Role of Liver Transplantation for Hepatocellular Carcinoma

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This review evaluates the available evidence to establish the role of liver transplantation in the management of hepatocellular carcinoma in India. Most liver transplants in India are living donor transplants due to the paucity of brain dead organ donors. There is sufficient evidence to permit allocation of organs to patients with tumors within the Milan criteria. If the waiting list time is more than 6 months, a down-staging locoregional treatment modality such a trans-arterial chemoembolization, radiofrequency ablation, resection or percutaneous ethanol injection may be used to prevent disease progression. Allocating scarce livers to patients with more advanced tumors may not be justifiable. However, living donor liver transplantation may be offered to medically fit patients with hepatocellular carcinoma with cirrhosis, offering a guarded prognosis to patients beyond the Milan or UCSF criteria. Vascular invasion and extra-hepatic disease should be absolute contraindications to liver transplantation. (J Clin Exp Hepatol 2014;4:S97–S103)

The role of liver transplantation in the management of hepatocellular carcinoma (HCC) is best understood in the context of the evolution of the modality. This is not a situation that lends itself to the conduct of multi-center double blind randomized controlled studies and much of the evidence comes from case series and database reviews. At the end of this review, it will be clear that patients with decompensated cirrhosis with small, not too numerous HCCs, with no vascular involvement and no extrahepatic spread are best served by an early liver transplant and that they do as well after liver transplant as patients transplanted for liver failure without HCC. It is also clear that patients with HCC infiltrating into major blood vessels or with extrahepatic spread have such poor outcomes that they are not candidates for liver transplant. Patients without cirrhosis with resectable HCC are obviously candidates for liver resection. Patients with early cirrhosis with small HCCs may be candidates for either resection or ablative therapies like radiofrequency ablation or for transplantation. Patients with larger HCCs, more numerous HCCs or adverse markers of tumor biology like markedly raised alfa-fetoprotein (AFP) levels or uptake of fluoro-deoxy-glucose (FDG) on positron emission tomography (PET) have a higher recurrence rate and a poorer long-term survival after liver transplantation than patients transplanted for liver failure without HCC and it is not clear exactly where to draw the line. If the option of living donor liver transplant (LDLT) is available, the patient is not competing with another patient for a scarce resource (a deceased donor liver). However the potential benefit should be weighed in the context of the potential for harm to the donor. Whether to have different criteria for LDLT is an essentially ethical question and should perhaps be settled only after the donor's wishes are taken into account.

EVOLUTION OF LIVER TRANSPLANTATION FOR HCC

In the early years of liver transplantation, the procedure was a desperate attempt to save a dying patient. Neither the surgical technique nor the anesthetic management had been standardized. It was a victory for the patient to survive the operation and go home. Coagulopathy and bleeding was a major problem.[1] In this context, the patient with an unresectable cancer in the liver was an attractive candidate. Since the cirrhosis was not very advanced, there would be less portal hypertension and coagulopathy and the patient was more likely to survive the operation. Liver transplantation was offered to patients with various unresectable malignancies in the liver. Of the first 7 liver transplants attempted, in Denver, Boston and Paris, 6 were for cancer, 3 HCC, 2 colorectal liver metastases and 1 cholangiocarcinoma.[2] As liver transplantation evolved and the procedure became safer and more standardized, long-term survival became the norm. However, when the long-

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Abbreviations: AFP: alfa-fetoprotein; DDLT: deceased donor transplants; FDG: fluoro-deoxy-glucose; HCC: hepatocellular carcinoma; LDLT: living donor liver transplant; PET: positron emission tomography; TACE: trans-arterial chemoembolization
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term survival of patients transplanted for liver cancer was evaluated, it was found to be dismal. In 1985, Starzl's group, which had by then moved to Pittsburgh, reported a 75% recurrence rate in patients transplanted for liver cancer.[3] In contrast, patients with incidental HCCs diagnosed on pathological examination of the explanted liver did well with 12 of 13 alive without recurrence. Penn reported the results of transplantation for primary or metastatic cancer in 637 patients.[4] The 5-year survival of patients transplanted for HCC was a dismal 18%. Patients transplanted for cirrhosis were doing well with improvements in immunosuppressive drugs and since there were not enough donor livers for the potential recipients, liver transplantation for HCC fell into disrepute for many years.

The Milan Criteria

In 1996, Mazzaferro et al from the University of Milan reported the outcomes in 48 patients with cirrhosis with small HCCs.[5] Their criteria were a single tumor up to 5 cm in diameter or up to 3 tumors none of which was more than 3 cm in diameter. Twenty-eight patients with sufficient liver reserve underwent some treatment, predominantly transarterial chemoembolization (TACE) before transplant. After liver transplant patients were followed for a median of 26 months. The overall mortality was 17%. The actuarial survival at 4 years was 75% with a recurrence free survival of 83%. Thirty-five patients met the criteria at pathological examination as well (73%) and had 4-year overall and recurrence free survivals of 85% and 92% respectively. The 13 patients who exceeded these limits on pathological examination had 4-year overall and disease free survivals of 50% and 59% respectively. The difference was highly significant ($P < 0.01$). It should be noted that only 60 of 295 patients referred for transplant for HCC met the criteria. Of these 1 died waiting for transplant, 11 were still waiting for organs and 48 had been transplanted. Transplant was performed a median of 143 days after staging.

The Milan criteria established that there is a category of patients with unresectable HCC against a background of cirrhosis who would do as well after transplant as patients transplanted for decompensated cirrhosis without HCC. The Milan criteria have been validated by many other centers. In a systematic review of such studies, Mazzaferro et al in 2011 looked at 90 studies spanning a period of 15 years and including 17,780 patients.[6] Only 17% of the studies, including 1612 patients had level 1b evidence. In 9 studies, patients who met Milan criteria and underwent liver transplant had post-transplant survival rates comparable to patients transplanted for non-tumor indications. Nineteen studies compared patients within Milan criteria and those beyond. Patients within Milan criteria had a better survival (hazard ratio 1.68, 95% CI—1.39–2.03). When the studies were split according to the type of transplant, the hazard ratio was 1.76 (95% CI—1.45–2.15) for deceased donor transplants (DDLT) while the advantage was considerably attenuated in LDLTs with a hazard ration of 1.28 with the CI beginning at 0.86. This suggests that perhaps the wait for the organ in the DDLT situation may select patients with better tumor biology for transplant.[7] It may also be that patients beyond Milan criteria progress while waiting for a deceased donor liver while they may have considerably superior outcomes in the LDLT scenario where this wait is eliminated.

Beyond the Milan Criteria

Obviously, everyone with tumors beyond the Milan criteria does not have recurrence after liver transplant and it seems unfair, for instance to condemn a patient with a 5.1 cm single tumor to death. The possibility of seeing how far beyond the Milan criteria it is possible to go has been explored in many ways. The best known of the "beyond Milan" criteria are the University of California at San Francisco (UCSF) criteria. Yao et al reported 70 patients transplanted for HCC.[8] They confirmed that the size limit for single tumors could be expanded to 6.5 cm and that for up to 3 tumors could be expanded to 4.5 cm provided the sum of the diameters of all the tumors was not more than 8 cm. Patients within the UCSF criteria had 1 and 5-year survivals of 90 and 75% while patients beyond the criteria had a 1 year survival of 50% ($P = 0.0005$).

Patel et al analyzed data from the United Network for Organ Sharing (UNOS) database.[9] From 2002 to 2007, 3434 patients were transplanted for HCC. Patients exceeding UCSF criteria, pediatric cases and patients whose size and number data was not available were excluded, leaving 1972 patients. Of these, 1913 patients were within the Milan criteria while 59 were beyond Milan but within the UCSF criteria. The survival of the two cohorts was similar, 1,2,3 and 4 year survival in the Milan cohort was 89%, 81%, 76% and 72% respectively while in the USCF cohort it was 91%, 80%, 68% and 51% respectively. This might be a better assessment of the impact of extending the criteria in the transplant population at large as opposed to a single center. While this report confirms the validity of the USCF criteria, it also illustrates the fact that only 3% of patients undergoing liver transplant for HCC will benefit from this extension of the criteria. In this study there were only 59 patients out of 1972 who were beyond the Milan criteria but within the UCSF criteria (2.9%). However, it may be that the small number of patients beyond Milan and within UCSF might reflect the fact that many centers had not yet accepted the UCSF criteria as a replacement for the "gold standard" Milan criteria.

Toso et al suggested using the total tumor volume (TTV) instead of size and number to predict the risk of recurrence.[10] However, this approach was limited by the