Liver Transplantation for Hepatocellular Carcinoma

The incidence of hepatocellular carcinoma (HCC) is rising and HCC is now the third most common cause of cancer-related death worldwide. The diagnosis of HCC is increasingly being made without histologic confirmation because of its characteristic appearance on imaging studies. Serum alpha-fetoprotein (AFP) is used as a screening test but has poor sensitivity and specificity and other serum markers are being investigated. Biopsy of suspected lesions is controversial because of the risks of bleeding, false negatives, and needle track seeding.

Treatment
Treatments for HCC include resection, ablation (e.g., radiofrequency, ethanol), chemoembolization, systemic chemotherapy, and liver transplantation. Only resection, ablation, and liver transplantation are considered potentially curative, and liver transplantation allows removal of both the HCC and the cirrhotic liver.

Liver Transplantation
Early liver transplantation outcomes for HCC were dismal due to transplantation of patients with advanced tumors. Significantly better survival following transplantation was observed for early stage tumors, and these findings led to a landmark prospective study by Mazzaferro and colleagues confirming that long-term recurrence-free survival greater than 80% could be achieved in carefully selected patients.

Patients with HCC often have preserved liver function and are disadvantaged by a transplant allocation system that does not provide exceptions for HCC. The selection criteria used in the Mazzaferro study, known as Milan criteria, are used by the United Network for Organ Sharing (UNOS) to prioritize patients with HCC and reduce the risk of drop-out due to tumor progression (see Table).

Expanded Selection Criteria
Current liver transplant selection criteria based on Milan criteria have recently been challenged. Yao and colleagues at the University of California, San Francisco (UCSF) have proposed a modest expansion of Milan criteria (see Table), and 5-year post-transplantation survival using UCSF expanded criteria has been shown to be comparable to Milan criteria in a recent prospective study. Other groups have proposed selection criteria based on surrogates of tumor biology other than tumor stage.

Downstaging
The same group at UCSF also proposed to prioritize patients with HCC exceeding UCSF expanded criteria if they can be downstaged to within Milan criteria. While the UCSF group has demonstrated excellent short-term survival after downstaging, other groups have had poorer results with pretransplantation treatment of tumors exceeding Milan criteria.

UNOS Region 6 (including transplant programs in Washington, Oregon, and Hawaii) recently adopted a downstaging policy proposed by the University of Washington. Under the new policy, a patient whose tumor meets Region 6 downstaging criteria (see Table) may be prioritized for liver transplantation if successfully downstaged to Milan criteria. This policy requires biopsy of the tumor to exclude microvascular invasion prior to downstaging. We hope this will allow more patients with HCC to undergo potentially curative liver transplantation without adversely impacting post-transplantation HCC recurrence or transplantation of other patients on the waiting list. A prospective analysis of these outcomes is planned.

Surveillance and Referral
Patients at risk for HCC (mostly patients with cirrhosis) benefit from a surveillance program and should undergo an imaging study and serum AFP measurements every 6 to 12 months. If either of these surveillance tests is
abnormal a more specific study must be performed, such as quadruple-phase CT or MRI. Lesions greater than 2 cm with a characteristic appearance on imaging do not require a biopsy to establish the diagnosis. Lesions less than 1 cm can usually be followed every 3 to 6 months to determine their stability. Lesions that are greater than 1 cm without the characteristic appearance of HCC (indeterminate lesions) require frequent follow-up, usually at 3-month intervals, or a biopsy. If a lesion suspicious for HCC is found on imaging, we recommend early referral to a center experienced with the evaluation and treatment of patients with HCC, including liver transplantation.

Patients referred to the Primary Liver Tumor Clinic at the University of Washington are presented in a multidisciplinary conference staffed by hepatologists, transplant and oncologic surgeons, interventional radiologists, and pathologists. Imaging studies and pathology specimens are reviewed and a management plan is formulated and discussed with the patient the same morning. This unique service provides patients with HCC efficient and cutting-edge care using the most effective available treatments.

—Oren K. Fix, MD, MSc

References


Modified TNM staging system for HCC
(adapted from reference 10)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>T1</td>
<td>1 nodule less than 2 cm</td>
</tr>
<tr>
<td>T2</td>
<td>1 nodule 2-5 cm; 2 or 3 nodules, all less than 3 cm</td>
</tr>
<tr>
<td>T3</td>
<td>1 nodule &gt;5 cm; 2 or 3 nodules, at least 1 greater than 3 cm</td>
</tr>
<tr>
<td>T3A</td>
<td>1 nodule 5-6.5 cm; 2 or 3 nodules, at least 1 greater than 3 cm, all less than 4.5 cm; total tumor diameter less than 8 cm</td>
</tr>
<tr>
<td>T4A</td>
<td>4 or more nodules, any size</td>
</tr>
<tr>
<td>T4B</td>
<td>T2, T3, or T4A plus gross intrahepatic portal or hepatic vein involvement</td>
</tr>
</tbody>
</table>

Milan criteria = T1+T2

Current UNOS policy uses T2

UCSF expanded criteria and Region 6 downstaging criteria = T3A