Optimizing Living Donor Liver Transplantation: Risks and Benefits

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Disclosures

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• No conflicts of interest were declared by the authors
Total Number of Adult Transplants

AJT 2016: OPTN/SRTR 2014 Annual Report

2004: 273, 4.9%
2014: 228, 3.8%
Figure LI 5.4 Graft survival among adult liver transplant recipients, 2006-2009: living donors
Figure IV-8. Number of Living Donor Liver Transplants by Age, 1998-2007

Source: 2008 OPTN/SRTR Annual Report, Table 9.4b.
When Disaster Strikes: Death of a Living Organ Donor

Organ Donor Death Raises Questions About Living Donors

Live Donor Deaths Beg the Question: Does the Benefit Outweigh the Risk?

Montefiore live-donor transplant program shut down after donor mom dies during surgery
Factors Influencing Donor Surgery: Extent of Donor Hepatectomy

- The **amount of remnant hepatic parenchyma** in the donor after hepatectomy has been repeatedly identified as the **single most important predictive factor for donor outcome**.

- Individuals with **larger remnant volumes** consistently display **fewer adverse events**, shorter lengths of stays, and faster return to pre-donation activity levels.
Program Volume and Aborted Hepatectomy


- 11,553 completed donor hepatectomies reported
- 136 donor hepatectomies were aborted
- 1.16% overall risk of aborted hepatectomy
  - However, high volume programs experience significantly fewer AHs (>200 = 62/8860, 0.7%)
Program Volume and “Near Miss” Events

- “Near Miss” events decreases with experience

- Both low and medium volume programs have higher incidence of near miss events compared to high volume programs (**p<0.001, both groups)


1 center in each group has had a donor requiring LT.
36 Total Donor Deaths by Geographic Region

- Deaths reported in survey (n=23)
  - \(15 \leq 60\) days Post Op
  - \(8 > 60\) days Post Op, but 2 result of continuing complications
- Deaths reported in literature (n=11)
  - 8 in first 60 days
  - 3 >60 days
- 2 Additional Deaths known but not reported to either

“Near Miss” Events Occur in Addition to Reported Complications and Deaths

- 61% of programs included in the survey reported a “near miss event”
- 127 Events in 126 Patients (43 Programs)
- 1% Overall incidence of a “Near Miss” Event ($127/11553=1.1\%$)

So How Do We Perform Live Donor Adult Liver Transplantation with Acceptable Risk?
Ethical considerations

Even in countries with adequate access to DDLT, live liver donation is appropriate due to organ shortages.

Donor safety is of paramount importance in living donor liver transplantation and yet living donor complications and deaths occur even in the most experienced hands (0.1–0.5% mortality, 10–38% morbidity).

“Vancouver Forum” (2006) established practice principles for LDLT:

- Live liver donation should only be performed if the risk to the donor is justified by the expectation of an acceptable outcome in the recipient.

Barr ML et al., Transplantation 2006; 81:1373–85.
## Preventable complications in living liver donors

*Abecassis, et al. AJT 2012*

<table>
<thead>
<tr>
<th>Preventable Complications</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory arrest</td>
<td>Over-sedation (Opioid)</td>
</tr>
<tr>
<td>Pulmonary embolism (PE), Deep vein thrombosis (DVT)</td>
<td>Immobility, No heparin/SCDs</td>
</tr>
<tr>
<td>Neuropraxia</td>
<td>Nerve compression during surgery (positioning)</td>
</tr>
</tbody>
</table>

### Cardiopulmonary
- Pneumothorax
- Pleural effusion
- Pulmonary edema

### Hepatic
- Encephalopathy/hepatic coma
- Ascites
- Liver failure
- Hepatic artery thrombosis
- Portal vein thrombosis
- Inferior vena cava thrombosis

### Other
- Deep vein thrombosis
- Neuropraxia
- Infections

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**CUTTING EDGE OF TRANSPLANTATION 2016**

**RESOLVING THE ORGAN SHORTAGE**

**PRACTICE | POLICY | POLITICS**
Preventable complications and catastrophes are the tip of the iceberg

- For every complication, there are about 100 near miss events that did not lead to a complication.

*Ladner, et al; Liver Transplant, 2013*
Prospective Multimodal Approach to Living Liver Donor Safety

- Learning from the production industry, airline and nuclear power industry we designed a multimodal approach to find vulnerabilities in the delivery of care that occur frequently and are at high risk to lead to preventable complications.
A2ALL SAFETY STUDY

- NIH/NIDDK R01DK090129
- Study Period: 09/01/11 – 05/31/15
- Four Participating A2ALL Transplant Centers (TC):
  - Northwestern University (NU) – Lead TC
    Daniela Ladner, MD and Donna Woods, PhD
  - Columbia University Medical Center
    James Guarrella, MD
  - Lahey Clinical Medical Center
    Elizabeth Pomfret, MD and Mary Ann Simpson, PhD
  - Virginia Commonwealth University
    Robert Fisher, MD
Living Liver Donor Pain Management

- Donors experience pain during hospitalization
  - Experienced pain by donors is significant
    - 73% of patients experience pain scores above 4
    - 49% of patients experience pain scores over 6
    - Pain is worst after day 3

- Pain management associated complications
  - 20% suffer from sequelae of opioid overdose
    - Somnolence (requiring treatment), respiratory events requiring treatment (e.g. reintubation, Narcan)
    - Events primarily within first 24 hours
Evidence-based Donor Pain Management Solution Elements (Opioid sparing)

- **Preoperative Assessment and Management:**
  - Risk factor assessments (e.g. OSA Assessment)
  - Bowel preparation
  - Educational handout on postoperative pain

- **At the end of the case in OR:**
  - Local Anesthetic (TAP block, intrathecal)
  - I.V. Ketorolac (when adequate hemostasis is determined by surgeon and urine output is > 500cc)
  - I.V. Steroids (Dexamethasone or Solumedrol)

- **Postoperative Assessment and Management:**
  - NSAIDS x 72 hours followed by PO cox-inhibitor until discharge
  - Opioids (PCA followed by oral opioids)
  - CO2 monitoring in PACU/ICU for early monitoring of respiratory depression
### Complications* Related to Donor Pain Management (PRE vs POST-Implementation of Opioid Sparing Protocol)

<table>
<thead>
<tr>
<th>CAUSE</th>
<th>PRE (N=90)</th>
<th>POST (N=23)</th>
<th>Change PRE/POST</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>Opioid</td>
<td>41 (46%)</td>
<td>2 (9%)</td>
<td>-37%</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>Opioid</td>
<td>50 (56%)</td>
<td>7 (30%)</td>
<td>-25%</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Pain</td>
<td>25 (28%)</td>
<td>2 (9%)</td>
<td>-19%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Opioid</td>
<td>13 (14%)</td>
<td>0 (0%)</td>
<td>-14%</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>Pain</td>
<td>31 (34%)</td>
<td>4 (17%)</td>
<td>-17%</td>
</tr>
<tr>
<td>Constipation</td>
<td>Opioid</td>
<td>43 (48%)</td>
<td>7 (30%)</td>
<td>-17%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Opioid</td>
<td>13 (14%)</td>
<td>1 (4%)</td>
<td>-10%</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>Steroid</td>
<td>13 (14%)</td>
<td>4 (17%)</td>
<td>3%</td>
</tr>
<tr>
<td>Bradypnea</td>
<td>Opioid</td>
<td>34 (38%)</td>
<td>6 (26%)</td>
<td>-12%</td>
</tr>
<tr>
<td>Nausea</td>
<td>Opioid</td>
<td>55 (61%)</td>
<td>12 (52%)</td>
<td>-9%</td>
</tr>
<tr>
<td>Pruritis</td>
<td>Opioid</td>
<td>19 (21%)</td>
<td>3 (13%)</td>
<td>-8%</td>
</tr>
<tr>
<td>Urinary Retention</td>
<td>Opioid</td>
<td>14 (16%)</td>
<td>3 (13%)</td>
<td>-3%</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>Opioid</td>
<td>8 (9%)</td>
<td>2 (9%)</td>
<td>-0.19%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Pain</td>
<td>23 (26%)</td>
<td>7 (30%)</td>
<td>5%</td>
</tr>
</tbody>
</table>

* Verified by Medical Monitor
Living Donor Pain; Likert Scale (0-10): PRE (N=90) and POST (N=23) Comparison

<table>
<thead>
<tr>
<th>PAIN</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRE</td>
<td>41%</td>
<td>56%</td>
<td>41%</td>
<td>45%</td>
<td>60%</td>
<td>57%</td>
<td>55%</td>
<td>50%</td>
<td>55%</td>
</tr>
<tr>
<td>POST</td>
<td>35%</td>
<td>30%</td>
<td>30%</td>
<td>38%</td>
<td>38%</td>
<td>29%</td>
<td>50%</td>
<td>33%</td>
<td>50%</td>
</tr>
</tbody>
</table>
Conclusion

• The most effective way to improve living donor safety is to **prevent preventable complications**

• ~50% of complications are preventable

• Near miss events are 100 x more frequent than preventable complications

• We can learn from other industries, even if they are less complex than medicine (proactive and prospective)
Recipient Outcomes
Background

- Living donor liver transplantation (LDLT) provides an important surgical option for end-stage liver disease

- Initial outcomes demonstrated inferior post-transplant results compared to deceased donor liver transplantation (DDLT)
  - Centers with < 20 associated with 83% higher risk of graft failure ($p<0.0045$)
    - Olthoff et al, Ann Surg 2005

- Advantage of LDLT over DDLT related to decreased death on the waitlist due to more timely transplantation, regardless of MELD score
  - Berg et al, Gastroenterology 2007
  - Berg et al, Hepatology 2011
Cumulative Risk of Death After Initial LD Evaluation for Patients Undergoing LDLT vs. DDLT Stratified by Center Experience

Adjusted for age, MELD score and HCC

Berg et al, Hepatology 2011
Defining Long-term Outcomes With Living Donor Liver Transplantation in North America


Ann Surg

Study Population

• 1600 completed transplants enrolled in A2ALL between 1/1/1998 – 1/31/2014
  – All patients had a living donor evaluated, but some ultimately received a DDLT
  – 173 LDLT “learning curve” cases excluded
    • First 20 at each A2ALL-1 institution*
    • A2ALL-2 centers contributed transplants occurring after 8/31/2009, by which time each had completed > 20 LDLT cases

• 1427 completed transplants analyzed
  – 963 living donor recipients
  – 464 deceased donor recipients

## Recipient Characteristics:

### Demographics

<table>
<thead>
<tr>
<th></th>
<th>DDLT (n=464)</th>
<th>LDLT (n=963)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>87</td>
<td>126</td>
<td>0.005</td>
</tr>
<tr>
<td>White</td>
<td>390</td>
<td>877</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black</td>
<td>33</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>17</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Other race</td>
<td>24</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td><strong>Diagnosis (multiple diagnoses possible)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC</td>
<td>98</td>
<td>154</td>
<td>0.02</td>
</tr>
<tr>
<td>HCV</td>
<td>210</td>
<td>339</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PBC</td>
<td>12</td>
<td>81</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Other diagnosis</td>
<td>21</td>
<td>90</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Age, Female, BMI, Additional Diagnoses (Acute Liver Failure, Alcohol-related Cirrhosis, Autoimmune Hepatitis, Cryptogenic Cirrhosis, Hemochromatosis, Other Metabolic Liver Disease, Malignancy other than HCC, and PSC) were not significantly different between DDLT and LDLT. Olthoff K, et al Ann Surg 2015; 262(3):465-75
Recipient Characteristics:

Disease Severity

At evaluation (p<0.001)

P< 0.001

## Perioperative Characteristics

<table>
<thead>
<tr>
<th></th>
<th>DDLT</th>
<th>LDLT</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of surgery (hrs)</strong></td>
<td>5.78 (5-7)</td>
<td>7.57 (7-9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Total ischemia time (mins)</strong></td>
<td>486.50 (364-600)</td>
<td>98.00 (71-140)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>PRBCs (units)</strong></td>
<td>6.00 (3-11)</td>
<td>4.00 (2-8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Recipient ICU LOS (days)</strong></td>
<td>2.00 (1-5)</td>
<td>2.00 (1-3)</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Recipient total LOS (days)</strong></td>
<td>10.00 (7-17)</td>
<td>10.00 (7-15)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

*Collected in A2ALL-1 only

PRBC = packed red blood cells; ICU = intensive care unit; LOS = length of stay

*Adjusted model shows survival curves for 53 year old male patient without non-HCC malignancy or PSC, not dialysis at transplant, MELD of 16, and received a liver from a donor under 50 years old.

*Adjusted model shows survival curves for a 53 year old patient without autoimmune hepatitis, HCC, or PSC, a MELD of 16 at transplant, not on dialysis at transplant, and received a liver from a donor under 50 years old.

Primary Causes of Death

- Malignancy: DDLT 16, LDLT 32
  - Infection/Sepsis: DDLT 29, LDLT 31
  - Pulmonary: DDLT 7, LDLT 16
  - Graft Failure: DDLT 21, LDLT 14

- MSOF: DDLT 14, LDLT 14
- Cardiovascular: DDLT 20, LDLT 22
- Other Causes: DDLT 15, LDLT 22
- Unknown Cause: DDLT 24, LDLT 24

Cumulative incidence (%)

Time since transplant (years)

- DDLT (n=146 deaths)
- LDLT (n=175 deaths)

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# Predictors of Mortality

## Combined Model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hazard Ratio (HR)</th>
<th>95% Lower CI for HR</th>
<th>95% Upper CI for HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDLT vs. DDLT</td>
<td>0.98</td>
<td>0.77</td>
<td>1.27</td>
<td>0.90</td>
</tr>
<tr>
<td>Female vs. male</td>
<td>0.74</td>
<td>0.58</td>
<td>0.94</td>
<td>0.01</td>
</tr>
<tr>
<td>Recipient diagnosis: malignancy other than HCC</td>
<td>2.16</td>
<td>1.13</td>
<td>4.11</td>
<td>0.02</td>
</tr>
<tr>
<td>Recipient diagnosis: PSC</td>
<td>0.45</td>
<td>0.30</td>
<td>0.69</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>On dialysis at transplant</td>
<td>3.59</td>
<td>2.05</td>
<td>6.28</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Recipient age at transplant (per 10 years), &lt; 55</td>
<td>1.20</td>
<td>1.00</td>
<td>1.44</td>
<td>0.05</td>
</tr>
<tr>
<td>Recipient age at transplant (per 10 years), &gt; 55</td>
<td>1.65</td>
<td>1.27</td>
<td>2.15</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Donor age &gt; 50 vs. &lt; 50</td>
<td>1.49</td>
<td>1.14</td>
<td>1.94</td>
<td>0.003</td>
</tr>
<tr>
<td>MELD at transplant (per 5 points)</td>
<td>1.06</td>
<td>0.98</td>
<td>1.16</td>
<td>0.15</td>
</tr>
</tbody>
</table>

*Variables tested for inclusion: Recipient age, gender, race, ethnicity, BMI, diagnosis, medical severity at transplant (on ventilator or on dialysis), MELD at transplant, cold ischemia time, donor age, and donor type.

## Predictors of Graft Failure

### Combined Model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hazard Ratio (HR)</th>
<th>95% Lower CI for HR</th>
<th>95% Upper CI for HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDLT vs. DDLT</td>
<td>1.09</td>
<td>0.87</td>
<td>1.37</td>
<td>0.44</td>
</tr>
<tr>
<td>Recipient diagnosis: autoimmune hepatitis</td>
<td>0.44</td>
<td>0.24</td>
<td>0.82</td>
<td>0.009</td>
</tr>
<tr>
<td>Recipient diagnosis: HCC</td>
<td>1.32</td>
<td>1.01</td>
<td>1.73</td>
<td>0.05</td>
</tr>
<tr>
<td>Recipient diagnosis: PSC</td>
<td>0.66</td>
<td>0.47</td>
<td>0.93</td>
<td>0.02</td>
</tr>
<tr>
<td>On dialysis at transplant</td>
<td>2.54</td>
<td>1.50</td>
<td>4.31</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Recipient age at transplant (per 10 years), &lt; 55</td>
<td>1.03</td>
<td>0.89</td>
<td>1.19</td>
<td>0.71</td>
</tr>
<tr>
<td>Recipient age at transplant (per 10 years), &gt; 55</td>
<td>1.39</td>
<td>1.08</td>
<td>1.78</td>
<td>0.009</td>
</tr>
<tr>
<td>Donor age &gt; 50 vs. &lt; 50</td>
<td>1.52</td>
<td>1.20</td>
<td>1.93</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MELD at transplant</td>
<td>1.09</td>
<td>1.00</td>
<td>1.17</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Variables tested for inclusion: Recipient age, gender, race, ethnicity, BMI, diagnosis, medical severity at transplant (on ventilator or on dialysis), MELD at transplant, cold ischemia time, donor age, and donor type.

Variables Impacting Mortality

Separate Model

Female vs. Male
Hispanic vs. Non-hispanic
PSC
HCC
Non-HCC malignancy
On dialysis
Recipient age (per 10 yrs), <55
Recipient age (per 10 yrs), >55
Donor age > 50 vs. < 50
MELD (per 5 points)

Hazard Ratio (log scale)

p-value

DDLT

LDLT

0.24

0.07

0.45

0.21

0.32

0.64

0.79

0.82

0.79

0.68
Variables Impacting Graft Failure

Separate Model


<table>
<thead>
<tr>
<th>Variable</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female vs. Male</td>
<td>0.09</td>
</tr>
<tr>
<td>Hispanic vs. Non-hispanic</td>
<td>0.09</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>0.51</td>
</tr>
<tr>
<td>PSC</td>
<td>0.31</td>
</tr>
<tr>
<td>HCC</td>
<td>0.34</td>
</tr>
<tr>
<td>On dialysis</td>
<td>0.76</td>
</tr>
<tr>
<td>Recipient age (per 10 yrs), &lt;55</td>
<td>0.99</td>
</tr>
<tr>
<td>Recipient age (per 10 yrs), &gt;55</td>
<td>0.84</td>
</tr>
<tr>
<td>Donor age &gt; 50 vs. &lt; 50</td>
<td>0.94</td>
</tr>
<tr>
<td>MELD (per 5 points)</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Hazard Ratio (log scale)
Variables **Not** Impacting Mortality

- Era of transplant
- Year of transplant
- Right vs left lobe
- Time on waitlist

Summary

• Patients receiving LDLT have lower disease severity than those receiving DDLT resulting in better overall unadjusted survival

• Long-term adjusted post-transplant outcomes for recipients of DDLT and LDLT are comparable

• LDLT and DDLT have similar causes of death, but more graft loss due to death with DDLT
Implications

- LDLT provides significant benefit, allowing transplantation at lower MELD score, decreased death on the waitlist, and equivalent post-transplant survival to DDLT

- Accumulated data from 12 centers over 15 years demonstrates compelling reasons to consider LDLT for appropriate recipients

- Decreasing donor risk must remain central to any efforts to increase LDLT