EDITORIAL

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Who should undergo liver transplantation for hepatocellular carcinoma? Ablate, wait ... and see!

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The incidence of hepatocellular carcinoma (HCC) is rising in the USA, and the use of liver transplantation (LT) for HCC treatment has grown accordingly [1,2]. This trend has magnified an inequity in the distribution of livers to needy patients with versus without HCC. While donor organ availability has remained relatively static over the last decade, the fraction of LT performed for HCC has ballooned, with associated increases in waiting time and the severity of liver dysfunction at LT in non-HCC candidates [2,3]. For a given period of time on the LT wait list, HCC candidates have lower mortality and a higher probability of receiving LT than non-HCC candidates [4,5]. These disparities shed unflattering light on the current liver allocation system. Consideration of an ethical framework for the management of scarce resources will guide policy makers in molding this system into one that effectively directs organs to the patients, with or without HCC, who will benefit most [6].

1996–2005: Milan criteria, MELD prioritization & MELD exceptions

By congressional mandate, medical urgency governs liver allocation in the USA [7].

However, LT must also result in acceptable long-term survival for a given indication to be approved for LT. Initial long-term outcomes of LT for HCC were dismal due to the transplantation of advanced malignancies with high rates of post-LT cancer recurrence. In 1996, Mazzaferro reported a set of restrictive criteria for HCC that identified a subgroup with comparable post-LT survival to non-HCC indications (75% at 4 years), firmly establishing LT as an effective treatment for early HCC [8]. These ‘Milan criteria’ (MC) permitted one tumor up to 5 cm or three tumors up to 3 cm. In 2002, the United Network for Organ Sharing (UNOS) adopted the MC for the prioritization of HCC for LT. Simultaneously, UNOS implemented the Model for End-Stage Liver Disease (MELD) scoring system to rank candidates with chronic liver disease by their expected 90-day mortality on the LT wait list [9].

Since candidates with HCC frequently have well-compensated liver disease and low MELD scores, a ‘MELD exception’ was awarded to allow HCC candidates to compete with MELD-prioritized non-HCC patients on a shared wait list. The

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MELD exception was initially calibrated to minimize the probability that HCC would progress beyond the MC, resulting in wait list removal. It soon became apparent that the MELD exception, as originally conceived, excessively favored HCC over non-HCC candidates [10]. To devalue the prioritization granted for HCC, UNOS reduced the quantity of MELD exception points for HCC exceptions in 2003 and again in 2005.

2005 to present: refining the selection of HCC candidates for LT

Since 2005, several important themes have emerged that challenge current allocation dogma for HCC. First, the MC are imperfect; LT for carefully selected patients outside MC has demonstrated excellent outcomes, while HCC recurrence persists in some within-MC LT recipients [11,12]. Second, locoregional therapies (LRT) for HCC have evolved; the prevalence of LRT has risen, the technology is increasingly refined reducing wait list dropout rates, and the capacity of LRT response to predict post-LT outcomes is now recognized [13–15]. Third, underlying liver dysfunction independently predicts post-LT outcomes in HCC candidates and is unaccounted for with the MELD exception (a combined HCC–MELD allocation model has been proposed to address this deficiency) [16,17]. Finally, there is an increasing appreciation that the current liver allocation system directs organs to the most ill patients who have the worst post-transplant outcomes, which undermines the desire to extract maximal utility from the limited pool of organs available for LT [18].

Proposals to improve liver allocation based on core ethical values

We propose a general approach to improve liver allocation based on the ethical principles of justice, utility, beneficence and autonomy [18]. In practice, LT for HCC pits the principle of beneficence against those of justice and utility. Beneficence implies selecting the treatment that maximizes benefit to the individual patient. Since LT clearly offers a survival benefit to patients with HCC compared with other therapies, LT strongly supports the principle of beneficence. However, LT for HCC violates the principle of justice (HCC patients have greater access to LT than non-HCC patients) and does not extract the most utility from the organ pool (survival after LT is superior for non-HCC patients). How can we ‘rebalance the equation’ to better

adhere to ethical principles for scarce resource allocation?

Should we be transplanting HCC at all? Early cirrhotic patients (Child–Pugh class A) with HCC derive marginal benefit from LT [15], while patients with advanced cirrhosis (MELD ≥ 20) have worse post-LT survival than similar non-HCC patients [16]. In general, despite their enhanced access to LT, HCC patients demonstrate shorter post-LT survival compared with non-HCC LT recipients [19]. Excluding HCC patients from LT would support the ethical principle of utility (by maximizing total life years gained from available livers), but this policy would also exclude patients who would derive a survival benefit from LT, thus transgressing the principle of beneficence. A proposed policy of completely excluding HCC patients from LT would ill serve the ethical concerns at stake and should be discarded.

We submit two potential strategies to restore equity to liver allocation for patients with and without HCC: ‘patch’ the current MELD-based allocation system or introduce a completely new method of liver allocation that more closely aligns with the ethical principles discussed above.

‘Patching’ MELD-based liver allocation for HCC

How can we repair the current MELD exception algorithm for HCC? One strategy would be to apply LT only in subgroups of HCC that derive the greatest benefit. Patients with good liver function (Child–Pugh class A) and small tumors (≤ 3 cm) display excellent survival with LRT alone [20], and do not significantly benefit from LT. At the other end of the HCC spectrum, patients at high risk for post-LT HCC recurrence also do not significantly benefit from LT. The widely publicized ‘ablate and wait’ approach [12] may optimize discrimination of these two groups. Liver-simulated allocation modeling has shown that imposing a 6-month delay in LT for HCC would equalize access to LT for patients with and without HCC, without increasing wait list mortality [21]. Thus, Child–Pugh class A cirrhotic patients with ≤ 3 cm HCC would be treated with LRT and then closely monitored. If recurrent or *de novo* HCC did not occur over a 6-month period, then LT would not be offered. Patients with multifocal or large HCC would also be treated with LRT and closely followed for a 6-month period; patients with tumor progression during this period would also not be

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offered LT, due to a high risk of post-LT HCC recurrence.

Straddling these two groups are patients with Child–Pugh class A cirrhosis and recurrent or *de novo* HCC after LRT, and patients with more advanced liver disease (Child–Pugh class B or C) and HCC. The former group greatly benefits from LT due to clear evidence of a ‘field defect’ that LT could correct, while the latter group greatly benefits both from HCC eradication and restoration of liver function. In summary, we submit that the three subgroups of HCC patients who should be offered LT are:

- Child–Pugh class A cirrhosis and small HCC (≤ 3 cm), who have undergone LRT but had recurrent or *de novo* tumors, or
- Child–Pugh class A cirrhosis and HCC > 3 cm who have undergone LRT and demonstrated no metastatic disease, vascular invasion, or growth beyond MC (‘favorable biology’) during a 6-month waiting period, or
- Child–Pugh class B or C cirrhosis and HCC ≥ 2 cm that demonstrated ‘favorable biology’ during a 6-month waiting period, with or without LRT.

Implementation of this policy would enhance justice and utility in liver allocation by excluding HCC patients with little to gain from LT due to a high probability of having an excellent outcome without LT (small HCC and preserved liver function with good response to LRT) or an adverse outcome with LT (the waiting period reveals unfavorable biology).

Rebooting the system: survival benefit-based liver allocation

A second approach introduces an entirely new liver allocation system. Such an approach has been suggested using a model that maximizes survival benefit with LT [22]. This strategy would move completely away from the MELD

system that solely focuses on expected mortality without LT. Instead, survival-based allocation accounts for both expected mortality without LT and mortality with LT, allocating organs to candidates expected to benefit most from LT. Survival benefit-based models are already in use for lung [23] and kidney [24] allocation, and can be readily adapted to model HCC mortality, as well as other etiologies of liver disease that require MELD exceptions due to a mortality risk without LT that is not reflected by their MELD score. However, short of adopting this radical transformation in liver allocation policy, we favor ‘patching’ the current system of MELD-based allocation for HCC as discussed above.

Ultimately, we concede that the absence of tumor progression during a 6-month waiting period is but an inelegant surrogate for underlying ‘favorable biology.’ AFP may add to the prediction of wait list dropout and HCC recurrence, but a clear consensus on its specific role has precluded widespread use. Molecular genetic assays of both the cancer and surrounding liver parenchyma may soon offer more accurate and rapid prognostication of the probability of recurrent or *de novo* HCC development [25]. Until these tools have been refined, incorporation of the waiting period and LRT response into our liver allocation scheme offers our best hope of allocating precious livers to the patients who will benefit most.

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