ICCR Rotation (August 5 – August 25, 2008)
Final Presentation
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Title: Optimal Use of Extended Criteria Donor Liver Grafts in Adult-to-Adult Whole Liver Transplantation

Study purpose and rationale:
Hepatitis C Virus infection is one of the leading causes of liver failure in the world and the primary indication for orthotopic liver transplantation in the United States. According to the most recent UNOS Data, over 45% of the OLTs performed in 2007 were in HCV positive recipients.[1] However the organ shortage limits the efficacy of OLT in the treatment of HCV, and chronic liver disease in general. In the last 20 years, while OLT has become a routine therapy for a growing population of patients with end-stage liver disease, organ availability has plateaued at approximately 6000 grafts per year. This disparity between the expanding UNOS waiting list and the fixed number of grafts has resulted in a 5-fold increase in deaths while awaiting OLT and poses that biggest challenge to the transplant community.[2,3]

Efforts to expand the donor pool include increasing the donation rate, expanding living donor liver transplant programs, improving new surgical techniques such as split liver transplantation and using extended criteria donor (ECD) liver grafts.[4] While each of these techniques poses unique challenges and concerns, ECD grafts have generated significant controversy as these organs are thought to carry a potentially high risk of primary non-function, initial poor function or donor-transmitted disease. The transplant community has yet to establish a definition of extended criteria donor livers, however it is believed that the following donor factors pose an elevated risk of either allograft failure or disease transmission to the recipient: (1) age >60 years; (2) macrovesicular steatosis >30%; (3) HCV positive grafts; (4) Hepatitis B core positive grafts; (5) donation after cardiac death. In addition it is generally believed that several transplant related factors increase the risk of graft loss: (1) hemodynamic instability, specifically prolonged hypotension (SBP <60 for 2 or more hours), use of dopamine > 10 μg/kg/min for over 6 hours and the required used of 2 inotropic agents to sustain donor blood pressure for

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[1] United Network for Organ Sharing. Available at: http://www.unos.org
[2] Verna, E and Brown, R. Hepatitis C virus and liver transplantation. *Clinics in Liver Disease* 2006;10(4):919-940.
[3] Lucey, M.R., Brown, K.A., Everson, G.T, et al. Minimal criteria for placement of adults on the liver transplant waiting list: a report of national conference organized by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases. *Liver Transplantation Surgery* 1998;66:956-62.
[4] Renz, JF, Kin, C, Kinkhabawala, M, et al. Utilization of extended donor criteria liver allografts maximizes donor use and patient access to liver transplantation. *Annals of Surgery* 2005;242:556-63.

more than 6 hours; (2) cold ischemic time >10 hours; and (3) sharing outside the local donor service area.[5,6,7,8]

Several large retrospective studies have investigated the impact of ECD grafts on recipient outcomes. Feng et al used data from over 20,000 donors from 1998 to 2002 to develop a quantitative donor risk index. They showed that age, donation after cardiac death, cold ischemic time and sharing outside the local donor service area independently predicted a significantly increased risk of graft failure.[7] Gruttadauria et al compared outcomes in standard graft recipients to ECD recipients, stratifying the latter group into patients who received a graft with 1 to 2 risk factors versus patients who received a graft with 3 to 4 risk factors. They found that graft survival and patient survival differed significantly between standard and nonstandard grafts and graft survival differed significantly according to cumulative risk factors.[8] Finally in a retrospective analysis of primary adult OLTs at UCLA (n>1000) Cameron et al found that ECD grafts were associated with a higher morbidity and mortality compared to standard grafts and saw an inverse relationship between survival and the number of ECD risk factors per graft.[9]

While these studies have verified the perceived risk of increased mortality and graft failure associated with ECD grafts, they have not addressed several key issues. First, previous studies have relied upon scoring systems that assess the cumulative risk of an ECD graft rather than analyzing each factors individual effect on recipient outcomes. Of the ECD factors previously outlined studies to date have only been powered to comment on the individual impact of donor age. Secondly, while hepatitis C patients comprise the majority of OLT recipients and ECD graft recipients, outcomes in this population have not been specifically analyzed. Understanding the relationship between Finally, while previous studies have addressed the impact of ECD grafts on graft failure, there has been little attention paid to disease transmission. This area is of specific concern in the HCV population where the affects of an HCV genotype mismatch or HBV donor-recipient transmission on HCV post-transplantion recurrence remains unknown.

When considering the impact of ECD grafts on recipient outcomes in the HCV population, it is important to understand the natural course of HCV in the post-

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[5] Gridelli, B, and Remuzzi, G. Strategies for making more organs available for transplantation. *The New England Journal of Medicine* 2000;343:404-410.
[6] Gruttadauria, S, Cintorino, S, Mandala, L et a. Acceptance of marginal liver donors increases the volume of liver transplant. *Transplant Proc* 2005;37:2567-2568.
[7] Feng, S, Goodrich, N.P., Bragg-Gresham, J.L. et al. Characteristics associated with liver graft failure: the concept of donor risk index. *American Journal of Transplantation* 2008;4:783-790.
[8] Gruttadauria, S, Vizzini, G, Biondo, D et al. Critical use of extended criteria donor liver grafts in adult-to-adult whole liver transplantation: a single-center experience. *Liver Transplantation* 2008;14:220-227.
[9] Cameron, A, Ghobrial, R, Yersiz, H et al. Optimal utilization of donor grafts with extended criteria a single-center experience in over 1000 liver transplants. *Annals of Surgery*. 2006;243(9):748-755.

transplantation setting. Liver transplantation is the only cure for HCV-related cirrhosis, however HCV invariably recurs after liver transplantation. The sequelae of chronic hepatitis post-transplantation are a significant cause of morbidity and mortality, with death and graft failure occurring more commonly in this population compared to HCV negative transplant recipients.[10] The natural history of HCV disease is accelerated in the post-transplantation setting, leading to cirrhosis in up to 25% of patients within 5-10 years.[11] Standard antiviral therapy post-transplantation with pegylated interferon-alpha and ribavirin has not produced reliable improvements in long-term survival nor has research into adjunct therapies led to eradication of the virus.[12] As a result much effort is now focused on predictors of severe recurrence and poor outcomes in an effort to identify modifiable risk factors for accelerated disease recurrence. It remains unknown how ECD grafts affect patient survival, graft survival and disease recurrence in the HCV population or whether these outcomes differ according to the type of ECD graft.

Hypothesis:
Null Hypothesis: One year patient survival, one year graft survival and the rate of accelerated disease recurrence do not differ between healthy donor liver grafts and extended criteria grafts or amongst the different classes of extended criteria grafts.

Alternative Hypothesis: Extended criteria donor grafts in general result in worse patient survival, graft survival at one year and an increased rate of accelerated disease recurrence post-transplantation compared to healthy grafts. Within the pool of extended criteria grafts, one year graft survival and the rate of accelerated disease recurrence differs depending on the type of graft.

Study Design:
This is a retrospective study of hepatitis C positive adult liver transplant recipients, transplanted between February 2002 and January 2008. The beginning date for the study period was chosen based on the implementation of the Model for End-Stage Liver Disease (MELD) model in all US transplant centers in February 2002. Patients will be assigned to either the standard criteria donor (SCD) group or extended criteria donor (ECD) group based on the type of graft received. The ECD group will be subcategorized based on the type of ECD liver received. The subgroups are defined as: (1) donor age >60; (2) percent steatosis >30%; (3) HCV positive graft; (4) HBV positive graft.

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[10] Neumann, UP, Berg, T, Bahra, M et al. Long term outcome of liver transplants for chronic hepatitis C: a 10 year follow-up. *Transplantation* 2004;77:226-231.
[11] Berenguer, M, Crippin, J, Gish, R, et al. A model to predict severe HCV-related disease following liver transplantation. *Hepatology* 2003;38:34-41.
[12] Wang, CS, Ko, HH, Yoshida, Em, et al. Interferon-based combination antiviral therapy for hepatitis C virus after liver transplantation: a review and quanitative analysis. *American Journal of Transplantation* 2006;6:1586-1599.

Recipient outcomes will then be assessed in each group and subgroup. Outcome variables are defined as:

- Patient survival at one year
- Graft survival at one year
    - Primary graft nonfunction: diagnosed if it occurred within 14 days after transplant and in the absence of vascular thrombosis and biliary obstruction, if a constant increase in liver enzymes and parallel drop in coagulative indices were present.
    - Graft rejection: diagnosed by histology. All Hepatitis C patients receive at minimum post-transplantation protocol liver biopsies annually for the first five years after transplantation. This histological information can be used to assess liver damage, specifically hepatitis, severe hepatitis, steatohepatitis, and rejection. Among biopsy specimen categorized as hepatitis, severe hepatitis is defined as the presence of stage three or greater fibrosis.
- Hepatitis C recurrence: diagnosed based on transaminase values and histologically as discussed above
    - Severity of Hepatitis C recurrence: diagnosed based on transaminase values and histologically as discussed above

Study Subjects:

Inclusion Criteria:

- Full size cadaver adult allografts used for adult recipients from February 2, 2002 to August 1, 2008
- Hepatitis C virus positive recipients

Exclusion Criteria:

- Adult-to-adult liver-related liver transplants
- Split liver or reduced graft transplants
- Hepatitis C virus negative recipients
- Retransplants
- Donors whose age was less than or equal to 18 years
- Any graft without fully complete data sets that concomitantly included recipient, donor or operative variables.
- Grafts with more than two concurrent ECD factors

Sample Size:

- N = 981 patients transplanted between February 2, 2002 to August 1, 2008
    - 387 patients received ECD grafts
    - 594 patients received Standard grafts
- $\alpha = 0.05$
- Power = 0.80
- Using proportion of patients who developed progressive or rapidly progressive HCV recurrence post-transplantation (p=0.07)
- Able to detect $p < 0.048$

Statistical Plan:
Time to graft failure was defined as the period between transplantation and graft loss secondary to either retransplantation or recipient death, whichever occurred first. All available post-transplant follow-up data will be used in the analysis. Likely donor parameters to be investigated include: age, sex, race, BMI, cause of death, serum levels of creatinine, BUN, AST, ALT, total bilirubin, comorbidities (hypertension, insulin-dependent diabetes), cigarette, alcohol and intravenous drug use, viral status (cytomegalovirus, hepatitis B, hepatitis C), transplantations factors (required used on intoropic agents, administration of anti-convulsants, anti-hypertensives or vasodilators).

To isolate the impact of ECD characteristics on liver allograft outcomes, all models will be adjusted for recipient and transplant factors that may impact allograft failure. The following recipient factors will be included in all models: age; sex; race; body mass index; underlying liver disease diagnosis (acute hepatic necrosis, cholestatic liver disease, noncholestatic liver disease, metabolic liver disease, malignancy, or other); hepatitis B status; hepatitis C status; cytomegalovirus status; history of previous liver transplant; SGOT (AST); total bilirubin, albumin and creatinine; dialysis status at time of transplantation; medical condition (intensive care unit, in hospital, or out of hospital); Status 1 medical urgency designation; requirement for life support; grade III or IV hepatic encephalopathy; requirement of inotropic support; portal vein thrombosis at time of transplantation and incidental tumor identified during transplantation. Transplant parameters included in all models were ABO compatibility, cold ischemia time and origin of the donor organ beyond the recipient's listing organ procurement organization (shared organ).

Kaplan-Meier methods will be used to estimate patient and graft survival as a function of time. The log-rank test will be used for univariate Kaplan Meier curve comparisons for each factor independently (e.g. comparing graft survival in Hep C patients who received a graft with >30% steatosis vs a graft with <30% steatosis). Univariate empirical hazard ratios will be computed and reported (hazard = number of events/number of person-months of follow-up; where events = deaths or deaths + failure).

Study Drugs or Devices:
No study drugs or devices will be used in this study.

Study Questionnaires:
No study questionnaires will be used in this study.

Potential Risks:
Patients may derive no benefit from participating in this study. Given that is a retrospective analysis no additional risk is anticipated.

Potential Benefits:

The information gained from this project will better inform the transplant community of the stratified risk associated with different classes of ECD grafts and will enable HCV patients awaiting transplantation to make more informed decisions.

Alternatives:
The current approach to ECD graft use varies by transplant center and generally relies on a scoring system that assesses cumulative risk rather than the individual risk of each ECD factor, resulting in significant speculation during donor-recipient matching.