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Expanding the Donor Pool with Utilization of Extended Criteria DCD Livers

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Abbreviations:

ALT alanine aminotransferase

AST aspartate aminotransferase

ASTS American Society of Transplant Surgeons

BMI body mass index

CIT cold ischemia time

DBD deceased donor

DCD donation after circulatory death donor

EAD early allograft dysfunction

ECD extended criteria donor

fWIT functional warm ischemia time

HTK Histidine-tryptophan-ketoglutarate

IC ischemic cholangiopathy

LT liver transplant

MELD model for end-stage liver disease

SCD standard criteria donor

tPA tissue plasminogen activator

UW University of Wisconsin

WIT warm ischemia time

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Abstract

Utilization of donation after circulatory death donor (DCD) livers for transplantation has remained cautious in the U.S. The aim of this study was to demonstrate the expansion of DCD liver transplant (LT) program with the use of extended criteria DCD livers. After institutional review board approval, 135 consecutive DCD LTs were retrospectively studied. ECD DCD livers were defined as those with one of the followings: 1) donor age >50 years, 2) donor BMI >35 kg/m², 3) donor functional warm ischemia time (fWIT) >30 minutes, and 4) donor liver macrosteatosis >30%. An

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optimization protocol was introduced in July 2011 to improve outcomes of DCD LT, which included thrombolytic donor flush, and efforts to minimize ischemic times. The impact of this protocol on outcomes was evaluated in terms of graft loss, ischemic cholangiopathy (IC) and change in DCD LT volume. Of 135 consecutive DCD LT, 62 were ECD DCDs. 24 ECD DCD LT were performed before (Era I) and 38 after the institution of optimization protocol (Era II), accounting for an increase in the use of ECD DCD livers from 39% to 52%. Overall outcomes of ECD DCD LT improved in Era II, with a significantly lower incidence of IC (5% vs. 17% in Era I; $P = 0.03$) and better 1-year graft survival (93% vs. 75% in Era I, $P = 0.07$). Survival outcomes for ECD DCD LT in Era II were comparable to matched deceased donor (DBD) LT. With the expansion of the DCD donor pool, the number of DCD LT performed at our center gradually increased in Era II to account for > 20% of the center's LT volume. In conclusion, with the optimization of perioperative conditions, ECD DCD livers can be successfully transplanted to expand the donor pool for LT.

Introduction

Donation after circulatory death (DCD) donors have expanded the donor pool, however utilization of these livers remain cautious in the U.S. [1] The number of DCD donors has doubled in the last decade (642, 8% of 8017 total donors in 2006 vs. 1684, 17% of 9971 total donors in 2016); only 27% (518/1884) of the DCD livers were transplanted in 2017. [1] The reluctance to transplant DCD livers stems from several initial studies that published worse outcomes, mainly attributing to ischemic cholangiopathy (IC). [2-5] Due to initial worse outcomes with DCD LT, the American Society of Transplant Surgeons (ASTS) recommended practice guidelines for DCD procurement and transplantation in 2009 which emphasized limiting the use of DCD donor livers with (i) longer ischemia times or (ii) from older donors. [2-4] Variables, such as older donor age, prolonged cold ischemia time (CIT) and donor warm ischemia time (WIT) have been identified as the important risk factors associated with worse outcome, particularly for IC. [2-6] However, application of these criteria has led to underutilization of extended criteria donor (ECD) DCD livers. [1] A clear trend of transplanting DCD livers from younger donors was seen nationally, and only 13% DCD LTs were

from donors >50 years old between 2005 and 2015. [OPTN.org]

Recently, The Mayo group has shown comparable outcomes of DCD LT using donors >50 years age to that with younger donors as well as deceased donor LT. [7] Our and other programs have also reported improved results after DCD LT with outcomes comparable to deceased donor LT [8, 9] [10]. Improved outcomes were attributed to donor selection, minimization of CIT, and the use of thrombolytics. [11, 12] [13] Although these are important achievements, a large number of ECD DCD livers still remain underutilized in the U.S., compared to European centers. [10, 14] Schlegel *et al*, from Birmingham U.K., have demonstrated DCD livers from donors >60 years age can be successfully used with good long-term outcomes when other risk factors are limited. [14] The Zurich experience with hypothermic oxygenated perfusion (HOPE) has shown good 5-year outcomes despite extended donor warm ischemia and median donor age 57 years and median fWIT 31 minutes. [15]

In this study, we present our experience with the use of ECD DCD livers with comparable outcomes to matched deceased donor (DBD) LTs.

Methods

Study population

Patients with at least 6 months follow up were included in the study. The retrospective analysis of data between 08/2003- 05/2018 from the transplant research database at our center was reviewed and approved by the institutional review board of the Indiana University School of Medicine. Outcomes of adult DCD LTs (n=135) were evaluated. Due to the introduction of DCD LT optimization protocol in 07/2011, two eras were defined for the DCD LT. Patients with less than 12 months follow up were excluded from the survival analysis. For comparison of ECD DCD LTs with DBD LTs, a case-control matched analysis on propensity score was performed to reduce selection bias. The propensity score was estimated with the use of a multivariable logistic regression model. Matching was performed with the use of a 1:2 matching protocol without replacements. DBD LTs were matched with ECD DCD LTs with respect to the year of transplant, recipient age, gender, MELD score, CIT, recipient WIT, donor age, and donor gender.

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Definitions

ECD DCD livers were defined as those with one or more of the following factors: 1) donor age >50 years, 2) donor BMI >35 kg/m², 3) donor fWIT >30 minutes, and 4) donor liver macrosteatosis >30%. The definition of ECD DCD livers was based on the current national DCD liver acceptance practices, ASTS recommendations [10], and single-center experiences reported in the literature. [2-9, 11-15, 19]. Era I DCD LT included those performed between 08/2003-06/2011 (n=62). Era II DCD LT included those performed with the 'DCD LT Optimization Protocol' from 07/2011 onwards with at least 6 months follow up (n=73). Donor total WIT (tWIT) was defined as the time from extubation to in-situ perfusion. The time period from donor mean arterial pressure less than 50 mmHg and/or oxygen saturation less than 70% to in-situ perfusion was considered as functional WIT (fWIT). CIT was defined as the time from cold perfusion to portal reperfusion. Similar to Kroome et al, [7] IC was defined as the presence of intrahepatic biliary strictures in the absence of hepatic artery thrombosis, which was confirmed either by endoscopic retrograde cholangiopancreatography, or magnetic resonance cholangiopancreatography, or percutaneous transhepatic cholangiography. [16, 17] Early allograft dysfunction (EAD) was defined, as described by Olthoff *et al.* [18]

Organ procurement

The technique of DCD liver procurement was previously described. [9] Briefly, 300 IU/ kg heparin was administered systemically at the time of withdrawal of life support. Procurement began 5 minutes after the declaration of circulatory death. Immediately after entering the abdomen, distal aorta was cannulated and flushed with preservation solution and the infrarenal inferior vena cava vented for rapid exsanguination. Thoracic aorta was then clamped and the inferior vena cava was divided in the thoracic cavity. Ice-slush was placed on the abdominal organs and 3-4 liters of cold preservation solution was flushed through the aorta. Liver grafts were rapidly removed and an additional 500 mL of preservation solution was flushed through the portal vein on the back table. The common bile duct

was irrigated with cold preservation solution on the back table. Liver biopsies during procurement were performed based on procuring surgeons discretion to evaluate steatosis or necrosis. Post-reperfusion liver biopsies were however performed in all cases. In the majority (6/7) of the cases, livers with macrosteatosis >30% were identified at the time of procurement.

DCD LT Optimization Protocol (July 2011 to current; Era II)

The optimization protocol comprised of two main components: 1) minimization of modifiable ischemic times (CIT, recipient WIT) and 2) thrombolytic donor flush. The details of the protocol were previously described. [9] Briefly, during DCD procurements 100 mg of tissue plasminogen activator (tPA) (Activase®, Genetech Inc., CA, USA) was mixed in 1 liter of normal saline at room temperature, and was flushed through the aortic cannula as the initial flush after aortic clamping. This was followed by a 1 minute dwell period, followed by a 3-4 liters cold preservative fluid flush. After recovery of the liver, an additional 100 ml of tPA solution was injected into the celiac artery and the branches of celiac trunk were clipped until the back table preparation to avoid spillage. To minimize CIT, when possible, patients with a complex surgical history, extensive portal venous thrombosis were avoided as recipients. In order to make a quick decision regarding the usability of the organ at donor site In Era II, all procurements, including nationally shared livers were procured by our team which was led by surgeons experienced in DCD procurements. At our center, all procurements are led by attending surgeons. Two surgeons (P.M. & C.K.) who had developed particular expertise using the optimization protocol performed majority (90%) of the DCD procurements in Era II. As soon as the liver was considered transplantable, the recipient preparation for surgery was expedited. Recipient operation and back table preparation of the liver began simultaneously. Similarly, until 2017, all recipient operations were performed by staff surgeons to keep, hepatectomy time and recipient WIT short.

Recipient operation

Recipient operation was previously described elsewhere. [19] Briefly, the transplant operation was performed using a piggyback technique for the venous outflow. Hepatic artery was dissected and prepared for anastomosis during hepatectomy to avoid prolonged warm ischemia to the biliary system after portal reperfusion. Hepatic artery anastomosis was performed after reperfusion of the portal vein.

Recipient selection

At the beginning of Era II, recipient selection was cautious; recipients with portal vein thrombosis, prior upper abdominal surgeries (except cholecystectomy) were considered to be unsuitable initially. Also, the possibility of re-transplantation was also kept in mind while selecting recipients in the beginning. However, with initial success and growing experience, DCD allografts were offered to patients with surgical complexities and frailty in the latter half of Era II, although keeping ischemic times short.

Clinical endpoints

The clinical endpoints of our study were (i) graft loss, (ii) development of IC and (iii) expansion of the DCD donor pool with the use of ECD DCD donors.

Statistical analysis

Standard statistical testing was conducted with commercially available software (IBM SPSS, Version 24.0. Armonk, NY). The comparisons were performed with the Mann-Whitney U-test for numerical data and the Chi-square test for categorical data. Survival rates were estimated with the Kaplan-Meier analysis. For comparison of ECD DCD LTs with DBD LTs, a 1:2 case-control propensity scores matched cohort of DBD LTs was used. All graft survival curves were calculated as non-death censored. A *P* value of <0.05 was considered statistically significant.

Results

In Era I (8-year span) 62 (46%) DCD LTs were performed, whereas in Era II (~7 -year span) there were 73 (54%) DCD LTs. Of 135 DCD LT, 62 were ECD DCD; 24 (39%) in Era I and 38 (52%) in Era II.

Donor, recipient and transplant characteristics

Donor, transplant and recipient characteristics were compared between standard criteria donor (SCD) and ECD DCD LTs, separately for the two eras. (Table 1) As expected, donor age was higher in ECD DCDs in both eras, however median donor BMI was higher in ECD DCDs from Era I only. Overall, majority of ECD DCD livers were from regional (31%) or national (29%) share compared to SCD DCD livers (23% & 12% respectively, chi-square, $P = 0.01$). However, in Era II, 62% of all DCD livers and 47% of ECD DCD livers were local ($P = 0.01$). In Era I, 18% DCD donor livers were flushed with University of Wisconsin (UW) solution, whereas Histidine-tryptophan-ketoglutarate (HTK) was exclusive preservation fluid used in Era II (100% vs. 82%, $P = 0.001$). Recipient demographics were comparable between SCD and ECD DCD LTs in both eras. There was an overall improvement in ischemic times in Era II. The ischemic times except for CIT for ECD DCDs in Era I were significantly longer than SCD DCDs. Median functional donor WIT was significantly longer in ECD DCDs [32(14-78) vs. 15(7-30); $P = 0.001$]. Median recipient WIT (anastomoses time) for ECD DCDs was also significantly longer than SCD DCDs [21(18-38) vs. 27(21-38); $P = 0.001$].

Donor, transplant and recipient characteristics for ECD DCD LTs across the two eras were also compared. (Table 1) These comparisons revealed, comparable donor demographics, but older recipients, higher MELD scores, more male recipients, and higher recipient BMI in era II.

In terms of transplant characteristics, CIT, total donor WIT, recipient WIT and hepatectomy times were significantly shorter for ECD DCDs in Era II. For example, median total WIT (donor functional WIT + recipient WIT) was 39(28-72) in Era II, compared to 58(38-108) in Era I, $P < 0.001$. The exclusive use of HTK as preservation fluid in ECD DCDs in Era II was also significant.

Post-transplant outcomes

Post-transplant clinical outcomes for ECD DCD LTs were compared across the two eras. (Table 2) In Era II, the total bilirubin on post-transplant days 14 and 30 were significantly lower and day 3 - INR was significantly higher (Table 2). EAD was overall common in ECD DCDs and was comparable across the two eras ($P = 0.69$). In Era II, the prevalence of biliary anastomotic strictures was significantly lower (21% vs. 54% in Era I; $P = 0.01$). There were two cases of IC in Era II (5% vs. 17% in Era I, $P = 0.01$). Hepatic artery thrombosis occurred in 1 patient in each Era which resulted in retransplantation of both cases. In Era II, the patient with late hepatic artery thrombosis also developed intrahepatic diffuse biliary strictures. This was not considered as IC, due to the hepatic artery compromise.

The outcomes of ECD DCD LT in Era II were compared with propensity score matched DBD LT ($N = 124$) (Table 2). Peak post-transplant transaminases (AST and ALT) were significantly higher in ECD DCD LTs in Era II compared to matched DBD LTs. Post-transplant bilirubin levels (on days 7, 14, 30) were comparable between ECD DCD LT in Era II and matched DBD LT (Table 2). The post-transplant day 3 INR and incidence of EAD were also significantly higher in the ECD DCD (Era II) cohort. IC, hepatic artery thrombosis, and re-transplantation rates were similar between Era II ECD DCD LTs and matched DBD LTs.

Survival outcomes

Overall graft survival for ECD DCD LTs improved in Era II, compared to Era I, however, this was not statistically significant by Log-Rank test ($P = 0.26$). (Fig. 1a) 1-year graft survival was numerically higher in Era II ECD DCD LTs when compared with Era I ECD DCD LTs (93% vs. 75%; $P = 0.07$) (Table 2). Overall graft survival for ECD DCD LT (Era II) was comparable to matched DBD LT (Log Rank, $P = 0.8$) (Fig. 1b). Similar trends were recorded for patient survival (data not shown). 1-year patient survival for ECD DCD LTs was numerically higher than that of ECD DCD LT in Era I (97% vs. 83%; Log Rank; $P = 0.09$) and matched DBD LT (97% vs. 90%; $P =$

0.25). Three patients receiving ECD DCD LTs in Era II died with-functioning grafts at the time of death from cardiomyopathy, pneumonia, and stroke. One patient was retransplanted for intrahepatic biliary strictures secondary to late hepatic artery thrombosis.

Ischemic cholangiopathy (IC) in ECD DCD LT

Two patients (5%) in Era II receiving ECD DCD LTs developed IC compared to 4 patients (25%) in Era I ($P = 0.01$) (Table 2). Of 4 patients developing IC in Era I, 3 lost their grafts due to this complication. Of whom, one patient was re-transplanted 4.5 months after transplantation. In 1 patient, there were predominant right and left main hepatic duct strictures and were managed with repeated biliary interventions. In Era II, both patients developing IC were managed with endoscopic interventions and have normal liver function.

Expansion of the DCD LT program with the use of ECD DCD

Due to poor outcomes, the number of DCD LT performed per year decreased in the latter half of Era I. After the introduction of DCD LT optimization protocol in 2011, the DCD LT program expanded. [Fig. 2] Especially for 3 years since 2015, the successful expansion was from ECD DCD livers. In 2016, 2017, and 2018 ECD DCD livers constituted 59%, 60% and 56% of our DCD LT activity respectively. In 2015, 2016, and 2017, 9%, 12%, and 11% of all adult LT were DCD LT, respectively. In 2018, 32 out of 143 of adults LTs were DCDs accounting for 22% volume. Donor selection evolved over the period of Era II. At the beginning of Era II, most of the DCD donors were SCD DCDs, from 2011 to 2014 out of 13 DCD LTs only two were ECD DCDs. With the initial success of having no IC or graft loss, we started utilizing ECD DCDs. Initially, we started utilizing livers donor age and BMI as ECD variables and from 2015 onwards we expanded our ECD variables to fWIT >30 minutes and macrosteatosis >30% was the last ECD variable to be incorporated. (Figure 2)

ECD DCD variables (Table 3)

There were 62 (54%) ECD DCD LTs (24 in Era I and 38 in Era II). The most common ECD criterion was donor age, followed by fWIT, donor BMI and macrosteatosis in this order. In Era II, graft loss was not associated with ECD criteria, unlike in Era I. For instance, in Era II, 16% ECD DCD livers were with donor fWIT >30 minutes (32, 33, 33, 37, 40 & 41 minutes) and none of these grafts failed. The threshold for fWIT was raised in the latter half of Era II. In 3 transplants, fWIT >30 minutes was combined with other ECD variables such as BMI, macrosteatosis, and age. In Era I, LTs with more than one ECD criteria were associated with 100% graft loss. In Era II, none of the 6 grafts with 2 ECD variables failed. Of 6 livers with macrosteatosis >30% in Era II, 1 graft loss occurred as a result of patient death. Interestingly, none of the livers with macrosteatosis >30% were from donors with BMI >35 kg/m². When ECD DCD variables (donor age >50 years, donor BMI >35 kg/m², donor fWIT >30 minutes, and donor macrosteatosis >30%) were considered individually with respect to the development of IC, EAD, and graft loss, no associations were found.

Discussion

This study demonstrates the use of ECD DCD livers to expand DCD LT program. The overall improvement in outcomes consolidates our previous experience with a protocol that utilizes thrombolytic donor flush along with short ischemic times. [9] Although, it is possible that we are now more adept and experienced in performing DCD LT. Similar to our experience, recently other centers [8] [12] and SRTR data-based reports [20] have demonstrated improved outcomes after DCD LT. The explanation for improved outcomes in our series remains speculative since multiple changes were instituted. In our opinion, the most important factor responsible for improved outcomes was shorter CIT. It should also be noted that in Era I ECD DCD LTs were associated with significantly longer warm ischemic times than for SCD DCD LTs. It is possible that a combination of ECD factors with longer warm ischemic times in Era I was responsible for poor outcomes. The role of thrombolytic

flush is also compelling. Improved outcomes have also been reported by others without the use of heparin or thrombolysis, questioning the theory of microthrombi within peribiliary capillaries. [21]

On the other hand, several groups have demonstrated improved outcomes with the use of thrombolysis. [8, 9, 12, 13] We believe that efforts should be made to shorten CIT in DCD LT in order to improve outcomes and expand the donor pool. Other studies have reiterated this observation. [20] [22] Selck *et al* showed 31% increased risk of graft loss associated with nationally shared DCD livers due to increased CIT. [23] Similar to our experience in Era II, Detry *et al* have described excellent outcomes (IC in 1/70 patients) with a median CIT of 3.9 hours [24].

Expanding DCD donor pool

Risk factors associated with poor outcomes in DCD LT are already defined, and some of these are modifiable. This principle was exploited in our and other DCD series. [8, 9, 24] The modifiable donor risk factors are: 1) location of withdrawal of life support, 2) asystole to cross-clamp time, 3) post-mortem use of heparin, 4) interventions such as use of thrombolytics in the donor or recipient, normothermic perfusion after procurement, use of ECMO after cardiac arrest. [8, 9, 13, 25-29] Additional modifiable recipient risk factors can be 1) hepatectomy time, 2) recipient WIT, and 3) CIT. [30-32] On the other hand, donor age, donor BMI, donor WIT, donor liver quality in terms of steatosis, transaminases are unmodifiable factors. Our approach has been to gradually expand the acceptance criteria to include unmodifiable risk factors. We started with donor age and BMI, then gradually expanded to livers with >30 minutes fWIT and >30% macrosteatosis. There were 6 transplants with donor fWIT >30, 32, 33, 33, 37, 40 & 41 minutes. We believe that donor fWIT can be safely extended up to 40 minutes in select cases, particularly with short CIT, and short recipient WIT. Another important observation in our study was that of 11 ECD DCD donors with BMI >35, none had macrosteatosis >30%, emphasizing that DCD liver should not be discarded based on BMI alone. Also, quantification of macrosteatosis on frozen section biopsies can be variable and is frequently overestimated on frozen sections. Although we do not use a cut-off value for %

macrosteatosis in our DCD liver program, we believe that DCD livers with little over >30% macrosteatosis on frozen sections can be used safely with relatively healthy-appearing remaining hepatocytes, with soft liver parenchyma and short ischemic times.

Recipient selection remains important to successful outcomes. As our experience grew with DCD LT, we gradually relaxed our recipient selection criteria to include recipients with surgical complexities and portal vein thrombosis. Currently, the only recipient contraindication to DCD LT is the previous LT. We also keep in mind that recipients of ECD DCD grafts should have overall health to tolerate re-transplantation in the event of IC and graft loss.

Definition of ECD DCD LT

Currently, there are no established criteria for ECD DCD LT. In this study, we defined ECD DCD criteria based on organ acceptance practices in the U.S. to identify potentially transplantable livers and previous ASTS practice guidelines on DCD liver transplantation. [4] We chose donor age >50 years as one of the criteria because, from 2005-2015, only 13% DCD LTs were performed from donors older than 50 years nationally. Croome et al from UNOS data reported a decline in DCD LTs from donors >50 years age from 18% (2003-2006) to 11% in 2011-2014. [20] Although many European centers have reported the successful use of DCD livers from donors older than 60 years, [14] only 4% DCD donors pursued for organ procurements in the U.S. from 2005-2015 were >60 years old. On the contrary 24%, DCD donors pursued during this period nationally were from 51-60 years of age group, making this donor age group the first target to expand the donor pool. The second criterion in our definition was donor BMI >35. Median donor BMI for national DCD LTs from 2005-2015 was 25.5 with 29.5 as the 75th percentile. To stay beyond the upper limit of BMI margin for livers being currently transplanted, we chose a BMI of 35. Another huge potential to expand the DCD donor pool relates to the donor WIT. It is astonishing that only 5% of DCD LTs performed nationally between 2011-2014 were with total donor WIT >30 minutes. [20] It must be noted that this was total

donor WIT and not functional, hence it is likely that several of the discarded livers would have had <30 minutes functional WIT. The major disadvantage of using total donor WIT as an organ acceptance criterion is that it does not truly reflect the conditions inflicting liver injury from warm ischemia during the agonal phase. Therefore, to exclude the period with normal vital parameters, we used fWIT of >30 minutes as our third criterion. Our fourth criterion was % macrosteatosis. We adopted a cut off level of 30% for the macrosteatosis based on the ECD definition for DBD livers.

[33]

Limitations

This study has several limitations. We could not exclude the possibility of bias from unobserved variables due to the retrospective nature of the study. There were confounding factors such as increased experience with DCD LT & improved recipient selection. In this study, we used historic controls, as a randomized controlled study was not possible due to the risk involved. However, most published studies on DCD LT are retrospective single center and/or national database studies.

Conclusions

ECD DCD livers can be used successfully to expand donor liver pool. Outcomes comparable to DBD LT can be achieved despite the use of donors >50 years of age, donors with high BMI, and livers with relatively longer donor WIT, and macrosteatosis. With the recent success in this field, updated guidelines on DCD liver procurement and transplantation are required to expand DCD LT nationally.

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Figure Legends:

Figure 1a: Graft survival by Kaplan-Meier analysis for ECD DCD LTs stratified by two eras.

Graft survival not censored for death for ECD DCD LTs compared across the two eras, Log Rank; $P = 0.26$.

Figure 1b: Graft survival by Kaplan-Meier analysis for Era II ECD DCD LTs compared with matched DBD LTs.

Graft survival not censored for death for ECD DCD LTs in Era II compared to graft survival for propensity score matched DBD LTs across the two eras, Log Rank; $P = 0.8$. Cases were matched for year of transplant, recipient age, gender, CIT, recipient WIT, donor age, and donor BMI.

Figure 2: Number of all DCD LTs performed at Indiana University since 2003.

Gray bar indicates standard criteria donor (SCD) donation after circulatory death (DCD) donor LT.

The black bar indicates extended criteria donor (ECD) DCD LT. The numbers indicate percentages of

DCD LTs on overall adult LTs of each year performed at Indiana University. The DCD LT Optimization protocol was introduced in July 2011.

Accepted Article

Table 1. Donor and recipient demographics data for DCD LT in Era I and Era II, stratified by ECD status.

	Era I SCD DCD n=38	Era I ECD DCD n=24	p-value	Era II SCD DCD n=35	Era II ECD DCD n=38	p-value	p-value Era I ECD DCD vs. Era II ECD DCD
<u>DONOR</u>							
Age (years)	40 (12-50)	42 (21-58)	<0.001	31 (9-53)	46 (12-62)	<0.001	0.37
Gender: Male	28 (73)	13(54)	0.11	29 (79)	30 (83)	0.67	0.11
Body mass index (kg/m ²)	24 (14-32)	24 (20-40)	0.01	26 (14-32)	25 (19-48)	0.18	0.35
Organ origin			0.13				
Local	20 (53)	7 (29)		27 (77)	18 (47)	0.01	0.18
Regional share	10 (26)	7 (29)		7 (20)	12 (32)		
National share	8 (21)	10 (42)		1 (3)	8 (21)		
Preservation fluid							
HTK	33 (87)	18 (75)	0.23	38 (100)	38 (100)	--	0.001
UW	5 (13)	6 (25)		0 (0)	0 (0)		
<u>RECIPIENT</u>							
Age (years)	54 (40-71)	53 (24-65)	0.08	57 (33-68)	61 (39-72)	0.25	<0.001
MELD*	15 (9-24)	14 (8-27)	0.2	20 (11-40)	19 (7-35)	0.61	0.01
Gender: Male	22 (58)	13 (54)	0.77	25 (71)	31 (82)	0.31	0.04
Race: White	35 (92)	18 (75)	0.06	30 (86)	27 (71)	0.61	0.2
Body mass index (kg/m ²)	30 (23-37)	27 (19-37)	0.05	29 (20-38)	30 (20-38)	0.63	0.045

Ischemic/ hepatectomy times

CIT (hours)	6.5 (4.3-10.4)	6.4 (4-12)	0.86	4.6 (3.1-9.2)	4.5 (3.6-5.8)	0.07	< 0.001
Total donor WIT (minutes)	23 (14-39)	34 (19-83)	0.01	23 (15-33)	24 (18-43)	0.86	0.01
Functional donor WIT (minutes)	15 (7-30)	32 (14-78)	0.001	18 (10-28)	20 (12-40)	0.52	0.01
Recipient WIT (minutes)	21 (18-38)	27 (21-38)	0.001	19 (13-28)	20 (16-31)	0.06	< 0.001
Total WIT (donor functional WIT + recipient WIT) (minutes)	37 (26-63)	58 (38-108)	0.001	37 (25-50)	39 (28-72)	0.07	< 0.001
Hepatectomy time (minutes)	73(48-146)	84 (72-122)	0.26	73 (42-120)	66 (37-101)	0.94	0.01

Legend: Data are presented as the median (range) or frequency (%) values. MELD: model for end-stage liver disease, AST: aspartate aminotransferase, ALT: alanine aminotransferase, HTK: Histidine-Tryptophan-Ketoglutarate, UW: University of Wisconsin, ECD: extended criteria donor, SCD: standard criteria donor, DCD: donation after cardiac death, CIT: cold ischemia time, WIT: warm ischemia time.

Table 2. Clinical outcomes of ECD DCD LTs stratified by eras and compared with propensity score matched DBD LTs

	Era I	Era II	p-value	Matched	p-value
	ECD DCD n=24	ECD DCD		DBD	(Era II ECD DCD vs. Matched DBD)
		n=38		n=124	
<u>Recipient laboratory values</u>					
Peak ALT (U/L)	1274 (191-9635)	1236 (98-5740)	0.81	497 (46-4725)	<0.001
Peak AST (U/L)	1614 (117-12618)	2544 (271-13300)	0.12	685 (43-6684)	<0.001
PTD 7 Total Bilirubin (mg/dL)	4.1 (0.8-16.1)	2.6 (0.9-27.6)	0.08	2.9 (0.6-23.2)	0.56
PTD 14 Total Bilirubin (mg/dL)	3.6 (0.9-14.1)	1.4 (0.5-47)	0.01	1.8 (0.4-21.7)	0.15
PTD 30 Total Bilirubin (mg/dL)	1.6 (0.3-22.7)	0.8 (0.4-56)	0.03	1 (0.2-16.2)	0.15
Early allograft dysfunction*	14 (58)	24 (63)	0.7	43 (35)	<0.01
Anastomotic biliary stricture	13 (54)	8 (21)	0.01	37 (30)	0.05
Ischemic Cholangiopathy	4 (17)	2 (5)	0.01	3 (2)	0.42
Hepatic artery thrombosis	1 (4)	1 (3)	0.9	1 (1)	0.61
Re-transplantation within 1 year	2 (8)	1 (3)	0.8	2 (2)	0.82
Length of hospital stay (days)	16 (0-80)	15 (7-31)	0.85	12 (0-66)	0.53
30-day graft loss	2 (8)	0	0.07	10 (8)	0.06
1-year graft loss	6 (25)	2/32 (7) [†]	0.07	15 (12)	0.16

1-year patient death

4 (17)

1/32 (3)[†]

0.09

12 (10)

0.25

Legend: Data are presented as the median (range) or frequency (%) values. AST: aspartate aminotransferase, ALT: alanine aminotransferase, PTD: post-transplant day, ECD: extended criteria donor, DCD: donation after circulatory death, DBD: donation after brain death

* Early allograft dysfunction defined as AST or ALT greater than 2000u/L in first 7 days, day 7 total bilirubin \geq 10.0 mg/dL, or day 7 INR \geq 1.6.

[†]Note: for 1-year graft loss, patients with at least 12 months follow up were considered

Table 3: Extended criteria DCD livers and graft loss in Era I and II

ECD variable/s	Era I (n=24)		Era II (n=38)	
	Transplants	Graft loss (%)	Transplants	Graft loss (%)
Age >50	8	6 (75)	23	2 (9)
BMI >35	4	1 (25)	7	0
fWIT >30	8	4 (50)	6	0
Macrosteatosis >30%	0	0	6	1 (17)
Age >50 + BMI >35	3	3 (100)	1	0
Age >50 + fWIT >30	0	0	1	0
Age >50 + Macrosteatosis >30%	0	0	2	0
BMI >35 + fWIT >30	1	0	1	0
BMI >35 + Macrosteatosis >30%	0	0	0	0
fWIT >30 + Macrosteatosis >30%	0	0	1	0

Legend: Data are presented as the frequency of transplants and graft loss (%). ECD: extended criteria donor, fWIT: functional donor warm ischemia time, age in years, BMI in kg/m², fWIT in minutes





