Adult Living Donor Liver Transplantation
Why, How & What (Outcomes)...

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Disclosures

- Advisory boards:
  Boston Scientific
  Mallinckrodt Pharma
  Rebiotix Inc

- Speaker’s bureau
  Intercept Pharma
  Eisai Co.
Objectives

- Promote Awareness of LDLT as an option for liver transplant candidates
- Familiarize participants with the process of donor evaluation
- Explore the implications of LDLT on both recipients and donors
Outline

- **Introduction**
  - Why Living Donor Liver Transplantation (LDLT)?

- **Evaluation**
  - Living Donors
    - Recipient & Donor Factors
  - Donor Evaluation

- **Recipient Outcomes**

- **Donor Outcomes**
  - Medical
  - Psychosocial

- **Challenges & Controversies**
Living Donor Liver Transplantation - Why?

"GOOD NEWS AND BAD—FIRST, THE GOOD... WE CAN USE YOU AS SPARE PARTS FOR OTHER PEOPLE."
Deceased donor liver transplantation (DDLT) yields excellent long-term outcomes → Optimal Treatment
- Patient survival: 91.5% at 1-year & 85% at 5-years

Growing discrepancy between # patients on waiting list & availability of deceased donor organs.
Deceased donor Organ Donor Rates

Number of people donating organs per million population (2002)

Spain > Austria > Portugal > Belgium > US > Ireland > France > Italy > Finland > Norway > Denmark > Canada > UK > Poland > Netherlands > Germany > Sweden > Australia > Switzerland > Israel > New Zealand > Japan
• Taiwan and Korea have the highest number of LDLT
• Late legislation on brain death
• Lack of dedicated resources for organ recovery
Liver Transplantation in 2017

(Petrowsky Curr Opin Organ Transplant 2019, 24: 620-622)
Adult LDLT Contribution Toronto: 25 – 35%
~ 5% of Liver Transplants are LDLT in US

Liver Transplant - USA

US OPTN Data
Abu-Gazala and Olthoff, Gastroenterol Clin N Am 2018: 297-311
Living Donation – Children

- Feasibility demonstrated in 1989 in US
  - Recipient child with mother as donor

- Very successful
  - Survival 92% at 1 year & 89% at 5 years

- Donors have few complications
  - Left lateral segment or left lobe (30 – 40% liver volume)

- Ethically accepted
Living Donation – Adults

- Expanded to adult-to-adult living donor liver transplantation (LDLT) in 1994
  - First adult-to-adult LD liver transplant in 1998 in the US
  - >4500 pts in 89 US centers
  - Right lobe donation (60% liver volume)
  - Excellent and comparable post-transplant survival outcomes to DDLT
Right lobe donation involves removing segments 5, 6, 7, and 8. Left lateral segment donation involves removing segments 2 and 3. Left lobe donation involves removing segments 2, 3, and 4. The liver grows back to its normal size in about 6 weeks.

Artist: Stephen Maider. © Copyright 2003. Property of UHN. This graphic cannot be reproduced or used for other purpose without permission.
Liver Regeneration
- Grafts ↑ by 60 – 200% within 1 month & approximate standard liver volume by 2 months\(^1\)

Immunologic Tolerance - ↑HLA matching in related
- Rejection reduced (?)
- Disease recurrence more aggressive (?)
  - Viral
  - Autoimmune
- Graft vs. Host Disease increased in perfect HLA matching (?)
- HCC

\(^1\)Haga et al. Liver Transpl. 2008
Recipient Survival: 1-Year

![Graph showing one year unadjusted patient survival by year for living and deceased donor liver transplants. The graph indicates a trend of increasing survival rates over the years, with living donors generally having a higher survival rate compared to deceased donors. The source is the OPTN/SRTR Annual Report Tables 1.12b.]
LDLT vs. DDLT
Patient Survival Mar 2000 – Sept 2005

N = 124 LD vs. 374 DD
A2ALL study

- Launched in 2002 with NIH funding
- 9 North American Centers with 3 more added in 2009
- Data from 2742 donors and 2182 recipients
- 41 publications
A2ALL findings

- Learning curve with more graft and patient losses in first 15-20 procedures
- A2ALL vs non A2ALL centers
- 9 centers, 702 LDLT vs 67 centers, 1664 LDLT
- Similar outcomes
- Currently LDLT concentrated in a few centers across the country
- only 12 centers perform > 10 LDLTs in 2016
Benefit of LDLT to Recipient – Shorter Wait-Time

- Wait-list mortality demonstrated\(^1\)
  - 1-year survival \textit{from time of listing} – 90% RLDLT vs. 80% DDLT/Waiting List group (p<0.001)

Shah et al. AJT 2007
• 1998-2003 = 4.4 year follow up
• Superior survival in LDLT compared with DDLT or waiting
• 807 potential candidates = 389 LDLT vs 249 DDLT
• Reduction in transplant recipient mortality

• A2ALL Berg CL, Gastroenterology 2007
A2ALL confirmed similar survival benefit from LDLT compared with DDLT

Female sex, PSC, autoimmune hepatitis associated with better graft survival

Survival benefit in pts with MELD scores < 15 unless HCC was present
Higher HCC recurrence rates in LDLT
38% vs 11%, $p = 0.0004$
But similar when adjusted for tumor characteristics

*Kulik et al Am J Transplant 2012; 12: 2997-3007*
# Recipient Complications

## Table 1
Probability of specific complications in recipients of living or deceased donor liver transplantation

<table>
<thead>
<tr>
<th>Complication</th>
<th>Overall Complication Rate</th>
<th>Log-Rank P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Significantly higher in LDLT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bile leak or biloma</td>
<td>0.26</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blood infection</td>
<td>0.26</td>
<td>0.0091</td>
</tr>
<tr>
<td>Biliary stricture</td>
<td>0.32</td>
<td>0.0002</td>
</tr>
<tr>
<td>Biliary tree infection</td>
<td>0.14</td>
<td>0.0062</td>
</tr>
<tr>
<td>Hepatic artery thrombosis</td>
<td>0.06</td>
<td>0.0378</td>
</tr>
<tr>
<td><strong>Significantly higher in DDLT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>0.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ascites</td>
<td>0.21</td>
<td>0.0151</td>
</tr>
<tr>
<td>Cardiac complication</td>
<td>0.02</td>
<td>0.0008</td>
</tr>
<tr>
<td>Intraabdominal bleeding</td>
<td>0.05</td>
<td>0.0190</td>
</tr>
</tbody>
</table>

Unique complications

- Small for size syndrome: jaundice/ascites/renal insufficiency
- Small graft is unable to meet metabolic demand
- Sustains damage from hyperperfusion due to portal hypertension
- Size of graft 0.6% of total body weight (ideally 0.8%)
LDLT – How Much, Who & How?

‘A Father Gives a Son Life
A Son Gives a Father Life’
Living Donor Selection & Evaluation

- Option of living donation discussed with recipient

- Recipient suitability for LDLT established at listing

- Stepwise evaluation process – After recipient listed on deceased donor list
  - Donors age 18 – 60 & Blood Group Compatibility
  - Ability to stop work/studies for an average of 12 weeks
  - 4-8 weeks
  - Donor may confidentially withdraw at any stage
Living Donor Evaluation
“Donor Safety Trumps Recipient Need”

Donor Identification & Health History
- Screen – Physical, Mental & Social
- Blood Type

Preliminary Physical Work-up
- Labs
- Infections
- ECG, CXR

Liver Function & Anatomy
- U/S, CT, MRI
- Liver Volume
- Vasculature
- Cholangiogram
- +/- Liver Biopsy

Consultations
- Independent Medical Team
- Psychiatrist/SW
- Surgeon(s)
- Additional

INFORMED CONSENT
Potential Living Donors – Not All Recipients Equal...

Donor Identification & Health History

≥ 1 POTENTIAL LIVING DONOR IN ~ 35%

Preliminary Physical Work-up
- Labs
- Infections
- ECG, CXR

Liver Function & Anatomy
- U/S, CT, MRI
- Liver Volume
- Vasculature
- CT Cholangiogram
- +/- Liver Biopsy

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- Additional

INFORMED CONSENT
Predictors of Having a Potential Live Donor
Recipient & Donor Factors

<table>
<thead>
<tr>
<th>Recipient Factors</th>
<th>Donor Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>Mean age 37 years</td>
</tr>
<tr>
<td>Female</td>
<td>Males 56%/Females 44%</td>
</tr>
<tr>
<td>Lower BMI</td>
<td>Caucasian or Hispanic 90% (US)</td>
</tr>
<tr>
<td>More Likely...Hepatitis C, HCC, Cholestatic Disorders</td>
<td>Relationship to Donor... Offspring (31%), Sibling (21%), Parent (3%), Other Biological (9%), Spouse (9%), Other Non-Biological (22%)</td>
</tr>
<tr>
<td>Less likely...Alcoholic Liver Disease, Acute Liver Failure</td>
<td></td>
</tr>
<tr>
<td>History of Variceal Bleed</td>
<td></td>
</tr>
</tbody>
</table>

Trotter et al. Hepatology 2007
Rudow et al. Liver Transpl. 2003

Trotter et al. Hepatology 2007
...this next organ, ladies, is a beautiful, healthy liver. Notice its reddish-brown colouration and lack of fat deposits...

Ooohh! That'll go nice with my new kidney!
Donor Identification & Health History
- Screen – Physical, Mental & Social
- Blood Type

Preliminary Physical Work-up
- Labs
- Infections
- ECG, CXR

Liver Function & Anatomy
- U/S, CT, MRI
- Liver Volume
- Vasculature
- Cholangiogram
- +/- Liver Biopsy

Consultations
- Independent Medical Team
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- Surgeon(s)
- Additional

INFORMED CONSENT

On average **at least 4 donors** start evaluation for each donor hepatectomy performed

UHN 24%
(14 – 40%)
# Reasons for Donor Exclusion

Table 3. Disposition of A2ALL Potential Donors (n = 1011)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potential Donors Who Were Not Accepted</strong></td>
<td></td>
</tr>
<tr>
<td>Donor-related reasons</td>
<td></td>
</tr>
<tr>
<td>Medical contraindications</td>
<td>173 (17%)</td>
</tr>
<tr>
<td>Anatomical contraindications</td>
<td>115 (11%)</td>
</tr>
<tr>
<td>Donor liver steatosis</td>
<td>65 (6%)</td>
</tr>
<tr>
<td>Declined to donate</td>
<td>68 (7%)</td>
</tr>
<tr>
<td>Psychosocial contraindications</td>
<td>55 (5%)</td>
</tr>
<tr>
<td>Recipient-related reasons</td>
<td></td>
</tr>
<tr>
<td>Recipient received DDLT</td>
<td>65 (6%)</td>
</tr>
<tr>
<td>Recipient died</td>
<td>24 (2%)</td>
</tr>
<tr>
<td>Recipient too sick/removed from transplant consideration</td>
<td>19 (2%)</td>
</tr>
<tr>
<td>Recipient improved</td>
<td>8 (1%)</td>
</tr>
<tr>
<td>Recipient declined/refused organ</td>
<td>5 (&lt;1%)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>9 (1%)</td>
</tr>
<tr>
<td><strong>Potential donors who were accepted</strong></td>
<td></td>
</tr>
<tr>
<td>Successful donation</td>
<td>392 (39%)</td>
</tr>
<tr>
<td>Went to operating room but procedure aborted</td>
<td>12 (1%)</td>
</tr>
<tr>
<td>Graft resected but not transplanted</td>
<td>1 (&lt;1%)</td>
</tr>
</tbody>
</table>
Donor steatosis and age

- Short term reduction in body weight can resolve donor steatosis
  
  *Hwang S Liver Transp 2004 10(6)*

- Age> 50- limited regeneration liver capacity
Predictors of Candidate acceptance

- Young donor age, lower BMI, biological/spousal relationship\(^1\)
- Day from recipient listing to 1\textsuperscript{st} donor evaluation < 23 days\(^1\)
- Low recipient MELD score (\(\leq 20\))\(^1\)
- Center of Evaluation\(^1\)
- Higher Education & Part-Time Employment in donor (?)\(^2\)

\(^1\)Trotter et al. Hepatology 2007
\(^2\)Verna et al. Am J Transpl 2005
Donor Outcomes

- Medical
  - Mortality
  - Morbidity

- Psychosocial
Donor Mortality

- 0.3% or 1 in 300 (Right Lobe)

- Worldwide
  - Systematic Review: 0.23 – 0.5%\(^1\)
  - 35 donor deaths\(^2\)

- Causes
  - Sepsis, PE, Bleeding

\(^1\) Middleton et al. Liver Transpl. 2006
\(^2\) Ringe & Strong. Transpl 2008
## Donor complications

<table>
<thead>
<tr>
<th>A2ALL Study, Year of Publication</th>
<th>Number of Donors Who Successfully Donated</th>
<th>Reported Common Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghobrial et al, 2008</td>
<td>393</td>
<td>- Bacterial infections (12%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Biliary leaks (9%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Incisional hernias (6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Pleural effusions requiring intervention (5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Neuropraxia (4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Wound infections (3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Reexplorations (3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Intraabdominal abscess (2%)</td>
</tr>
<tr>
<td>Abecassis et al, 2012</td>
<td>740</td>
<td>- Bacterial infections (12.5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Biliary complications (9.7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Intraoperative complications (6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Incisional hernias (5.6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Pleural effusions (5.3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Psychological difficulties (4.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Reexplorations (3%)</td>
</tr>
</tbody>
</table>
### Donor Morbidity
#### Clavien Grading of Severity

<table>
<thead>
<tr>
<th>Grade</th>
<th>Negative Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Any alteration from ideal postoperative course with complete recovery, not requiring significant intervention</td>
</tr>
<tr>
<td>2</td>
<td>Requiring significant intervention or potentially life-threatening, but without residual disability or persistent disease</td>
</tr>
<tr>
<td>3</td>
<td>Any complication with residual or lasting functional disability or development of malignant disease</td>
</tr>
<tr>
<td>4</td>
<td>Complications that lead to re-transplantation (4a) or death (4b)</td>
</tr>
</tbody>
</table>
Donor Morbidity → High!

  - 405 right lobe donors
  - 38% had complications
    - 21% 1 complication, 17% ≥2 complications

- **University of Toronto (2000 – 2008)**
  - n = 202; 1st right lobe living donors
  - 40% had complications during 1st year of follow-up
    - Grade 1 – 21 (10%)
    - Grade 2 – 27 (13%)
    - Grade 3 – 32 (16%)
    - Grade 4 – 0%

1Ghobrial et al. Gastro 2008
2Adcock et al. Am J Transpl 2010
## Early Post-Operative Complications (< 30 days)

<table>
<thead>
<tr>
<th>Complication</th>
<th>N = 202</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-phrenic/pleural effusions</td>
<td>6%</td>
</tr>
<tr>
<td>UTI</td>
<td>4%</td>
</tr>
<tr>
<td>Bleeding (re-operation)</td>
<td>3%</td>
</tr>
<tr>
<td>Wound infection</td>
<td>3%</td>
</tr>
<tr>
<td>Bile leak</td>
<td>3%</td>
</tr>
<tr>
<td>Fascial separation</td>
<td>2%</td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>1%</td>
</tr>
<tr>
<td>Other</td>
<td>6%</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>28%</strong></td>
</tr>
</tbody>
</table>

**Mean Donor Length of Hospital Stay – 7 days**

Adcock et al. Am J Transpl 2010
## Late Post-Operative Complications ( > 30 days)

<table>
<thead>
<tr>
<th>Complication</th>
<th>N = 202 (median f/u 25 mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental health issues</td>
<td>4%</td>
</tr>
<tr>
<td>Incisional hernia &amp; repair</td>
<td>3%</td>
</tr>
<tr>
<td>Keloids</td>
<td>2%</td>
</tr>
<tr>
<td>Small bowel obstruction</td>
<td>2%</td>
</tr>
<tr>
<td>Pulmonary emboli &amp; DVT</td>
<td>1%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1%</td>
</tr>
<tr>
<td>Wound infection</td>
<td>1%</td>
</tr>
<tr>
<td>Pleural effusions</td>
<td>0.5%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>14.5%</td>
</tr>
</tbody>
</table>

Adcock et al. Am J Transpl 2010
Donor Outcomes – Psychosocial

- Physical Domain
- Mental Domain
  - Overall
  - Cosmesis
- Social
  - Relationship with recipient
  - Vocational
  - Financial
- Attitudes
Physical & Mental Domains

- **Physical**
  - Better physical SF-36 scores than Canadian norms\(^1\)
  - 54% experienced more pain than expected\(^1\)
  - 71% mild ongoing abdominal symptoms $\rightarrow$ 29% saw a physician\(^2\)

- **Mental**
  - Better or equivalent mental SF-36 scores than Canadian norms\(^1\)
  - Improved self-esteem\(^3\)
  - Predictors of poor outcome\(^1\)
    - Younger age
    - Psychiatric diagnosis
    - Greater pre-donation self-related concerns
    - Recipient engaged in risky behaviour
    - Graduate degree
    - Income < $99,000/year

\(^1\)Dubay et al. Am J Transpl. 2009
\(^2\)Trotter et al. Liver Transpl. 2001
\(^3\)Schulz et al. Liver Transpl. 2009
Cosmesis & Body Image

- “Change” in body image in up to 42%\(^1\)
- Worse body image & cosmetic satisfaction than open nephrectomy\(^2\)
  - Associated with lower physical & mental (SF-36) and spousal relationship and sex life
- Predictors
  - Younger age
  - Greater pre-donation self-related concerns
  - Recipient engaged in risky behaviour

\(^1\)Trotter et al. Liver Transpl. 2001
\(^2\)Dubay et al. Transpl. 2010
Social Domain & Attitudes

- **Relationship with recipient**
  - 51% better & 45% no change

- **Return to pre-donation job or studies**
  - 96 – 100%
    - Range 2 – 24 weeks (median 12 weeks)
  - 21% changed or modified their work

- **Financial**
  - Mean out of pocket expenses $3660 US

- **Attitudes**
  - 80% would go through it again

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1 Holtzman et al. Liver Transpl. 2009
3 Trotter et al. Liver Transpl. 2001
LDLT – Challenges & Controversies

- Acute Liver Failure & Expedited Donor Work-Up
- Anonymous Living Donation
Acute Liver Failure & Expedited Donor Work-Up

- University of Toronto
  - April 2006 1st case
  - 7 patients listed & donors assessed
    - 4 right-lobe LDLT (friend, sibling, daughter, son)
  - Average evaluation time = 21 hours
  - Resource intensive & stressful!

- Importance of face-to-face team conference:
  - Prior to donor transfer to the OR
  - Review checklist, sign-off
Anonymous Living Liver Donors

- University of Toronto
  - 29 Potential Donors
    - Strong rationale
    - History of social altruism
    - Strong social support
    - Willingness to maintain confidentiality
  - 17 Rejected
    - Decision (7), medical (5), anatomy (3), breath of confidentiality (2)
  - 12 Accepted
    - 7 LL (Pediatric) & 5 RL (Adult)
    - 6 initiated contact with recipient
    - 2 contacted media > 1 year later

Reichman et al. Am J Transpl. 2010
Take Home Points...

ADULT LDLT
LDLT – Why?

- Organ shortage
- High wait-list mortality
- Reduction in wait-list mortality primary benefit to recipients
LDLT – How Much, Who & How?

- Comprises a small percentage of liver transplant activity at Ochsner

- Potential Donor may not be related
  - Offspring, Sibling, Spouse, FRIENDS

- Comprehensive evaluation to determine donor suitability
  - Medical, Anatomical & Psychosocial

- On average, 4 donors enter evaluation for every donor hepatectomy performed
LDLT Outcomes

- **Recipient**
  - Comparable survival to DDLT
  - Higher risk of surgical complications
    - Biliary > Vascular

- **Donor**
  - Mortality ~ 1/300
  - Medical complications frequent (~ 40%)
    - Mostly minor & early
  - Psychosocial impact includes physical, mental, body image, and social domains

- LDLT for acute liver failure feasible but challenging

- Anonymous donation evaluation focused on donor motivation