Utility of Marginal Donors in Liver Transplantation

HwanHyo, Lee

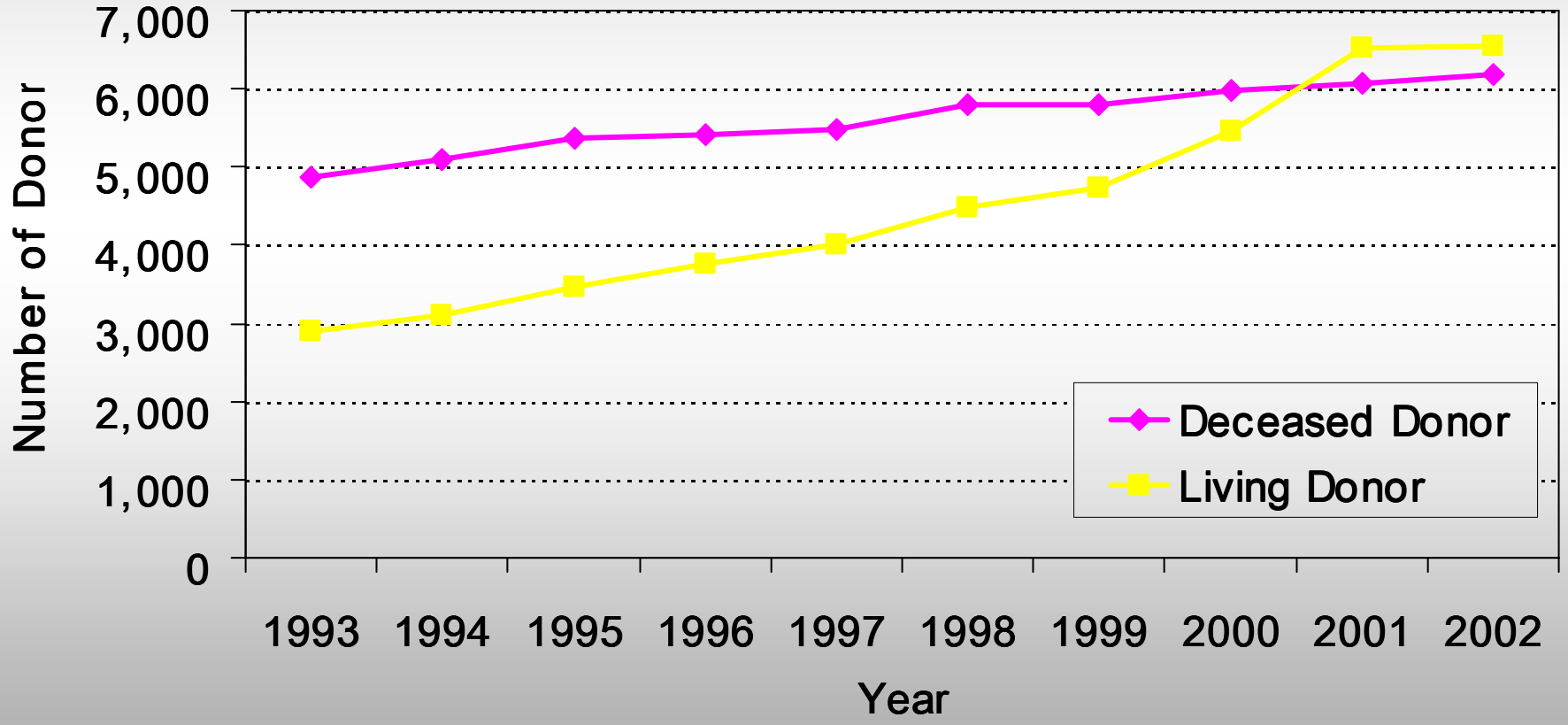
Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Contents

- *Review of Liver Transplantation(LT) Data*
- ***Marginal Donors in LT***
- ***Steatosis***
- ***Small-for-Size(SFS) Graft***

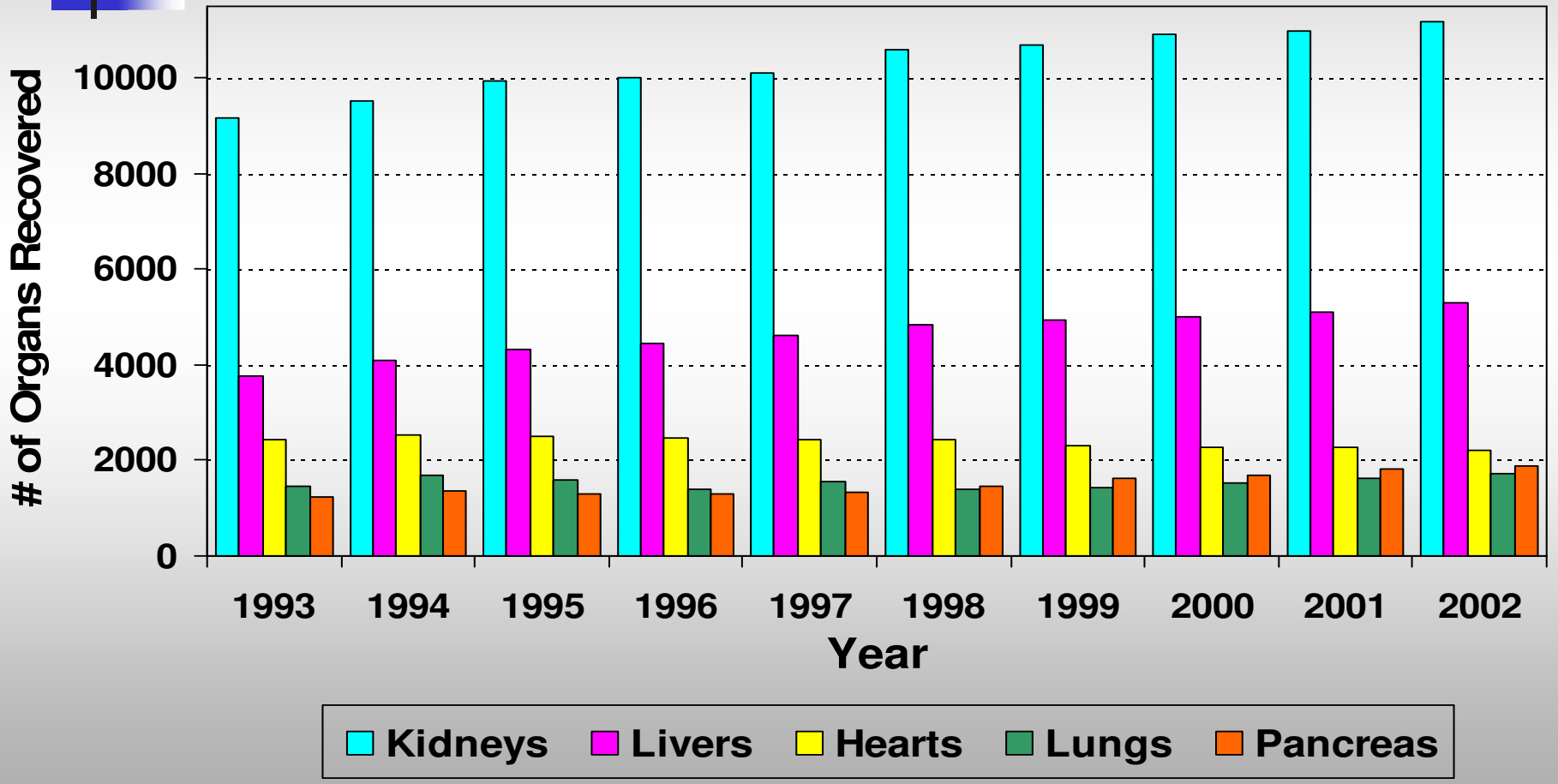
Deceased & Living Donors

1993 – 2002, UNOS



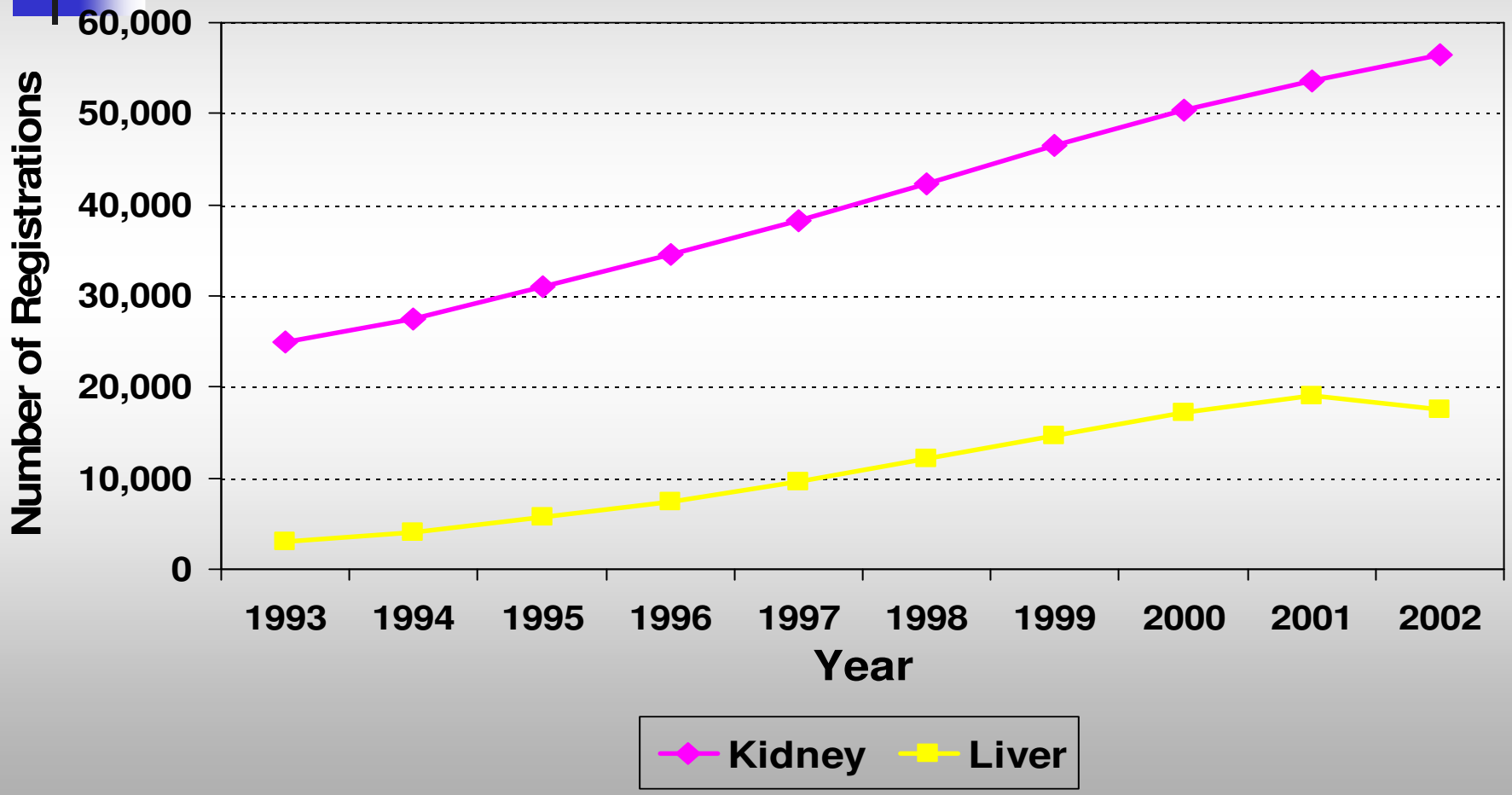
Deceased Donor Organs Recovered

1993-2002, UNOS



Waiting List at 1993-2002

UNOS



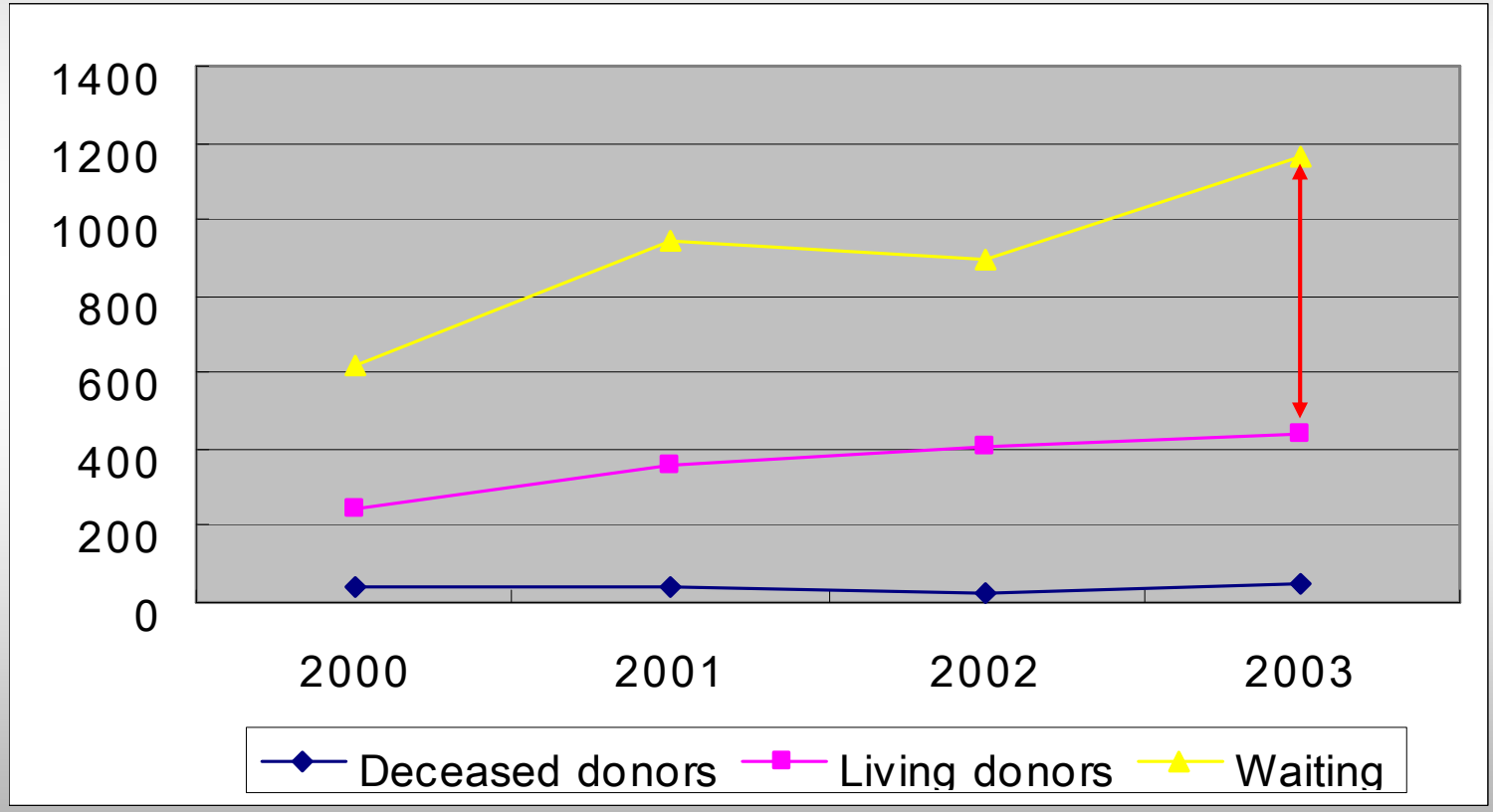
Deaths on the Waiting List

2000, 2001, 2002

Organ Type	2000	2001	2002
Kidney	3001	3119	3171
Pancreas	15	40	27
Kidney-Pancreas*	193	221	201
Liver	1784	2012	1756
Intestine*	23	45	52
Heart	617	637	552
Lung	492	491	468
Heart-Lung	43	40	37
Total *	6054	6455	6077

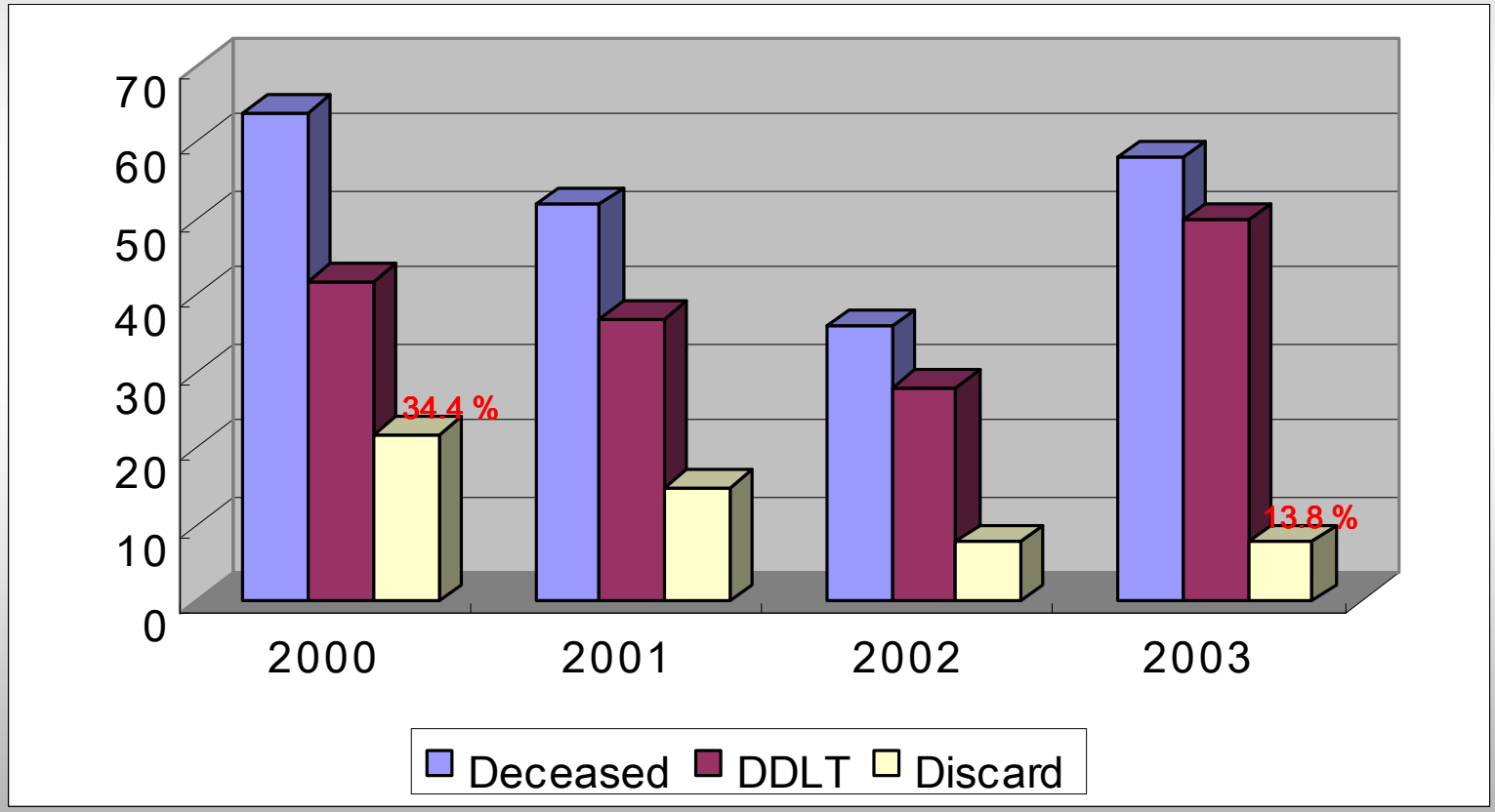
* Total Unique Patient Deaths

Waiting list in LT, KONOS



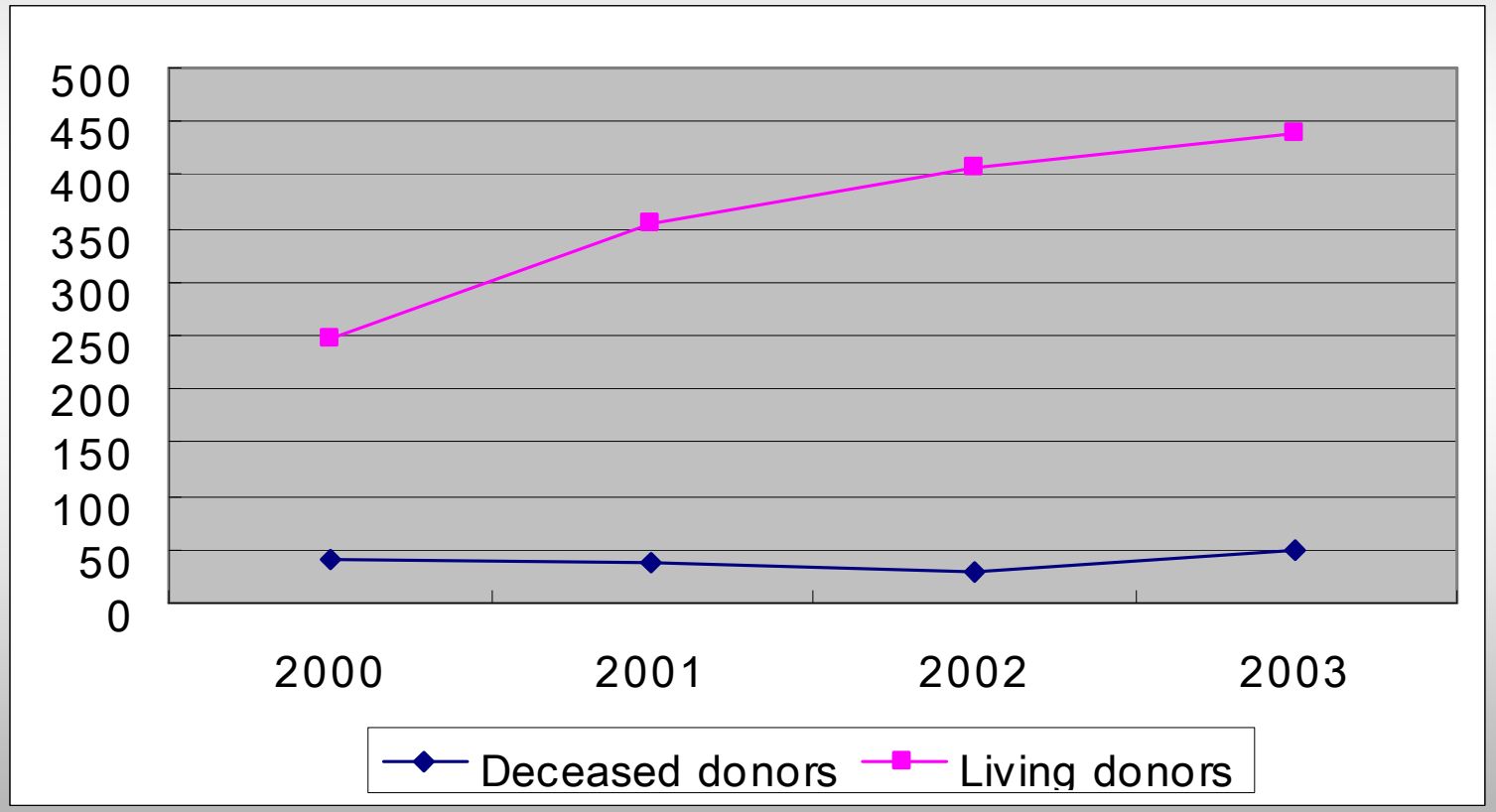
Deceased donors in LT

KONOS



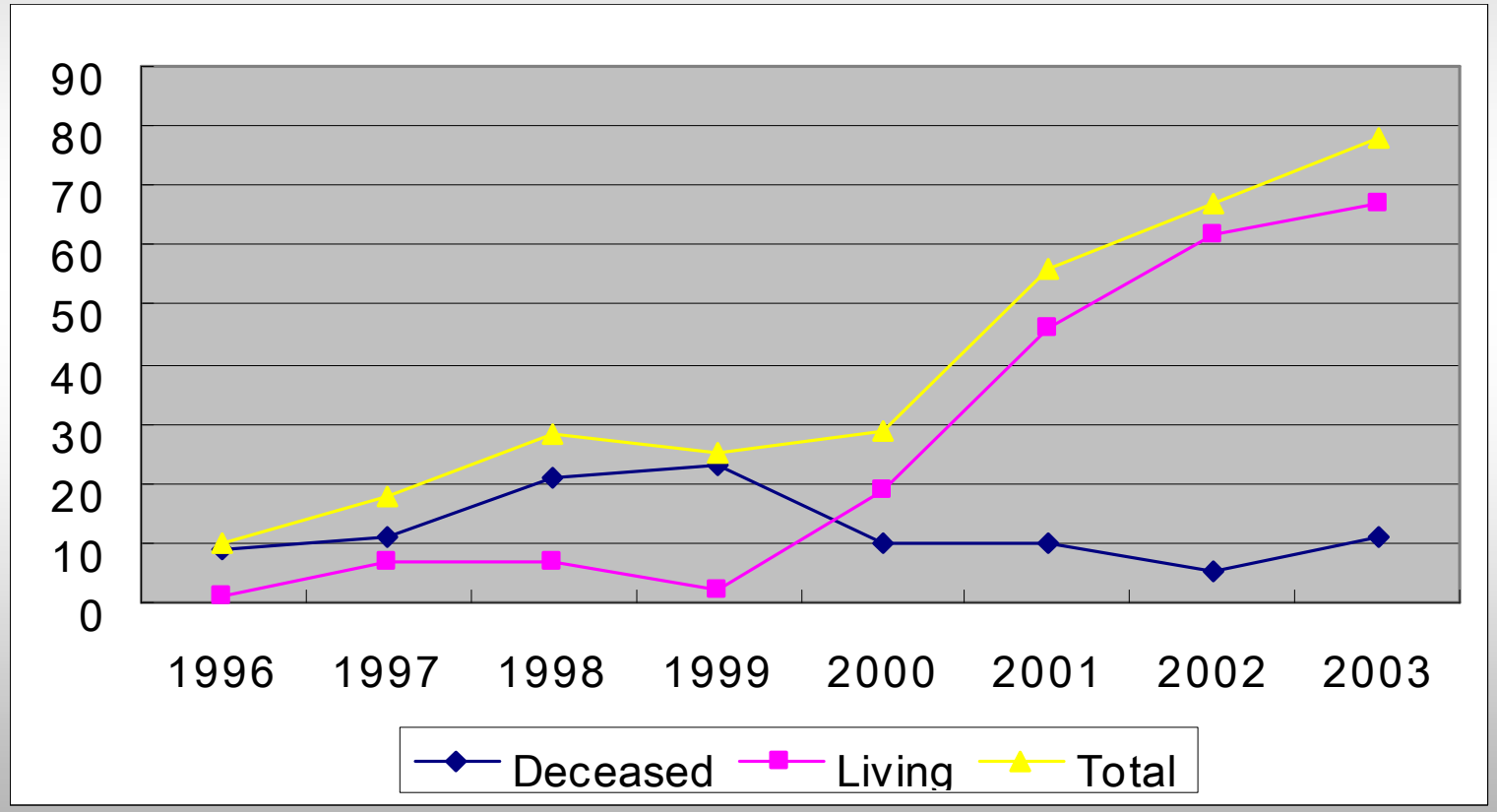
Deceased and living donors in LT

KONOS



Liver Transplantation in SMC

Organ Transplantation Center (OTC)



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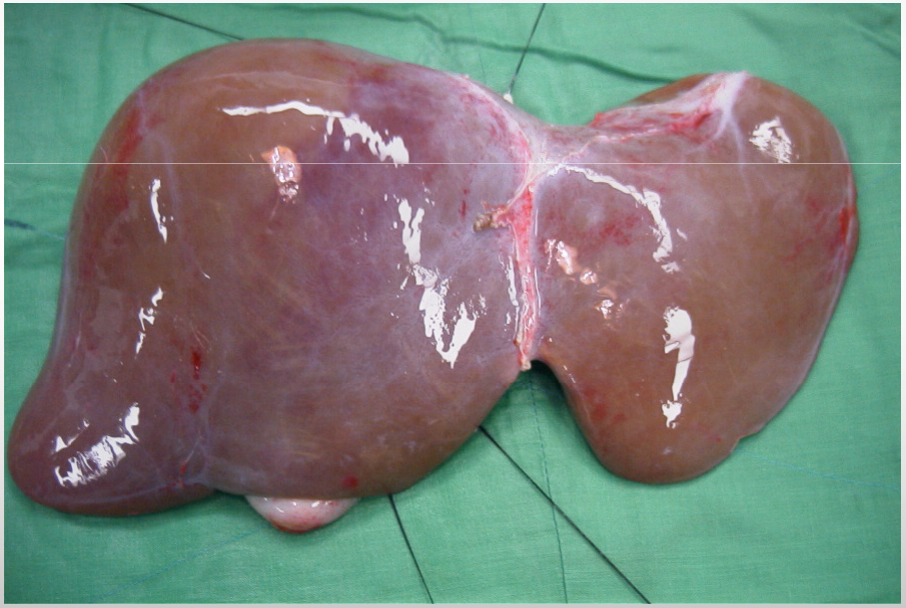
Ideal Graft in LT



- *Deceased donor*
- *Young adult age*
- *Enough graft size*
- *No steatosis*

What is the definition of marginal liver donors ?

Donor with Potential Risk Factor

initial poor function (IPF) or primary nonfunction (PNF)

- **Increasing age**
- **Prolonged ischemia**
- **Hypotension**
- **Inotropic support**
- **Steastosis**
- **Partial grafts**
- **Gender mismatch**
- **Non-heart beating donors (NHBD)**

The limits of donor age

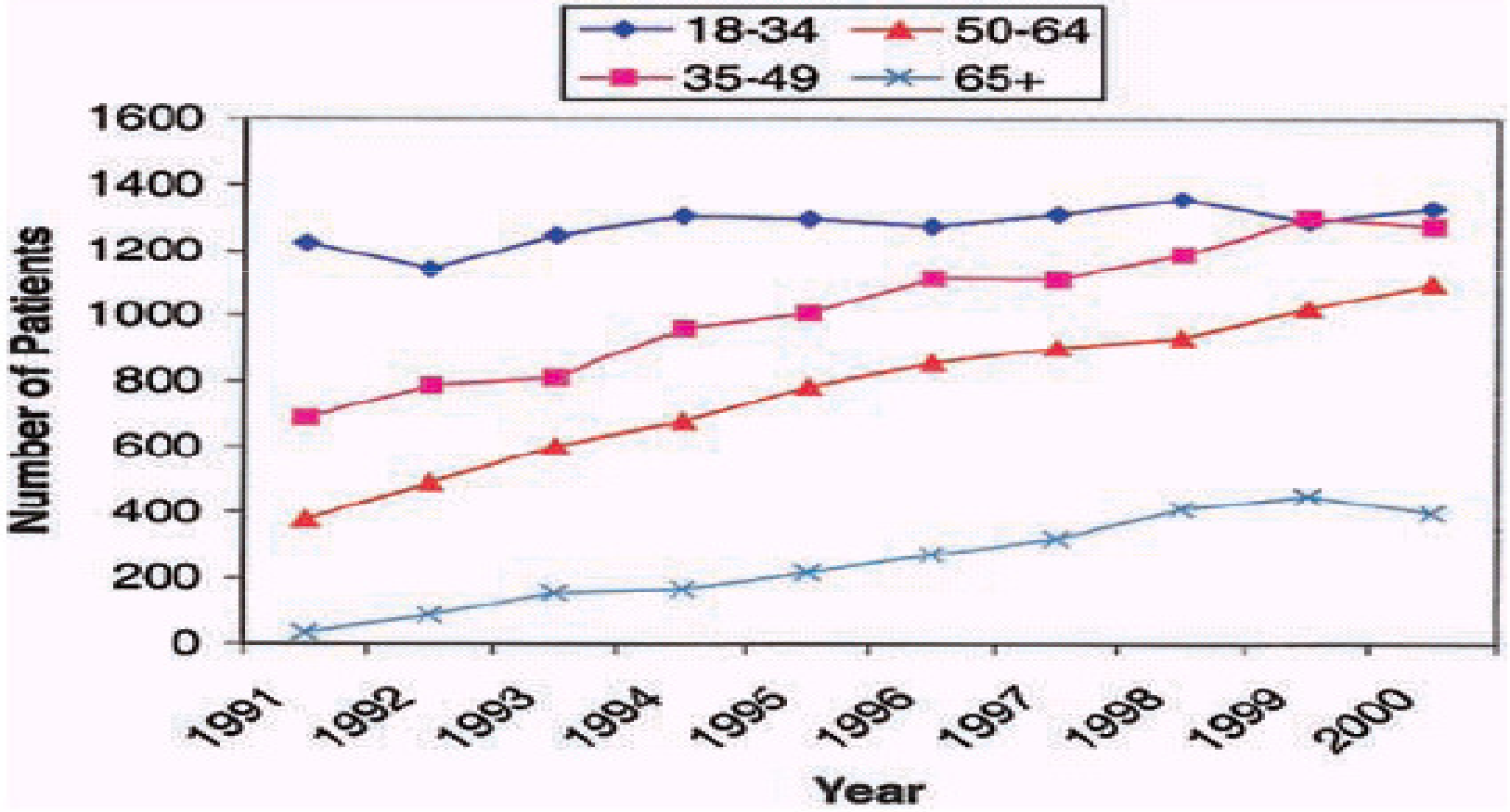
- **Donor age of more than 70 years**
  - **Associated with lower patient and graft survival**

- **Morphologic changes**
  - **Smaller and daker-colored**
  - **Fibrous thickening of capsule**

- **Endothelial cell injury during CIT**
- **Decreased ATP synthesis after reperfusion**

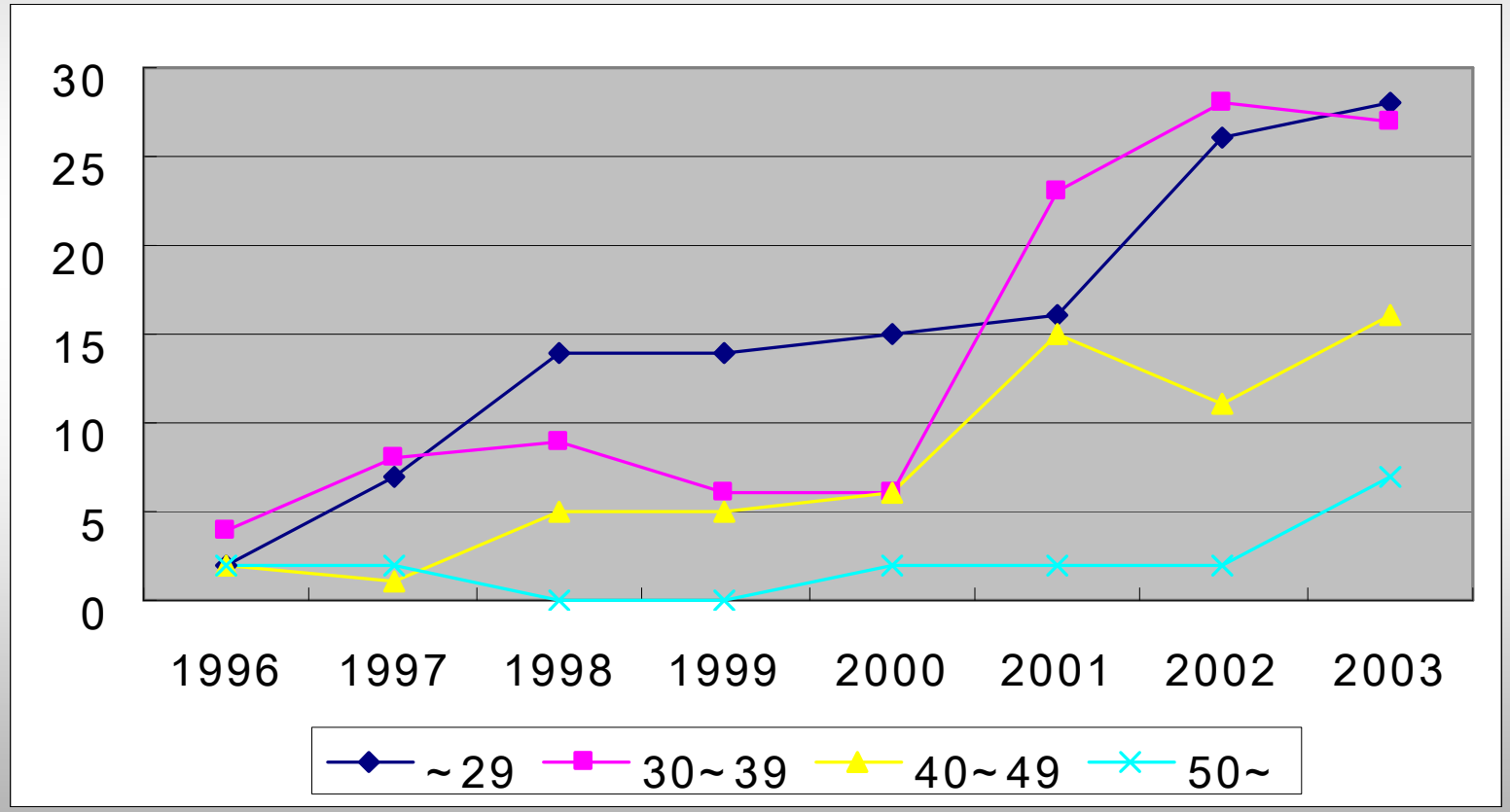
Donor Age

UNOS



Donor age in LT

SMC OTC



Prolonged Cold Ischemia Time (CIT)

- **Independent risk factor for liver preservation injury**
- **More than 14 hours : associated with a two-fold increase in preservation damage**

- **Prolonged postoperative course**
- **Biliary stricture**
- **Decreased graft survival**

Prolonged CIT

- **Sinusoidal cell damage & Hypercoaguability**
- **Metabolic activity 10-fold ↓**
- **Anaerobic metabolism and lactic acidosis ↑**

↓

- **Decrease of ATP & hypoxanthine**
- **Increase of reactive oxygen species**

↓

Ischemia-reperfusion(IR) injury

Reperfusion – insult on transplant liver

- **Endothelial / Kupffer cell swelling**
- **Vasocontriction**
- **Leukocyte entrapment**
- **Platelet aggregation within sinusoids**

interactions between different complex mechanisms

Failure of Microcirculation

Endothelial & Kupffer Cell Swelling

Ischemia Reperfusion

Failure of active transmembrane transport

↓

Intracellular edema

Vasocontriction

Ischemia Reperfusion

Imbalance between nitric oxide(NO) and endothelin(ET)

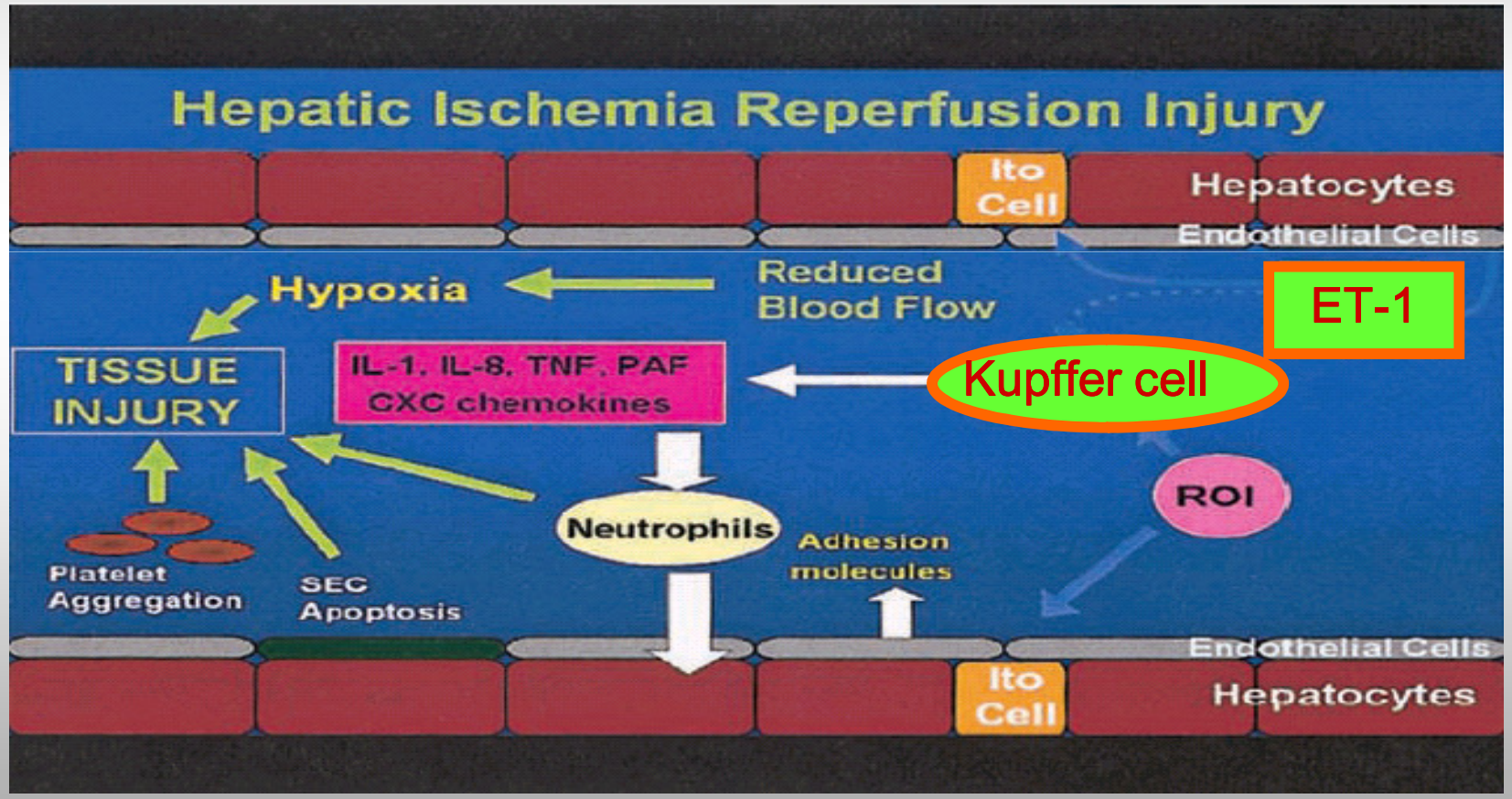
1st Step of IR injury

- Liberation of endothelin-1(ET-1)
- Activation of Ito cells
- Constriction of hepatic sinusoids

- Activation of Kupffer cells
- Release of oxygen derived free radicals (ODFR)

Reduced blood flow

1st Step of IR injury



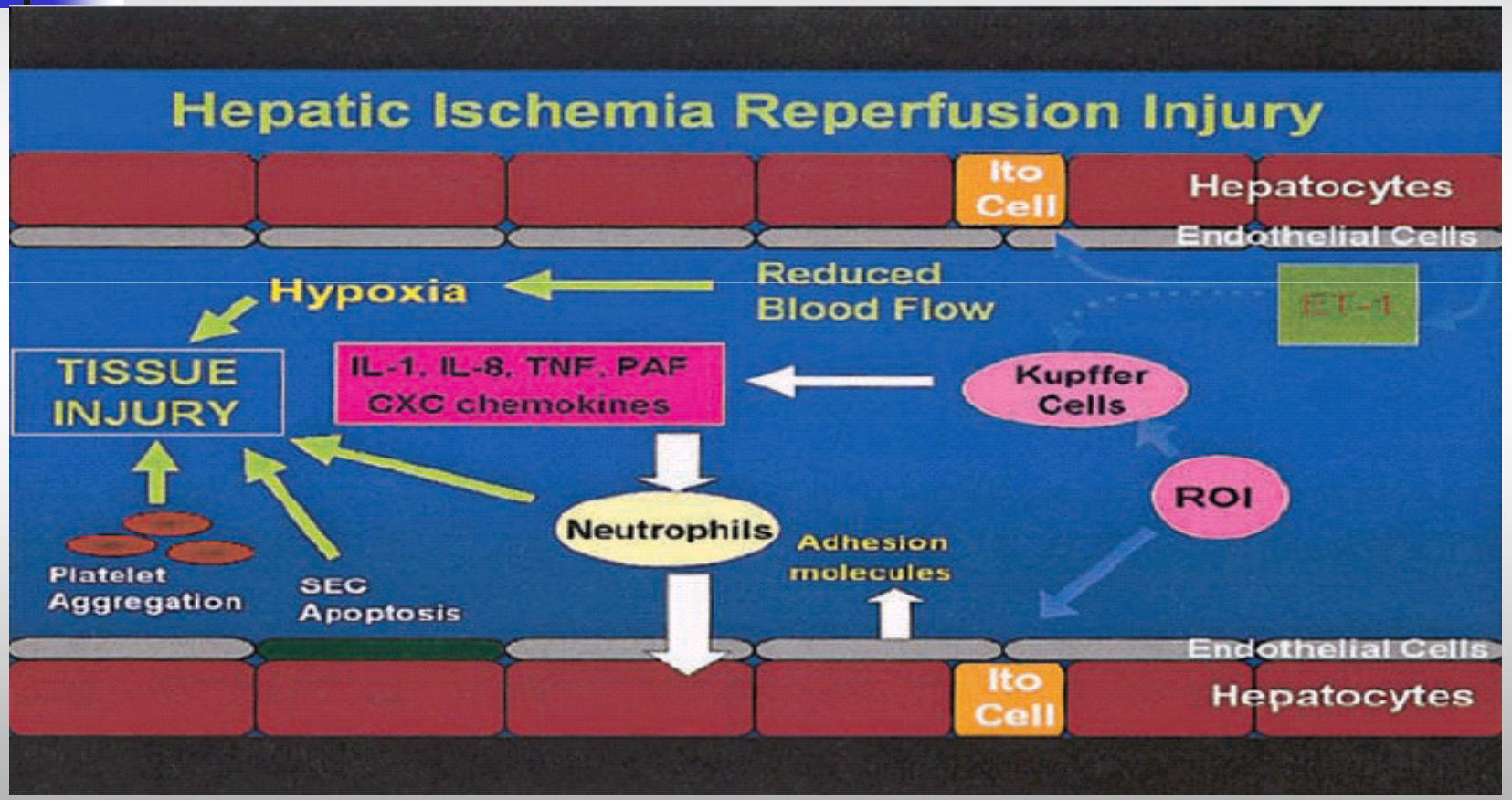
2nd Step of IR injury

- **Up-regulation of adhesion molecules**
  - **Activation of adhesion molecules (i.e., selectins, integrins & Ig)**
  - **Liberation of chemokines from Kupffer cells**
  - **Rolling and sticking Neutrophils to endothelial cells ↑**

- **Platelet aggregation**
- **Sinusoidal endothelial cell (SEC) apoptosis**

Tissue injury

2nd Step of IR injury



Prevention of Preservation Injury

- **Allows extended ischemia and rewarming times**
- **Preventing organ damage during CIT**
- **Prolonged storage**

- **University of Wiscosin(UW) solution**
- **Histidine-tryptophan-ketoglutarate (HTK) or Bretschneider solution**

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What is the role of Steatosis ?

- **Macrosteatosis:macrovesicular fatty change**
- **Microsteatosis : small vacuole deposits**

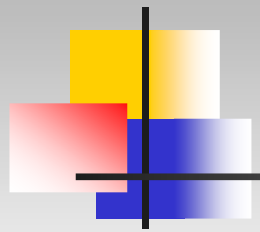
↓

- **Increase in cell volume: obstruction of hepatic sinusoidal space**

1% of steatosis* → **functional graft mass by 1%↓**

* Marcos et al, Transpl 2000

Impact of Steatosis on Graft Outcome



Steatosis

Mild (< 30%)

good result

Severe (>60%)

- **Primary nonfunction**
- **Early poor graft function**

Graft Failure

Degree of Steatosis Acceptable for LDLT

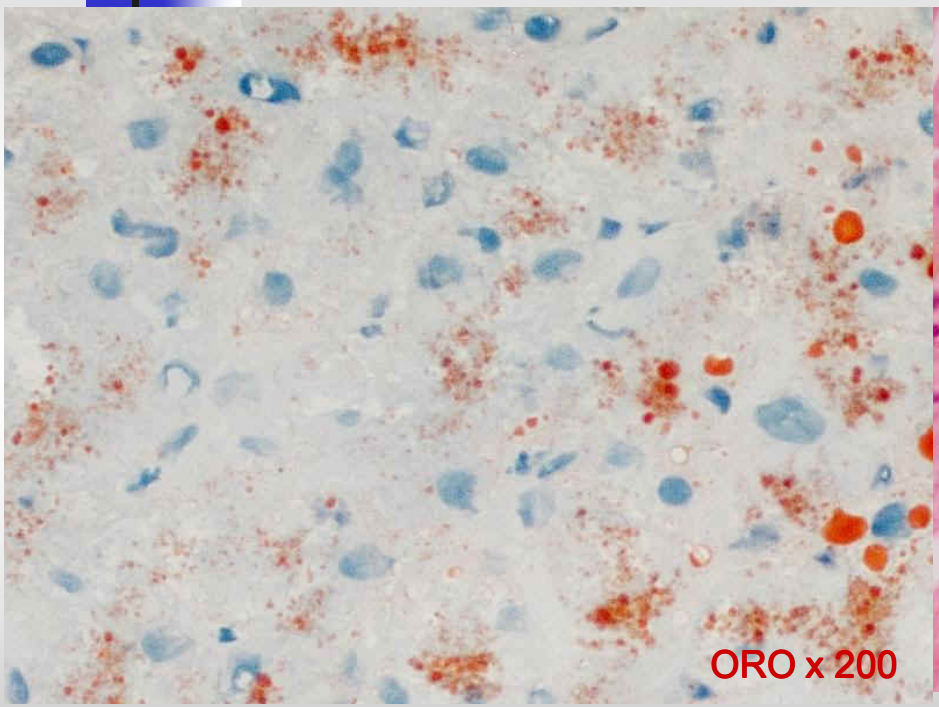
Microsteatosis : less injury and graft survival rates similar to normal livers

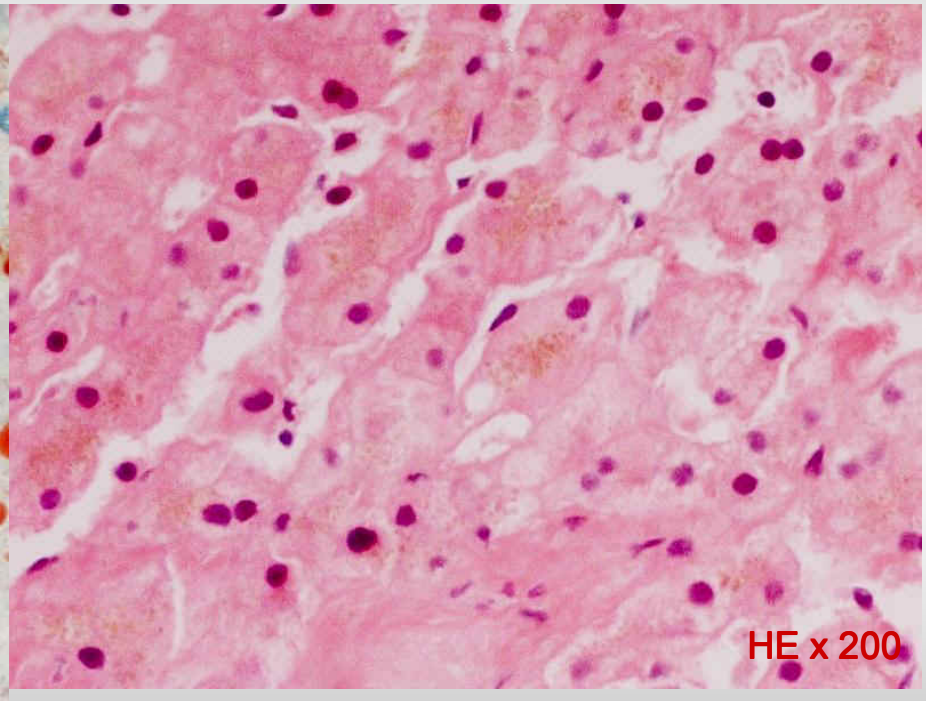
- **Macrosteatosis (< 30%): can be used**
- **Moderate macrosteatosis(<50%) : could be used , if GV-to-SLV is more than 40%**

Accurate Detection of Steatosis

- **Preoperative liver biopsy: standard method**
- **Imaging studies : fatty infiltration findings**
- **BMI(predictor of steatosis) > 25**

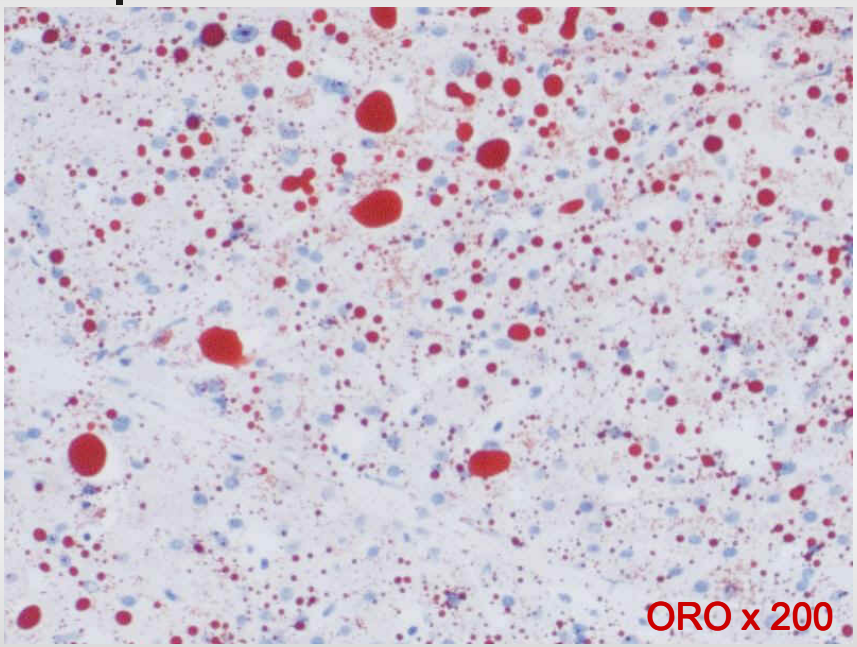
Photographs of Moderate Steatosis

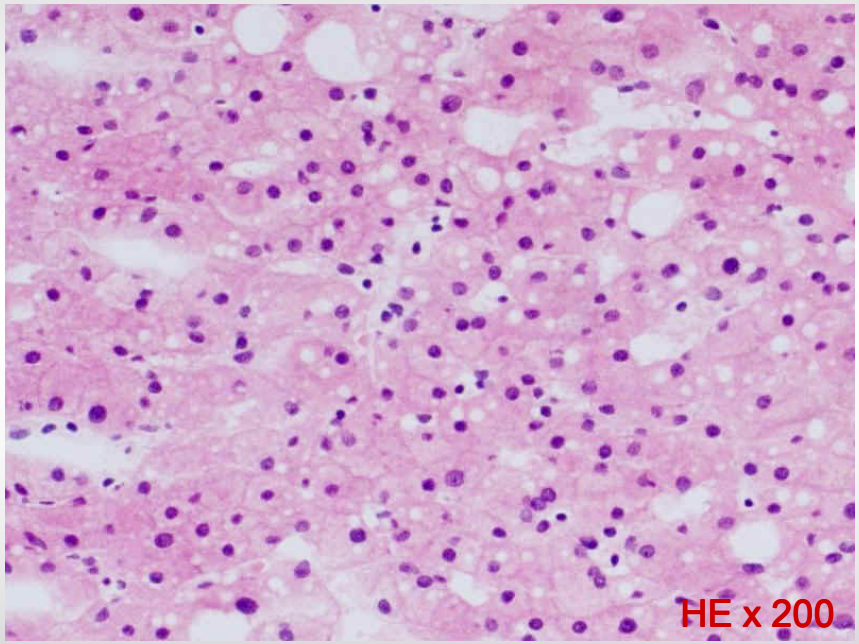




❖ Macrovesicular steatosis: 5%, Microvesicular steatosis: 20%

Photographs of Severe Steatosis





❖ Macrovesicular steatosis: 20%, Microvesicular steatosis: 50%

Approach to Donors with Steatosis

- **Recommendation**
  - **Low calorie diet (25-30 Cal x ideal body weight (kg) per day)**
  - **Aerobic exercise**
  - **Abstinence from alcohol**

Overcome of Donor Shortage

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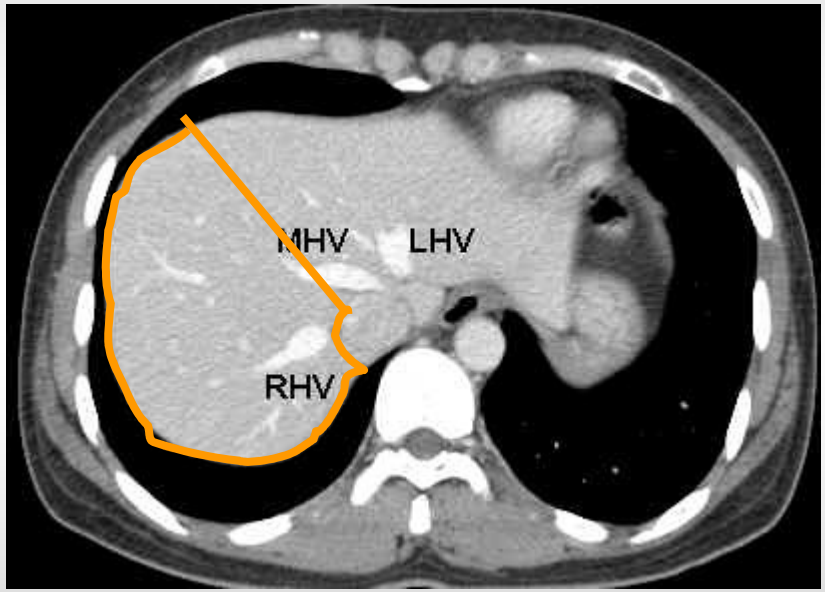
Optimal graft size in LT

- **Standard liver volume (SLV) or Estimated standard liver weight (ESLW)**
  - **Liver volume optimal for the recipient's metabolic demands**

- **formula ***
  - **SLV(ml) = 706.2 x BSA (m^2) +2.4**

*** Urata et al, Hepatology 1995**

Preoperative evaluation of liver volume



- **Liver CT (7.5mm slices)**
- **RLV(ml):**

  Sum of Areas x thickness (7.5)

- **Graft-to-recipient's weight ratio (GRWR)**
- **Graft volume to recipient's SLV (GV/SLV)**

Volumetry Example

- **Standard liver volume (SLV) of recipient**

  = 706.2 x (BSA) + 2.4 = 1204 cm^3

	Donor*		Recipient	
	Volume	%	GRWR	GV/SLV
Whole liver	1167cm^3			
Right lobe (excluding MHV)	705 cm^3	60.4%	*1.07%*	*58.6%*
Left lobe (excluding MHV)	431 cm^3	*36.9%*	0.65%	35.8 %

*CT volumetry

What is the most important thing in LDLT

Donor safety

Large-for-size

- **Hepatic artery thrombosis**
- **Portal vein thrombosis**

Small-for-size

- **Primary nonfunction**
- **Early poor graft function**
- **Risk of rejection ↑**

Graft Failure

Minimum Graft Size (?)

- **Lo et al*, 40% or less of GV/SLV**
- **Kiuchi et al**, less than 1% of GRWR**
- **Kawasaki et al#, 30-40% of SLV or 0.8~1.0% of GRWR**

Lower graft survival

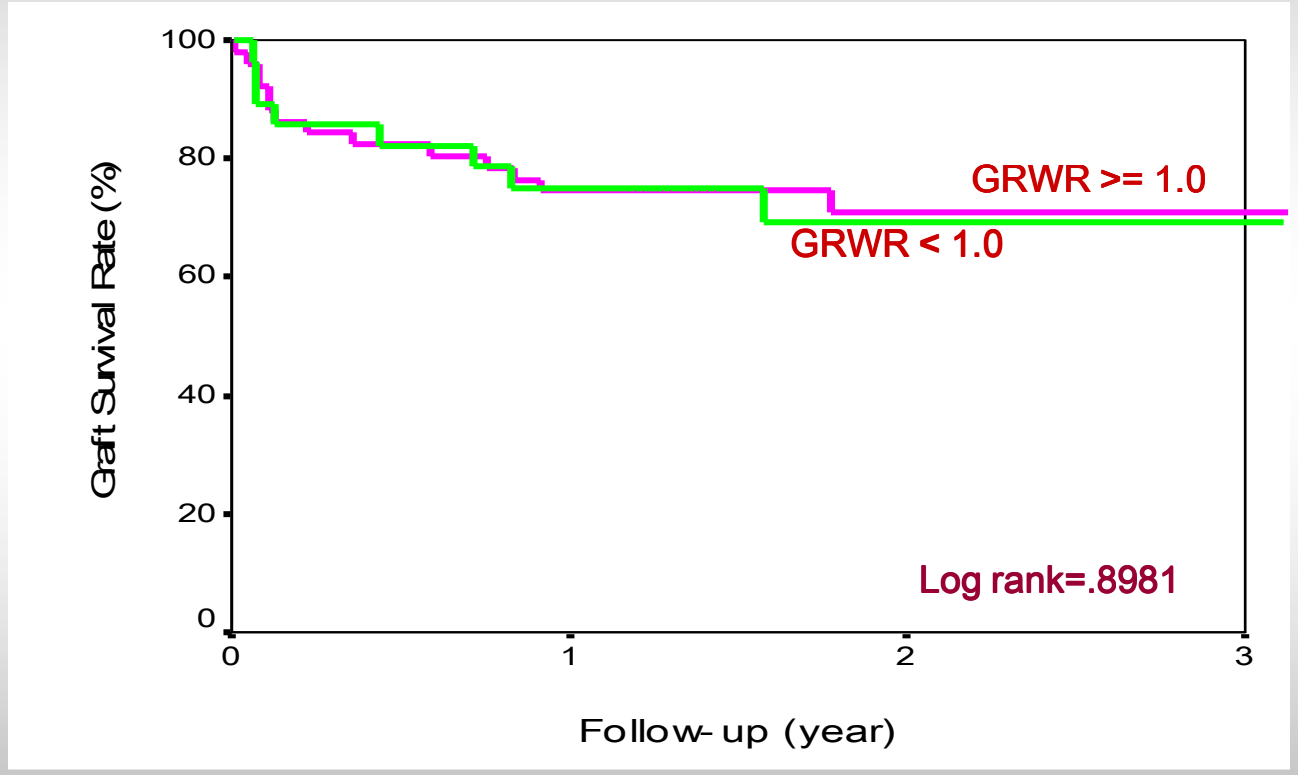
*** Lo et al, Transplantation 1996**

**** Kiuchi et al, Transplantion 1999**

 # Kawasaki et al, Ann Surg 1998

Graft Survival

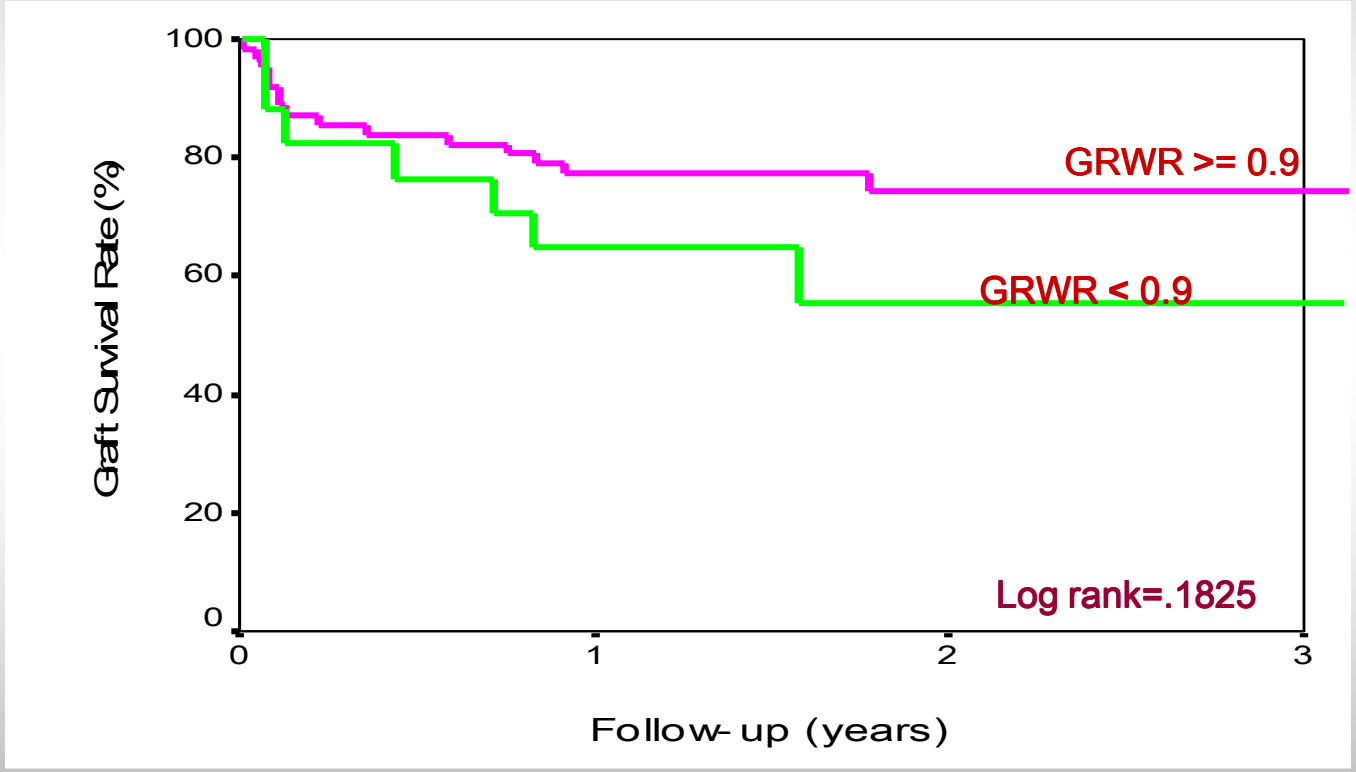
According to GRWR : 1.0, OTC in SMC



*** From June 1997 to June 2002 , 79patients received adult LDLT**

Graft Survival

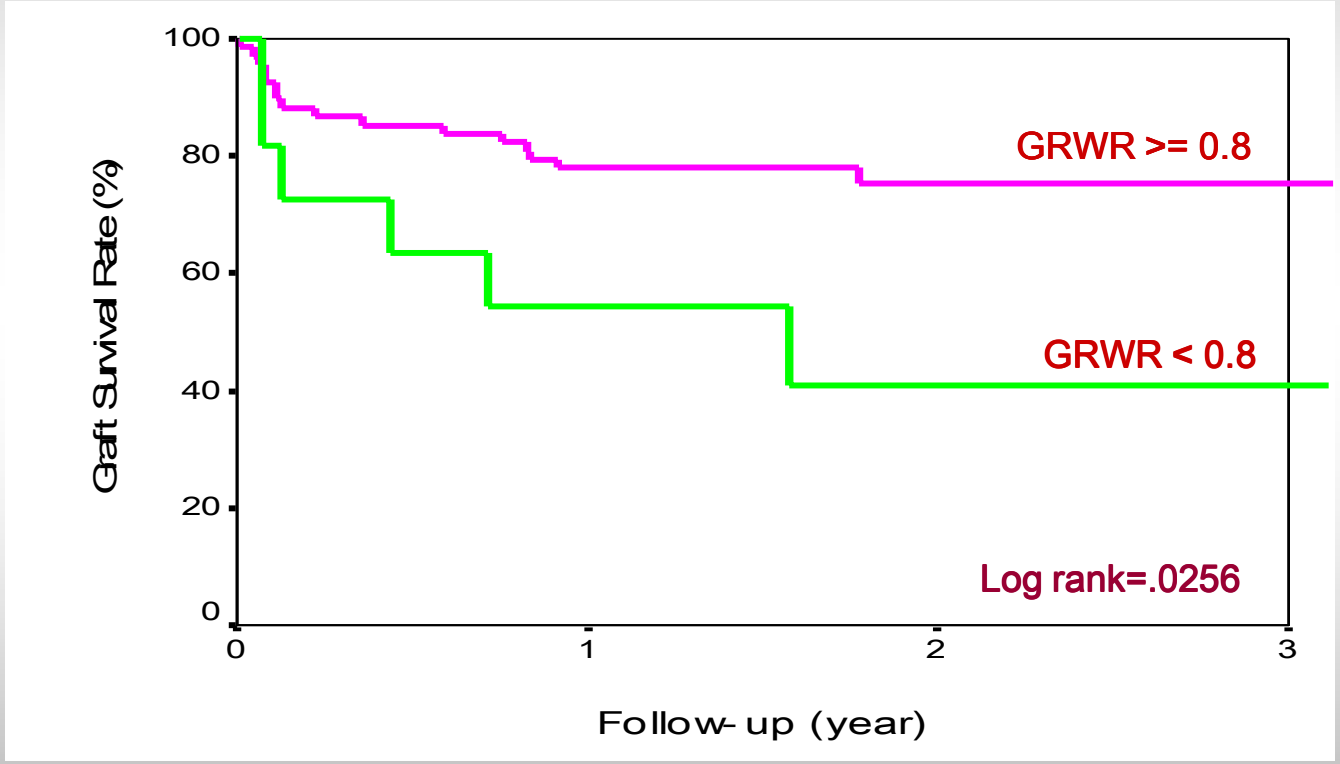
According to GRWR : 0.9, OTC in SMC



*** From June 1997 to June 2002 , 79patients received adult LDLT**

Graft Survival

According to GRWR : 0.8, OTC in SMC



*** From June 1997 to June 2002 , 79patients received adult LDLT**

Marginal- or Small-for-size grafts

- **Graft weight: less than 30% of SLV or 0.8% of GRWR**

- **Kiuchi: 28% GW of recipient SLV, successful transplantation - primary biliary cirrhosis**
- **Lo: 25% GW of recipient SLV, successful transplantation – fulminant hepatic failure biliary cirrhosis**

Small-For-Size(SFS) syndrome

- **Graft weight: less than 30% of SLV or 0.8% of GRWR**
- **Graft weight, greater than 40% of SLV or 1.0% of GRWR; associated with severe portal hypertension or relative impedence to hepatic venous drainage**

- **Poor bile production**
- **Delayed synthetic function;coagulopathy**
- **Prolonged cholestasis**
- **Intractable ascites**

Mechanism of SFS syndrome

- **Graft inflow : portal venous flow (PVF)**
- **PVF increase**
  - **high cardiac output**
  - **low peripheral vascular resistance**
  - **reduced hepatic arterial flow**

Mechanism of SFS syndrome

Main factors

- **Persistent portal hypertension**
- **Portal venous hyperperfusion**

SFSS

Reduced hepatic arterial flow

- **Preoperative conditions(UNOS status, ascites, bilirunim↑)**
- **Small functional graft mass**
- **Postoperative variables (sepsis, bile leak, renal failure)**

Histologic changes of graft in SFSS

- **Hepatocyte ballooning**
- **Centrolobular necrosis**
- **Parenchymal cholestasis**

→ **Reversible change**

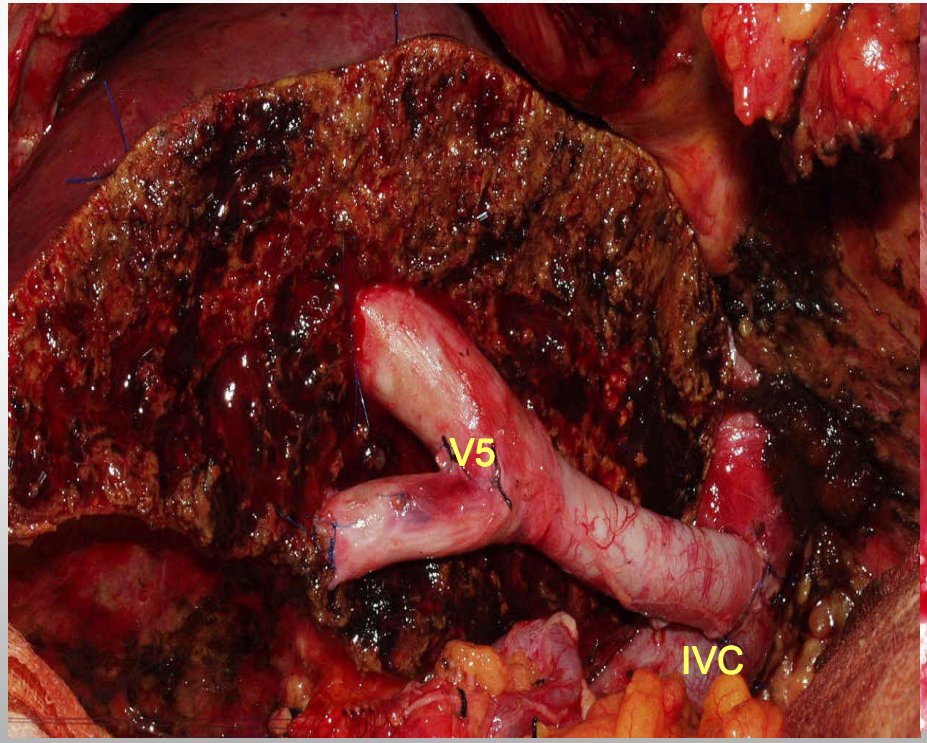
- **Graft regeneration : not affected**

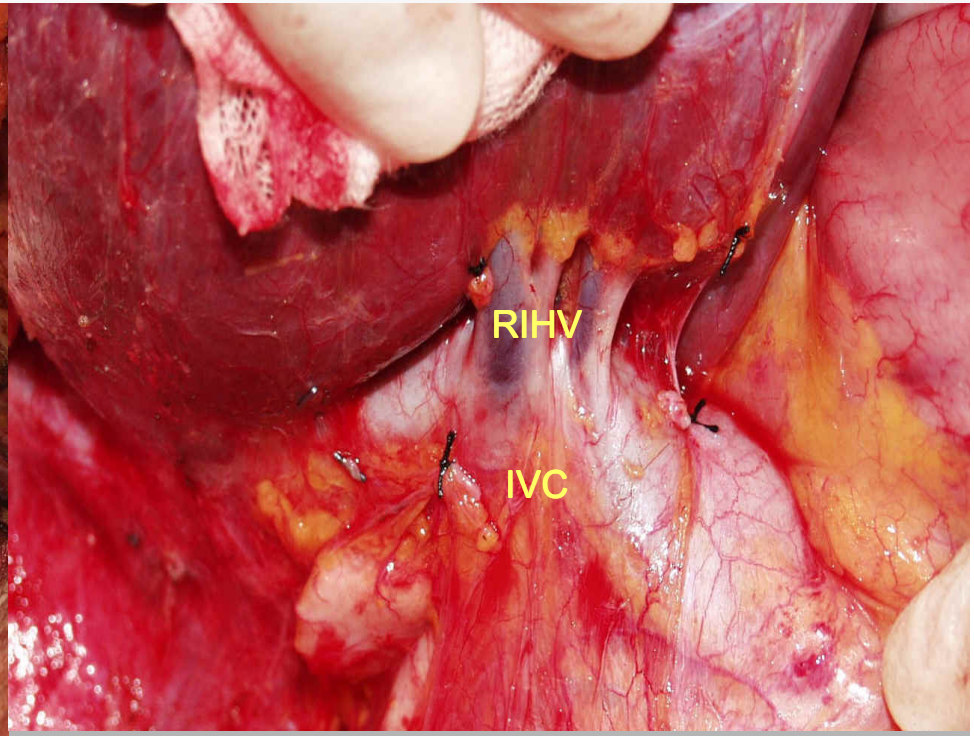
Prevention of SFS syndrome

- **Hepatic venous drainage (S5,S8)- Rt lobe graft**
- **Extended right-lobe graft including MHV**
- **Dual left lobe graft**
- **Auxiliary Partial Orthotorpic transplantation**
- **Splenic artery ligation**
- **Portosystemic shunt**

Hepatic venous drainage - Rt lobe graft

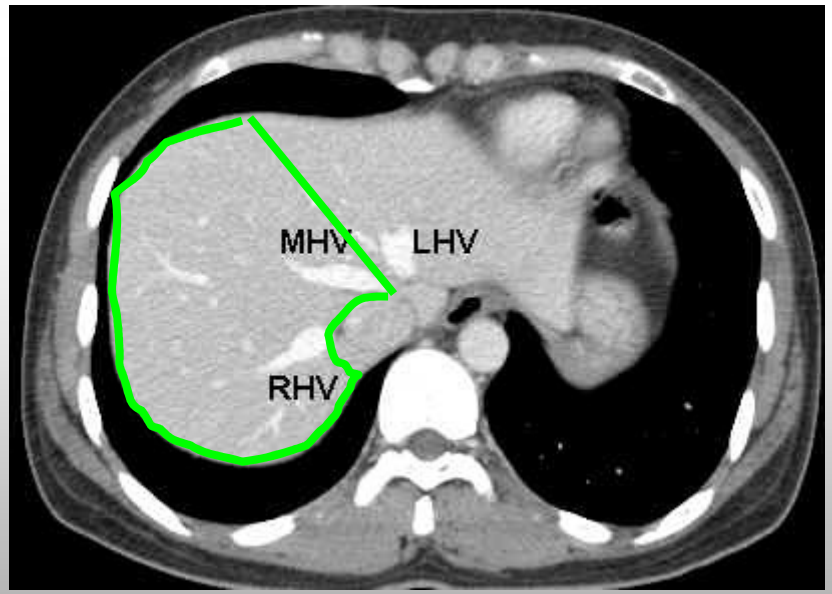
- **Hepatic venous drainage: S5, S8, RIHV**





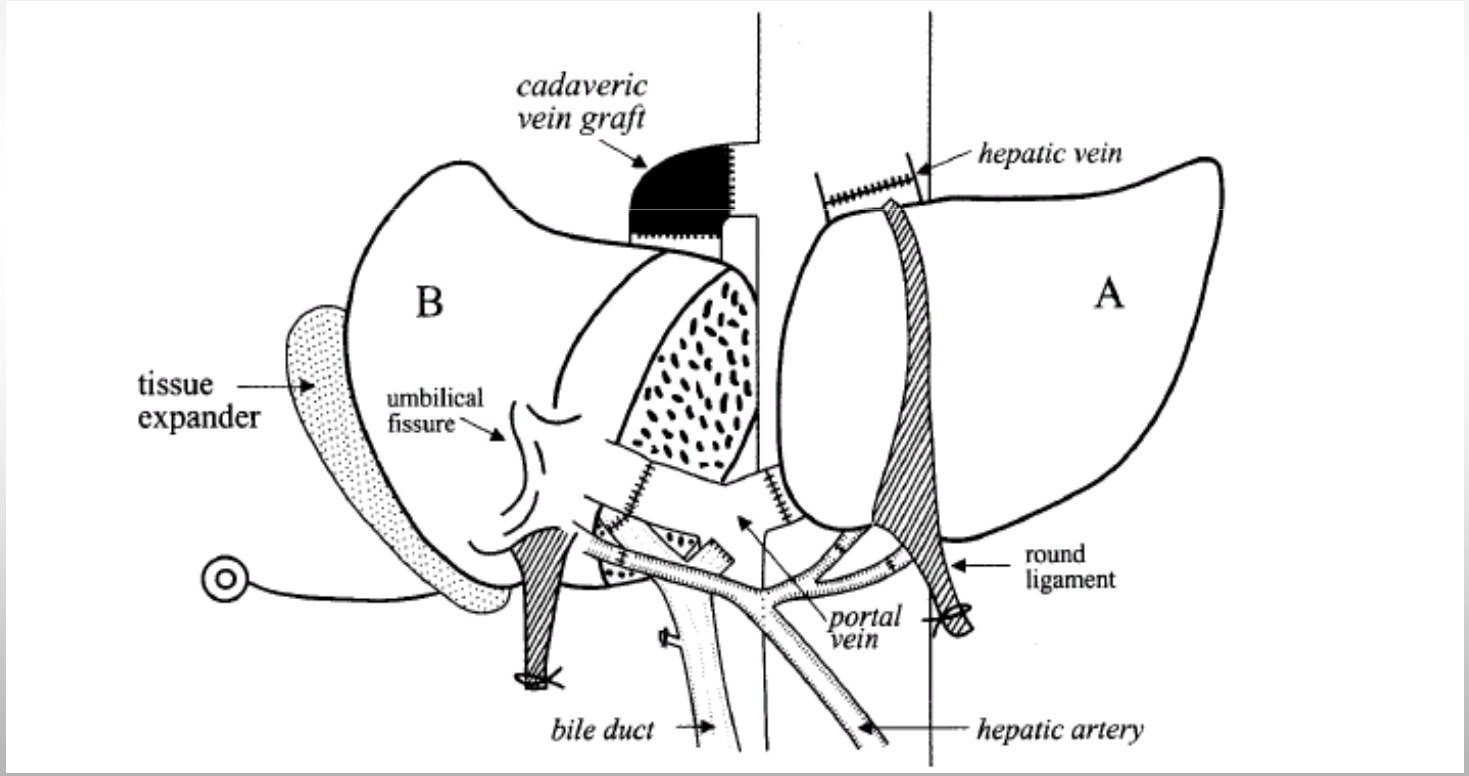
Extended right-lobe graft including MHV

- **Increased risk of donor safety**
- **Extremely limited**



Dual left lobe graft

- **Left lobe grafts from two donors**



Lee et al, Surgery 2001

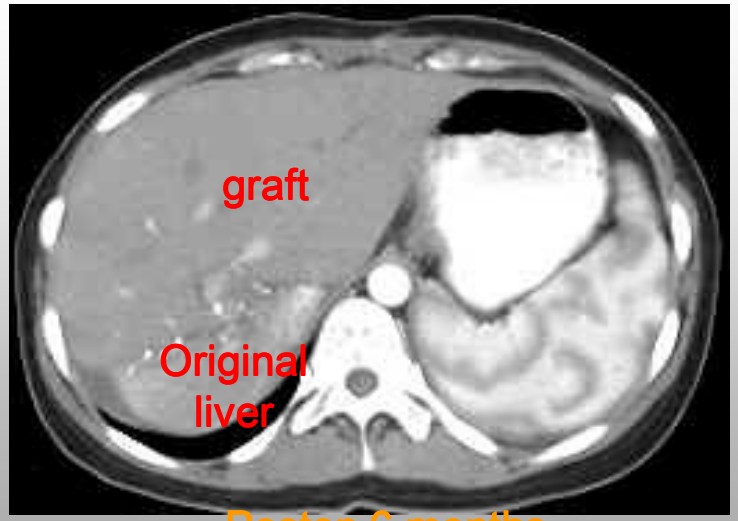
Auxiliary Partial Orthotopic Liver Transplantation (APOLT)

- **Concept: native liver support graft function**
- **Fulminant hepatic failure, metabolic disorders**
- **Inomata et al, 20 recipients**
- **Aid for a SFS graft**

Inomata et al, Transplantation 1999

APOLT in SMC

- **29/ F(168 cm, 56kg), fulminant hepatitis; Lt hemihepatectomy**
- **Donor : 21/M, her brother, extend left lateral segment; 259 gm GRWR: 0.46 %**



Postop 6 months

Management of Portal Hyperperfusion

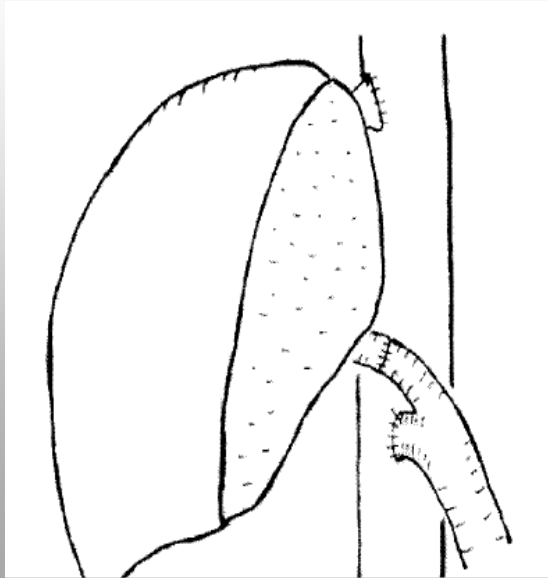
- **SFS (GRWR<0.8%), associated with excessive PVF (>250 ml/min/100 gm GW)**
  - **Poor graft survival**

- **Splenic artery ligation (Troisi et al)**
  - **to resolve ascites**
  - **to increase HAF**
  - **to prevent thrombocytopenia**

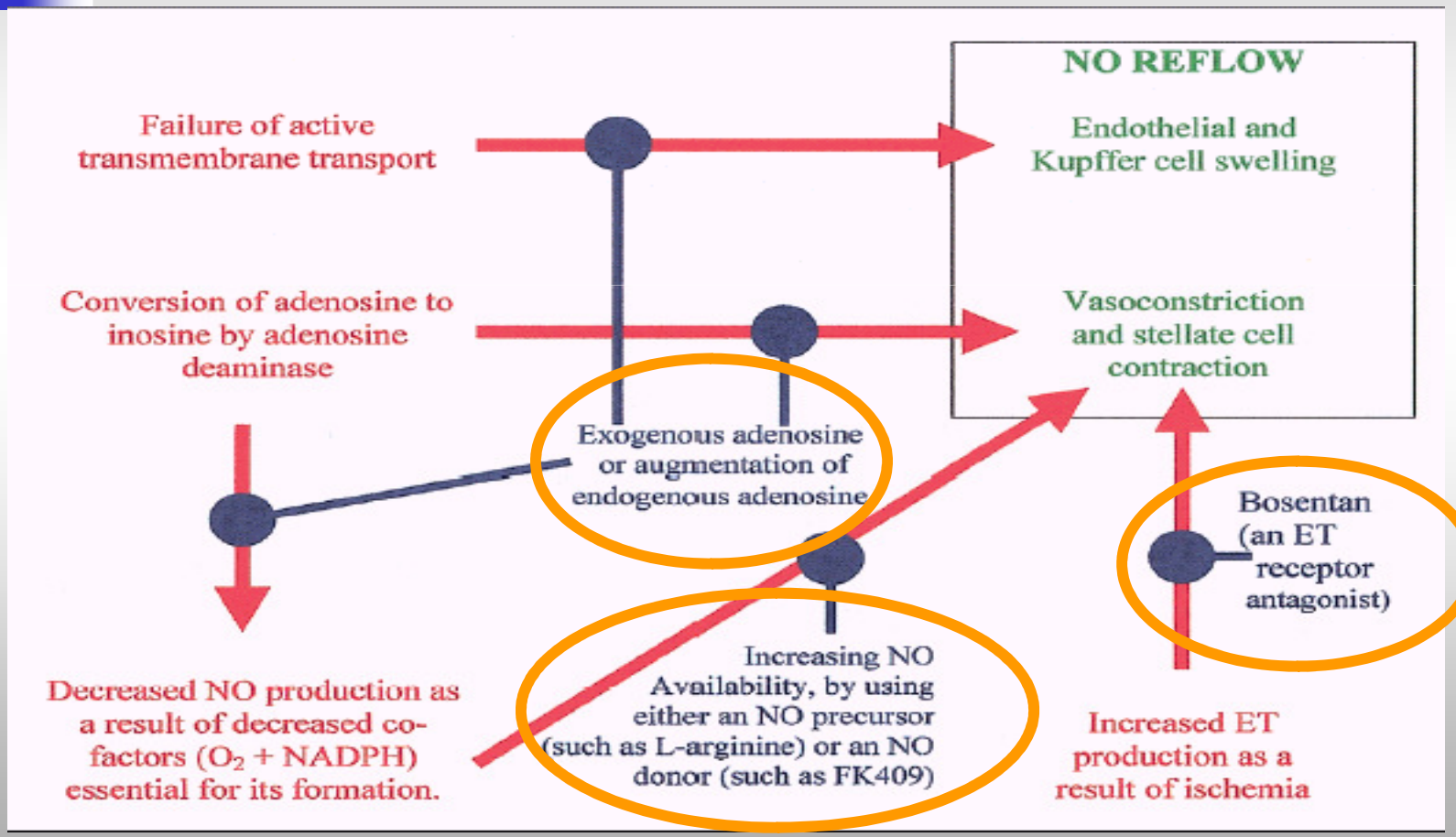
Troisi et al, Ann Surg 2003

Management of Portal Hypertension

- **Portosystemic shunt; RPV – IVC (end-to-side)**
  - **Nishizaki et al; taken down after reperfusion**
  - **Takada et al; sustained opening➔ portal hypoperfusion / hyperammonemia**

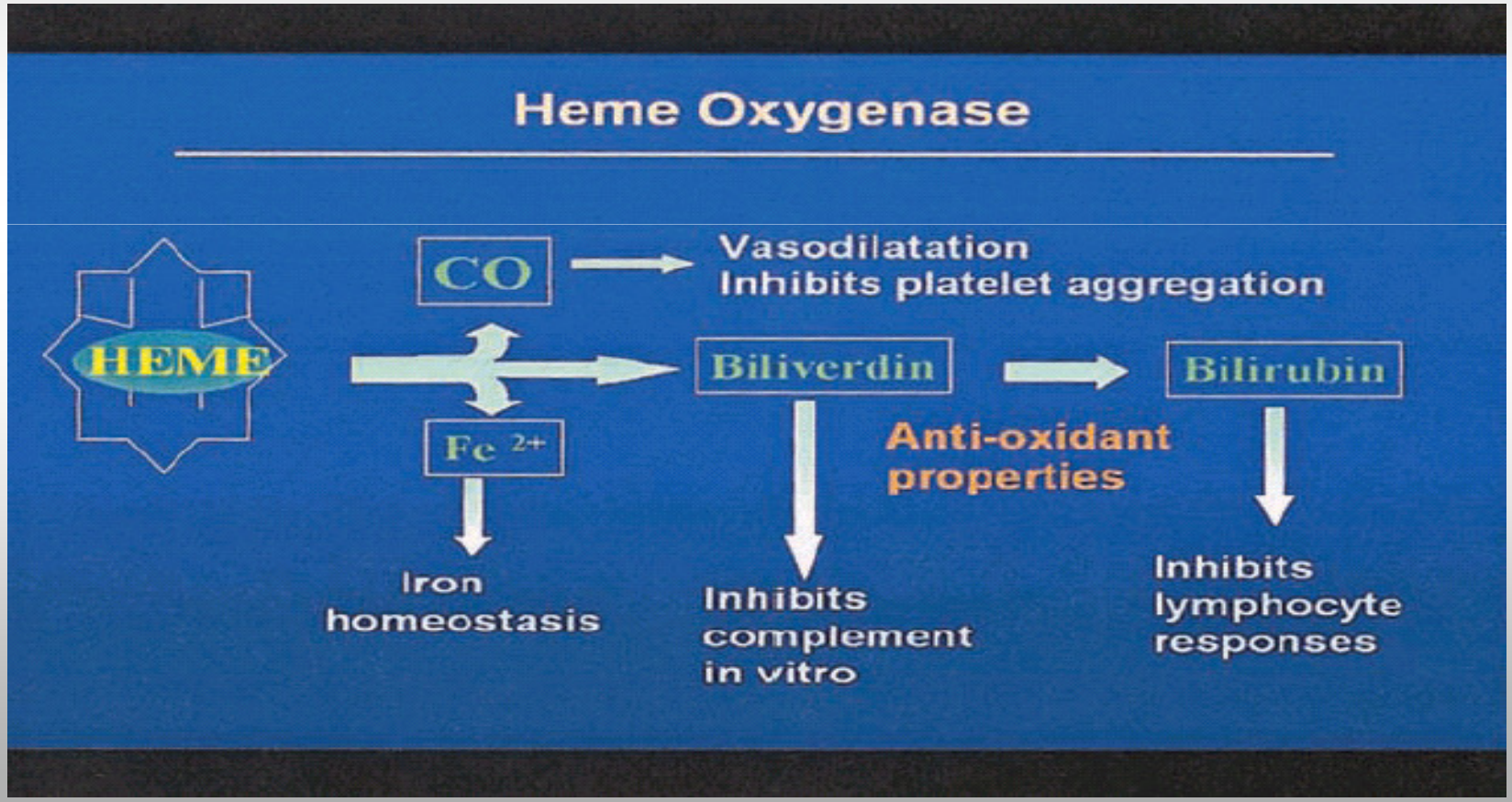


Experimental studies for the manipulation of marginal donors



Upregulation of Heme Oxygenase System

- **Heme Oxygenase-1 (HO-1): hsp32, potent cytoprotective effects**



Conclusions

- ***We should try and develop various clinical or experimental modalities that can be manage marginal donors*.**

Overcome of Donor Shortage