

HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

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Review of Liver Transplantation in Patients With Hepatocellular Carcinoma



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G&H Why has there been an increase in liver transplants performed for the indication of hepatocellular carcinoma?

FY Hepatocellular carcinoma (HCC) is one of the leading indications for liver transplantation, accounting for an estimated 20% to 25% of all liver transplants in the United States. Over the past 20 years, there has been an increase in liver transplants performed for this indication for 2 reasons. One is that the incidence of HCC has been on the rise over the past 2 to 3 decades. The second is that changes in organ allocation policy have allowed patients with HCC to have easier access to liver transplantation compared with 20 years ago. Before 2001, patients with HCC did not receive any priority at all, so it was very difficult for them to receive a liver transplant at that time. After changes in liver allocation, patients with HCC that meets the Milan criteria became eligible for priority listing for liver transplantation.

G&H Are patients with HCC overprioritized now or are they still underprioritized for liver allocation?

FY There was a period of time when patients with HCC were given too much priority. They were transplanted much quicker overall than patients with liver failure from

other etiologies, even though there were wide variations in waiting times across the United States.

As a result, the organ allocation policy was changed a few years ago to mandate a wait of at least 6 months for patients with HCC before they could receive exception points or priority status for liver transplantation. This narrowed the disparity between patients with HCC and those without it. However, this is a very complex issue because waiting times across the country are still very different, and there have been many efforts to try to narrow the disparity in waiting times across the country.

G&H What are the current outcomes of liver transplantation for HCC?

FY The outcomes largely depend on the stage of the HCC at the time of liver transplantation. In the United States, patients receive priority points for liver transplantation based on the Milan criteria, which have been considered the benchmark for selection of liver transplant candidates over the past 25 years. For tumors within the Milan criteria, 5-year patient survival after liver transplantation is expected to be 70% to 80%. This is close to survival following liver transplantation for most other indications. Recently in the United States, patients with a larger tumor burden within the University of California San Francisco (UCSF) downstaging criteria who have been successfully

downstaged to meet the Milan criteria are also eligible for priority listing for liver transplantation with expected survival similar to patients within the Milan criteria before liver transplantation who did not need downstaging. When the criteria for liver transplantation are relaxed, survival after the procedure may not be as good. It is also known that patients with lower levels of the tumor marker alpha-fetoprotein have better posttransplant outcomes than patients with high alpha-fetoprotein levels before liver transplantation. In addition, approximately 10% to 15% of patients with HCC within the Milan criteria or downstaged to the Milan criteria before liver transplantation may develop recurrence of HCC following the procedure.

G&H When should patients with HCC undergo liver resection rather than liver transplantation?

FY Patients who are good candidates for liver resection either have no cirrhosis or have cirrhosis but good liver function, no signs of liver failure, and no portal hypertension. These patients are at low risk for decompensation after liver resection. In addition, liver resection should be reserved for patients with only a single HCC and not multiple tumors. If a patient has more advanced cirrhosis and portal hypertension, or more than 1 lesion, then liver transplantation is the preferred option.

G&H How do the outcomes of liver resection compare with those of liver transplantation?

FY Five-year survival with liver resection is approximately 50% to 60% in the best candidates for this procedure. A higher survival rate is not seen because patients often develop recurrence of HCC after liver resection, and some may experience progression of cirrhosis and liver failure over time.

Although overall long-term outcomes are not as good with liver resection compared with liver transplantation, liver resection is still a very important treatment because good outcomes are possible and there is a shortage of liver organs for transplantation. In addition, liver resection can be performed right away, whereas there is usually a waiting time before liver transplantation (1-2 years in areas with long wait times).

G&H Which patients are most likely to experience recurrence of HCC following liver transplantation?

FY There are many factors that affect the risk of recurrence after liver transplantation. As mentioned, overall, the recurrence rate ranges from 10% to 15% in patients

who were within the Milan criteria prior to liver transplantation. The risk for recurrence increases if the tumor size or burden was underestimated prior to liver transplantation. There are other markers for recurrence as well. A very high alpha-fetoprotein level may be a reflection of worse tumor biology. In general, our approach to patients with HCC is to try to treat them prior to liver transplantation so that they have a reduced tumor burden prior to the procedure.

The patients who do the best are those who had complete tumor response with locoregional or bridging therapy before liver transplantation. The patients with normal alpha-fetoprotein levels have far better outcomes than patients with high alpha-fetoprotein levels going into liver transplantation.

Another factor that impacts recurrence is the presence of tumors invading blood vessels microscopically, which cannot be ascertained before liver transplantation. There are also other, less-established factors that reflect tumor biology or impact tumor recurrence after liver transplantation.

G&H Is there an optimal bridging therapy to liver transplantation for HCC?

FY It has not been established yet which bridging therapy is the best. Chemoembolization, which combines embolization of the artery supplying the tumor with delivery of chemotherapy via the artery to the tumor, has traditionally been the most commonly used bridging therapy. In recent years, more centers are using yttrium-90 (Y90) radioembolization, which delivers radiation via the artery to the tumor. These 2 intra-arterial therapies are the modalities most commonly used as bridging therapy to liver transplantation. Another option is to use microwave or radiofrequency ablation, which are both good treatments to target a small single tumor. For larger lesions, chemoembolization and radioembolization have better results than microwave ablation. External beam radiation therapy can also be considered, but the data on its efficacy are still evolving. There are very limited data comparing chemoembolization vs Y90 radioembolization as bridging therapies to liver transplantation.

G&H What are the main benefits of bridging therapy?

FY The consensus is that bridging therapy is indicated if the waiting time is sufficiently long (at least 6 months) to potentially reduce the likelihood of tumor progression to beyond liver transplant criteria (based on tumor burden, vascular invasion, or spread beyond the liver). Reducing tumor burden prior to liver transplantation with

bridging therapy may also result in better outcomes after liver transplantation.

This brings up the concept of response to bridging therapy as a selection tool for liver transplantation for HCC. A number of studies over the years have suggested that patients with HCC that responds to bridging therapy tend to do better than patients with HCC that continues to progress despite bridging therapy before liver transplantation.

G&H Should bridging therapy be used prior to liver transplantation for small HCC?

FY Bridging therapy is still used fairly routinely in these patients despite the fact that small HCC seems to have a lower likelihood of progression. It is estimated that 90% of patients receive some form of bridging therapy prior to liver transplantation across all regions in the United States, regardless of wait time for liver transplantation.

G&H What are the outcomes of liver transplantation specifically for small HCC?

FY It is the general consensus that the higher the tumor burden, the lower the survival after liver transplantation. However, tumor burden is only one factor contributing to posttransplant outcomes. As mentioned, other factors, including the alpha-fetoprotein level, have a strong influence on outcomes of liver transplantation. For example, a small tumor with a high alpha-fetoprotein level may have a higher risk for tumor recurrence when compared with a larger tumor with a low alpha-fetoprotein level. A large tumor successfully downstaged may do just as well as a smaller tumor.

G&H How can patients best be managed following liver transplantation for HCC?

FY This is an important consideration. Every transplant program may have a slightly different approach in terms of frequency, modality, and duration of HCC surveillance after liver transplantation, and there is currently no standardized protocol in this regard. The UCSF Medical Center, in collaboration with the Mayo Clinic in Rochester, Minnesota and the Mayo Clinic in Jacksonville, Florida, developed the Risk Estimation of Tumor Recurrence After Transplant (RETREAT) scoring

system, which is based on 3 variables in patients who have undergone transplantation: the patient's alpha-fetoprotein level at the time of transplantation, the sum of the number of viable tumors and the largest viable tumor diameter, and whether there is any evidence of microvascular invasion of the tumor. Patients are then classified into different groups that correlate with the risk of tumor recurrence. The RETREAT score goes from 0 to greater than 5. We have proposed different surveillance strategies (both in length and interval) based on the predicted risk of tumor recurrence according to this RETREAT score. Posttransplantation screening includes computed tomography scan of the abdomen and chest and the measurement of alpha-fetoprotein level. Patients who have a low RETREAT score have a low risk of recurrence. If a patient has the lowest score of 0, which predicts a less than 3% risk of tumor recurrence at 5 years, we do not even apply screening after liver transplantation. Patients with a very high risk of tumor recurrence based on a RETREAT score of 5 or higher should be screened every 3 months for at least 5 years.

G&H What are the priorities of research in terms of HCC and liver transplantation?

FY We need better biomarkers that can improve the selection of patients with HCC for liver transplantation. We also need to develop adjuvant therapy that can be used after liver transplantation to reduce the risk of tumor recurrence.

Disclosures

Dr Yao has no relevant conflicts of interest to disclose.

Suggested Reading

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