LDLT for Higher Risk Recipients: Who decides what benefit is acceptable, what should the recipient be told, what if the graft fails?

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Disclosure
none
Learning Objectives

1. Define a “high-risk” LDLT recipient
2. Describe the role and limitations of LDLT in “high-risk” recipients
3. Discuss the requirements to perform LDLT in “high-risk” recipients
LDLT: Brief history

• 1981  Bismuth – reduced size LT
• 1988  Pichlmayr – split LT
• 1989  Strong- Pediatric LDLT- left lateral segment
• 1993  Makuuchi- Adult LDLT- Left lobe
• 1996  Fan- Adult LDLT- Right lobe
• 2000  Lee- Dual LDLT
Rationale of LDLT

- Liver segments regenerate; donor recovers fully
- Transplanting a liver segment restores function in the recipient
- The principles of beneficence, autonomy, and justice provide the ethical underpinning of the procedure
Absolute numbers of Liver transplants from DD, from LD and Domino. Percentage of LD. Global data. 2011-2017

<table>
<thead>
<tr>
<th>Year</th>
<th>LD</th>
<th>DD</th>
<th>Domino</th>
<th>% LD</th>
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<tbody>
<tr>
<td>2011</td>
<td>51</td>
<td>19510</td>
<td>4211</td>
<td>17.7</td>
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<tr>
<td>2012</td>
<td>50</td>
<td>19562</td>
<td>4376</td>
<td>18.2</td>
</tr>
<tr>
<td>2013</td>
<td>51</td>
<td>20038</td>
<td>4562</td>
<td>18.2</td>
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<tr>
<td>2014</td>
<td>47</td>
<td>20845</td>
<td>5168</td>
<td>19.8</td>
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<tr>
<td>2015</td>
<td>59</td>
<td>21808</td>
<td>5824</td>
<td>21.0</td>
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<tr>
<td>2016</td>
<td>56</td>
<td>24292</td>
<td>6012</td>
<td>19.8</td>
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<tr>
<td>2017</td>
<td>53</td>
<td>26142</td>
<td>6153</td>
<td>19.0</td>
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</tbody>
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23,727 → 32,348
LDLT in USA

MELD

10.1%


Number of LDLT

150 300 450 600

0 5.9%

7.1%
Advantages of LDLT

- Shorter wait-time
- Lower wait-list mortality
- Higher quality graft
- Transplant before patient is too “sick”

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The Ultimate Sacrifice

A healthy man gives his brother half his liver—and dies. Should this kind of transplant be allowed?

By CHRISTINE GORMAN

Mike and Adam Hurwitz grew up together on Long Island, in the suburbs of New York City. They were very close, even for brothers. So when Adam’s liver started failing, Mike offered to give him half of his. The operation saved Adam’s life. But Mike, who went into the hospital in seemingly excellent health, developed a complication—perhaps a blood clot—and died last week. He was 57.

Mike Hurwitz’s death has prompted a lot of soul searching in the transplant community. Was it a tragic fluke or a sign that transplant surgery has reached some kind of ethical limit? The Mount Sinai Medical Center, which performed the operation, said no. But others are not so sure. "There really is very little margin for error," says Dr. John Fung, chair of transplantation at the University of Pittsburgh Medical Center. "If the rates stay at 1%, it's just not going to be accepted."

On the other hand, there’s an acute shortage of traditional donor organs from people who have died in accidents or suffered fatal heart attacks. If family members fully understand the risks and are willing to take them, says Dr. Fung. By way of analogy, he suggests, think of a tree. "An adult-to-child living donor transplant is like cutting off a limb. With an adult-to-adult transplant, you're splitting the trunk in half and trying to keep both halves alive."

Even if a potential donor understands and accepts these risks, that doesn’t necessarily mean the operation should proceed. All sorts of subtle pressures can be brought to bear on such a decision, says Dr. Mark Siegel, director of the MacLean Center for Clinical Medical Ethics at the University of Chicago. "Sometimes the sicker the patient, the greater the pressure and the more willing the donor will be to accept risks. If you feel you can’t say no, is your decision truly voluntary? And if not, is the medical community’s responsibility to save you from your own best intentions?"

Transplant centers have developed screening programs to ensure that living donors fully understand the nature of their decision. But still, for the most part, the larger issue of just how much a volunteer should be allowed to sacrifice to save another human being. So far, we seem to be saying some risk is acceptable, although we still have a lot to learn about where the limits are.

however, is a lot trickier than one to transplant a kidney. Not only is the liver packed with blood vessels, but it also makes lots of proteins that need to be produced in the right ratios for the body to survive. When organs from the recently deceased are used, the surgian gets to pick which part of the donated liver is the best—and to take as much of it as is needed. Assuming all goes well, a healthy liver can grow back whatever portion of the organ is missing, sometimes within a month.

A living-donor transplant works particularly well when an adult donates a medical portion of the liver to a child. Usually only the left lobe of the organ is required, leading to a mortality rate for living donors in the neighborhood of 1 in 500 to 1 in 1,000. But when the recipient is another adult, as much as 60% of the donor’s liver has to be removed. "There really is very little margin for error," says Dr. Fung. By way of analogy, he suggests, think of a tree. "An adult-to-child living donor transplant is like cutting off a limb. With an adult-to-adult transplant, you’re splitting the trunk in half and trying to keep both halves alive."

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Time Magazine  January 28, 2002
Living Liver Donation

Recipient benefit  Donor risk

It’s all about Safety
Misconception

LDLT is reserved for low-risk recipients
Who is a high risk recipient?

**Patient-related:** high MELD, hepatorenal syndrome, fulminant liver failure

**Graft-related:** GRWR < 0.8, poor venous outflow, severe portal hypertension, steatosis, donor age

**Disease-related:** HCC beyond Milan/UCSF; cholangiocarcinoma, colorectal liver metastases
What is a “reasonable” benchmark for patient/graft survival in LDLT?

• Same as DDLT?
• Can it be reduced?
• Where should we draw the line?
Who decides?

- Recipient
- Donor
- Transplant team
- Bioethicist
- 3rd party
- National/International organizations
High MELD LDLT Recipients

Selzner et al. Annals of Surgery 2010
# LDLT for hepatorenal syndrome

<table>
<thead>
<tr>
<th></th>
<th>DDLT (n = 90)</th>
<th>LDLT (n = 30)</th>
<th>p</th>
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<tbody>
<tr>
<td>Age (years) (^1)</td>
<td>53 (±11)</td>
<td>50 (±11)</td>
<td>0.38</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>60 (67)</td>
<td>24 (80)</td>
<td>0.25</td>
</tr>
<tr>
<td>BMI</td>
<td>30 (±6.6)</td>
<td>29 (±5.7)</td>
<td>0.61</td>
</tr>
<tr>
<td>INR (^1)</td>
<td>2.60 (±1.27)</td>
<td>2.52 (±1.28)</td>
<td>0.66</td>
</tr>
<tr>
<td>Creatinine (mg/dL) (^1)</td>
<td>2.99 (±1.55)</td>
<td>2.80 (±1.69)</td>
<td>0.21</td>
</tr>
<tr>
<td>Bilirubin (mg/dL) (^1)</td>
<td>16.49 (±16.78)</td>
<td>18.94 (±18.01)</td>
<td>0.6</td>
</tr>
<tr>
<td>MELD at listing (^1)</td>
<td>24 (±9)</td>
<td>20 (±8)</td>
<td>0.07</td>
</tr>
<tr>
<td>MELD at transplant (^1)</td>
<td>32 (±6.7)</td>
<td>31 (±7.3)</td>
<td>0.58</td>
</tr>
<tr>
<td>Pretransplant dialysis (%)</td>
<td>30 (33)</td>
<td>10 (33)</td>
<td>1</td>
</tr>
<tr>
<td>Pretransplant dialysis (days) (^1)</td>
<td>5 (±11)</td>
<td>3 (±9)</td>
<td>0.36</td>
</tr>
<tr>
<td>Pretransplant dialysis &gt;2 weeks (%)</td>
<td>13 (14)</td>
<td>2 (7)</td>
<td>0.51</td>
</tr>
<tr>
<td>MELD adjusted by dialysis (^1)</td>
<td>33 (±6.5)</td>
<td>31 (±7.5)</td>
<td>0.36</td>
</tr>
<tr>
<td>Time on waiting list (days) (^2)</td>
<td>58 (35–1282)</td>
<td>153 (0–1198)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Study period May 2000- Dec 2012

Goldaracena et al. Am J Transplant 2014
In HRS, no difference in graft survival or recovery of renal function with LDLT and DDLT

Goldaracena et al. Am J Transplant 2014
LDLT for FLF

Listed for LT
n=1123

FLF
n=46

No LT
n=13

LT
n=33

DDLT	n=26

LDLT	n=7

No difference in graft or patient survival

Graft Considerations
Determinants of graft function

Graft Size

Functional Mass

Venous Outflow
- Segmental vein revascularization
- MHV revascularization

Portal hypertension
- Splenectomy
- Splenic artery ligation
- Portal vein banding
- Portal caval shunt

Other factors
- age
- steatosis
- fibrosis

Marcos, Liver Transpl 2001
Left-liver Adult-to-Adult Living Donor Liver Transplantation

Can It Be Improved? A Retrospective Multicenter European Study

- 1-year graft survival 59%
- Urgent retransplantation 26%
- Increased risk of graft failure with donor age > 45, MELD >14, GRWR <0.6

Sanchez-Cabus et al. Annals of Surgery 2018; 268: 876-884
Optimizing venous drainage

Cattral et al., Am J Transpl 2004
Portal vein flow modulation

Target PV pressure < 15 mm Hg

Graft considerations for “high-risk” recipients

- GRWR > 0.8
- High quality parenchyma: age <50 yrs, steatosis < 10%
- Excellent venous outflow
- PV pressure < 15 mm Hg
Liver Tx and HCC

• most effective therapy in patients with cirrhosis
• shortage of donor organs
• identification of appropriate recipients is the main challenge
Recipient selection

• Size and number have been the dominant considerations: Milan, UCSF, Rule of 7, etc
• HCC are heterogeneous with variable biologic characteristics
• Tools to help define tumor biology: AFP, Neutrophil/lymphocyte ratio, PIVKA, liver biopsy, PET scan
Extended Toronto Criteria

• Tumor confined to liver (no size or number limitations)
• Absence of vascular invasion by imaging
• No poor differentiation in liver biopsy
• Absence of constitutional symptoms
ETC – validation study

Sapisochin et al. Hepatology 2016
ETC – validation study

Sapisochin et al. Hepatology 2016
Intent-to-treat survival is better with LDLT than DDLT

- Lower risk of wait list drop-out (14.6% vs. 27.5%, p <0.001)
- Higher 5-yr ITT survival rate (68% vs. 57%, p=0.02)
- Wait-times > 9 mo were predicative of death

Goldaracena et al. J Hepatology 2019;70:666
LDLT and transplant oncology

- Intrahepatic cholangiocarcinoma\(^1\)
- Colorectal liver metastases\(^2\)
- Emerging data indicates that well-selected patients may benefit
- Role of LDLT undefined

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\(^1\)Lunsford et al. Lancet Gastroenerol Hepatol 2018;3:337
Avoiding Futility

Lai CJ. Liver Transplant 2017;23 (S1):S40
Essential elements of successful LDLT in high risk recipients

Quality graft
- Adequate volume i.e. right lobe
- Complete venous drainage
- Minimal steatosis

Identify futility
- Cardiac event
- Refractory sepsis

Dedicated Team
- Surgery
- Hepatology
- Anesthesia
- Intensivists
- Infectious disease
- Allied Health

High MELD LDLT

Donor
Recipient
Surgeon
Experience

Au et al. Curr Opin Organ Transplant 2019;24:637
Who should perform “high-risk” LDLT?

- All vs. limited number of centers?
- Volume matters
- Experience matters
- Failure can be catastrophic
Conclusions

- LDLT can be successful in high risk recipients
- The decision to proceed depends on high quality graft and experience of the transplant team
- Avoid futility
- Donor safety (physical and psychological) remains the priority