

Extended criteria donors in liver transplantation— from marginality to mainstream

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Further to refinements in immunosuppression and the significant gains witnessed in outcomes over recent decades, liver transplantation has firmly established itself as the definitive treatment for end stage liver disease and selected instances of hepatic malignancy. However, there exists a constant divide between organ supply and demand, with the numbers of new entrants to liver transplant waiting lists consistently and significantly outstripping that of transplants performed annually, as exemplified by United Network for Organ Sharing (UNOS) data from the United States (1). Compounding this issue are the adverse projections for the state of organ donors in the near future. The concept of an ideal liver graft as a whole organ coming from a young donor, brain-dead from traumatic or anoxic causes, on the background of a short cold ischaemic time (CIT) is well established [as the donor risk index (DRI)] (2) but perhaps a slowly diminishing reality. An aging population along with the rising incidence of obesity, diabetes and non-alcoholic fatty liver disease (NAFLD) are all expected to contribute to poorer donor quality and as a consequence, lesser organ utilization by 2030 (3).

Harnessing the potential of ‘marginal’ or extended criteria donors (ECDs) aims to somewhat mitigate the brunt of these adverse forecasts. How best to define an ECD is still a contentious issue with no consensus criteria. Nonetheless, the umbrella of ECDs has traditionally included categories such as advanced age, donation after circulatory death (DCD), hepatic steatosis, split liver grafts, CIT >8–12 hours,

donors with increased risk of communicable disease transmission, those with active or past extrahepatic malignancy, hypernatraemia, and prolonged donor intensive care unit stay amongst others (4). As a result, they understandably invoke perceptions of higher risk of inferior graft and patient survival although such grafts still offer benefit from waiting-list mortality (5).

The recent work of Halazun and co-workers from New York serves to highlight the successful use of marginal livers over an 18-year period in a high volume transplant centre well adapted to the use of such grafts due to the relative lack of indigenous donors in their UNOS region (6). Accordingly, the majority of the 790 adult patients in their ECD cohort received grafts declined by other local/regional centres (68%) and from donors >70 years of age (28%). Using such an approach, the authors showed comparable outcomes between recipients of marginal and standard livers.

The questions frequently asked on the back of such efforts are obvious—can the selection of ECDs be further improved or can these marginal factors be better optimized to allow enhanced outcomes? Encouragingly, this field is the subject of much research and our knowledge in the area is expanding at a promising rate. Herein we touch upon some of these variables that have witnessed advances in recent years.

The premise that advanced donor age denotes marginality has been challenged with recent data. The same

New York group in a new report note that elderly grafts (>70 years age) formed only 4.3% of all 71,926 liver transplants done in the MELD era within UNOS, thus representing an underutilized resource (7). Although unadjusted survival was poorer for recipients of elderly grafts, judicious matching of these livers with patients with no other adverse donor/recipient risk factors [using DRI and survival outcomes following liver transplantation (SOFT) criteria] resulted in comparable outcomes to those recipients with grafts <40 years of age. Donor livers >70 years with no risk factors were found to offer equivalent survival to those grafts <70 years with a DRI up to 1.5.

DCD liver transplantation has historically been associated a higher risk of ischaemic cholangiopathy and poorer outcomes in comparison to their heart-beating counterparts (8), a trend that has remained largely unchanged over the years in multinational registry analyses (9,10). However, smaller-scale studies indicate that careful donor and recipient selection enable durable outcomes, which assumes importance given the increasing scale of DCD donation worldwide. Paramount to improving the risk associated with a DCD liver donor is minimizing the functional warm ischaemia time (fWIT) incurred between the onset of post-withdrawal agonal haemodynamics and cold perfusion. One of the latest studies that attempts to quantify the risk of DCD liver donation highlighted fWIT (defined as systolic blood pressure <50 mmHg >30 minutes) as the most powerful donor indicator of adverse outcome (11). However how one defines the threshold at which fWIT begins is still a matter of debate, with definitions incorporating peripheral oxygen saturation, mean arterial blood pressure or systolic blood pressure all being used (12).

Hepatic steatosis represents the most highly prevalent type of ECD, and with current population forecasts is firmly here to stay. Increasing degrees of donor hepatic macrosteatosis >30% is well understood to be associated with an increasing risk of heightened reperfusion injury, primary non-function and lower graft survival following transplantation. There is however data to support the use of markedly macrosteatotic livers (>60%) in well-selected recipients with acceptable outcomes, and in fact reversal of fatty change has been observed in such recipients (13). Whether pre-operative liver machine perfusion can help mitigate the adverse risk of severe steatosis is currently unclear, with preliminary data highlighting no significant drop in the degree of fatty change in liver tissue after

24 hours of normothermic perfusion (14).

The recent arrival of directly acting anti-viral agents (DAAs) is now changing the landscape of how hepatitis-C virus (HCV) positive donors are utilized. Whilst traditionally reserved only for HCV-positive recipients, the high (>90%) success rate and of DAAs in eliminating the virus combined with their good tolerability is leading to the increased use of such livers in HCV-negative patients, with positive implications on wait-list mortality (15). This is especially relevant considering the higher prevalence of HCV positivity in intravenous drug users and the increasing rate of drug overdose deaths in the United States. Notably, the number of HCV-positive liver recipients has fallen in recent years within the UNOS region, coupled with a steady rise in HCV-positive donors (1). The high costs of DAAs and securing upfront authorization for therapy also factor into the logistics of this paradigm. What is imperative regardless to acceptable outcomes is the use of younger donors with no/early-stage fibrosis from HCV, with attention to minimization of other risk factors.

The advent of normothermic machine perfusion (NMP) into the realm of phase III human clinical trials has provided the transplant community with valuable data about the short-term benefits of this modality over cold static storage of liver grafts, with significantly lower hepatocyte injury profiles and higher preservation time in the NMP group (16). The application of NMP and similarly hypothermic oxygenated perfusion (HOPE) to ECD livers is also currently underway and could highlight opportunities to further modify the risk to marginal donors (17,18).

In summary, it is evident that marginal liver donors are increasing in prevalence worldwide, and they must be optimally exploited in order to expand the donor pool and improve transplant outcomes. It remains crucial that such grafts are utilized in good-risk recipients capable of incurring the brunt of potential suboptimal organ function. However, the next breakthroughs in the management of these livers will likely stem from advancements in the field of liver machine perfusion.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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