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Extended criteria donors in liver transplantation Part II: reviewing the impact of extended criteria donors on the complications and outcomes of liver transplantation

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Abstract

Extended criteria donors (ECDs) have an impact on early allograft dysfunction (EAD), biliary complications, relapse of hepatitis C virus (HCV), and survivals. Early allograft dysfunction was frequently seen in grafts with moderate and severe steatosis. Donors after cardiac death (DCD) have been associated with higher rates of graft failure and biliary complications compared to donors after brain death. Extended warm ischemia, reperfusion injury and endothelial activation trigger a cascade, leading to microvascular thrombosis, resulting in biliary necrosis, cholangitis, and graft failure. The risk of HCV recurrence increased by donor age, and associated with using moderately and severely steatotic grafts. With the administration of protease inhibitors sustained virological response was achieved in majority of the patients. Donor risk index and EC donor scores (DS) are reported to be useful, to assess the outcome. The 1-year survival rates were 87% and 40% respectively, for donors with a DS of 0 and 3. Graft survival was excellent up to a DS of 2, however a DS >2 should be avoided in higher-risk recipients. The 1, 3 and 5-year survival of DCD recipients was comparable to optimal donors. However ECDs had minor survival means of 85%, 78.6%, and 72.3%. The graft survival of split liver transplantation (SLT) was comparable to that of whole liver orthotopic liver transplantation. SLT was not regarded as an ECD factor in the MELD era any more. Full-right-full-left split liver transplantation has a significant advantage to extend the high quality donor pool. Hypothermic oxygenated machine perfusion can be applied clinically in DCD liver grafts. Feasibility and safety were confirmed. Reperfusion injury was also rare in machine perfused DCD livers.

I) Introduction

As discussed earlier, extended criteria donors are used widely. In this chapter a review is given about the impact of ECD on the outcome. Living related liver transplantation is discussed shortly, whether the partial grafts can still be regarded as ECD or not. Machine perfusion, as a possible management was also reviewed briefly. Outcome parameters are divided as possible complications, and survival results. Complications are listed as early graft dysfunction, biliary complications, HCV recurrence. Survival rates are summarized separately. Split, and living related LT discussed briefly, and finally the machine perfusion, as a possible future aspect is summarized.

II) Complications

1) Early graft dysfunction (initial poor function, or delayed graft function)

ECD donors are also not optimal for candidates with a high MELD score. *Briceno et al* reported their prediction for graft dysfunction based on ECD-scores and MELD score. In their findings ECD 2 (relative risk [RR]=1.59; 95% confidence interval [CI]=1.25-1.62), ECD 3 (RR=2.74; 95% CI=2.38-3.13), as well as MELD 21 to 30 (RR=1.89; 95% CI=1.32-2.06), and MELD more than or equal to 30 (RR=3.38; 95% CI=2.43-3.86).were independent risk factors for IPF or PNF. In summary they state that a combination of ECD>3 and MELD >29 is the worst scenario [1]. A similar report was published by *Palmiero et al* about 1786 OLTs. ECD criteria were the same as described earlier. The predictive factors for death among the whole population were DRI >1.5, cold ischemia time ≥9 hours, MELD ≥25, female recipient, and longer waiting list time [2]. *Silberhummer et al* figured out the recipients' condition by the delta-MELD: as the difference between the MELD at transplantation and the MELD at listing. Patients with a both delta-MELD>1 and an ECD>2 together had a higher chance to develop EAD, and also significantly higher risk for mortality [3]. Others report a similar incidence of EAD, PNF, acute rejection, biliary complication and also that ECD had no significant effect on either ICU stay or duration of postOLT ventilation, and also the postOLT laboratory test, bleeding, biliary and vascular complication rates were similar in ECD and non-ECD groups, and finally the rate of IPF was 27% vs 31% in ECD and non-ECD grafted patients [4]. There was no difference (P = .882) in total hospital stay and ICU stay (P = .788) among recipients having three or more extended criteria, and also renal replacement therapy was necessary in a similar proportion in all these groups (P = .783) [5].

Grafts with mild steatosis can be safely used in OLT with risk of postoperative EAD compared to non-steatotic grafts, if other risk factors are excluded [6,7]. The long-term outcome is also good. Grafts with moderate macrovesicular steatosis (30–60%) may be utilized in the absence of additional risk factors in the donor or recipient; livers with more than 60% macrosteatosis should

probably be excluded, because the use of grafts with macrovesicular steatosis has been associated with increased rates of EAD, or PNF, and poorer outcome [8].

The outcome of liver grafts with different grades of steatosis showed significantly lower patient and graft survival when grafts with steatosis >30% were used [7,9,10]. EAD was seen in 53% of grafts with moderate steatosis and in 73% of grafts with severe steatosis compared to 26% EAD in grafts with mild steatosis [7]. On the contrary, others demonstrated no differences in graft survival between grafts with less than 30% steatosis and grafts with moderate and severe steatosis [11,12,13]. All these studies showed that grafts with >30% steatosis had significantly increased transaminases, diminished PT time and longer time for bilirubin to normalize. Experience about the use of severely steatotic grafts is also emerging. *Chavin et al.* and *McCormack et al.* showed that LT with grafts with steatosis > 60%, (despite the higher incidence of EAD) can achieve excellent patient and graft survival when these grafts are allocated in low risk recipient [14,15]. The proper allocation of steatotic grafts was confirmed by *Dutkowski et al.*[16] : graft with <30% steatosis can be used safely up to BAR (Balance of Risk) score of 18 of less, however if graft steatosis exceeds 30% acceptable outcome can be achieved only if BAR score was 9 or less.

The definition of EAD was recently re-validated by *Croome KP et al*, in a multicenter study: EAD was a valid predictor of both graft and patient survival at six months in DBD allograft recipients, but in DCD ones. Within DCD group the 6 months patient and graft survival was 11,5% vs 16,7 % with and without ECD scores. On the other hand they proved an association with INR more/less 1,6 on day 7 after OLT and graft failure [17]. According to the definition of *Olthoff et al* EAD was set whether of one or more of the following previously defined postoperative laboratory analyses were present: bilirubin >or=10mg/dL on day 7, international normalized ratio >or=1.6 on day 7, and alanine or aspartate aminotransferases >2000 IU/L within the first 7 days. Of recipients meeting the EAD definition, 18.8% died, as opposed to 1.8% of recipients without EAD (relative risk = 10.7 [95% confidence interval: 3.6, 31.9] P < 0.0001). More

recipients with EAD lost their grafts (26.1%) than recipients with no EAD (3.5%) (relative risk = 7.4 [95% confidence interval: 3.4, 16.3] P < 0.0001) [18]. This is in accordance with the definition of *Nemes et al* [19]. *Routh et al* report 6,5% PNF, and 26,1% of three or more complications in ECD grafted recipients [20]. PNF is usually defined as unrecoverable hepatocellular dysfunction leading to patient death or re-transplantation within the first week post-transplant after excluding other causes of graft failure such as vascular thrombosis, biliary complications, rejection or recurrent disease. By using different in vivo organ preservation methods to maintain DCD donors and by strictly applying donor selection criteria authors report promising results from Maastricht category I and II donors with a PNF rate of 10%-25% [21]. *Leithead et al* reported about the kidney injury that developed frequently after DCD grafting. Acute kidney injury occurred 53,4% vs 31,8% in DCD vs DBD grafted patients, while chronic renal impairment was found to be 53,7% vs 42,1% respectively [22].

2) Biliary complications

i) Donor organ quality

The development of biliary complications after liver transplantation has been described as the Achilles of the operation. Extended criteria donors, steatotic liver, prolonged CIT are risk factors for biliary complications [23]. The risk will even be higher, when additive risk factors are present on the recipient side. *Nemes et al* [19] compared different study groups, which were established according to donor graft quality and recipient status. Donors had a marginal score if any of the following were present: age older than 60 years, BMI greater than 27, ICU stay longer than 3 days, high inotropic support, hypotension, cardiac arrest requiring cardiopulmonary resuscitation, hypernatremia, elevated liver enzymes or serum bilirubin levels. Recipient status was based on MELD scores; and the results showed that patients with a high MELD score demonstrated increased risk of postoperative complications - including biliary complications. Moreover the use of marginal donor organs in high-risk patients increased early patient mortality. If possible, an extended criteria organ must never be given to a recipient with extensive risk factors. Other authors found similar biliary and vascular complication rates in ECD and non-ECD groups [4, 24,25].

ii) The role of hepatic artery thrombosis

Hepatic artery thrombosis (HAT) must also be mentioned as a serious technical complication, occurring in approximately 2% to 9% of cases. Early HAT frequently results in fulminant hepatic failure, bile duct necrosis and leaks, relapsing bacteremia and ultimately graft loss and retransplantation or recipient death [26]. Several factors have been reported to predispose to HAT [27]. The role of advanced donor age is controversial. *Petridis et al* [28] reported OLTs from cadaveric donors older than 80 years with 10% of HAT, also requiring retransplantation. As for the late complications 60% had stricture of the biliary anastomosis. In case of older donors - the iliac "tool kit" may be unusable because of atherosclerotic disease. An alternative solution is to perform the anastomosis of the celiac artery with aortic patch from the donor directly to the

supraceliac aorta of the recipient [29]. In the more recent approach to hepatic artery (HA) reconstruction the use of interposition grafts was minimized. *Cescon et al.* suggest performing more "straight" anastomoses on sites generally spared from advanced stages of atherosclerosis, thus reducing the risk of kinking and of disruption of the intima [27].

iii) Split liver transplantation

Postoperative morbidity, composed of vascular and biliary complications, remains high for pediatric and adult recipients of split liver transplantation (SLT). *Vagefi et al* analyzed data of 106 SLT recipients and found 29% biliary and 11% vascular postoperative complications and 11% unplanned re-exploratory surgery in adult recipients, and 40% biliary and 26% vascular complications in children [30]. The complication rate for recipients of living donor liver allografts is still higher than that for recipients of whole-organ allografts, which is further compounded by the morbidity and mortality risk of the living donor [30]. *Mallik et al* found similar incidence of biliary complications when comparing DCD and SLT liver transplants [31]. The splitting procedure –in the case of ex vivo splitting technique - takes typically 2–3 hours and additional time required for transport of these livers (possibly to two centers sequentially), consequently SLT has much longer CIT than DCD has.

iv) Donors after circulatory death (DCD), ischemia-reperfusion

Many publications focus on liver transplant complications related to DCD transplantation, the increasing special form of ECD pool. DCD liver transplantation has been associated with inferior outcomes including higher rates of graft failure and biliary complications compared with DBD transplants [26,32]. DCD recipients have a 2.4 times increased Odds-ratio of biliary complications and a 10.8 times increased odds of ischemic cholangiopathy (IC) [26,33]. IC patients experience jaundice, disabling pruritus, and frequent episodes of cholangitis [33]. DCD recipients with IC experienced more frequent re-hospitalizations, longer lengths of stay, and required more invasive biliary procedures. According to a metaanalysis of *Jay et al* IC patients

undergo an average of 12 invasive biliary procedures (range = 0–21) in their first 2 years after transplantation [33]. *Skaro et al* [34] observed no significant differences in the rates of PNF or vascular complications, but the majority of re-listing (69.2%) and re-OLT (71.4%) in the DCD group were a consequence of biliary complications. After OLT the development of IC is most commonly precipitated by the occlusion of hepatic arterial flow. *Yamamoto et al.* found significantly more HAT (33.3% vs. 0%) and biliary (37.5% vs. 6.3%) complications in their DCD group compared to the DBD group [35]. After DCD OLT, warm ischemia, preservation and reperfusion injury involving the peribiliary plexus have been implicated. Endothelial activation triggers a cascade of events leading to microvascular thrombosis and ischemia resulting in stricture formation, biliary necrosis and cholangitis culminating in progressive graft failure [34].

Abou Abbass et al [36] also reported 46% of biliary complications after DCD OLT. These donors undergo variable periods of hypoperfusion between extubation and asystole, and another period of no perfusion between asystole and cold flush, meaning a significant ischemic insult. Biliary strictures may occur with a patent hepatic artery (IC or ischemic-type biliary strictures (ITBS)). These lesions associate with increased incidence of abscess formation and lower graft survival and higher mortality. The treatment options include endoscopic retrograde cholangio-pancreaticography (ERCP), percutaneous transhepatic cholangiography (PTC) and drainage (PTD), conversion to hepaticojejunostomy with Roux-en-Y limb, artery revision if necessary. Less severe IC can be treated without retransplantation as long as the strictures are few and accessible for endoscopic or percutaneous therapy. Patients with bilateral multifocal strictures, or diffuse necrosis of the bile ducts had poor prognosis resulting in either death or retransplantation. *Foley et* al found that 81% of their DCD retransplants were for complications of IC [37]. High retransplantation rates have important ramifications for healthcare costs and the pool of available livers. Costs associated with retransplantation are more than double those for primary transplantation [33].

Factors such as a long WIT, chaotic donor physiology before asystole, and bile salt toxicity are believed to lead to a higher risk of non-anastomotic biliary stricture [26,38,39]. The biliary epithelium is more sensitive to ischemia/reperfusion injury than hepatocytes. The injury to the biliary epithelium may occur before or after organ retrieval because of the depletion of energy stores. The combination of donor warm ischemia and subsequent cold ischemia/reperfusion increases the generation of oxygen free radicals within the biliary epithelium. Ischemic injury to the microvascular endothelium in the preservation phase also leads to cell disruption, loss of surface glycosamino-glykans (heparin) and may contribute to microvascular thrombosis. This may prevent effective revascularization and worsen ischemic injury to the biliary epithelium [36]. *Foley et al* also found a significantly higher rate of HAS in the DCD group. These stenoses were all distal to the anastomosis and they hypothesized that the artery may have sustained some ischemic injury secondary to the DCD recovery and implantation process [37].

It has been suggested an arterial flush at the back table in addition to portal flush. Flushing the arterial tree with thrombolytic solution could help eliminate microthrombi and aid biliary tree perfusion. [38]. Some investigators have proposed that initial reperfusion through the arterial system or simultaneous portal and arterial reperfusion might decrease the occurrence of non-anastomotic biliary strictures [38,39]. It would lead to faster reperfusion of the biliary tree, thereby minimizing warm ischemia time. *Lopez-Andujar et al* recommend the use of T-tube in the presence of any risk factors for biliary complications, such as a donor or recipient bile duct diameter of less than 7 mm, large discrepancies between bile duct sizes, split or reduced grafts, DCD donors, retransplantations and to control the quantity and quality of bile in the immediate posttransplant period [40,41,42]. Long WIT seems to be detrimental to biliary tree and graft survival in general.

According to *Foley et al* CIT and donor age are the strongest predictors for the development of IC [37]. *Chan et al* found donor age of more than 50 years to be a significant risk factor for biliary

complications [26,43]. Donor weight >100 kg in combination with long total ischemic times and older donor age are predictive risk factors for the development of IC [26,37]. Moreover, transplanting a liver with> 25% of steatosis is a risk factor for the development of biliary complication [44].

Some have reported the use of histidine-tryptophan-ketoglutarate (HTK) to be associated with lower rates of biliary strictures than the use of University of Wisconsin (UW) solution while others have found no such difference [26]. Due to these observations some liver transplant centers decline DCD livers if the agonal phase exceeds 30 minutes and/or CIT exceeds 10 hours, livers from donors more than 40 years old and use HTK solution during procurement.

Extracorporeal membrane oxygenation (ECMO) may provide adequate normothermic organ perfusion and oxygenation in the absence of cardiac function. This has the potential advantage of eliminating the period of hypoperfusion of organs during the agonal phase and lessening the warm ischemic time associated with the DCD process. Clinical initiatives using ECMO suggest a potential to protect both hepatocytes and biliary epithelium [36,39]. *Fondevilla et al* reported using ECMO from declaration of death until organ procurement and the clinical applicability of type 2 DCD liver transplants was 9% (34 OLT out of 400 potential donors) [45]. Biliary complications occurred in four recipients (12%). There were three cases of IC (8%), who underwent retransplantation, a fourth patient developed an anastomotic biliary stricture and successfully underwent hepaticojejunostomy.

The higher rate of ITBS in DCD liver transplantation leads to higher recipient morbidity including biliary sepsis, growth of multi-resistant organisms and deteriorating health status, which eventually might exclude those recipients from relisting. In the current era of MELD-based allocation, these patients can only regain true access to a retransplantation through an exceptional MELD status, as suggested by *Monbaliu et al* [46].

The summarized results of ECD and Hepatitis C recurrence as well as the patient-, graft cumulative survival are shown on Table 1 and 2. Due to the extensive publication of these topics the results of some authors (Ref.No.118 to 138) will only appear on the Tables.

3) Hepatitis C recurrence (Table 1.)

In the era of organ shortage the donor factors affecting HCV recurrence are in the focus of interest.

i) Donor age

As mentioned in the first part, donor age steadily increased over recent years. Older donors have been found to be associated with HCV recurrence and worse patient and graft survival [47]. In the report by *Lake et al.*, donor age (>40 years) was the strongest predictor of graft loss and death in patients with HCV, however, this was not a risk factor in HBV or in patients without viral etiology [48]. There is a clear association between donor age and accelerated fibrosis progression in HCV patients. Donor age was a powerful determinant (p=0.02) of fibrosis progression rate in HCV patients. When the liver donor was younger than 40 years, median progression rate was 0.6 units/year and interval to cirrhosis was 10 years. When the donor was aged> 50 years, median progression rate was 2.7 units/year and interval to cirrhosis only 2.2 years [49]. *Uemura et al.* reported advanced donor age (>60 yrs.) has led to poor outcome of OLT for HCV regardless of MELD score and recipient age using the UNOS database [50]. Estimation by *Botha et al.* showed the risk of HCV recurrence increased by 23% for every 10-year increase in donor age [51]. Others reported that young donor age would be also a risk factor for HCV recurrence, and found no decrease in short term graft or patient survival using young pediatric donors (<13 yrs.) in adult recipients[52].

ii) Hepatic steatosis

It is found in about 15-25% of potential liver donors [53]. In 2007, *Briceno et al.* published a paper analyzing 120 patients with HCV and they reported liver grafts with moderate-to-severe steatosis,

those with severe liver preservation injury and prolonged CIT showed a dismal prognosis at 1, 3, and 5 years. Upon multivariate analysis, fat content and CIT >12 hours were independent predictors of graft survival [54]. Also more frequent and earlier HCV recurrence have been reported using moderately and severely steatotic grafts (>30%), concluding to avoid OLT with 30% steatotic donor livers in HCV recipients [55]. Contrary, *Botha et al.* analyzed 113 HCV positive LT candidates declaring that macrovesicular steatosis (5–45%) had no impact on HCV recurrence. Only donor age (P = 0.02) and CIT (P=0.01) were found to increase the relative risk of HCV recurrence [51]. Similarly to this report, *Burra et al.* reported no correlation between steatosis and fibrosis progression in HCV patients. They examined serial liver biopsies after liver transplantation in 56 hepatitis C virus–positive and 60 HCV negative patients. No difference in 36-month survival was seen, regardless of whether the etiology of the patient's liver disease was HCV-related or non–HCV-related and whether the steatosis in the graft was reportedly absent, mild, or moderate/severe [56].

iii) Allocation, preservation injury

As for HCV recurrence, a positive correlation between both CIT and WIT and severe HCV recurrence and reduced survival has been shown [47]. As mentioned previously, prolonged ischemia time is an independent risk factor associated, particularly for allografts from donors >60 years old [55]. In the study by *Botha et al,* the risk of HCV recurrence increased by 13% for every 1-hour increase in CIT [51]. HCV recipients with evidence of graft reperfusion injury have been shown to have poorer survival outcomes when compared with non-HCV transplant patients. In case of reperfusion injury, hepatocyte death and proliferation, it is possible that the viral burden may increase dramatically by incorporating into proliferating cells [57]. In fact, PI may be a result of a combination of several perioperative factors that define the ECD donor, including prolonged ischemic time, donor age, and donor steatosis [47].

iv) Antiviral therapy

Considering the growing number of ECDs and a high proportion of HCV positive recipients, an effective treatment of HCV recurrence is the challenge. Since the standard PEG-IFN+RBV therapy had low response rate and high intolerability, the use of direct-acting antivirals (DAAs) are in the focus of interest. In 2011, the first generation protease inhibitor (PI) boceprevir (BOC) and telaprevir (TLV) have been approved by the Food and Drugs Administration for immunocompetent patients in association with PEG-IFN and RBV [58]. *Pungpapong et al* compared viral response in 35 LT patients who received TLV plus PEG-IFN and RBV to 25 patients who received BOC plus PEG-IFN and RBV. After 24 weeks of treatment, 67% of TLV-treated and 45% of BOC-treated patients achieved HCV-RNA negativity [59]. In a recent study safety and efficacy of triple therapy after OLT have been analyzed, and 42% SVR rate after TLV based and 53% in BOC based triple therapy was found [60]. The rate of serious adverse events was 27% and hematological toxicity was seen in 95%. Excellent results have been shown regarding IFN free regimens: *Charlton M et al.* evaluated the efficacy and safety of an IFN-free regimen of the nucleotide polymerase inhibitor sofosbuvir (SOF) combined with RBV for 24 weeks in 40 patients treating post-transplantation compensated recurrent HCV infection. SVR at 12 weeks after treatment was achieved in 70% patients [61]. SOF and RBV regimen is also well-tolerated and it seems to be effective against fibrosis [62]). More data regarding the use of these novel DAAs in different groups of ECD donation are needed. However, these results are encouraging to transplant centers that make an effort to expand the donor pool by safely using even HCV positive donors for a transplant.

III) Survival (Table 2.)

1) Waitlist mortality

This is reported already in 2009 by *Burroughs et al* that the number of patients awaiting an OLT has tripled to 18.000, and organ availability increased only from 1.700 to 6.200 grafts per year [63]. Despite expanding the definition of acceptable deceased donor grafts and employing partial grafts from living donors, death on the liver waiting list still occurs in approximately 8% of the

candidates. The summary of *Barshes NF et al* questions whether the waitlist mortality (WLM) decreases at a given transplant center by using ECDs [64]. The study of *Barshes NF et* al might be regarded as referential for the ECD topic since they have been collecting the data of all US transplant centers between February 2002 and June 2005. That covered the data of 100 US liver transplant centers, meaning a total of 15,932 liver transplantations. These operations included 11660 (73,2%) standard criteria donor grafts, and 3555 ECDs (22,3%), while 717 transplantation were carried out by living donor liver transplantation (LDLT). The waitlist mortality varied from 0 to 15,3%, while the median number of liver transplants performed using an ECD allograft/ waitlist candidate was 0.09 (0-0,26). They introduce the coefficient ECD that means the number of liver transplants performed using ECD liver allografts (as defined above) at center during the study period divided by the total number of candidates added to the waitlist at center during the study period. Using a cross-sectional multivariate regression analysis they prove that waitlist mortality will be decreased by about 1% for every additional ECD liver transplant per 100 waitlist candidates (p=0,003). Yet ECD liver allografts are often allocated to less severely ill transplant recipients that have a lower risk of pretransplant mortality, so it could not be tacitly assumed that the use of these allografts would necessarily decrease WLM [64]. The question that arises in the paper of *Barshes NF et al* is still open for discussion: would it be better to increase the use of ECD sin liver transplantation by gaining 1-5% of waitlist mortality and having a post-transplant survival of 70%, or be much more selective, and strict to optimal donors that result in a 15% waitlist mortality but resulting in a 90% post-transplant survival? Other centers even quantified the increase in their activity by the introduction of ECD program. Waitlist mortality was 8% reported by *Gastaca* in Spain where 1392 recipients were listed during 2007, and 1045 were transplanted [65].

2) Patient survival, mortality

Some reports suggest that a graft-related death occurs in 8.5% of recipients of EDC grafts versus 4.2% of recipients of optimal grafts [4]. Articles presenting data about survival after ECD are

summarized in Table 2. In the study of *Afonso et al* the early mortality rate (within 30 days) didn't differed among liver transplanted patients with one, two, three or more extended criteria. They have prospectively recorded data from 139 patients who underwent 152 OLTs. Early overall survival rate was 83.76%; 12 reOLTs were required (10.25%). Comparing the four groups, patient survivals (P =0.41) and retransplantation rates (P =0.518) were similar [5]. *Angele et a*l proved that organ survival did not depend on the degree of donor steatosis (5-year-survival rates: 68% and 58% with steatosis <30%, or >/= 30%, respectively) (hazard ratio .754, confidence interval .458-1.242, P = .268) [66]. *Bacchella et al* also report high mortality within the first month, in cases of marginal grafts transplanted into high-MELD recipients. On the other hand, high-MELD recipients of non-marginal livers achieved an adequate survival rate [24]. In contrary *Gruttadauria et al* report on a worse but, non-significant patient survival drop in ECD. It means that regardless of having one, or more criterions present, the cumulative patient survival didn't differ significantly. However graft survival was 93,22% vs 78,9% at 6 months. Despite this fact, it was suggested that a more aggressive acceptance of ECDs, did not negatively influence the overall outcome [25,67]. Others also report a similarly good early survival, and only 13% one-year mortality in ECD group [20]. In a from the UNOS database with 117 comparing 117 grafts from controlled DCD with a group of DBD grafts, the PNF rate was 11.8% versus 6.4%, respectively (*P*= .008) while the 1-year graft survival was 72.3% versus 80.4%, respectively (P= .056). Patient survivals were similar but the retransplantation rate was higher among the DCD group, 13.9% versus 8.3% *(*P= .04) [68]. According to the UCLA database in 2009, 1153 liver allografts were considered, and 568 of them exhibited no extended criteria (donor score = 0), and 429, 135, and 21 donors had donor scores (DS) of 1, 2, and 3, respectively. The overall 1-year survival rates were 87%, 80%, 77%, and 40%, respectively, with donors with a DS of 0, 1, 2, and 3. Graft survival was excellent up to donor score 2, but grafts from donors with a DS >2 should be avoided, particularly in higher-risk recipients [72]. *Nguyen et al* compared DCD, SCD and ECD groups. The one-, three-, and five-year survival of DCD recipients was 89.5%, 89.5%, and 89.5%,

respectively. This was not significantly different than patient survival at one-, three-, and five-year for SCD (84.3%, 80.7%, 76.5%) and ECD (85%, 78.6%, 72.3%) groups [69].

Briceno et al. reported about 498 patients that received an ECD liver, 13.25% of whom had a HRS prior to OLT. They revealed that graft macrosteatosis per-30%-increments and donors >65 yrs. ($p = 0.089$; HR = 1.622 [1.17-1.94]) were independent predictors of graft loss in recipients with HRS. In this context, for patients with type 1 HRS, to receive a graft from an aged donor and/or moderate-to-severe graft steatosis may be better than waiting for an optimal donor. However, the combination of donors >65 yrs. with a >60% graft steatosis may not be recommended in type 2 HRS because of the high rate of graft dysfunction in a patient not so sick, who may wait for a better donor [70]. *Jay et al* revised the US Scientific Registry of Transplant Recipients database between 1996 and 2007, and collected the data of 1113 DCS and 42,254 DBD operations. The 1 and 3 years patient survival was 82% and 71%, as well as 86% and 77% respectively [32]. *Harring et al* studied the UNOS/OPTN database for DCD and DBD graft and patients 1, 3, 5 and 10 years survival. For patients it was 84,4%, 74,8%, 68,9% and 48,8% vs 86,1%, 78,3%, 72,5%, and 59% respectively. For grafts it was 75,3%, 63,9%, 56,2% and 38,7%, vs. 81,5%, 72,8%, 66,5%, and 52,8% [71]. In other reports DCD grafts with ≥ 3 donor risk factors had significantly lower 1-year post-transplant survival than no or only 1 or 2 risk factors (58.3% vs 72.6%, 69.2% and 73.9%, respectively). No grafts with 4 risk factors survived within 1 year [26].

In the comprehensive review of *le Dinh H et al* the results of 13 major overviews has been summarized: DCD recipients more often require re-transplantation. Respectively, 21.6%-42% vs 8.8%-16% of DCD and DBD recipients were listed for re-transplantation. The retransplantation rate ranged from 7.6% to 31% in DCD-LT compared to 2.5%-12% in DBD-LT [26]. Retransplantation arouses controversy on medical, economic, and ethical grounds: patient and graft survival rates after a second liver transplant are inferior to those after initial grafting, the procedure is more expensive and in the context of organ shortage retransplantation inevitably

denies organs to first-time recipients [72]. Retransplantation rate was significantly higher in case of DCD vs DBD (14,7% vs. 6,8%) in the largest studies, like the one of *Jay's* in 2011, and re-transplantation survival was markedly inferior to survival after primary transplant irrespective of graft type [32]. The use of extended criteria liver donors for retransplantation is controversial. In the study of *Northup et al* 1327 retransplantations were analyzed. There were 611 (46%) recipients who received re-livers from a donor with at least one ECD criterion [72]. Among the 165 patients reported by *Schemmer et al* there were 23 secondary OLTs (13.9%; 13 no-EDC [17.6%] vs 10 EDC [11%] P = .2), and four tertiary OLTs (2.4%): two in each group; (2.7% vs 2.2%; P = .9). [4]. Utilization of DCD allografts for re-transplantation was rare (2.5% of initial DCD vs 3.1% of initial DBD) and outcomes from each group were comparable. The general practice is to avoid re-transplantation with a DCD graft [26]. This topic is further discussed by *Marti et al*: 88 non-urgent liver retransplantations were studied. Grafts with a Donor Risk Index> 1,8 were considered as high risk. They also divided OLTs for two time periods. In the first period high-risk grafts did worse than low-risk grafts (5-year survival: 0 vs. 54.5%, p=0.002) while in the second period outcomes were similar (5-year survival: 48.6 vs. 56.7%, p=0.660). Donor age was the only independent donor factor for graft survival, with lower survival when using grafts from donors over 60-years-old [73]. In summary controlled DCD became a fast growing source for OLT. Consequently, DCD nowadays represents as much as 20% of the liver donor pool in some European countries. There are differences among the countries. For example, the use of controlled (Maastricht category III) DCD donors is not legal in Spain, France and Hungary. Between 2004 and 2009 the proportion of DCD increased from 0,5% to 1,9% in Spain (Maastricht-II), but from 2,4% to 18,6% in Belgium, and from 7,5% to 21,7% in The Netherlands [74].

IV) Split and living related transplantation

Earlier the reduced size livers, and split liver grafts were told to be extended criteria. Split-liver transplantation (SLT), a technique that allows for the use of two liver grafts from one donor liver,

is a good alternative to increasing the donor pool. Conventional splitting along the falciform ligament increases the number of left lateral segment grafts, shortens the pediatric waiting list and reduces the pre-transplant mortality of children [75,76]. On the other hand, early reports of inferior results for extended right lobe graft (eRLG) transplantation compared with whole liver transplantation (WLT) have discouraged aggressive use of the SLT technique, and eRLGs are considered to be marginal grafts [31]. Recently, technical improvements achieved with careful donor and recipient selection have had favorable results [77]. *Cauley et al.* reported the findings of an analysis of 62,190 liver transplantation procedures in adults (889 SLT) based on the UNOS data obtained in 2013. In that report, the graft survival of SLT was comparable to that of WLT (P=0.66), and the authors demonstrated that SLT was a significant risk factor of increased graft failure in the pre-MELD era (1995-2001), but not the MELD era (2002-2010) [78].

Another multicenter study reported similar results for 382 eRLG transplantations. The survival rates in a group of patients undergoing 358 primary eRLG transplantations at 1, 3 and 5 years were 85.2%, 82.5% and 82.5%, respectively, in the current period (2005-2011), which were significantly better than those noted in the previous period ((1997-2004); 80.0%, 68.9% and 66.1%, respectively). However, the outcomes of 24 re-transplantation procedures performed using eRLG were extremely poor, with 1-, 3- and 5-year survival rates of 16.7%, 12.5% and 12.5%, respectively [79]. Factors related to the outcomes of SLT have been reported to include a recipient MELD score of > 30, age of > 60 years, donor age of >45 years, CIT of >10 hours, urgent recipient condition and treatment at a low-volume center [80]. Complications after SLT were recently discussed in a meta-analysis conducted by *Wan et al.*, which showed higher rates of overall biliary complications (OR=1.66, 95% CI= 1.29-2.15, P<0.001), bile leakage (OR=4.30, 95% CI=2.97-6.23, P<0.001), overall vascular complications (OR=1.81, 95% CI=1.29-2.53, P<0.001), HAT (OR=1.71, 95% CI=1.17-2.50, P=0.005) and outflow tract obstruction (OR=4.17, 95% CI=1.75-9.94, P=0.001) in cases of eRLG transplantation. However, comorbidities were not found to be significant risk factors for either patient or graft survival [81].

The method for splitting can be divided into two types. Ex vivo splitting involves usual organ procurement followed by parenchymal dissection and vessel division on the back table. This technique is not influenced by donor hemodynamic instability and allows for rapid parenchymal resection, which contributes to a short warm ischemia time [77]. However, identifying various vital structures may be difficult in this setting. In order to overcome this problem, careful inspection using angiography and cholangiography is an alternative [30]. In situ splitting has the advantages of a short cold ischemia time and the ability to precisely detect the vessels. On the other hand, the prolonged splitting time, inconvenience for graft procurement and possibility of a prolonged WIT due to donor hemodynamic instability are potential disadvantages. The results of these two techniques are conflicting [30,81].

From the perspective of increasing the donor pool for adult recipients, full-right-full-left split liver transplantation (FRFLSLT) may have a significant advantage. However, because of technical and organizational difficulties, experience with this technique is limited [82]. In particular, anatomic variation, the small graft size and difficultly in performing vascular anastomosis and biliary reconstruction are crucial matters. In addition, despite the importance of evaluating the graft size and obtaining vascular information, the use of preoperative multiphase computed tomography in deceased donors is controversial, both logistically and ethically [83]. In 2014, a multicenter study from Italy reported a high postoperative complication rate in patients treated with FRFLSLT (64.1% Clavien grade III and IV) and a lower 5-year survival rate than that associated with WLT (63.3% and 83.1%) [84]. On the other hand, *Lee et al.* recently reported their experience with 42 FRFLSLT procedures. In that report, the postoperative complication rate was 35.7% (Clavien grade III and IV) and the 1-, 3- and 5-year survival rates were comparable with those of living donor liver transplantation (71.4%, 69.0%, 69.0% and 79.9%, 75.1%, 70.4%, respectively), despite being allocated to patients on the waiting list with the highest MELD scores. The authors suggested that the criteria for this procedure should include recipients with a

GRWR of more than 1% in cases of FRFLSLT, considering the uncertain condition of the donated liver [83].

V) Machine perfusion in the management of ECD liver grafts (Table 3.)

Different liver retrieval techniques for DCD have been described in the early nineties, including femoral cannulation prior to withdrawal of life support, and to as the "super-rapid technique" [74]. The extent of ischemia reperfusion injury depends on the degree of activation of key players involved in the hepatic ischemia reperfusion injury including Kupffer cells, platelets and leukocytes, besides the generated pro-inflammatory response (oxidative stress, inflammatory cytokines, and cytoplasmic proteases, up regulation of pro-inflammatory transcription factors). Clinically, ischemia reperfusion injury can result in immediate graft function, delayed graft function (considered to occur in 10–30% of grafts) or primary graft non-function (considered to occur in < 5% of grafts respectively) [45].

Referring to *Vekemans study* [85], simple cold storage (SCS) fails to optimally preserve extended criteria organs, alternative preservation methods potentially might be more beneficial. Relevant methods are shown in Table 3. During machine perfusion (MP) continuous circulation is maintained, the microcirculation is better preserved. In contrast to SCS, MP organs can be monitored over time; viability markers can be identified. *Monbaliu et al* evaluated discarded human livers after hypothermic machine perfusion (HMP). The livers were classified as non-transplantable and (in retrospect) transplantable according to generally accepted clinical criteria. They used HMP as a screening-tool to distinguish transplantable from non-transplantable ECD human liver grafts that were rejected for LT [74]. With SCS, the sinusoids become constricted due to the hypothermia, which prevents the penetration of the preservation solution in to the tissues and may cause an impaired microcirculation upon reperfusion [85]. Although MP has been developed to limit ischaemic graft damage and it has a proven biochemical benefit, machine liver perfusion is not yet considered clinically due to its low practicability. In a mini-review of

Dutkowski et al there is a summary about the different types of machine perfusion methods [86]. The use of normothermic and hypothermic perfusion solutions are the possibly two ways of MP technics, both with advantages and disadvantages. In *Obara's article* also a subnormothermic preservation temperature is mentioned [87]. Most of the published MP techniques do not consider practicability because it is generally recommended to apply perfusion immediately after organ harvest and during the whole preservation period. From a clinical point of view, perfusion during organ transport would be unavoidable which bears the risk of perfusion failure due to logistic reasons. In contrast, authors suggest a short-term MP performed after arrival of the harvested donor organ at the centre. A period of approximately 1–2 h usually accumulates after completion of back table preparation which allows interventions on the preserved and prepared graft during recipient hepatectomy without delay of the transplant procedure. Either hypothermic oxygenated low-pressure perfusion or normothermic asanguineous oxygenated perfusion are conceivable [86]. *De Rougemont et al* demonstrated in their large animal model the efficacy of a simple cold oxygenated MP system to rescue, otherwise lethal, ischemic injured DCD liver grafts [88]. In this study authors carried out OLT in Swiss landrace pigs, carefully adapted as close as possible to human situation. Some livers were treated by 1 hour hypothermic oxygenated machine perfusion prior to implantation (HOPE-group). They demonstrated that pigs transplanted with DCD grafts developed severe and uncorrectable acidosis, systemic shock, and severe liver injury evident by histology and liver function. All pigs with such untreated grafts died within a few hours after OLT due to PNF of liver grafts. In contrast, a short term machine perfusion was highly successful in preventing all of these events, resulting in extubation of transplanted pigs 2 hours after reperfusion, normalized lactate, initiated bile flow and improvement in histology [88]. According to *Schlegel et al*, HOPE may offer many beneficial effects, not only by rescuing marginal grafts but also by preventing rejection and decreasing the need for immunosuppression [89]. *Dutkowski et al* presented in 2013, the first report showing that this novel technique of HOPE can be applied clinically in human DCD liver grafts without

apparent increase of adverse outcome. In this initial report, they thus indicate feasibility and safety of such an approach, and also confirm that reperfusion injury was low in machine perfused DCD livers despite prolonged donor WIT. Authors also documented excellent early and longer-term outcome, and particularly no intrahepatic cholangiopathy in machine perfused DCD liver grafts [90]. Similar to the former studies many experiments with animal models investigate the potential clinical role of MP. The aim of the study of *Bessems et al* [91] was to compare cold storage and MP for preservation of the steatotic donor rat liver. Their method was the following: liver steatosis was induced in male Wistar rats by a choline-methionine-deficient diet. After 24 hours hypothermic cold storage (CS) using the UW solution or MP using UW-Gluconate (UW-G), liver damage and liver function were assessed in an isolated perfused rat liver model. According to their results, MP had an advantageous effect on bile production, oxygen consumption of the liver during reperfusion and on AST and lactate dehydrogenase (LDH) release. In accordance with other studies, *Bessems* concluded the evidence that steatotic livers are better preserved by MP instead of SCS. Preservation of steatotic livers by hypothermic MP results in less liver damage and better liver function as compared to SCS [91]. *Franchello et al* evaluated the role of ischemic preconditioning (IP) of the liver. 75 deceased liver donors were randomized to receive IP (IP+) or not (IP−). The main groups of (IP+) and (IP−) were divided in two subgroups considering the quality of the graft (marginal+ and marginal−); IP was performed during the procurement procedure by 10min inflow occlusion followed by 30min of reperfusion prior to the start of cold ischemia [92]. The analysis confirmed the hepatoprotective action of IP; a significant reduction of hepatocytes suffering was seen in IP+ graft when analysing cellular swelling after homeostatic deregulation. Preconditioning significantly increased low-grade and reduced mild-grade swelling. *Olschewski et al* evaluated in their study the influence of the perfusate temperature during oxygenated MP on the graft quality. Wistar rats were harvested after 60min warm ischemia induced by cardiac arrest. The portal vein was cannulated and the liver flushed with Lifor (Lifeblood Medical, Inc.) organ preservation solution for

oxygenated MP at 4, 12 or 21C'. After MP at 21C', portal venous resistance was significant reduced and bile flow was higher. Perfusion at 12 and 21 C' resulted after 6 h machine perfusion a significant higher enzyme release compared to machine perfusion at 4 C' After 60 min of normothermic reperfusion, livers stored static at 4 C' revealed a significant elevated enzyme release compared to livers stored by MP [93].

In connection with various organs (heart, brain) erythropoietin (rHuEpo) has been shown to be protective against ischemic damage and improving posttraumatic organ function. *Schmeding et al* evaluated the potential effect of rHuEpo preconditioning and treatment on post-transplant graft function in a rat model of marginal graft liver transplantation [94]. rHuEpo has been used in clinical routines for many years and can be regarded as a fairly safe substance with few side effects. Therefore, the application of rHuEpo in conditioning the "marginal" donor organ before and at/after transplantation may serve as a valuable tool in improving organ function after LT of extended liver grafts. The study of *Mangus et al* compares HTK and UW in a large number of SCD and ECD livers at a single centre over 5 years in Indianapolis [95]. All together 698 liver and liver-kidney transplants were analysed. HTK and UW were found to have no statistically significant difference in post-transplant graft and patient survival, risk of intraoperative death, and graft failure in the first 7 days post-transplant. Livers preserved with HTK had a higher initial AST and ALT in SCD and physiologic ECD livers, whereas the UW-preserved livers had a higher AST and ALT in the old donor livers. In all groups, these differences disappear by postoperative day 7. Only in case of biliary complications seemed the HTK to be superior to UW, including any need for biliary evaluation and the presence of bile duct stones or sludge. *Stegemann et al* have compared different types of perfusion solutions in case of MP in marginal liver grafts [96]. They concluded in their study that the results provided evidence for enhanced organ protective potential of the new Custodiol-N solution (complete modified HTK solution, i.e., with the addition of two iron chelators: 25 mM deferoxamine, and 7.5 mM of the new,

membrane-permeable chelator LK 614) compared with HTK solution upon hypothermic machine preservation of marginal liver grafts.

Vogel highlights in his abstract the current challenges of MP in liver transplantation. According to this, first the feasibility of the normothermic MP methodology in human livers has to be confirmed and, second, we have to develop and introduce a functional device into the clinical arena [97]. Since the phase I clinical trial of liver HMP has suggested superiority over SCS preservation, HMP has the potential to predict graft function as well as enable resuscitation of grafts from ECD [98]. In the year 2010 *Guarrera et al* published the results of the first study comparing HMP to standard cold preservation in human LT (clinical phase 1, prospective cohort trial) [99]. HMP occurred during patient preparation and recipient hepatectomy thus only a portion of the cold ischemic period was perfusion time. This simplifies the technique and allows utilization of less portable perfusion devices. The results have confirmed the beneficial effect of MP. EAD rates were 5% in the HMP group versus 25% in controls ($p = 0.08$). At 12 months, there were two deaths in each group, all unrelated to preservation or graft function. There were no vascular complications in HMP livers. Two biliary complications were observed in HMP livers compared with four in the CS group. Serum injury markers were significantly lower in the HMP group. Mean hospital stay was shorter in the HMP group (10.9 ± 4.7 days vs. 15.3 ± 4.9 days in the CS group, $p = 0.006$). HMP of donor livers provided safe and reliable preservation in this pilot case-controlled series. Connected to the former study, in another report [100] the authors examined levels of soluble cytokines, including interleukin-1 receptor antagonist (IL-1Rα), which is an anti-inflammatory member of the interleukin (IL) family produced in response to nuclear factor kappaB (NF- κβ) activation or IL-1β and IL-6 stimulation, and monocyte chemotactic protein-1 (MCP-1/CCL2), which is a monocyte and natural killer cell chemoattractant secreted by endothelial cells and monocytes in response to IL-1 signalling. These markers of immune activation during ischemia and reperfusion can provide an insight into the mechanism of HMP–mediated ischaemia-reperfusion injury (IRI) resistance and act as signals of future IRI damage in

the liver graft after reperfusion. *Obara et a*l have developed a MP preservation system that controls the perfusate temperature from hypothermic to subnormothermic conditions [87]. The porcine livers were perfused with modified UW gluconate solution containing dextran. The temperature was increased gradually from 4–8°C to 23°C during the perfusion. The pressure transition in the hepatic artery measured with this system was employed as a liver viability evaluation index. Temperatures controlled MP had a positive effect on pressure transition in the hepatic artery, and after this method lower LDH levels were found. In conclusion the results of *Obara* support the advantages of temperature-controlled MP to preserve the liver graft [87]. *Guarrera* reports 21 ECD livers that were preserved with HMP in phase 2 clinical trial also highlights that their experience with liver HMP is the only reported clinical experience worldwide representing a total of 41 successful liver transplant cases showing improved outcomes and diminished markers of ischemia/reperfusion injury. [99,101].

Various cytoprotective substances have been successfully administered into the donor prior to cardiac arrest for prevention of liver microcirculatory disturbance. Up to now, only Heparin and phentolamin (an antithrombotic substance and alpha-adrenergic antagonist) are allowed in clinical DCD organ procurement [26]. Tacrolimus, milrinone (a type 3 phosphodiesterase inhibitor), lazaroids (iron-dependent lipid peroxidase inhibitor), N-acetyl-cysteine were also studied in animal models [26]. Perhaps the most effective step in organ preservation is the cooling of the organ as the metabolic rate is halved for every 10 C drop in temperature [74].

VI) Expert commentary

When talking about extended criteria liver grafts we should emphasize that the functional reserve of these livers are limited. There is a sensitive balance between protective factors (like shortened CIT, WIT, machine perfusion, proper recipient selection) that will keep the results optimal and further injuries that cause decomposition. Injuries can be ischemia related or other (like viral exposure), however they will, at least partly act through the Ito cells. These cells (perisinusoidal

fat-storing cells, stellate cells, and lipocytes) are mesenchymal cells located in the space of Disse. [102]. When hepatic stellate cells (HSCs) are subjected to stress such as hypoxia, oxidative stress or endoplasmic reticulum stress, they modulate fibrosis progression by induction of their activation toward a myofibroblastic phenotype, or by undergoing apoptosis, and thus helping fibrosis resolution [103]. General inflammation pathways also lead to liver fibrosis. HCV infection is also associated with the development of hepatic fibrosis. Whether HCV is able to enter and replicate in hepatic stellate cells (HSCs), thereby directly disturbing their metabolism and activating them, is unknown. The results of *Florimond et al*, suggest that HCV infection of HSCs does not play a role in their activation and the related fibrogenic process during the course of chronic HCV infection [104]. Ductular reactions are encountered in virtually all liver disorders in which there is organ-wide liver damage and cell loss, but are also present in focal lesions such as focal nodular hyperplasia and adenoma. Moreover, diverse ductular reaction phenotypes can be present within any single disease entity, and are shaped by the etiology and evolution of the disease. Although much remains to be clarified, recent studies suggest that the diversity of appearances of the ductular reactions are likely to reflect the differing signals at the anatomic, cellular, and molecular levels driving the proliferative response [105]. The study cohort of *Prakoso et al* had 194 biopsy samples from 105 individuals with HCV recurrence after LT. The immunophenotype, morphology, and location of the ductular reaction were consistent with a hepatic progenitor cell origin. The ductular reaction correlated with intrahepatic fibrosis ($P < 0.001$) and the number of activated hepatic stellate cells (HSCs; $rs = 0.446$, $P < 0.001$) [106].

Donor Risk Index has been developed by *Feng et al* in 2006 [107]. Whereas a DRI of 1 or less was associated with an 87.6% 1-year survival, it was 76.9% for a DRI of 1.6 to 1.8 and 71.4% for a DRI > 2. This is also reported by our group in 2010, that allocation of an ECD donor to „bad" condition recipients is a worst scenario, while ECD donors might serve well in an HCC patient with mild cirrhosis [19]. According to other relevant authors the donor risk factors for a graft failure in case of ECD are antiHBcore AB positivity, low arterial pressure for more than 20

minutes, and CIT > 6 hour [108]. Prolonged CIT are inevitable proven as a worsening factor in case of ECD [32]. Therefore some argue for the withdrawal of life support in the operating room rather than in the ICU or preoperative holding unit. The need to transport donors from these locations to the operating room after declaration of cardiac death could further increase warm ischemia times and diminish the quality of livers [108]. ET uses several criteria to define a marginal donor or an ECD. None of the other ECD criteria (except for donor age) were found to have a significant impact on transplantation outcomes. The term ECD is still controversial because there is no recognized definition of an ECD. The DRI could be useful in defining what kind of donor should be considered an ECD [109]. Due to ethical and legal differences DCDs are utilized only in certain countries. A homogenous guideline for the management is not possible to set. However in the review of *Monbaliu D et al* this is suggested to optimize the outcome by donor pretreatment, avoid extended WIT, rapid flush out with low viscosity solution, allocation the liver to the procuring center (diminish CIT), add cytoprotective agents to the perfusion solution, use ex vivo, machine perfusion, and/ or in vivo ECMO perfusion, carefully select the recipient [73]. In large cohorts, a higher DCD graft failure within the first 180 days (20.5% DCD vs. 11.5% DBD; $P < 0.001$) is demonstrated, with convergence thereafter. Allocation policy that recognizes this limitation and increases access to ReOLT is necessary for expansion of this donor population [110]. Ethical aspects should also be considered. The first results of the ELITA-ELTR coordinated questionnaire was published by *Bruzzone P et al* based on the answers of 35 centres accepting ECD donors. Thirty-one centers informed the transplantation candidate of the ECD status of the donor, 20 (65%) when the patient registered for transplantation, 1 (3%) when an ECD liver became available, and 10 centers (32%) on both occasions. Thirteen centers required the liver transplantation candidate to sign a special consent form. Twenty centers informed the potential recipient of the donor's serology. Only 6 centers informed the potential recipient of any high-risk behavior of the donor [111]. Ischemia-reperfusion injury (I/R) is one of the negative impacts that might worsen the outcome of ECDs.

We suggest the study of *Nemeth et a*l concerning the importance of changes in hemorheological parameters caused by acid-base and blood gas alterations in experimental surgical models [112]. According to the authors conclusion [113] the majority of these harmful effects can be preventable by antioxidant drugs. Ischemic time and temperature are determinant factors in the extent of changes. The real extent of local micro-rheological changes is still unclear, and mainly in the context of microcirculatory disturbances further investigations are required.

Machine perfusion is an example of co-operation among health-care managers, medical professionals and bioengineer-experts. Since the 1960s, the most commonly used method of preserving organs for clinical transplant has been static cold storage (SCS). Machine perfusion generates a controlled recirculating flow of preservative solution at hypothermic temperatures in the 0°C to 4°C range. It is generally accepted that expanded criteria donor kidneys are liable to draw the greatest benefit from MP. It may be beneficial only in certain DCD subsets; reducing DGF, in DCD donors younger than 60 years old and 1-year survival in donors older than 50 years. The renal MP protocols cannot be applied directly to liver transplant, but need to be adapted to account for these distinctions, which include hepatic and portal systems flow competition, hepatic sinusoidal endothelial cell susceptibility to damage, high liver metabolism, the MP effect on preventing biliary tree injury, and Kupffer cell activation. The question of optimal temperature optimal flow rates and perfusion pressures, single or dual vessel perfusion, perfusate oxygenation, and different perfusate compositions are still under investigation [114]. The challenge in the era of new antiviral agents is the realistic approach, to completely resolve the HCV recurrence as a problem. [115]. HCV as a main indication for LT, and a current highlight in recurrent diseases, will be replaced by NASH within a few decades.

During living related donor liver transplantation this is expected to perform the splitting on an excellent donor liver. This is mandatory for the benefit of the donor and the recipient as well. Therefore it seems hard to find a connection between LRLT and extended criteria donors.

However LDLT practice is becoming the major alternative to bridge the gap between waitlist and final surgery not covered by current deceased donor procurement. From a centre perspective the inevitable utilization of ECDs can be partly replaced by an LRLT program. That can be exceptionally true for certain indications, like adult-to adult LRLT in high-urgency patients (Model for End-Stage Liver Disease score >30), or extended application of LDLT for unresectable hepatocellular carcinoma above Milan criteria [116]. The main field of LRLT is still pediatric LT (pLT) programs. Analyses of the collaborative transplant study (CTS) database show LDLT rates in pLT of 33%. The long-term graft survival is significantly better after LDLT vs DDLT (5-year graft survival 78.2% in LDLT vs 71.4% in DDLT, $P < 0.001$). The advantages of LDLT are the use of an optimal healthy donor, minimal ischemic time, elective surgery and timing of transplantation according to the recipients' need, which is particularly relevant for pediatric patients. [117]

VII) Five year view

In the near future, due to the significant lack of deceased donors in Western countries, full right/full left splitting (FRFLSLT) may become widely accepted at experienced centers at which living donor liver transplantation is frequently performed. Machine perfusion might offer potential strategies to decrease the grade of steatosis in livers procured for transplantation. Pharmacological preconditioning during normothermic machine perfusion was successfully used in experimental setting. Normothermic machine perfusion might also allow assessing the viability of steatotic graft before transplantation. More ECD livers will be preserved with MP techniques in clinical trials. Protocols are needed to determine with exact parameters of whether an ECD liver is transplantable or not. The need of ECD livers will stimulate the production of MP systems that are mobile, portable and available for all liver transplant centers. Other methods such as the use of HuEpo can also increase the transplantable liver pool. With the modern hemorheological instruments and standards new opportunities have been provided for the

experimental surgical research work, also for investigating the pathophysiology of circulation and microcirculation in ischemia-reperfusion injury. The use of DAAs will completely change the indications map of OLTs in ten years. As a consequence of successful treatment of HCV with DAA, the NASH (non-alcoholic steatohepatitis) will become the leader cause for an OLT. The usage of HCV positive liver grafts will not be considered as an ECD in five years, since a proper DAA treatment will offer complete remission, and protection for a HCV relapse.

ECDs are useful and safe when the meantime one consider the maximum protection of the recipient and graft, with donor preconditioning, prevention of ischemia-reperfusion, machine perfusion if needed, proper recipient selection, modern intensive care, and combined updated antiviral treatment. Ongoing and novel targets of basic research are welcome to enhance these fields and put them into practice.

VIII) Key issues

- The main complications after transplanting an ECD graft are the initial poor function (delayed graft function, or early allograft dysfunction), the late non-surgical biliary complications, and the recurrence of HVC/HBV. In case of an ECD graft transplantation a prolonged and complicated ICU care of the recipient should be anticipated
- Improvements in the outcomes of conventional split liver transplantation have encouraged the use of eRLG grafts as well as whole liver grafts, except for cases of re-transplantation. On the other hand, more experience with FRFLSLT is required. These grafts continue to be considered "marginal" because of the small graft size and associated technical complexity. However, in the near future, due to the significant lack of deceased donors in Western countries, FRFLSLT may become widely accepted at experienced centers at which living donor liver transplantation is frequently performed.

- In the last years more and more studies are available evaluating the positive effects of machine perfusion on human liver grafts. Still evidences and clinical trials are needed to accept and routinely use the MP techniques in the clinical therapy during liver transplantation.
- We live in the era of new antiviral agents implemented in case of HCV recurrence after OLT. Clinical trials have offered robust evidence supporting the use of direct antiviral (DAA) agents as pioneer treatments, alone, or in combination with standard pegylated interferon (peg-IFN) and ribavirin (RBV)-based regimens. DAAs have proved highly efficacious, with pan-genotypic activity, shortened treatment duration, and an improved side-effect profile when compared with historical peg-IFN/RBV treatment.
- According to the allocation policies the correct approach is a balance between individual justice (serving individuals in need) and population utility (getting the best results for the entire population at risk)

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Reference annotations

* Of interest

** Of considerable interest

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Table 1: Outcome of liver transplantations (survival, HCV recurrence, liver fibrosis) after the use of ECD in HCV positive recipients and the impact of anti-HBsAg/anti-HBc positive donors.

Author	Year	No.	ECD	End-point	Impact/outcome	Notes
Briceno et al.[54]	2009	125 HCV +	steatosis	Time of reHCV	Facilitate	ECD risk >30% steatosis
				Pt/Graft Survival	Worsened	
Burra et al.[55]	2009	56 HCV+ 60 HCV -	steatosis	Pt/graft suvival	No impact	Longterm liver graft histology
				Fibrosis		
Briceno et al.[53]	2007	120 HCV+	Multiple*	Graft survival	Worsened	*CIT, reperfusion injury and steatosis>30%
Botha et al.[50]	2007	113 HCV+	steatosis	reHCV +fibrosis	No impact	
			CIT, age	reHCV +fibrosis	Accelerate	
Subramanian et al. [114]	2012	48 HCV+	Steatosis	Fibrosis +cytokine	Accelerate	Fibrosis at 1 year post OLT
Uemura et al.[49]	2012	7508 HCV+	Age (>60)	Graft survival	Worsened	Additional risk factor was DCD, CIT
Ghabril et al.[51]	2009	51 HCV+	Age (>=13)	Pt/graft survival	No difference	
				Time of reHCV		
				Fibrosis		
DCD						
Yagci et al.[115]	2008	14 HCV/DCD 188 HCV/DBD	DCD	Pt/Graft survival	worsened	
Hernandez-Alejandro et al.[116]	2011	17 HCV/DCD 15 HCV- 42 HCV/DBD	DCD	PT/graft survival	worsened	Control group 42 HCV+/DBD-
Taner et al.[117]	2011	77 HCV/DCD 77 HCV/DBD	DCD	Pt /graft survival	No difference	
				Fibrosis		

Uemura et al. [118]	2012	630 HCV/DCD 1164HCV-/DCD+ 13257 HCV+/DBD	DCD	Graft/Pt survival	HCV+ no difference HCV- worsened	UNOS database Controlled DCD
Tao et al.[119]	2010	37 HCV/DCD 74HCV/DBD	DCD	Pt/graft survival reHCV fibrosis	No significant difference	

Author	Year	No.	End-point		Impact	Notes
Anti-HCV positive donors						
Northup et al. [120]	2010	741 HCV+/HCV+ 18760 HCV-/HCV+	Pt/Graft Survival		No difference	US OPTN Registry Database
Ballarin et al.[121]	2011	63 HCV+/HCV+ 63 HCV-/HCV+	Pt/Graft suvival		No difference	European multicenter study
			reHCV	timing	Accelerated (NS)	
				severity	Accelerated (NS)	
Burra et al.[122]	2011	540 HCV+ donor 540 HCV- donor	Pt/Graft survival		No difference	UNOS dabase 442 HCV+/HCV+ 442 HCV-/HCV+
O'Leary et al.[123]	2012	32 HCV+/HCV+ 17/32 HCV RNA -	Graft/Pt survival Fibrosis		No difference	17/32 HCV RNA neg
Anti-HBsAg negative, anti-HBc positive donors						
Yu et al.[124]	2009	1270 aHBc+ donor 34350 aHBc- donor	Pt/Graft survival		No difference	UNOS database
MacConmara et al.[125]	2012	25 aHBc + donor 843 aHBc - donor	Pt/graft survival De novo HBV		No difference None	aHBc + and MELD >30 worsened early survival
Angelico et al. [126]	2013	1218 HBc - donor 219 HBc + donor	Graft survival		Worsened	Liver Match prospective observational cohort study from in Italy
		66 HBc+/HBsAg + 153 HBc+/HBsAg -			No difference Worsened	

Table 2: Main post OLT complications, cumulative patient and graft survival in relation to ECD

	Year	Remark	N of OLTs	ECD (%)	Standard vs EC donors										
					EAD (IPF) (%)	BC (IC) (%)	reOLT (%)	Patient survival (%)					Graft survival (%)				
								1-6 mths	1 yr	3 yr	5yr	10 yr	1-3 mths	1 ys	3	5	10
Abt[67]	2004		43 367	25,6 (DCD only)	n.d	n.d			85 vs 79,7	77,4 vs 72,1							
Barshes[63]	2007	WL mortality= 1% decrease by 1 ECD /100 OLT	15 932	22,3													
Lucidi[127]	2007		70	44	10 vs 13			90 vs 90									
Northup[71]	2007	all HCV+ all reOLT	1 327	46					70,9 70,8								
Schemmer[4]	2007		165	55					82 vs 76	75 vs 74							
Silberhumer[3]	2007		386	ECD all: 65 ECD>1: 29	ΔMELD>1 +ECD>2: HR=3.78, p=0,01												
Afonso[5]	2008	ECD score: 0-4	139	43,6			1= 0 2= 9,4 3= 15,8 4= 7,7		1= 85 2= 83 3= 89 4= 69								
Bachella[23]	2008		103	63,1			5,2 vs 10,8	95 vs 80									
Gruttadauria[24]	2008		115	49,5	3,4 vs 7	29,3 vs 30	0 vs 5,2	95 vs 83	94,8 vs 81	(2yrs) 92 vs 81							
Selck[109]	2008	DBD vs DCD	21 944	39			8 vs 21,6		84,4 vs 73,8	74,4 vs 57,6							
Gastaca[64]	2009	donor age < 55 vs >75		n.a	no impact										69,5 59,8		51 45,6
Burroughs[128]	2009	DBD vs DCD	552	9	2,6 vs 5,5	9 vs 21		83 vs 83		74 vs 70			79 vs 77		69 66		

Continued Table 2.

Skaro[33]	2009	DCD vs DBD	269	11,9 (DCD)	3,1 vs 0,4 (PNF, DCD vs DBD)	53,1 vs 21,5	21,9 vs 6,8	DCD vs DBD	74,0 vs 90,4	74,0 vs 80,7			DCD vs DBD	61,3 vs 85,2	52,6 vs 74,2		
Abou Abbas[35]	2010	DCD	491	5,2 (DCD)	0,0 (PNF)	46	26		92					77			
Yamamoto[34]	2010	DCD vs HBD	40	60 (DCD)	8,3 vs 18,7 (DCD vs HBD)	37,5 vs 6,2 (HAT 33,3 vs 0,0)	12,5 vs 31,2	DCD vs HBD	61,9 vs 63,6		42,9 vs 54,5	42,9 vs 54,5 (20yr 38,1 vs 36,4)	DCD vs HBD	54,2 vs 43,8		37,5 vs 37,5	37,5 vs 37,5 (20 yr 29,2 vs 25,0)
Nemes[18]	2010	4 Groups: G/G = good-to-good B/G bad-to-good G/B = good-to-bad B/B = bad-to-bad	260	43 (112) B/G 28,8 (75) B/B 14,2 (37)	G/G 10 B/G 17 G/B 30,5 B/B 35			G/G B/G G/B B/B	93 84 82 83	86 79 79 83	83 75,5 72 83		G/G B/G G/B B/B	88 83 81 83	82 76 78 83	79 73 72 83	
Nguyen[68]	2010	SCD vs ECD vs DCD	467	49 (DCD:4 DBD+ECD : 45)	4,7 1,7 5,3	15,9 22,6 26,3	19,6 8,5 15,8		84,3 85 89,5	80,7 78,6 89,5	76,5 72,3 89						
Marthur[129]	2010	SRTR data (DCD)	22 656	7			13,6 (DCD)			78,4	64.9						
Briceno[1]	2010	ECD scores: 0,1,2,3	675	47	0=14,8; 1=19,2 2= 27,5; 3=37,4												
Nafidi[130]	2010	new factors*	634	<2000:46 ≥2000:56,9												71,6 vs 70,6	

Continued Table 2.

Palmiero[2]	2010	new factors** ECD <1,7 vs ≥1,7	1 786	preMELD era: 37,5 postMELD era: 43,7				70 vs 64	65 vs 60	61 vs 56						
Serrano[131]	2010	by donor age only	149	31		4,9 17		no difference					86,7 71,4			
Briceno[69]	2010	1) all HRS patients 2) by graft steatosis %	550	(all) 59 ECD-0: 40,9 ECD-1: 27,9 ECD-2: 16,5 ECD-3: 14,6							steatosis 0%: 85 10-30%: 78 30-60%: 76 > 60%: 49					
Kim[132]	2011	ECD factors 0-4	100	100% elder than 65 years										0=100%,1=82% 2=81,7% 3=39,3% 4=25%		
Hong[107]	2011	ECD score 0-1; 2-4; and >4	81			BC: 29 IC: 9,9								0-1:83 2-4:62 >4: 0		
Jay[31]	2011	SRTR data	43 367	2,6 (DCD only)			6,8 vs 14,7	86 vs 82	86 vs 77							
Jay[32]	2011	Meta-analysis (1950-2009)	4944	9,8 (DCD only) 1 yr mortality		IC: 3 vs 16		OR: 1,6 vs 2,1								
DeOliveira[37]	2011	DCD vs DBD adult + pediatric	500	33,4 (DCD)	DCD vs DBD:	19,7 vs 12,5 (IC: 2,4 vs 0,0)	1,19 vs 1,2	DCD vs DBD	P = 0.193	P = 0.144	P = 0.113		DCD vs DBD	P = 0.108	P = 0.173	P = 0.236
Foley[36]	2011	DCD vs DBD	1244	6,99	DCD vs DBD:	47 vs 26 (IC:	19,0 vs 4,8	DCD vs DBD	84 vs 91	72 vs 85	68 vs 81	54 vs 67 (15yr 54 vs 58)	DCD vs DBD	69 vs 86	60 vs 80	56 vs 76	43 vs 60

	34 vs 1)		(15yr 43 vs 51)

Continued Table 2.

Vagefi[29]	2011	only split livers, adult & pediatric, ex vivo & in vivo	106 adult 63 children 43		PNF: adult 1,6 children 2,3	adult 28,6 children 39,5	adult 3,2 children 16,3	adults overall adults ex vivo adults in situ children overall children ex vivo children in situ	93 93 94 84 83 86		77 85 75 75 73 86	73 74 NA 69 73 NA	adults overall adults ex vivo adults in situ children overall children ex vivo children in situ	89 86 94 77 75 86		76 77 75 63 59 86	65 63 NA 57 59 NA
Mallik[30]	2012	eRLG vs DCD	49	eRLG 34,7 DCD 65,3												71 93	
Fondevila[44]	2012	only Maastricht type 2 DCD	34		NA	12 (IC 8)	8		82					70			
Harring[70]	2012	DCD, UNOS/OPTN database	87499 (DBD: 85148, DCD: 2351)	DCD 2,68	PNF: 12	60		DCD vs DBD adult pediatric	84,4 vs 86,1 84,3 vs 86,1 90,2 vs 86,6	74,8 vs 78,3 74,5 vs 77,8 90,2 vs 82,8	68,9 vs 72,5 68,4 vs 71,6 90,2 vs 80,8	48,8 vs 59,0 47,8 vs 57,0 90,2 vs 76,6	DCD vs DBD adult pediatric	75,3 vs 81,5 75,1 vs 81,7 85,6 vs 79,5	63,9 vs 72,8 63,7 vs 72,7 76,7 vs 73,7	56,2 vs 66,5 55,9 vs 66,1 72,4 vs 70,5	38,7 vs 52,8 38,1 vs 51,4 64,4 vs 64,4
Ghinolfi[133]	2014	Age<60 61-69 70-79 >80	842	n.a.					90,5 88,6 87,6 84,7		78,6 81,3 75,1 77,1						
Hoyer[134]	2014	Donor CA yes vs no	884						76 75		57 53						

Continued Table 2.

Aseni[83]	2014	WG vs FRFLSLT	1263	5,1		83,1 63,4 (FL 67,2 FR 59,3)	80,4 58,8 (FL 60,7 FR 56,6)
Maggi[78]	2015	WG vs eRLG	2473	7,4		76,5 81,8	75,3 79,6

*Nafidi et al (2010).: Significant risk factors for graft loss: CIT>12 hours; graft gross appearance; donor partial O_2 ratio<300 mm Hg; donor Hbg >100 g/L

** Palmiero et al (2010): Significant risk factors for graft loss: CIT >9 hours ECD score >1.5; MELD ≥25; WL time >12 months

Table3: Different types of preservation methods of the donor graft after ECD liver transplantation.

Reference	Method	Population	Groups	advantages of the method
Rougemont (2009)[87]	HOPE (one hour hypothermic oxygenated perfusion)	Swiss landrace pigs	HOPE (n=6)vs CS (n=6)	survival, ATP recovery during reperfusion, glutathione, histology
Bessems (2007)[90]	24-hour liver preservation	Wistar rat	MP (n=7) vs CS (n=7)	bile production, ATP levels, tissue oedema after reperfusion, histology score, oxygen consumption
Franchello (2009)[91]	10min ischeamic preconditioning	deceased liver donors	IP+(n=30) vs IP-(n=45) (subgroups margial vs non-marginal)	bile production, hepatoprotective effect, AST and ALT level reduction 1.,3. postop day
Olschewski (2010)[92]	MP on different temperature (4,12,21C)	Wistar rat		portal venous resistance, bile flow (MPat21C),ALT after reperfusion,
Schmeding (2010)[93]	rHuEpo 4 hours after liver transplantation	Lewis rat	rHuEpo (+) n=35 vs rHUEpo(-) n=35 and n=70 recipients	ALT,AST (48h postolt), overall survival, cell apoptosis/necrosis
Mangus (2008)[94]	HTK vs UW	human DCD	n=698	HTK may be protective against biliary complications when compared to UW.
Stegemann (2010)[95]	modified HTK (Custadiol-N)	Wistar rat (non-heart beating)		significant enhancement of CO2 production and thus effective aerobic metabolism
Guarrera (2010)[98]	HMP (3-7 hours)	human	HMP (n=20) vs CS (n=20)	early allograft dysfunction, hospital length of stay, serum levels of markers of liver injury and renal function
Obara (2013)[86]	new machine perfusion preservation system (NES-01) with tempreture controll	porcine	n=3	pressure transition, LDH levels
Dutkowski (2013)[89]	HOPE	human DCD	DCD donor+HOPE(n=8) vs DBD (n=8)	reperfusion injury was low in machine perfused DCD livers