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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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CEOT CUTTING EDGE OF TRANSPLANTATION

TRANSPLANT SUMMIT 2020
BALANCING EQUITY AND UTILITY IN THE FACE OF AN ORGAN SHORTAGE

Disclosure

none

Learning Objectives

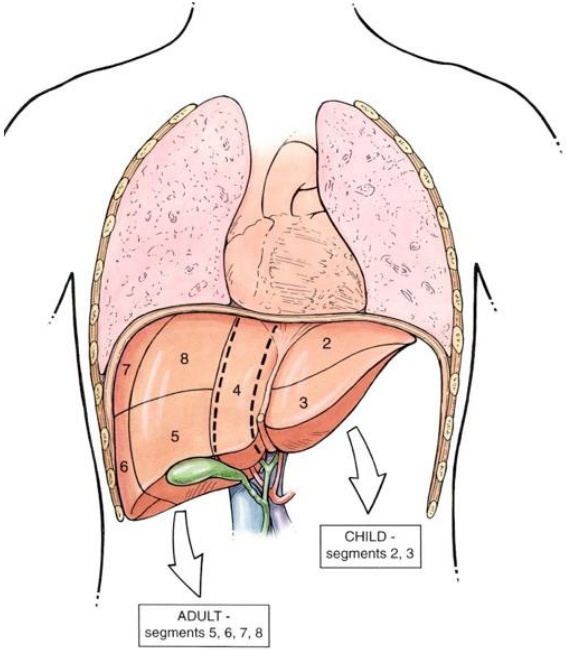
1. Define a “high-risk” LDLT recipient
2. Describe the role and limitations of LDLT in “high-risk” recipients
3. Discuss the requirements to perform LDLT in “high-risk” recipients

LDLT: Brief history

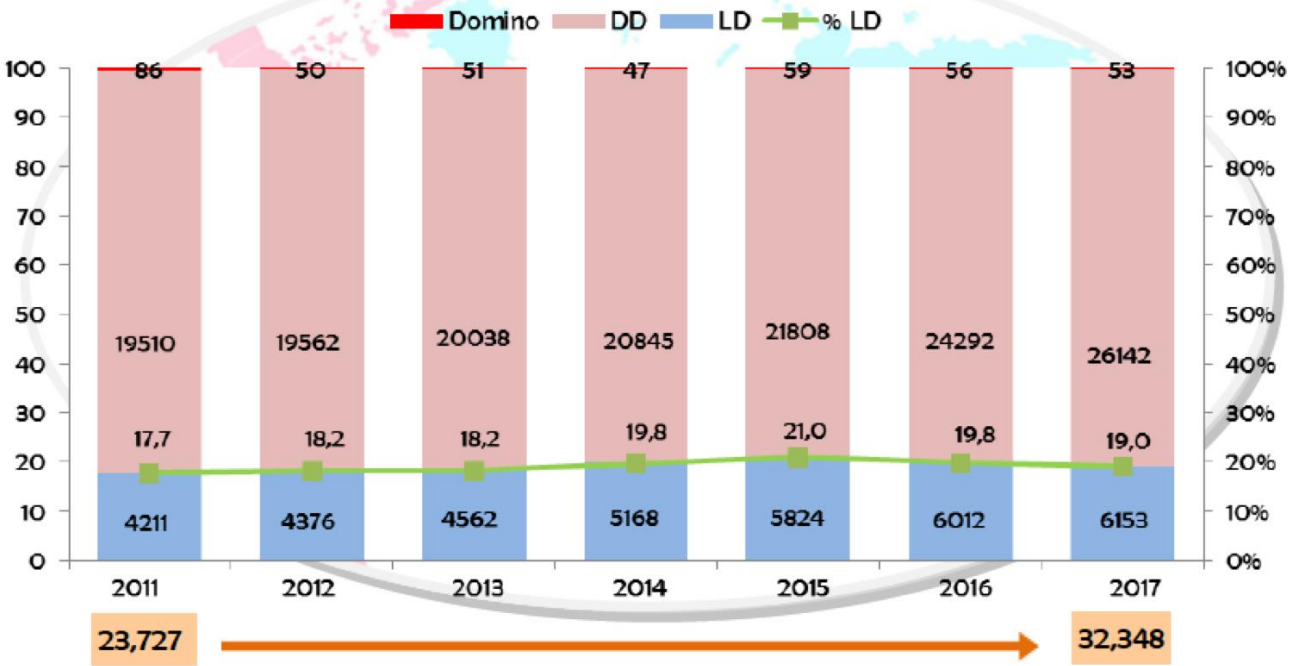
- 1981 Bismuth – reduced size LT
- 1988 Pichlmayr – split LT
- 1989 Strong- Pediatric LDLT- left lateral segment
- 1993 Makuuchi- Adult LDLT- Left lobe
- 1996 Fan- Adult LDLT- Right lobe
- 2000 Lee- Dual LDLT

Rationale of LDLT

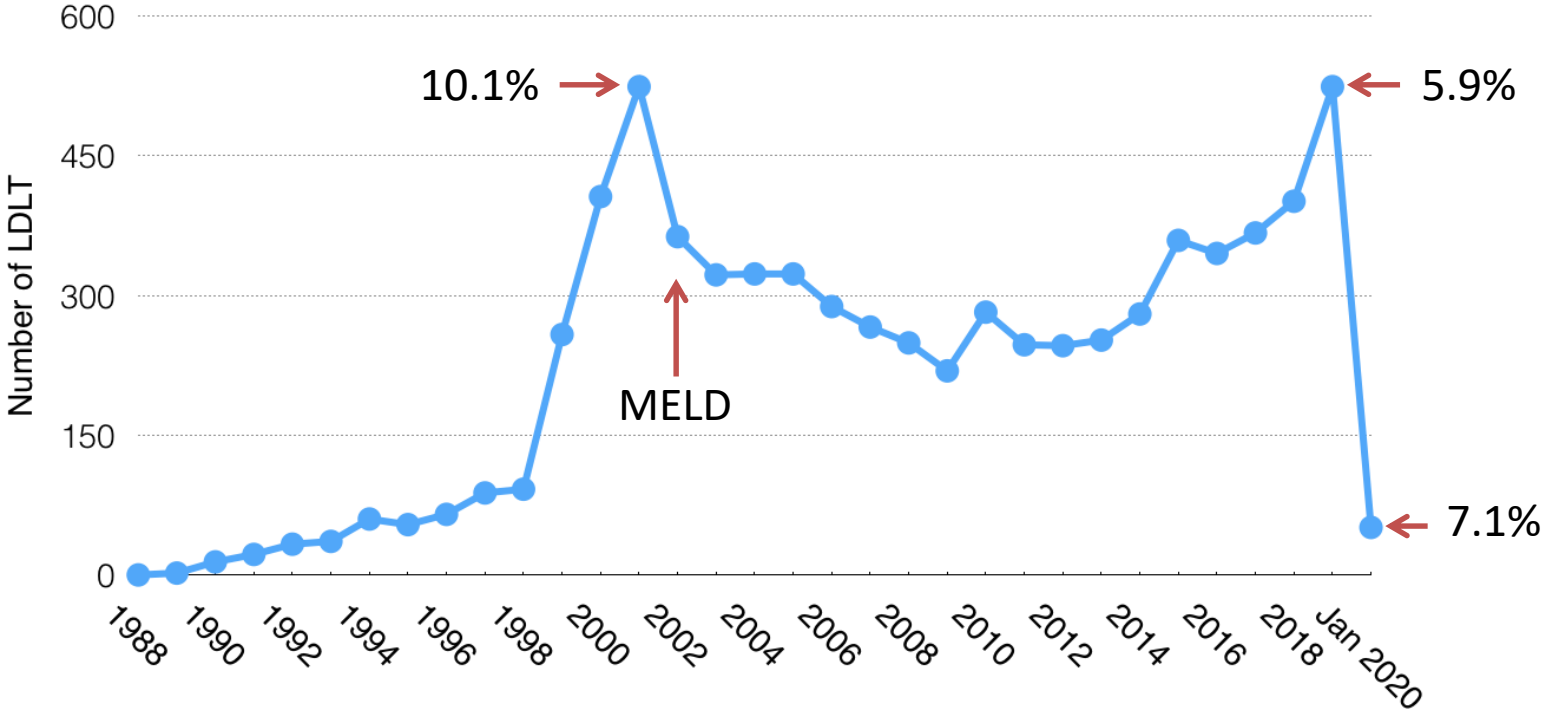
- Liver segments regenerate; donor recovers fully
- Transplanting a liver segment restores function in the recipient
- The principles of beneficence, autonomy, and justice provide the ethical underpinning of the procedure



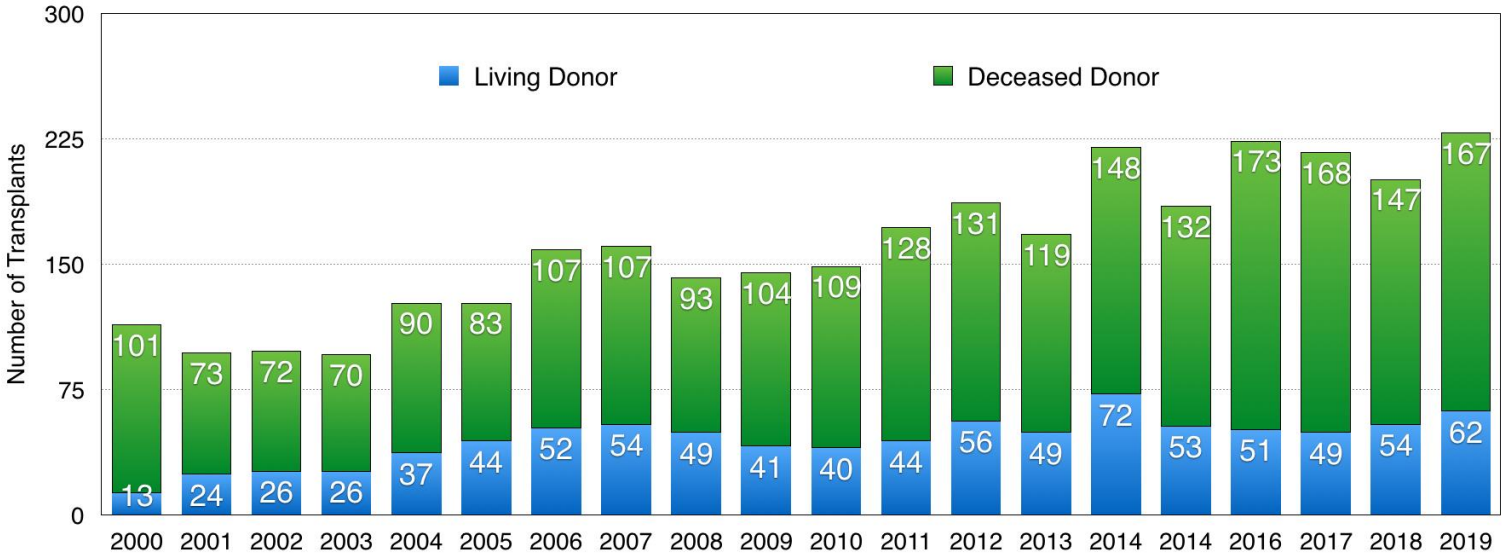
Absolute numbers of **Liver** transplants from **DD**, from **LD** and **Domino**. Percentage of LD. Global data. 2011-2017



LDLT in USA


600
450
300
150
0
Number of LDLT
10.1%
5.9%
7.1%
MELD
1988
1990
1992
1994
1996
1998
2000
2002
2004
2006
2008
2010
2012
2014
2016
2018
Jan 2020

Toronto Liver Transplant Program



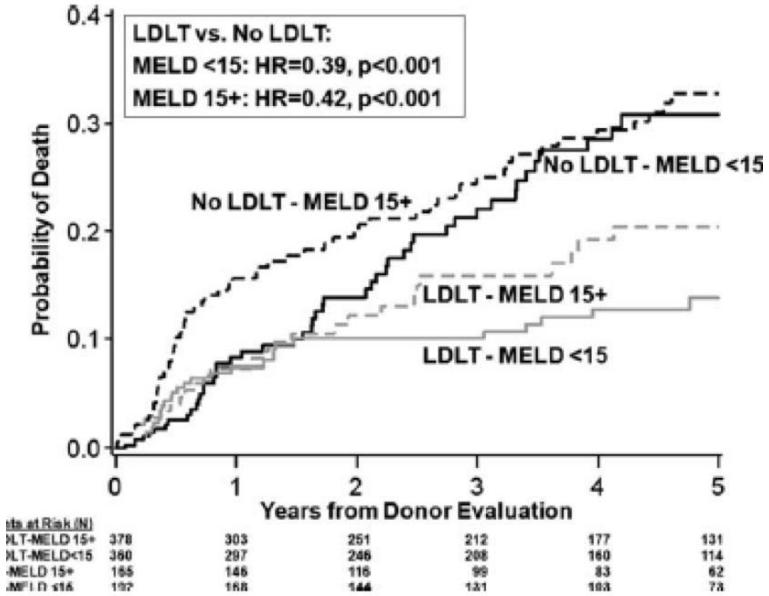
SickKids

UNIVERSITY OF TORONTO

UHN

Advantages of LDLT

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



Berg et al. Hepatology 2011;54:1313

Advantages of LDLT

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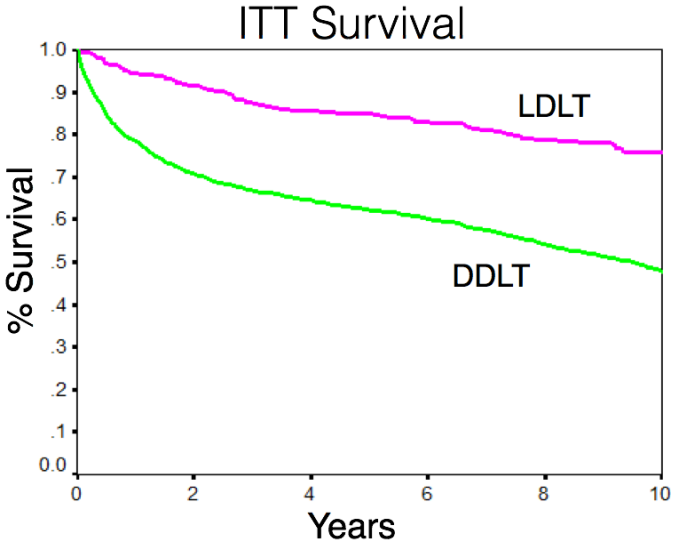
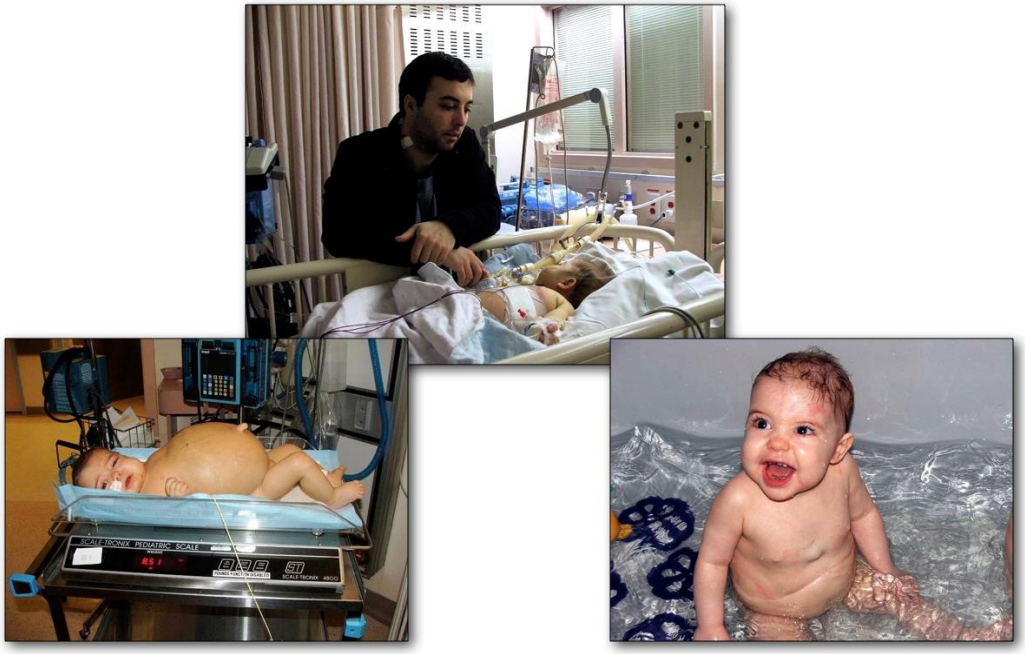


Toronto General Hospital
2000 - 2015

LDLT: the gift of life



The Ultimate Sacrifice

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

By CHRISTINE GORMAN

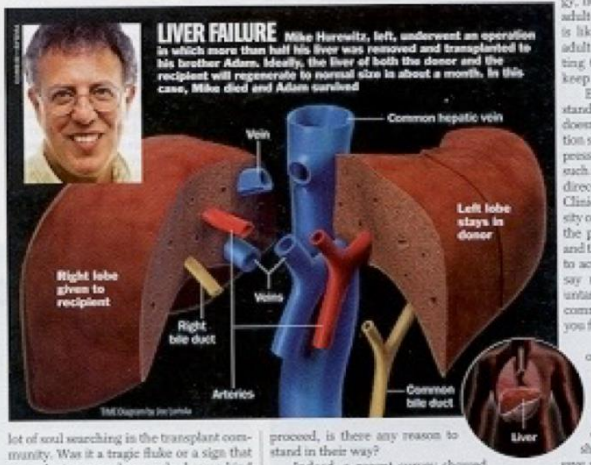
MIKE AND ADAM HUREWITZ GREW UP together on Long Island, in the suburbs of New York City. They were very close, even for brothers. So when Adam's liver started failing, Mike offered to give him half of his. The operation saved Adam's life. But Mike, who went into the hospital in seemingly excellent health,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

Mike Hurewitz'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

like bad odds, but there's more to this ethical dilemma than a simple ratio. The first and most sacred rule of medicine is to do no harm. "For a normal healthy person, a mortality rate of 1% is hard to justify," says Dr. John Fung, chief of transplantation at the University of Pittsburgh Medical Center. "If the rate stays 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 proceed, is there any reason to stand in their way?

Indeed, a recent survey showed that most people will accept a mortality



LIVER FAILURE Mike Hurewitz, left, underwent an operation in which more than half his liver was removed and transplanted to his brother Adam. Ideally, the liver of both the donor and the recipient will regenerate to normal size in about a month. In this case, Mike died and Adam survived

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 surgeon gets to pick which part of the donated liver looks the best—and to take as much of it as 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 modest 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."

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 Siegler, 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 it 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 unexamined, for the most part, is 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, al-

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

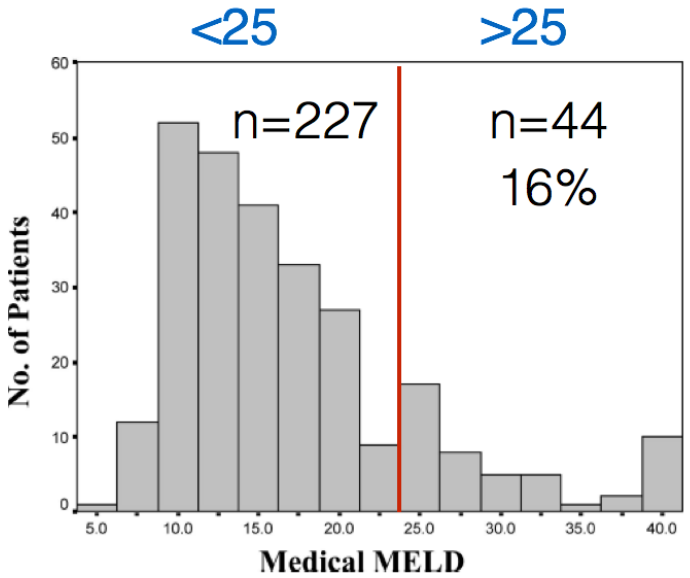
What is a “reasonable” bench mark for patient/ graft survival in LDLT?

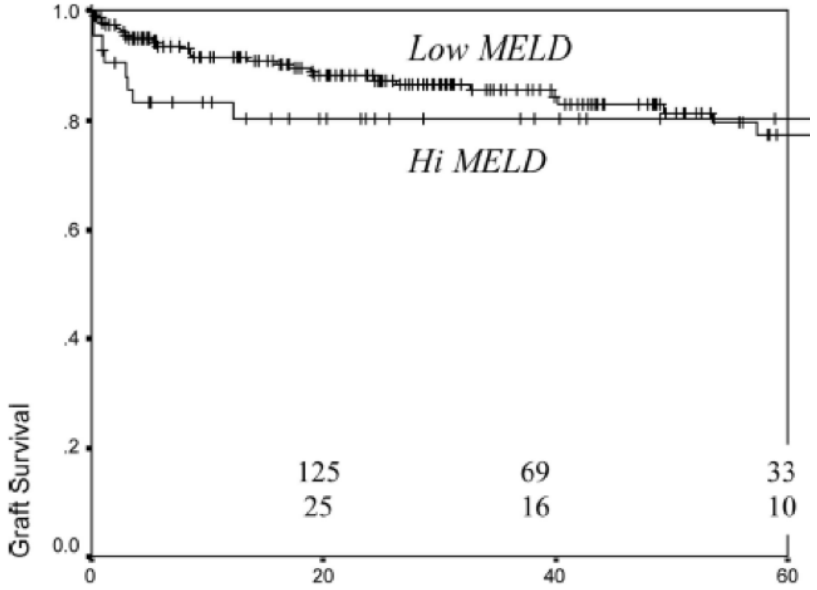
- Same as DDLT?
- Can it be reduced?
- Where should we draw the line?

Who decides?

- Recipient
- Donor
- Transplant team
- Bioethicist
- 3rd party
- National/International organizations

High MELD LDLT Recipients





Selzner et al. Annals of Surgery 2010

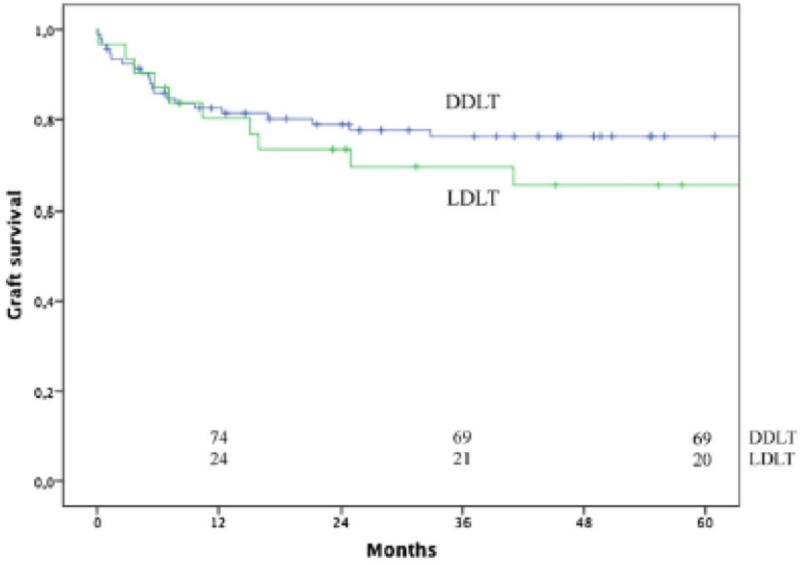
LDLT for hepatorenal syndrome

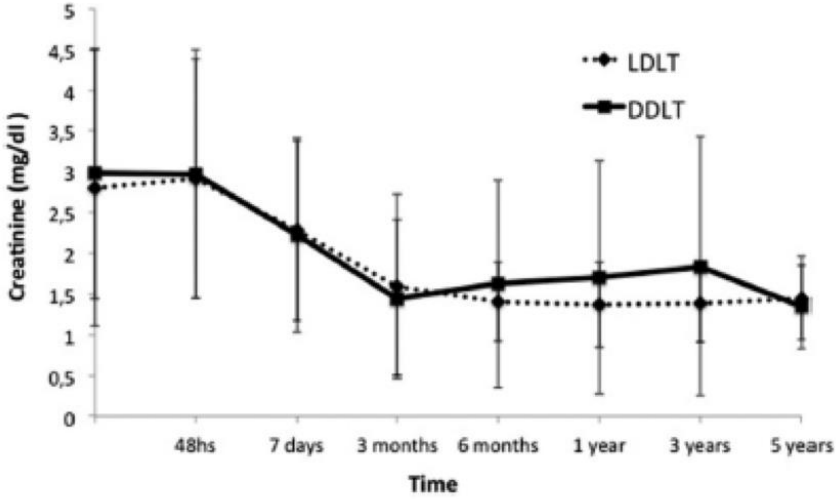
	DDLT (n = 90)	LDLT (n = 30)	p
Age (years)[1]	53 (±11)	50 (±11)	0.38
Male sex (%)	60 (67)	24 (80)	0.25
BMI	30 (±6.8)	29 (±5.7)	0.61
INR[1]	2.60 (±1.27)	2.52 (±1.28)	0.66
Creatinine (mg/dL)[1]	2.99 (±1.55)	2.80(±1.69)	0.21
Bilirubin (mg/dL)[1]	16.49 (±16.78)	18.94 (±18.01)	0.6
MELD at listing[1]	24 (±9)	20 (±8)	0.07
MELD at transplant[1]	32 (±6.7)	31 (±7.3)	0.58
Pretransplant dialysis (%)	30 (33)	10 (33)	1
Pretransplant dialysis (days)[1]	5 (±11)	3 (±9)	0.36
Pretransplant dialysis >2 weeks (%)	13 (14)	2 (7)	0.51
MELD adjusted by dialysis[1]	33 (±6.5)	31 (±7.5)	0.36
Time on waiting list (days)[2]	58 (35–1282)	153 (0–1198)	0.07

Study period May 2000- Dec 2012

Goldaracena et al. Am J Transplant 2014

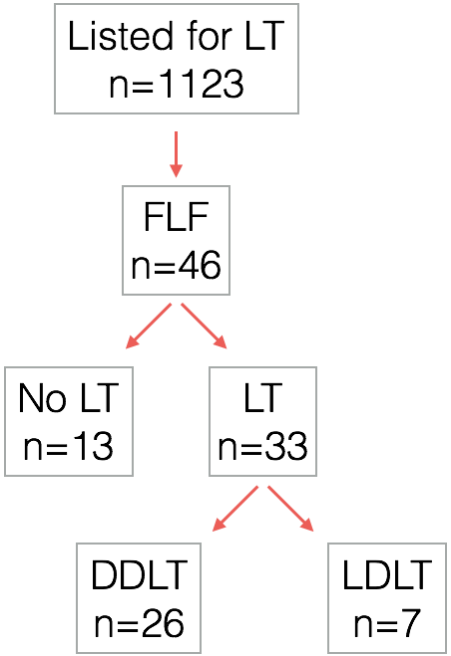
In HRS, no difference in graft survival or recovery of renal function with LDLT and DDLT



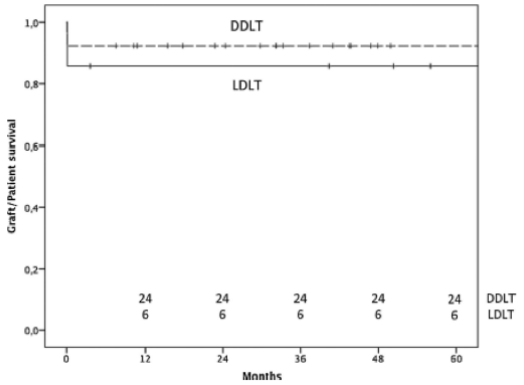


Goldaracena et al. Am J Transplant 2014

LDLT for FLF



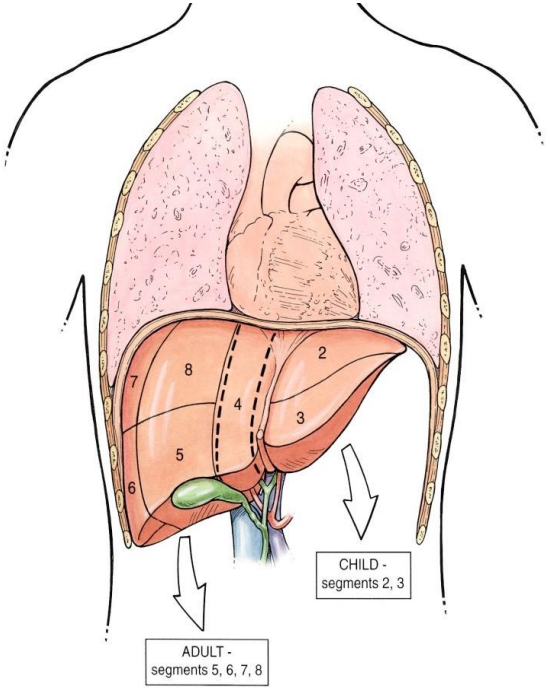
	DDLT n=26	LDLT n=7	p
Age (years)[1]	44 (± 13)	47 (± 18)	0.59
Male sex (%)	7 (27%)	2 (28%)	1
Unknown etiology of ALF (%)	18 (69)	3 (42)	0.37
INR[1]	4.72 (± 2.25)	5.93 (± 3.31)	0.21
Creatinine (mg/dL)[1]	1.57 (± 1.23)	1.01 (± 0.44)	0.68
Bilirrubin (mg/dL)[1]	24.44 (± 10.64)	20.35 (± 3.39)	0.32
MELD[1]	37 (± 6)	37 (± 4)	0.94
Pretransplant ICU admission (%)	18 (69)	6 (86)	0.64
Pretransplant ICU stay (days)[2]	1 (0–7)	1 (0–10)	0.38
Pretransplant mechanical ventilation need (%)	18 (69)	4 (57)	0.66
Pretransplant mechanical ventilation (days)[2]	1 (0–7)	1 (0–2)	0.34
Pretransplant inotropic drugs (%)	7 (27)	3 (43)	0.64
Pretransplant dialysis (%)	2 (8%)	0	1
Time on waiting list (days)[2]	1 (0–10)	1 (0–12)	0.6



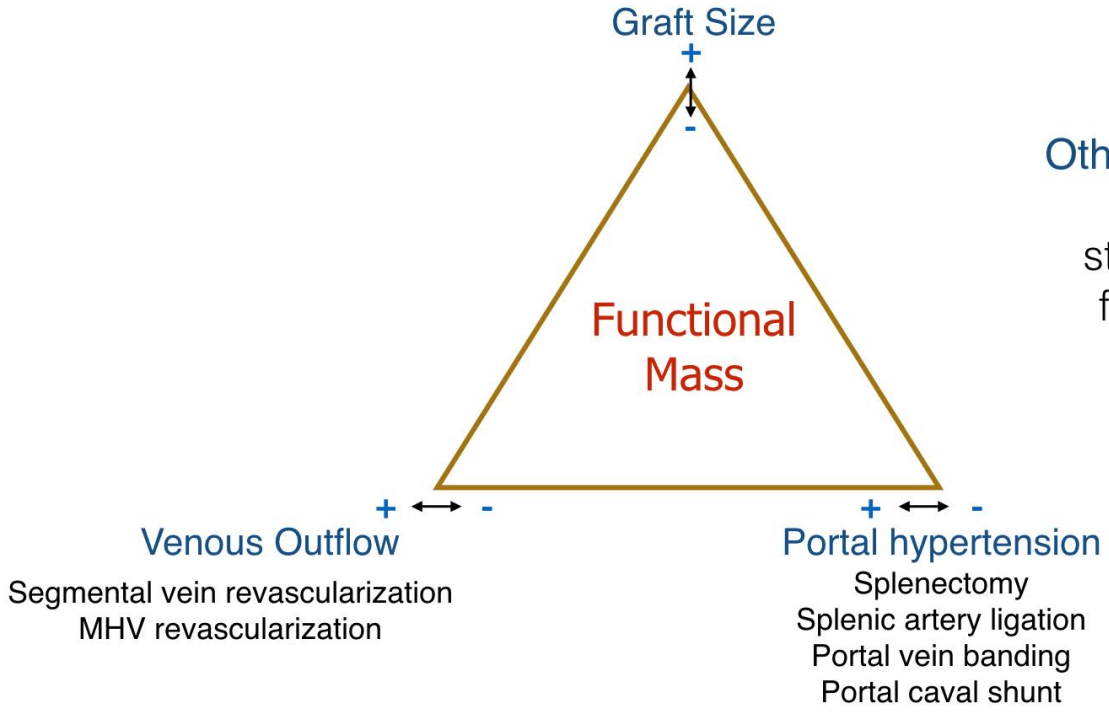
No difference in
graft or patient survival

Goldaracena et al. Am J Transplant 2015

Graft Considerations



Determinants of graft function

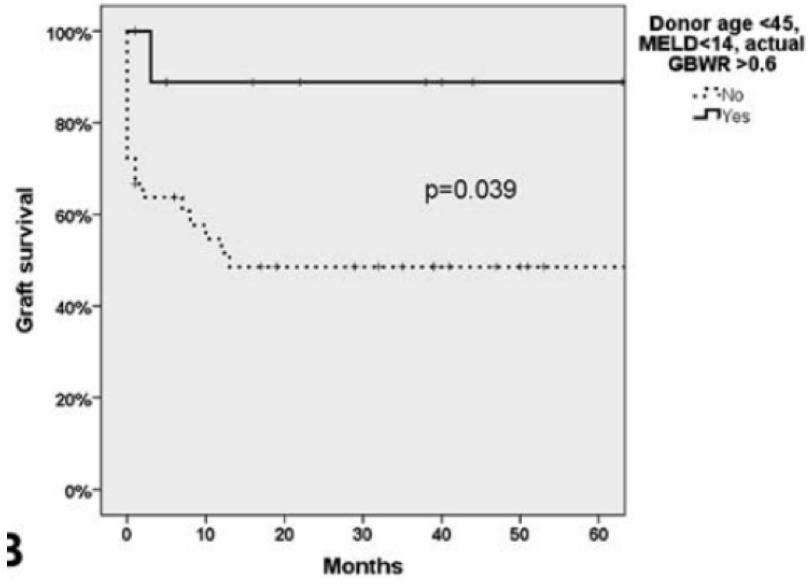


Other factors
age
steatosis
fibrosis

Marcos, Liver Transpl 2001

Left-liver Adult-to-Adult Living Donor Liver Transplantation

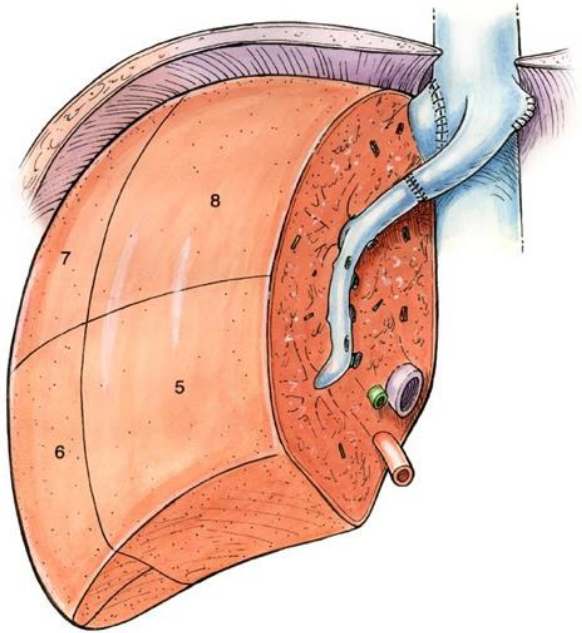
Can It Be Improved? A Retrospective Multicenter European Study

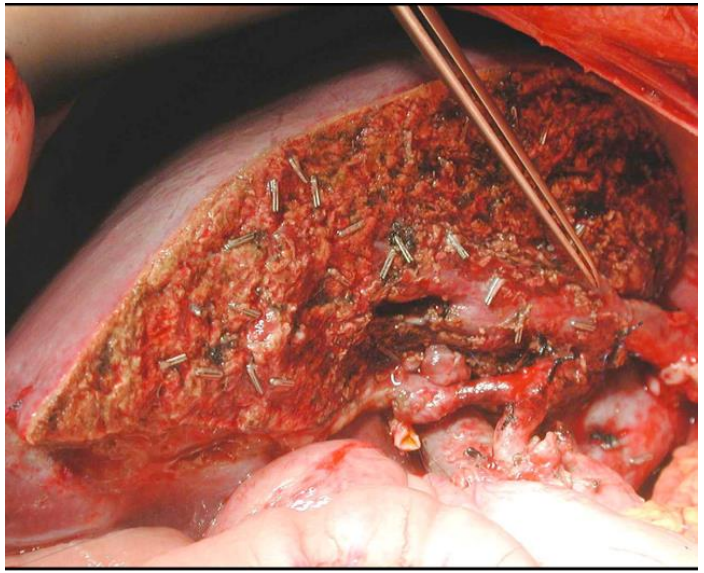


- 1-year graft survival 59%
- Urgent retransplantation 26%
- Increased risk of graft failure with donor age > 45, MELD >14, GRWR <0.6

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

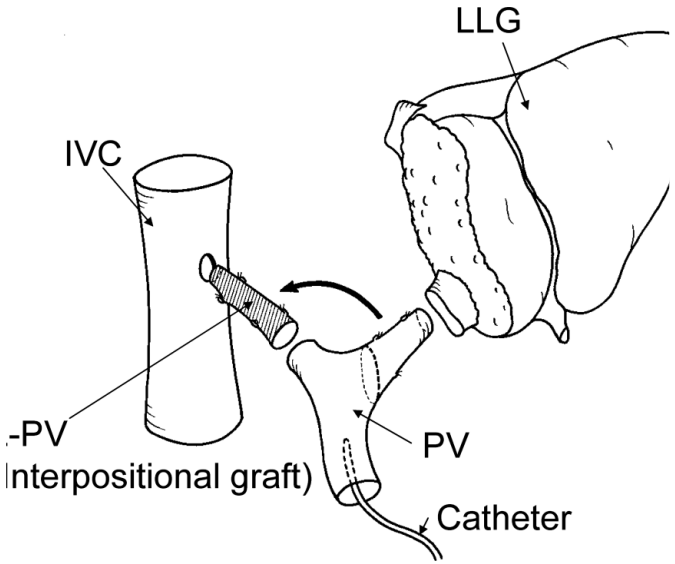
Optimizing venous drainage



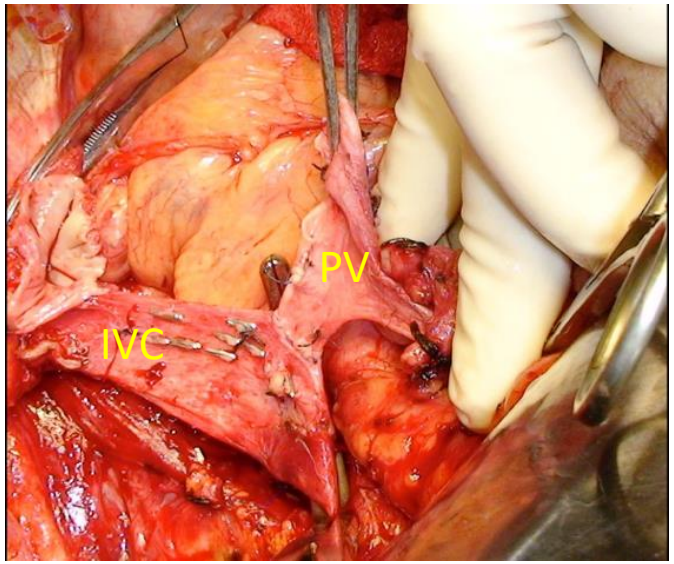


Cattral et al., Am J Transpl 2004

Portal vein flow modulation



Target PV pressure < 15 mm Hg



Yamada et al. Am J Transplant 2008

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

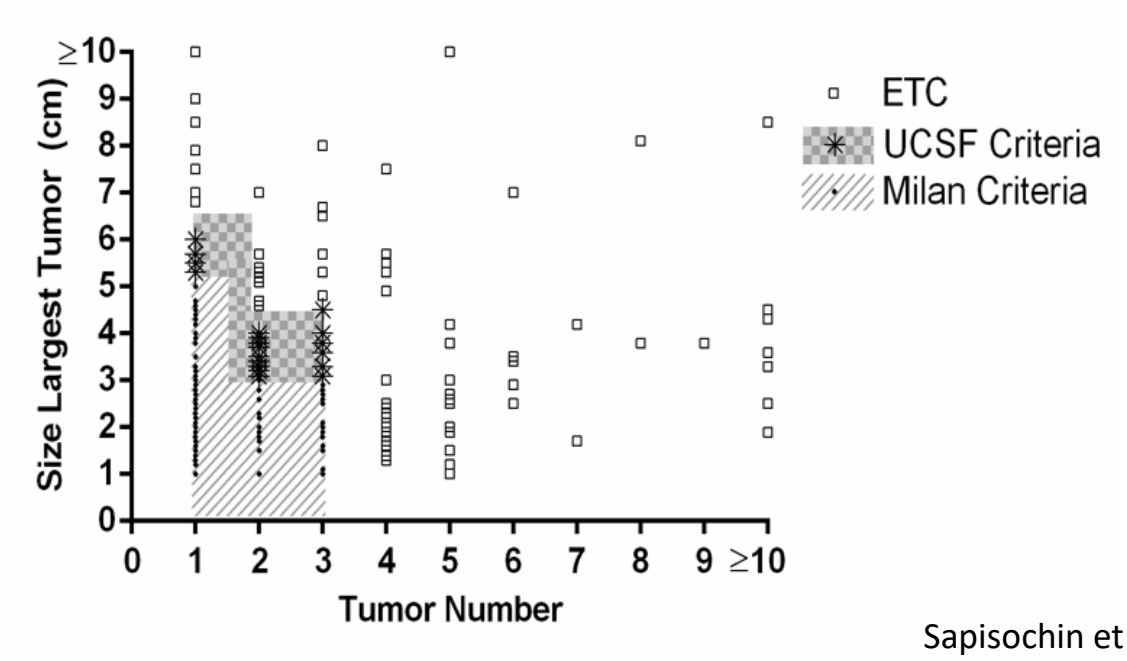
Recipient selection

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

Extended Toronto Criteria

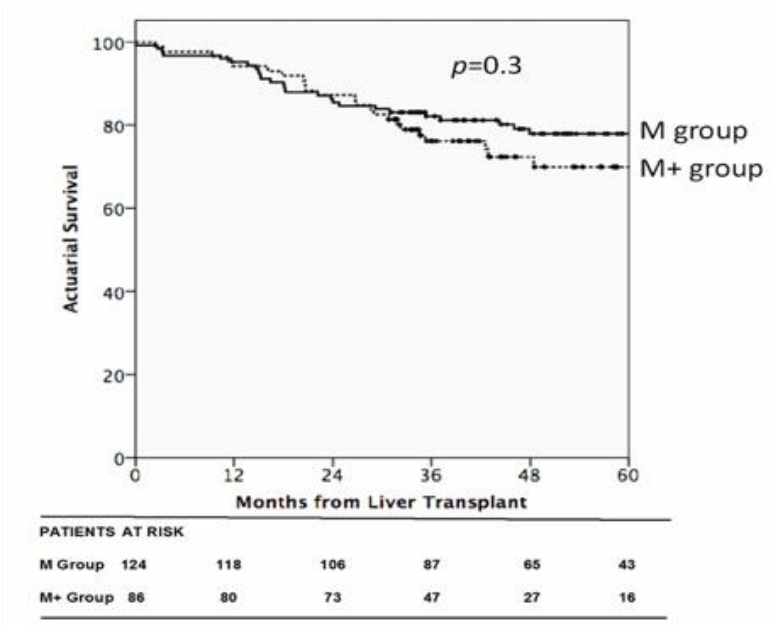
- Tumor confined to liver (no size or number limitations)
- Absence of vascular invasion by imaging
- No poor differentiation in liver biopsy
- Absence of constitutional symptoms

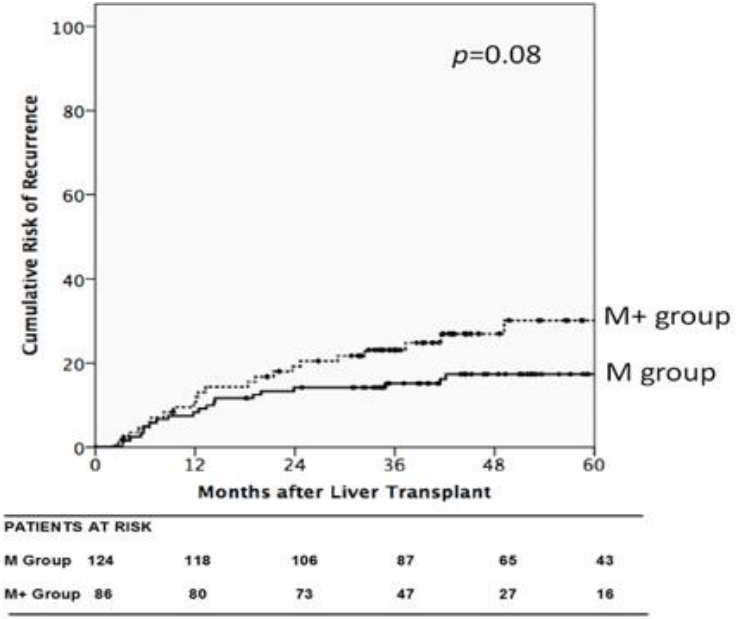
ETC – validation study



Sapisochin et al. Hepatology 2016

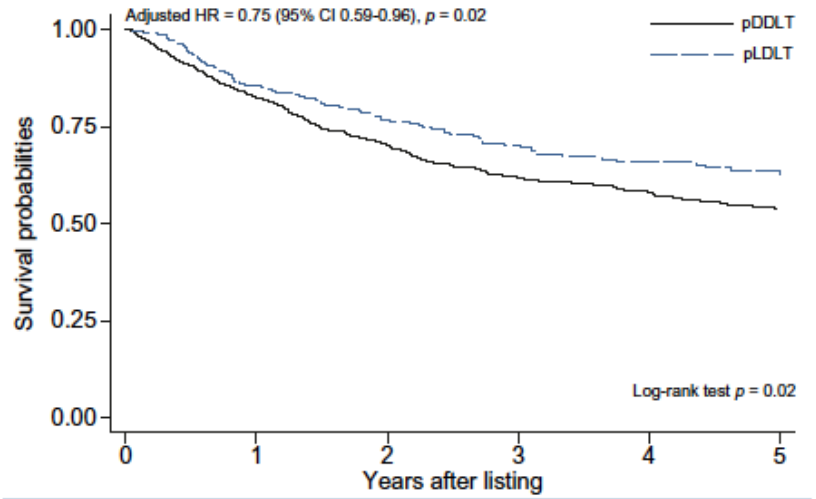
ETC – validation study





Sapisochin et al. Hepatology 2016

Intent-to-treat survival is better with LDLT than DDLT



N° at risk						
pDDLT	632	515	419	321	272	237
pLDLT	219	182	147	118	96	82

- 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

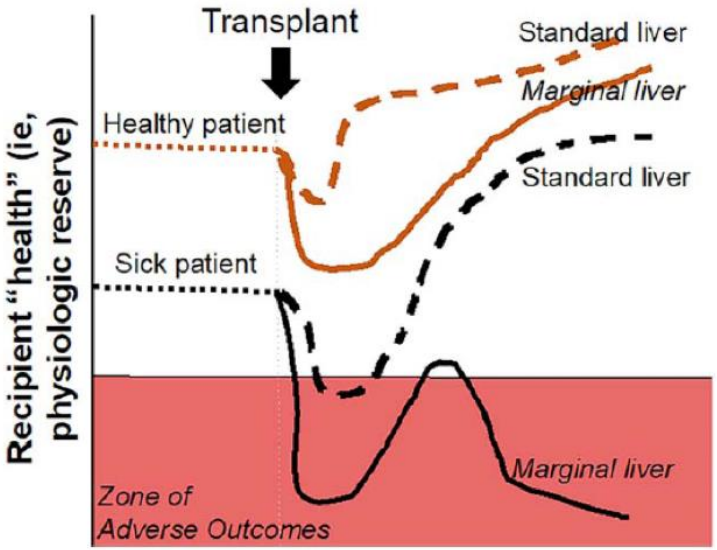
Goldaracena et al. J Hepatology 2019;70:666

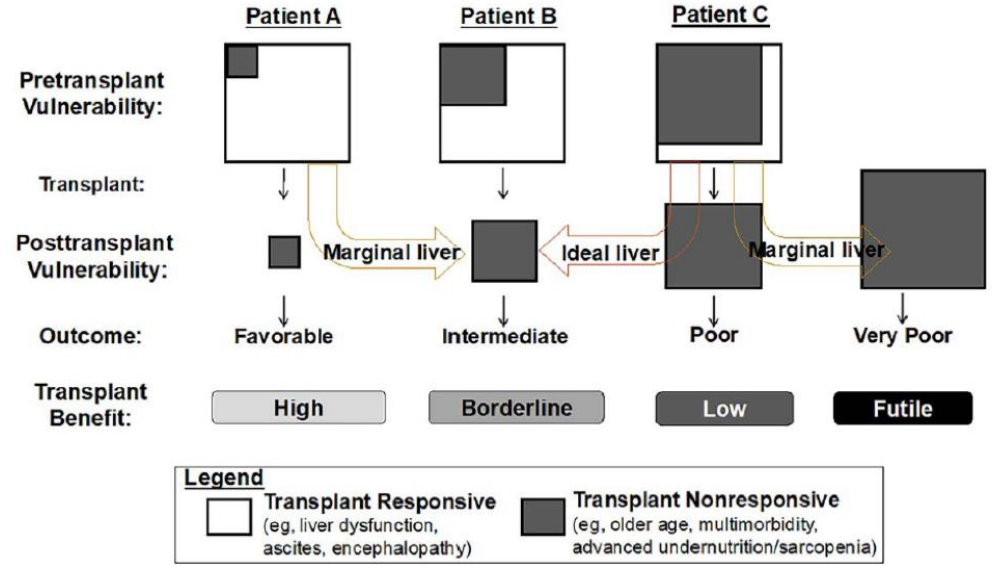
LDLT and transplant oncology

- Intrahepatic cholangiocarcinoma[1]
- Colorectal liver metastases[2]
- Emerging data indicates that well-selected patients may benefit
- Role of LDLT undefined

[1]Lunsford et al. Lancet Gastroenerol Hepatol 2018;3:337
[2]Dueland et al. Ann Surg 2020;271:212

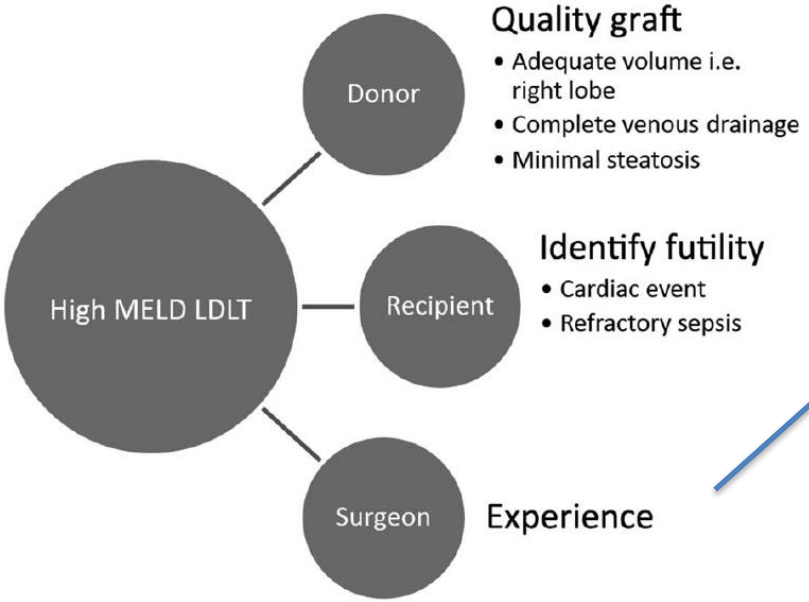
Avoiding Futility





Lai CJ. Liver Transplant 2017;23 (S1):S40

Essential elements of successful LDLT in high risk recipients



Dedicated Team

Surgery
Hepatology
Anesthesia
Intensivists
Infectious disease
Allied Health

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