and to the duration in the waiting list, the higher rate (46%) being observed in more advanced HCC and when the mean waiting time was 340 days. A systematic review of bridging therapy with TACE by *Lesurtel et al.* concluded that there was insufficient good quality evidence to demonstrate that TACE either improved post-LT survival, altered post-LT complication rates, or impacted on waitlist drop out.

Although pre-liver transplantation TACE does not influence post-LT overall survival and disease-free survival, it remains indicated in context of clinical trial when the period on the waiting list is more than 6 months.

5.1.2. Percutaneous ablation therapy

Patients with small tumors can have ablation either by percutaneous ethanol injection, radiofrequency or any other technique. Pre-transplant RFA ablation for HCC as a strategy to reduce dropout has been addressed in view studies. More than 80% of patients were in the Milan criteria with approximately 1 year on the waiting list. The dropout rate ranged from 0 to 14%. In a nonrandomized series from Toronto of 74 patients bridged using ablation compared with 79 non-bridged patients, the analysis of dropout for tumor progression identified a difference ($p < 0.005$) that became apparent only with prolonged waiting time superior to 300 days.

The main concern with this approach is seeding due to tumor puncture as has been reported for diagnostic biopsy. However, puncture-related seeding is usually a case of poorly differentiated tumors and to peripheral tumors that cannot be approached through a rim of non-tumoral liver.

In conclusion, due to small size of these studies and the heterogeneous nature of the study populations, as well as the absence of randomized clinical trials evaluating the utility of bridge therapy for reducing the liver transplantation waiting list dropout rate, limit the conclusions that can be drawn. Therefore, if liver transplantation can be done without significant delay (i.e. within 6 month) would the optimum. However, in patients whose waiting time is predicted to be prolonged, an RCT of TACE and/or ablation as bridging therapy to decrease dropout of transplantation could be justified.

5.2. Liver resection

Advances in liver surgery have significantly improved the safety of resection. Resection can be used as a treatment for HCC prior to liver transplantation in three different settings. First, resection can be used as a primary therapy, and liver transplantation reserved as a ''salvage'' therapy for patients who develop recurrence or liver failure. A second justification for resection prior to transplantation is that it helps refine the selection process. Resection, indeed, gives access to detailed pathological examination of the tumor and the surrounding liver parenchyma. Important prognostic information can be obtained from the entire resected tumor, including differentiation (which proved to be heterogeneous within the tumor), satellite nodules, microvascular invasion, and capsular effraction. As a result, resection may help deny transplantation in patients with tumors apparently within the Milano criteria but with histological features of especially poor prognosis (undetected macrovascular invasion in particular). On the other hand, resection may help decide transplantation in patients with tumors slightly outside the Milano criteria but with histological features of good prognosis. Third, resection can be used as a ''bridge'' therapy for patients who have already been enlisted for liver transplantation. Resection as the first line treatment for patients with small HCC with preserved liver function, followed by salvage transplantation only for recurrence or liver failure is an attractive option. Initial resection with negative margins, gives rapid access to an effective therapy, without the need for a donor, and offers 5-year survival rates exceeding 50% with a good quality of life. The main obstacle to this strategy is the risk of ''loss of chance'' in case of rapid and extensive recurrence not amendable to salvage liver transplantation. At the time of recurrence, salvage liver transplantation is only applicable in patients with a tumor within the Milan criteria. Initial data showed that patients with HCV infection who developed recurrence after partial resection had multifocal tumors and/or vascular invasion at the time of recurrence.

Although limited resection appears to be sufficient in this setting, it is associated with increased risk of post resection liver failure and is only appropriate for patients with peripheral tumors and Child A cirrhosis and no portal hypertension. As disadvantage for this approach the subsequent liver transplantation would be more difficult due to increase operative time and blood loss.

The use of laparoscopic approaches for peripheral tumors may further contribute to expand this strategy by minimizing technical difficulties during the transplant procedure.

5.3. Tumor dowenstaging

The role of downstaging of tumors before liver transplantation has been explored. Downstaging is done using HCC directed therapy that aims at reducing the size and/or number of HCC lesions. *Graziadei et al.* achieved downstaging to within Milan using TACE in 15/36 patients (41%). Among those downstaged, four dropped out prior to LT, one remained waiting, and 10 underwent LT; there were six deaths including three HCC recurrences, and 4- year post-transplant survival of 41%. *Yao et al.* reports successful downstaging in 21/30 patients with HCC beyond UCSF using a multimodality approach including resection in four cases. There were two deaths related to downstaging treatment (one postresection). Among 16 patients transplanted there was one death and no recurrence, but follow-up was limited (median 16 months). Recent prospective studies have demonstrated that downstaging (prior to transplant) with percutaneous ethanol injection (PEI), RFA, TACE and transarterial radioembolization (TARE) with yttrium 90 microspheres improves disease-free survival following transplant. However, such studies have used different selection criteria for the downstaging therapy and different transplant criteria after successful downstaging. In some studies response to locoregional therapy has been associated with good outcomes after transplantation. Further validation is needed to define the end-points for successful downstaging prior to transplant.

6. Living donor transplantation

Efforts to address the large waiting list of liver transplantation candidates and to decrease the dropout rate have included several strategies such as living donor LT, domino LT, split LT, the use of extended criteria donors, and donors after cardiac death. Living donor LT appears to be an effective option for patients with HCC within the Milan criteria, essentially equivalent in terms of survival to OLT, and it is cost effective if waiting times exceed 7 months. There are few data to support the use of living donor LT for patients with HCC who exceed the Milan criteria, although its use for this purpose is becoming increasingly common.

7. Immunsupression

Immunsupresion is used post liver transplantation to reduce graft rejection but, especially in transplantation for HCC, is associated with a risk of tumor growth. While results of liver transplantation including survival and rates of rejection were dramatically improved in cyclosporine treated patients compared with "historical controls", a high incidence of neoplasm and its aggressive phenotype were found to be due to cyclosporine and its activation of transforming growth factor-beta (TGFβ). *Vivarelli* and colleagues reported an increase in 5-year recurrence free survival in patients treated with smaller

cumulative doses of cyclosporine in the first year following liver transplantation for HCC. Furthermore, they observed a significantly higher mean cyclosporine level in patients with HCC recurrence. Tacrolimus, another calcineurin inhibitor was also found to promote cell cycle progression by an increase in cdk4 kinase activity and thus was linked to increased tumor recurrence.

On the other hand, the calcineurin-independent immunosuppressive agent sirolimus, a binder of mTOR, inhibits tumor growth in cell lines, and it inhibits primary and metastatic tumor growth *in vivo*. In a study by *Wang Z et al*, looking at HCC in mouse model of human HCC, they identify that sirolimus induces cell cycle arrest and blocke proliferation of an HCC cell line, also sirolimus found to prevent tumor growth and metastatic progression by down-regulating the mRNA expression of VEGF and HIF-1α.

Several retrospective reports suggest a lower risk of post-transplant tumor recurrence in patients with HCC with the use of sirolimus as compared to other types of immunosuppressive agents (such as the calcineurin inhibitors tacrolimus and cyclosporine). However, these reports are limited by small size and uncertainty as to whether the observed benefits were due to a specific antitumor effect or an impact on liver transplant in general.

8. Surveillance

There is no consensus as to the optimal approach for post-transplant surveillance. Guidelines from the National Comprehensive Cancer Network (NCCN) suggest the follow up after liver transplant with triphasic CT every 3-6 months for 2 years, then every 6-12 months. AFP levels every 3 months for 2 years, if initially elevated, then every 6-12 months.

9. Survival

There is a clear survival benefit and low recurrence rate after transplantation for hepatocellular carcinoma. When surgeons adhere to Milan criteria, 5-year survival rates after transplantation range from 70% to 80%, and tumor recurrence rates are approximately 10%. Since the initial report by Yao and colleagues that demonstrated acceptable survival rates using the UCSF criteria (90% 1-year survival rates and 75% 5-year survival rates) and showed no survival deference from Milan criteria in 1,3 and 5 years, long-term survival need to be further identified.

10. Recurrence

Tumor recurrence remains a main limitation to the long-term survival of patients following liver transplantation for HCC. While the majority of patients recur in the first two years after

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transplantation, late recurrence is not infrequent. Most common sites of recurrence are liver graft, lung, bone, abdominal lymph nodes, adrenal glands and peritoneum. The incidence of recurrent HCC following transplantation has been reported to vary, ranging from 6-56%. However, in cases in which the Milan selection criteria were adopted, risk of recurrence decreased to 10–15% at 5 years. While several recipient and tumor specific factors are prognostically important, primary tumor size, number of lesions, grade of tumor and presence of vascular invasion have been noted to be the most significan clinical risk factors for both recurrence and survival. De-novo tumor development from recurrent hepatitis and cirrhosis in the liver graft can occur, however presence of microscopic foci of disease in lymph nodes or distant organs at the time of transplantation, as well as hematogenous or peritoneal tumor dissemination during transplantation, are mechanisms attributed to disease recurrence. Recurrent disease following liver transplantation for HCC may involve an extrahepatic site in 10-43% of patients.

Successful surgical salvage has been reported for intrahepatic and/or confined extrahepatic HCC metastases. In a study by *Regalia et al*, involving several Italian centers, 7 out of 21 patients (30%) underwent salvage resection of recurrent HCC of the liver (2), lung (2), bone (1), skin or other sites (2). Surgical resection was associated with a survival of 15.5 months, which was better than the 5.5 months noted among patients treated with a non-surgical approach. *Schlitt et al*. reported on 39 patients with recurrent disease, 9 intrahepatic recurrences, 15 extrahepatic disease and 15 had both intra and extrahepatic recurrence. Eleven of these patients were able to undergo complete removal of the recurrent disease, including 5 patients with an intrahepatic recurrence; 7 (63%) were alive at 4.3 years of follow-up. As with HCC of the native liver, the utilization of resection versus ablation to treat recurrence in the allograft is dependent on surgical judgment, as well as the size and location of the tumor. While resection may be more applicable to more superficial and larger tumors, ablative techniques may be sufficient and appropriate in the setting of smaller and more deeply situated tumors. Although liver resection for intrahepatic HCC recurrence has been reported by several centers, most series are limited by a small sample size.

Reports of repeat liver transplantation as a treatment of recurrent intrahepatic HCC are limited to a few very select case series and is not the standard of care.

Another potential approach to intrahepatic HCC recurrence is the utilization with TACE and RFA. *Ko et al*, reported on 28 patients with recurrent HCC who underwent one or more cycles of TACE after transplantation (mean, 2.5 cycles). In this study, the targeted tumor reduced in size by ≥25% in 19 of the 28 study patients (68%). However, intrahepatic or extrahepatic metastasis occurred in 21 of the 28 patients (75%) during the 3-month follow-up period and mean survival was only 9 months.

Systemic therapeutic options for recurrent HCC are limited. While cytotoxic agents have traditionally had marginal effect in the treatment of HCC, systemic therapy with molecular targeted therapy has been shown to prolong survival in recent trials. Sorafenib, a multi-targeted kinase inhibitor, demonstrated a significant overall survival benefit in patients with advanced or metastatic HCC when compared with placebo in two separate Phase 3 trials. These studies were carried out in patients who presented initially with advanced disease (mostly

liver confined disease), and did not include patients who had previously undergone curative-intent therapy, such as surgical resection or liver transplantation. A number of retrospective studies have reported acceptable safety data for sorafenib in liver transplant patients, with very few unexpected toxicities or interaction with immunosuppressive medications. The numbers in these studies are small, and there is clearly a need for a prospective trial to fully assess the potential survival benefit of sorafenib in this setting.

Radiation therapy is another option for patients with recurrent unresectable HCC. Three dimensional conformal radiation, as well as stereotactic body radiation therapy and radioembolization, have been utilized in the treatment of primary unresectable HCC. In addition, radiation therapy is a treatment option for symptomatic palliation of extrahepatic disease. *Yamashi et al*, reported on 28 patients with metastatic HCC involving the portal and/or peripancreatic lymph nodes who were treated with radiation therapy. A total of 18 (64%) and five (18%) patients achieved partial responses and complete responses, respectively. The 1- and 2-year overall survival rates were 53% and 33%, respectively. In one study, *Seong et al*. investigated the effectiveness of palliative radiation therapy for HCC bone metastasis. In this study, 51 patients received radiation therapy for 77 bony metastatic lesions, with a median total dose of 30 Gy. There was pain relief in 56 lesions (73%), however, median and 1 year survival were only 5 months and 15%, respectively. In aggregate, these studies suggest that recurrent metastatic HCC may be sensitive to palliative radiation therapy. Therefore, radiation therapy should be considered for palliation of metastatic HCC lesions.

Abbreviation

HCC Hepatocellular carcinoma

HIF-1α Hypoxia-inducible factor 1, alpha

MELD Model for end-stage liver disease

RFA Radiofrequency ablation

PEI Percutaneous ethanol injection

TACE Transarterial chemoembolization

TGFβ Transforming growth factor-beta

TNM Classification of Malignant Tumors (Tumor, lymph Node, Metastasis)

VEGF Vascular endothelial growth factor

UNOS United Network for Organ Sharing

UCSF University of California, San Francisco

Author details

Ahmad Madkhali[1], Murad Aljiffry[2] and Mazen Hassanain[1,3]

1 Department of surgery, College of Medicine, King Saud University, Riyadh, Saudi Arabia

2 Department of surgery, College of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

3 College of Medicine, Liver Disease Research Centre, King Saud University, Riyadh, Saudi Arabia

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