Criteria for Liver Transplantation in Hepatocellular Carcinoma

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The early experience with liver transplantation for hepatocellular carcinoma (HCC) in the 1980s was wrought with exceedingly high recurrence rates and 5-year overall survival (OS) rate <35%. This led to HCC being a contraindication for orthotopic liver transplantation (OLT) until 1996, when the Milan criteria (1 lesion ≤5 cm, 3 lesions with no one >3 cm, no vascular invasion, and no metastasis) were introduced (Table 1).[1,2] Post-OLT 5-year overall survival (OS) exceeds 70% in those within the Milan criteria.[3] To this end, the United Network for Organ Sharing (UNOS) has recognized that patients with HCC who meet specific criteria merit prioritization on the liver transplant waiting list by the allocation of additional (also called 'exceptional') MELD points (Table 2).

Transplantation offers the oncologic advantage of removing the tumor as well as the cirrhotic liver that predisposes to further hepatocarcinogenesis. The limitation of transplantation remains the shortage of organs available.

Several reiterations to the UNOS prioritization have occurred since 2002 due to concern for patients with HCC being granted a disproportional advantage over patients waitlisted for reasons other than HCC (Table 2).

Management of HCC on the Waiting List

Strategy may vary based on the anticipated waiting time, which is impacted by patients' geographic location. For those anticipated to wait over 6 months, liver-directed therapy (LDT) is recommended to some waitlisted patients who can be safely treated in order to prevent tumor progression and drop-out (Table 2).[4] The form of LDT chosen is dependent on the tumor size, location, and center expertise. Response to LDT, known as "ablate and wait," may provide insight into the biological behavior of individual tumors.[5] The adequate period of time needed to observe tumor biology is not known. A recent multicenter study suggested a minimum of 6 months observation from the time of HCC diagnosis coupled with LDT to OLT to avoid early HCC recurrence post-OLT.[6] Independent of initial tumor size, a lack of response to TACE has been correlated with a higher chance of dropout (while being waitlisted, and higher rates of HCC recurrence if transplantation is performed early).[7,8] A decrease in OS has been reported among those with HCC undergoing OLT in a short waiting time region compared to regions with longer waiting times.[9] An expedient OLT may not allow adequate time for an aggressive tumor to become apparent and lead to higher post-OLT mortality due to HCC recurrence. As a result of these data, UNOS has recently changed the regulation govering the allocation of exceptional MELD points to HCC patients to incorporate an observation period of 6-months (Table 2).

Response to alpha fetoprotein (AFP) levels has also been reported to be predictive of outcome. The AFP level closest to time of OLT has emerged as an independent predictor of overall survival after transplant.[10,11] A decline in an initially elevated AFP associated with LDT has shown to incur no increase in mortality, whereas a rising AFP is associated with a significant increase in post-OLT mortality. These data support the contention that AFP level should be incorporated into the decision-making regarding patients on the waiting list.

Lesions Too Small for HCC Upgrade

Solitary lesions < 2 cm, T1, are not given prioritization on the waiting list. Options include close observation with

Abbreviations: AFP, alpha fetoprotein; DDLT, deceased donor liver transplantation; HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; LRT, locoregional therapy; MELD, Model for End-Stage Liver Disease; OLT, orthotopic liver transplantation; OS, overall survival; UCSF, University of California San Francisco; UNOS, United Network for Organ Sharing.

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TABLE 1 American Liver Tumor Study Group—Modified TNM Staging System

I	1 nodule ≤1.9 cm
II	1 nodule 2.0-5.0 cm; 2 to 3 nodules, all ≤3.0 cm; Milan criteria
III	1 nodule >5.0 cm; 2 to 3 with any nodule >3.0 cm
IVA1	≥4 nodules of any size
IVA2	Stage II, III, or IVA1 plus gross intrahepatic portal or hepatic vein involvement on imaging
IVB	Lymph node or distant metastasis or extrahepatic portal or hepatic vein involvement

TABLE 2 MELD Upgrade for HCC

Date	T2 = Milan	T1= 1 lesion ≤ 1.9 cm
2/27/2002	29	24
2/27/2003	24	20
04/14/04	24	-
03/06/05	24	-
09/08/2015	natural MELD for the first 6-months, then 28, cap at 34	-

Taken from Freeman et al.[19] and www.UNOS.org, accessed 10/10/2015.

imaging for 3 months until the lesion reaches 2 cm before receiving LDT versus proceeding with LDT prior to qualifying for a MELD upgrade. With watchful waiting, there is an inherent risk of progression beyond the Milan criteria that has been reported to be <10%.[12] Factors associated with increased risk of tumor progression beyond Milan without LDT include rapid tumor growth (>1 cm within 3 months) and an initial AFP > 500 ng/mL.

Predictors of Drop-Out

Tumors that progress beyond the Milan criteria become ineligible for MELD exception points. Factors identified as risk factors for drop-out include: tumor >3 cm, >1 tumor, a lack of complete radiographic response after the first locoregional therapy (LRT), and AFP > 20 ng/mL after the first LRT. Patients with a solitary tumor < 3 cm with response after initial LRT (CR and AFP < 20 ng/mL) have a reported 1- and 2-year risk of progression beyond T2 of 1.3% and 1.6%, respectively.[13]

Role for Transplant Exceeding the Milan Criteria

There is concern that the Milan criteria are too stringent and that a subgroup of patients that exceed these criteria would benefit from OLT without adversely effecting post-OLT outcomes. Various criteria beyond the Milan criteria have been proposed (Table 4). Whereas the majority of UNOS regional review boards have not accepted expansion beyond the Milan criteria, downstaging into the Milan criteria has shown promising results. Excellent outcomes (4-year OS 92%; N = 61) were initially reported by the UCSF group when a uniform protocol for downstaging was

TABLE 3 Liver-Directed Therapies for HCC

Ablative Therapies
- Percutaneous ethanol injection (PEI)
- Radiofrequency ablation (RFA)
- Microwave ablation (MWA)
- Cryoablation

Intra-arterial Therapies
- Transarterial Chemoembolization
  - Conventional
  - Drug-Eluting Beads (DEB)
- Radioembolization

TABLE 4 Criteria Beyond Milan

UCSF Criteria	1 lesion ≤6.5 cm; 3 lesions, none >4.5 cm, total diameter ≤8 cm
Dallas Criteria	Largest lesion ≤ 6 cm; no. of lesions ≤ 4
"Up to 7"	Largest tumor + number = 7 W/O microVI
Total tumor volume	≤115 cm^3 and AFP ≤ 400 ng/mL (1 lesion ≤ 6 cm or 3 lesions up to 4.2 cm)
Asian Criteria	Largest lesion ≤ 5 cm; no. of lesions ≤ 6
Kyoto Criteria	Largest lesion ≤ 5 cm; no. of lesions ≤ 10 PIVKA ≤ 400 m AU/mL
Kyushu University Criteria	All tumors < 5 cm OR DCP < 300 mAU/mL
Toronto Criteria	No restriction size/number: Tumor grade well or moderately differentiated in those > Milan; PS = 0

followed.[14] Part of the protocol included a mandatory waiting time of 3 months prior to listing after successfully downstaging to the Milan criteria. Expansion of the UCSF downstaging protocol to a multicenter study including 187 patients demonstrated a 5-year post-OLT OS of 80% with 11% HCC recurrence among 109 patients who underwent OLT.[15]

Living Donor Liver Transplantation in HCC

Living donor liver transplantation (LDLT) offers an alternative to waiting for a decreased donor transplant and hence can decrease the risk of drop-out and also provides a means to expand the donor pool. The burden of HCC is predicted to continue to increase with the peak incidence of HCV-related HCC to occur in 2020.[16]

'Fast tracking' to transplantation with LDLT compared to waiting for a deceased donor liver transplant (DDLT) has been reported to be associated with an increased risk of HCC recurrence.[7] This may be related to a combination of differences in tumor characteristics (patients with more advanced HCC undergoing transplantation with LDLT because DDLT option is limited in those exceeding the Milan criteria), waiting time (shorter in LDLT), and pre-transplant management (less LDT in LDLT). When the same selection criteria have been used for LDLT and DDLT, no significant difference in HCC recurrence was noted.[18] Similar to DDLT, response to LDT, including radiographic and AFP response, should be utilized when considering LDLT for HCC in order to minimize post-OLT HCC recurrence.

Conclusion

The incidence of HCC is rising. Although OLT offers the best opportunity for long-term survival, the limitation of organ availability will likely impact future decisions for prioritization for those with HCC. Optimization of patient selection including response to LDT and an observation period will be imperative to maximize outcomes among patients with HCC.

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References

1. Iwatsuki S, Gordon RD, Shaw BW Jr, Starzl TE. Role of liver transplantation in cancer therapy. Ann Surg 1985;202:401-407.
2. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693-699.
3. Mazzaferro V, Bhoori S, Sposito C, Bongini M, Langer M, Miceli R, et al. Milan criteria in liver transplantation for hepatocellular carcinoma:An evidence based analysis of 15 years of experience. Liver Transpl 2011;17:S44-S57.
4. Clavien PA, Lesurtel M, Bossuyt PM, Gores GJ, Langer B, Perrier A; OLT for HCC Consensus Group. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. Lancet Oncol 2012;13:e11-e22.
5. Roberts JP, Venook A, Kerlan R, Yao F. Hepatocellular carcinoma: ablate and wait versus rapid transplantation. Liver Transpl 2010;16:925-929.
6. Mehta N, Yao FY, Heimbach J, Harnois DM, Burns JM, Lee D, et al. Short waiting time predicts early recurrence of hepatocellular carcinoma after liver transplantation: a multicenter study supporting the "ablate and wait" principle [Abstract no. 504]. Hepatology 2014;60:446A.
7. Otto G, Herber S, Heise M, Lohse AW, Mönch C, Bittinger F, et al. Response to transarterial chemoembolization as a biological selection criterion for liver transplantation in hepatocellular carcinoma. Liver Transpl 2006;12:1260-1267.
8. Vitale A, D'Amico F, Frigo AC, Grigoletto F, Brolese A, Zanus G, et al. Response to therapy as a criterion for awarding priority to patients with hepatocellular carcinoma awaiting liver transplantation. Ann Surg Oncol 2010;17:2290-2302.
9. Halazun KJ, Patzer RE, Rana AA, Verna EC, Griesemer AD, Parsons RF, et al. Standing the test of time: outcomes of a decade of prioritizing patients with hepatocellular carcinoma, results of the UNOS natural geographic experiment. Hepatology 2014;60:1957-1962.
10. Berry K, Ioannou GN. Serum alpha-fetoprotein level independently predicts posttransplant survival in patients with hepatocellular carcinoma. Liver Transpl 2013;19:634-645.
11. Merani S, Majno P, Kneteman NM, Berney T, Morel P, Mentha G, et al. The impact of waiting list alpha-fetoprotein changes on the outcome of liver transplant for hepatocellular carcinoma. J Hepatol 2011;55:814-819.
12. Mehta N, Yao FY, Roberts JP, et al. Intention-to-treat outcome of T1 hepatocellular carcinoma using the approach of "wait and not ablate" until meeting T2 criteria for liver transplant listing. Presented at AASLD The Liver Meeting, Washington DC, November 1-5, 2013.
13. Mehta N, Dodge JL, Goel A, Roberts JP, Hirose R, Yao FY, et al. Identification of liver transplant candidates with hepatocellular carcinoma and a very low dropout risk: Implications for the current organ allocation policy. Liver Transpl 2013;19:1343-1353.
14. Yao F, Kerlan RK Jr, Hirose R, Davern TJ 3rd, Bass NM, Feng S, et al. Excellent outcome following down-staging of hepatocellular carcinoma prior to liver transplantation: an intention-to-treat analysis. Hepatology 2008;48:819-827.
15. Mehta N, Sarkar M, Guy J, Osorio RW, Frenette CT, Minteer WB, et al. Multicenter study of down-staging of hepatocellular carcinoma (HCC) to within milan criteria before liver transplantation (LT) [Abstract no. 111]. Hepatology 2014;60:253A.
16. Davis G, Alter M, El-Serag H, Poynard T, Jennings. Aging of hepatitis C virus (HCV) - infected persons in the United States: a multiple cohort model of HCV prevalence & disease progression. Gastroenterology 2010;138:513-521.
17. Kulik L, Abecassis M. Living donor liver transplantation for hepatocellular carcinoma. Gastroenterology 2004;127(5 suppl 1):S277-S282.
18. Bhangui P, Vibert E, Majno P, Salloum C, Andreani P, Zocrato J, et al. Intention-to-treat analysis of liver transplantation for hepatocellular carcinoma: living versus decreased donor transplantation. Hepatology 2011;53:1570-1579.
19. Freeman RB Jr, Wiesner RH, Roberts JP, McDiarmid S, Dykstra DM, Merion RM. Improving liver allocation: MELD and PELD. Am J Transplant 2004;4(suppl 9):114-131.