Liver Transplantation for Hepatocellular Carcinoma

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EPIDEMIOLOGY OF HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) is an aggressive malignancy and emerging global health crisis. Responsible for an estimated 750,000 deaths in 2012, HCC represents the second leading cause of cancer-related mortality worldwide.[1] HCC is a highly fatal cancer with 1- and 5-year overall survival rates of 43% and 17%, respectively. The majority of HCC burden is seen in developing countries, particularly in Southeast Asia and sub-Saharan Africa where the incidence of hepatitis B virus (HBV) infection is high. In the United States, the incidence rate of HCC almost doubled over the past two decades, where HCC currently is the most rapidly increasing cause of cancer-related deaths with more than 24,000 deaths in 2015 attributed to HCC and intrahepatic bile duct cancers.[2] Up to 90% of patients with HCC have underlying cirrhosis. In addition to HBV infection, the other major risk factors for HCC are hepatitis C virus infection, alcoholic liver disease, and nonalcoholic steatohepatitis.

DIAGNOSIS

Multiphasic computed tomography (CT) and magnetic resonance imaging (MRI) with contrast agents are the first-line modalities for diagnosis and staging of HCC, as specific imaging features permit the accurate diagnosis of HCC in the majority of patients. It is clearly important that imaging techniques are able to differentiate HCC from other nonhepatocellular malignancies and benign liver lesions. Unless the diagnosis is uncertain, liver biopsy is generally avoided because of the high risk for false-negative results in small HCC, as well as potential bleeding (0.5%) and risk for tumor seeding along needle tract (2.7%). A major limitation of imaging with extracellular contrast agents is low per-lesion sensitivity, which can lead to missed lesions and under staging of HCC. Hepatobiliary contrast agents are therefore being increasingly used for the diagnosis of HCC given higher sensitivity for early HCC and the added advantage to characterize HCC tumor biology, which provides valuable prognostic information.[3] Table 1 outlines the typical radiological features of HCC.

TABLE 1. FEATURES OF HCC ON CT AND MRI

Arterial-phase hyperenhancement	Enhancement in the arterial phase that is greater than that of the surrounding liver
Washout appearance	Visually assessed temporal reduction in enhancement relative to surrounding liver from an earlier to a later phase, resulting in portal venous or delayed-phase hypoenhancement
Capsule appearance	A peripheral rim of smooth hyperenhancement in the portal venous or delayed phase

TABLE 2. LT SELECTION CRITERIA FOR HCC

Criteria	Definition
Milan	Single tumor ≤ 5 cm
	Up to 3 tumors each ≤ 3 cm
	No macrovascular invasion or extrahepatic disease
UCSF	Single tumor ≤ 6.5 cm
	Up to 3 tumors with the largest tumor ≤ 4.5 cm
	Total tumor diameter ≤ 8 cm
	No macrovascular invasion
Up-to-seven	Largest tumor diameter (cm) + number of tumors ≤ 7
TTV+AFP	TTV ≤ 115 cm^3
	AFP ≤ 400 ng/mL
	No macrovascular invasion or extrahepatic disease

POTENTIAL TREATMENT OPTIONS

The management of HCC is complex and requires a multidisciplinary team approach for optimal outcomes. Because of improved surveillance of cirrhotic patients, HCC is now being diagnosed more frequently at an earlier stage. For those patients, the main potentially curative treatment options are liver resection, tumor ablation, and liver transplantation (LT).[4] Both liver resection and tumor ablation have inherent limitations related to the residual cirrhotic liver, which mainly include tumor recurrence and diminished hepatic functional reserve. LT, in contrast, bypasses those limitations by removing the tumor and replacing the cirrhotic liver that harbors carcinogenic potential. In carefully selected patients, LT has been recognized as the most effective treatment for non-resectable HCC.

LT SELECTION CRITERIA

In 1996, Mazzaferro and colleagues[5] proposed the now widely used Milan criteria to select patients with HCC for LT. Milan criteria depend on the number and size of HCC nodules as determined based on radiological assessment. Patients with HCC within Milan criteria who undergo LT have a 4-year recurrence-free survival rate of 92% and a 4-year overall survival rate of 85%. The latter is similar to the survival rate of patients undergoing LT for nonmalignant indications. As some argue that Milan criteria might be too restrictive, more expanded criteria to select HCC patients for LT have been proposed and have demonstrated comparable rates of tumor recurrence and overall survival after LT. These include the University of California San Francisco (UCSF) criteria[6] and the ''up-to-seven'' rule.[7] More recently, selection criteria based on total tumor volume (TTV) and alpha-fetoprotein (AFP) have been prospectively validated.[8] Table 2

summarizes some of the different selection criteria of HCC for LT.

LISTING FOR LT

The increasing incidence of HCC and the use of expanded candidate selection criteria have led to an increase in the number of liver transplants performed for HCC. Over the past several years, HCC has become one of the main indications for LT and currently accounts for about 40% of all liver transplants in some countries. This, in turn, led to increasing pressure on the limited organ donor pool. To prioritize the listing of patients with nonmalignant indications for LT, several organ allocation systems implement the Model for End-Stage Liver Disease (MELD) score, which is calculated using serum creatinine, serum total bilirubin, and international normalized ratio.

Because many patients with early-stage HCC have preserved liver function, their calculated MELD score can be low and they are more likely to progress to advanced cancer stages before undergoing LT. Subsequently, many transplant governing bodies [including the Organ Procurement and Transplantation Network and United Network for Organ Sharing (OPTN/UNOS) in the United States] developed exception MELD point systems to offer additional MELD points for documented HCC within Milan criteria (Table 3).[9] This, in turn, allows patients with HCC earlier access to LT. However, it has been noted that candidates with HCC exceptions have a lower risk for disease progression or dropout (removal from the waiting list for being too sick or because of death) than

TABLE 3. CURRENT OPTN/UNOS MELD EXCEPTION POINT SYSTEM FOR LT OF HCC

Qualifying for exception	Stage T2 HCC: 1 lesion ≥2 cm and ≤5 cm, or 2-3 lesions all ≥1 cm and ≤3 cm
Exception points at listing	Calculated MELD score for the first 3 months (initial application) and for the first 3-month extension, as long as the candidate continues to meet criteria; at 6 months (second extension) candidates receive a score of 28
Exception point progression and cap	Additional MELD points are granted every 3 months after the 28 score is assigned; these additional points are equivalent to a 10% increase in candidate mortality every 3 months; the maximum HCC exception score is capped at 34

TABLE 4. LIMITATIONS OF THE MELD EXCEPTION POINT SYSTEM FOR LT OF HCC

Lower risk for dropout of HCC patients compared with patients with nonmalignant liver diseases

Does not incorporate additional HCC characteristics (including biological factors) that are now known to be associated with tumor growth

Does not account for the effects of locoregional therapy

Lacks polices for removal from the list and giving more weight to longer-term post-LT outcomes for HCC

those without the HCC exceptions. Recently, the OPTN/UNOS implemented new changes to the HCC exception rules: capping the HCC MELD exception score at 34 with the intention of offering candidates with calculated MELD scores of ≥35 a better opportunity to receive regional LT offers.[10] Table 4 summarizes some of the limitations of the MELD exception point system for LT of HCC.

TUMOR DOWNSTAGING

An important concept related to LT in patients with HCC is pretransplant tumor downstaging. Patient dropout while on the waiting list secondary to HCC progression is a major obstacle to LT. Multiple modalities can be used to downstage HCC to within Milan criteria, as well as prevent progression of tumors already within the criteria, that is, bridging to LT. Downstaging is best used for stage T2 tumors when the likely waiting time on the LT list is longer than 6 months. Among those modalities, transarterial chemoembolization (TACE) is the most commonly used. Other modalities include radiofrequency ablation, radioembolization, and surgical resection. TACE can lead to hepatic decompensation and is generally limited to patients with compensated cirrhosis.[11] Tumor downstaging in HCC patients has been associated with comparable 5-year survival rates to HCC patients eligible for LT without downstaging. The role of downstaging is still to be better defined through large prospective clinical trials.

LIVING DONOR LT

Living donor liver transplantation (LDLT) is increasingly used in patients with HCC, especially in high-demand Asian countries. Several studies have demonstrated posttransplant survival rates after LDLT that are comparable with deceased donor LT. LDLT is being promoted in Western countries to handle the shortage of donor organs in addition to decreasing patient dropout while on the waiting list.[12] An important factor to consider with LDLT is that shorter waiting times from listing to transplant can allow the transplantation of patients with unfavorable tumor biology, who otherwise would have dropped out because of tumor progression while waiting for a deceased donor LT. This can be associated with higher rates of tumor recurrence after LDLT.[13]

POSTTRANSPLANTATION IMMUNOSUPPRESSION

Calcineurin inhibitors (tacrolimus, cyclosporine) and steroids have traditionally been the backbone regimen for post-LT immunosuppression. In the specific setting of LT for HCC, a number of studies have shown that another group of immunosuppressive agents known as the mammalian target of rapamycin (mTOR) inhibitors including sirolimus and everolimus is likely to reduce post-LT HCC recurrence in comparison with standard immunosuppressive regimens. This favorable effect of mTOR inhibitors is attributed to the overexpression of mTOR signaling in HCC and the inhibitory effect of these drugs on the expression of vascular endothelial growth factor.[14] Prospective clinical trials are under way to confirm the role of these agents in patients transplanted for HCC.

HCC RECURRENCE AFTER LT

A major complication related to LT in patients with HCC is recurrence of the tumor, estimated to occur in

8% to 20% of patients. Most cases of HCC recurrence are diagnosed within the first 2 years after LT, although late recurrence is possible. The risk for HCC recurrence is directly related to pre-LT tumor stage and unfavorable tumor biology. Subsequently, the large majority of HCC recurrence represents metastases from the primary tumor rather than de novo cancer arising in the transplanted graft. Although it is typically associated with high mortality, recurrent HCC prognosis has improved through the use of resection, ablation, and locoregional therapies like TACE. Sorafenib (a tyrosine kinase and RAF kinase inhibitor) is primarily used in patients with advanced HCC, but it has also been associated with a modest survival benefit in patients with unresectable HCC recurrence after LT.[15] The combination of sorafenib and mTOR inhibitors has also demonstrated promising results in the setting of recurrent HCC and needs further evaluation.[16]

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