La metafora del Titanic
Trapianti, liste di attesa e criteri di selezione

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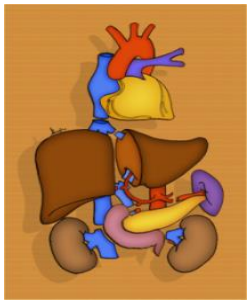
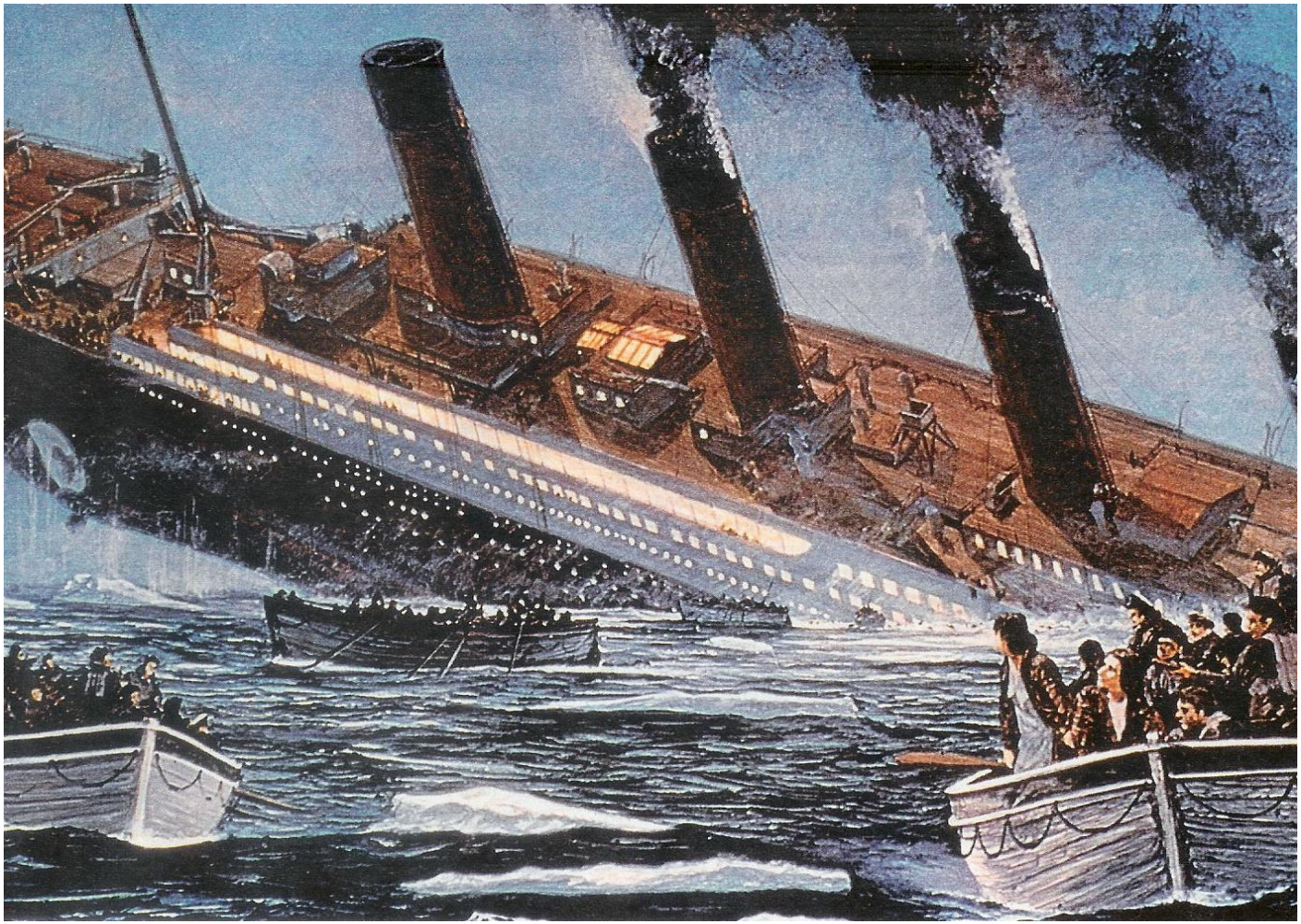
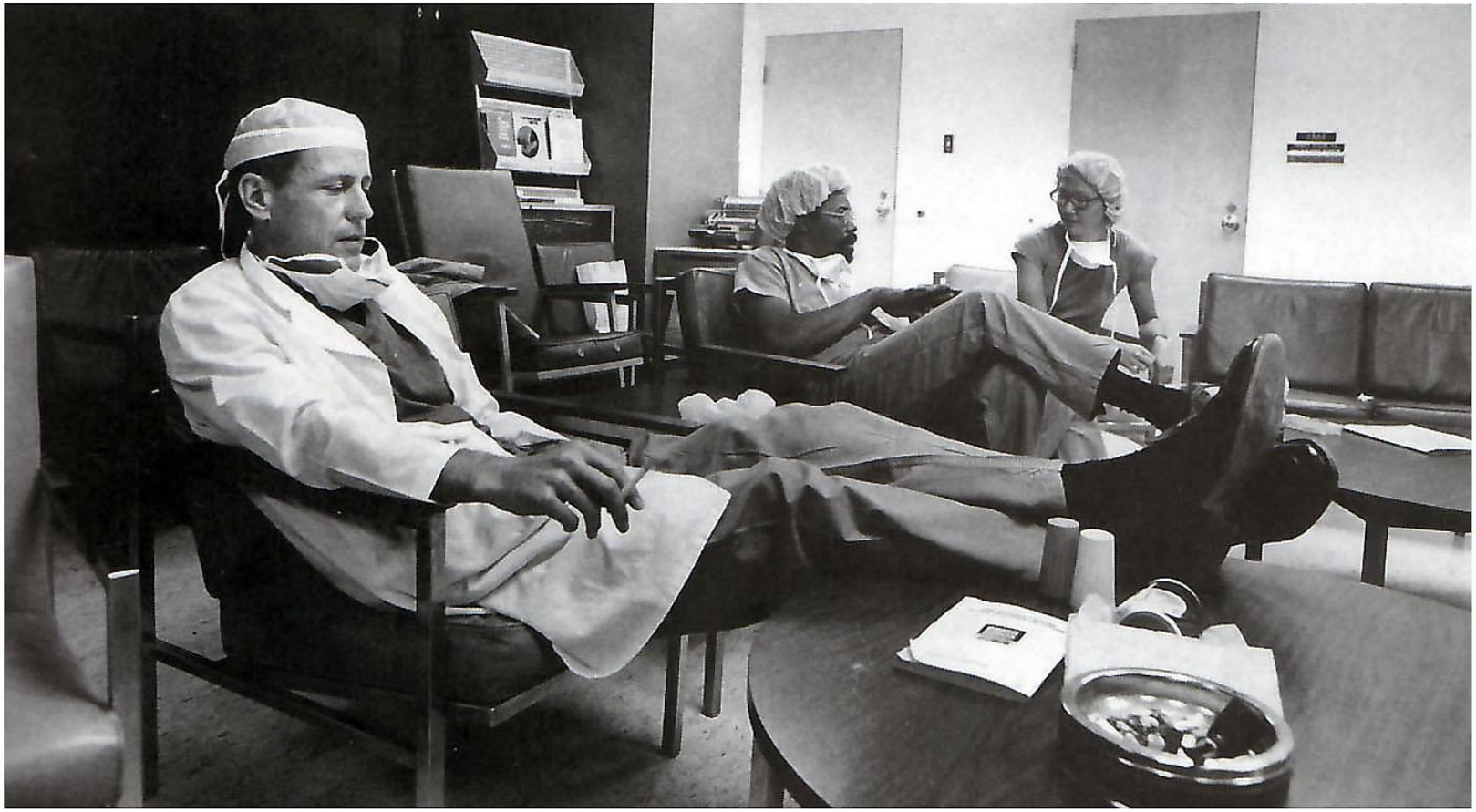


No conflict of interest to declare

During emergency: Who first?

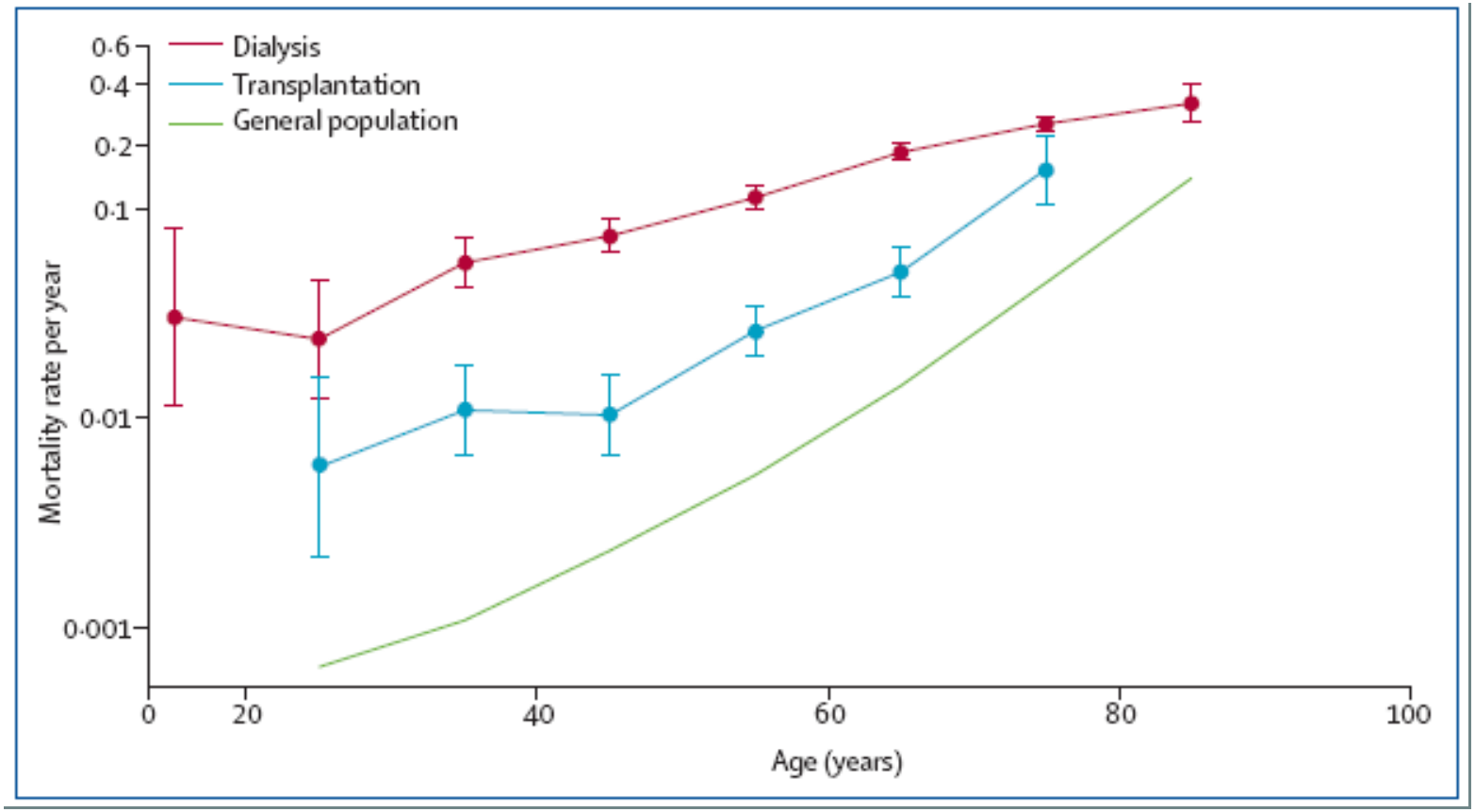


How did we learn from the past?



The consequences of successful transplantation

www.thelancet.com Vol 378 October 15, 2011



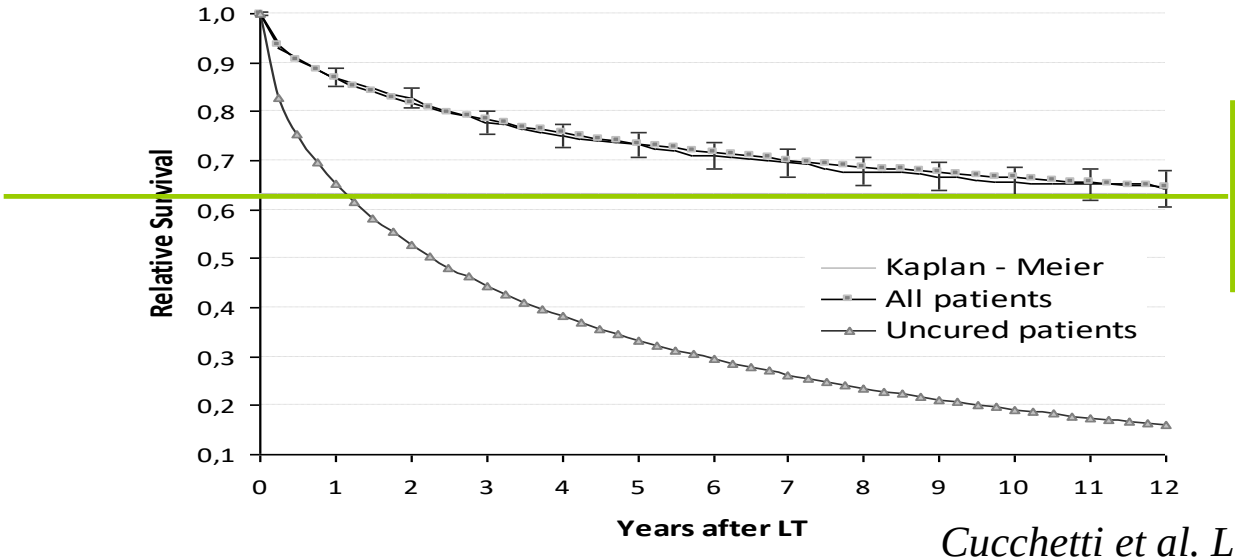
Can Liver Transplantation Provide the Statistical Cure?

Alessandro Cucchetti,[1] Alessandro Vitale,[2] Matteo Cescon,[1] Martina Gambato,[3] Lorenzo Maroni,[1] Matteo Ravaioli,[1] Giorgio Ercolani,[1] Patrizia Burra,[3] Umberto Cillo,[2] and Antonio D. Pinna[1]

[1]Department of Medical and Surgical Sciences, Sant'Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy; and [2]Hepatobiliary Surgery and Liver Transplant Unit, Department of General Surgery and Organ Transplantation, and [3]Multivisceral Transplant Unit, Department of Surgery, Oncology, and Gastroenterology, University of Padua, Padua, Italy

Bologna - Padua experience between January 1999 and December 2012: 1371 LTs

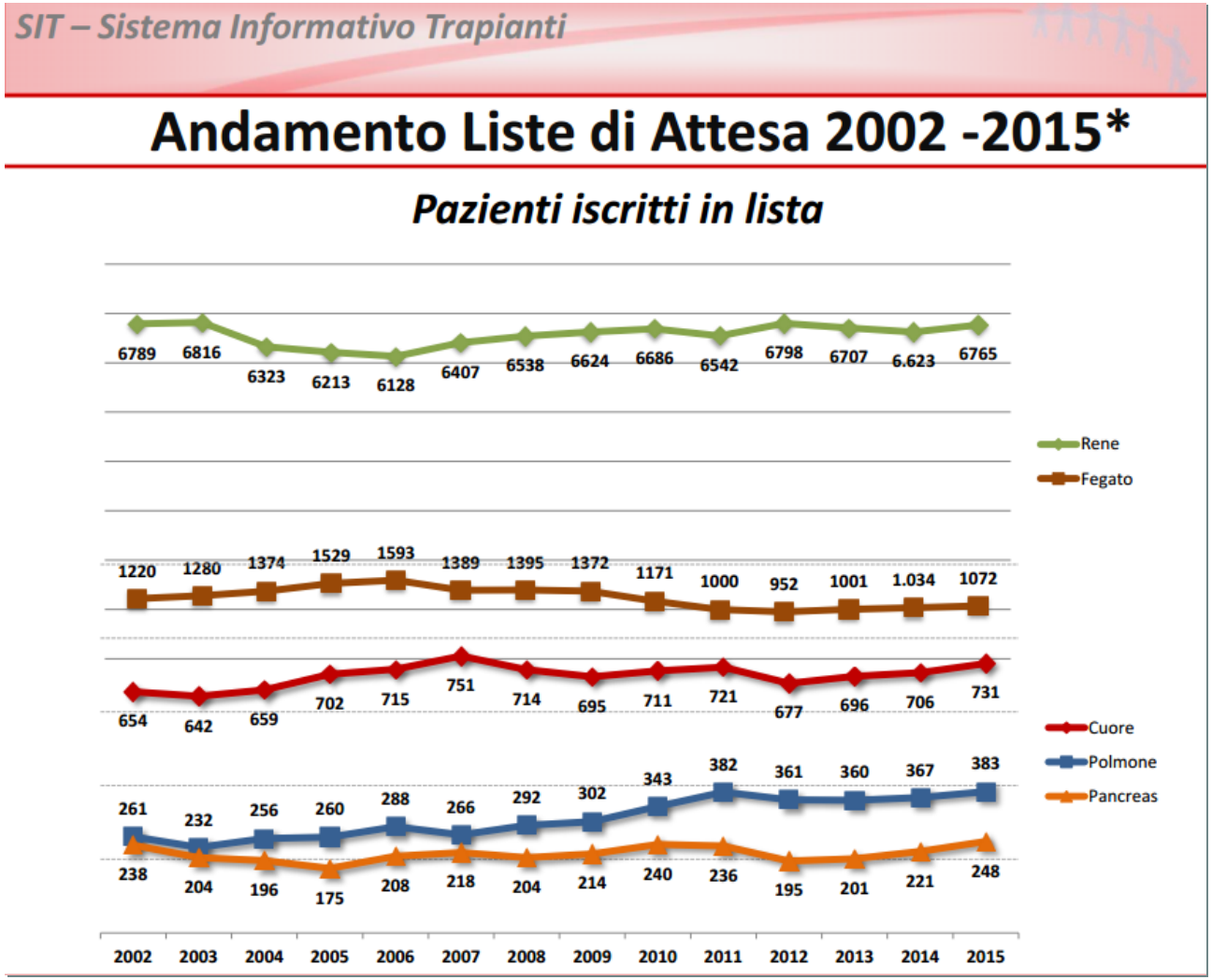
When the mortality among transplanted patients returns to the same level as in the general population, they can be considered "statistically cured".



Cure Fraction = 63.4% (95% C.I. : 52.6 – 72.0)

Cucchetti et al. Liver Transpl. 2014

Gap among candidates and recipients



Donor and recipient

European gap among donors and recipients

Extended criteria donors

Living donors

Split

NHBD

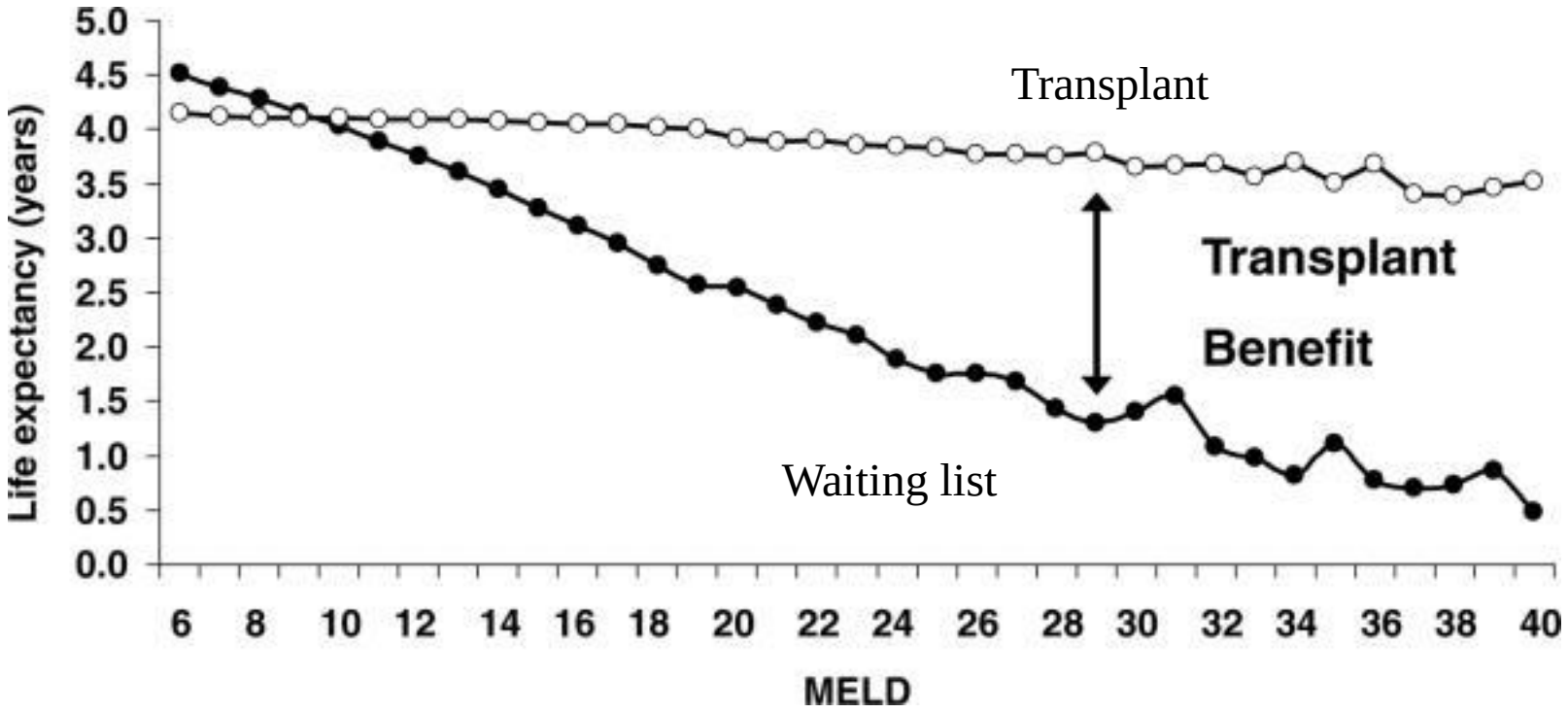
Domino

Effective allocation system

American Journal of Transplantation 2009; 9 (Part 2): 970–981
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2009.02571.x

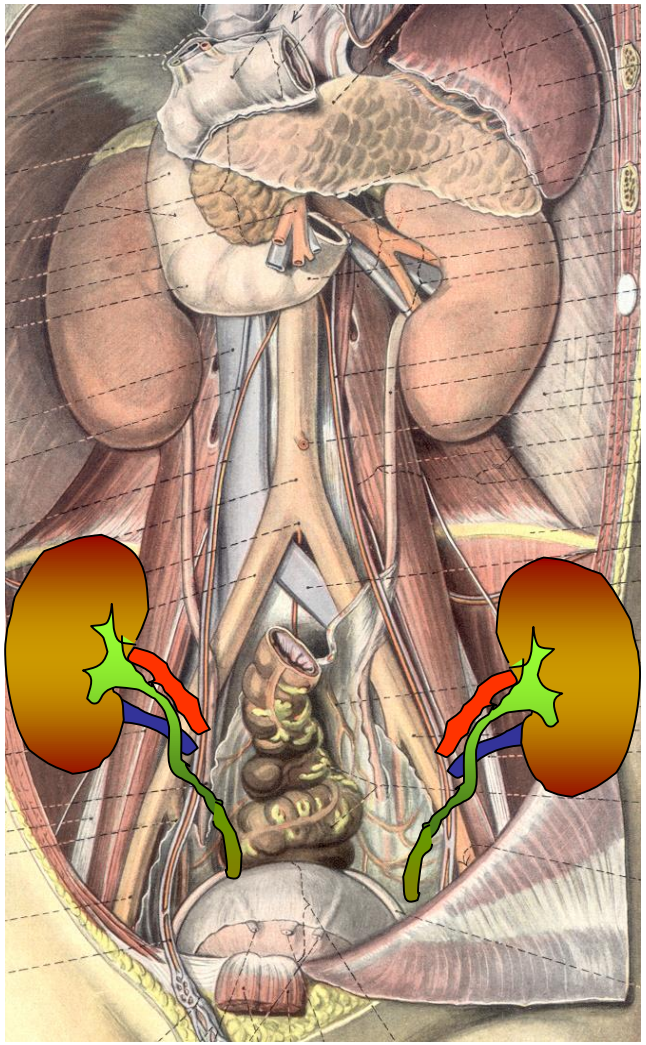
Survival Benefit-Based Deceased-Donor Liver Allocation



Extended Criteria Donor/Graft = ECD

Graft with an increased risk of early failure or inferior graft and patient survival resulting from per-transplant factors

How to optimize ECD ?



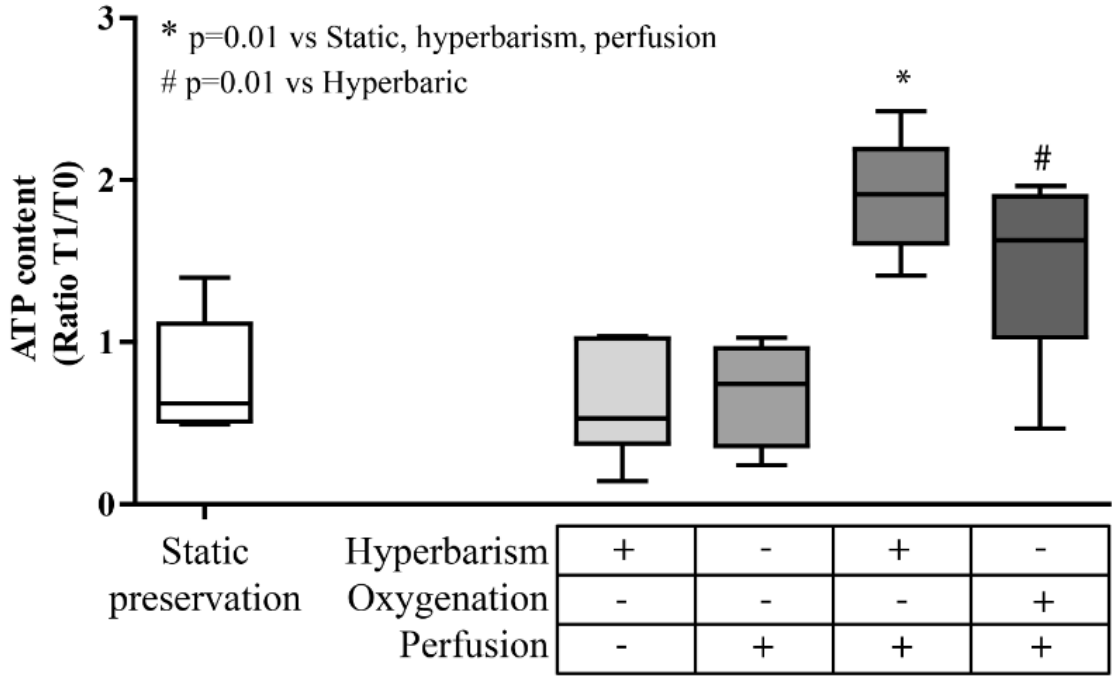
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Outcome of Renal Transplantation from Older Donors

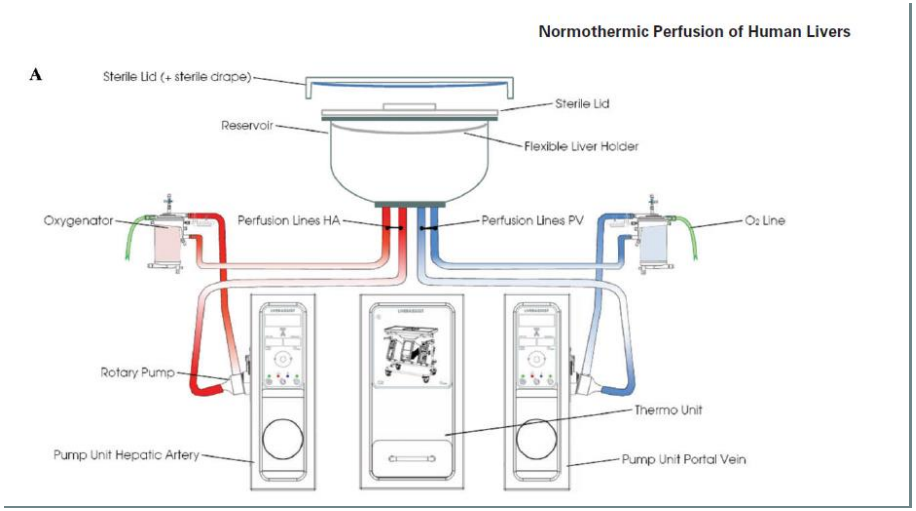
Giuseppe Remuzzi, M.D., Paolo Cravedi, M.D., Annalisa Perna, Stat.Sci.D., Borislav D. Dimitrov, M.D., M.Sc., Marta Turturro, Biol.Sci.D., Giuseppe Locatelli, M.D., Paolo Rigotti, M.D., Nicola Baldan, M.D., Marco Beatini, M.D., Umberto Valente, M.D., Mario Scalamogna, M.D., and Piero Ruggenenti, M.D., for the Dual Kidney Transplant Group*

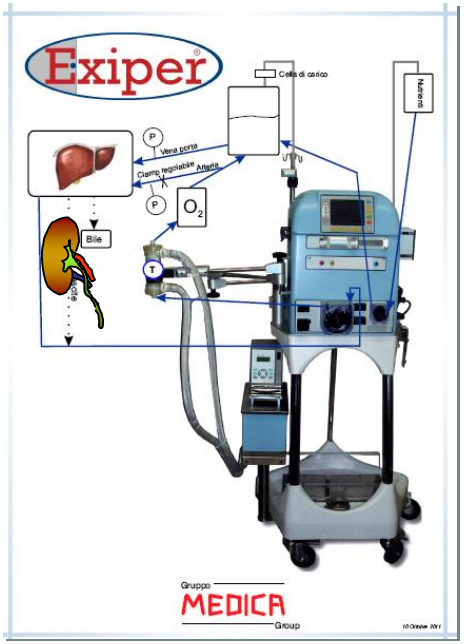
How to optimize ECD ?



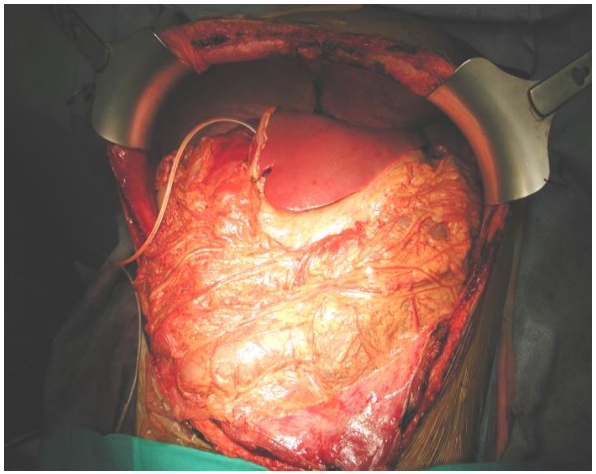
Recruit discharged graft – kidney (3 H)

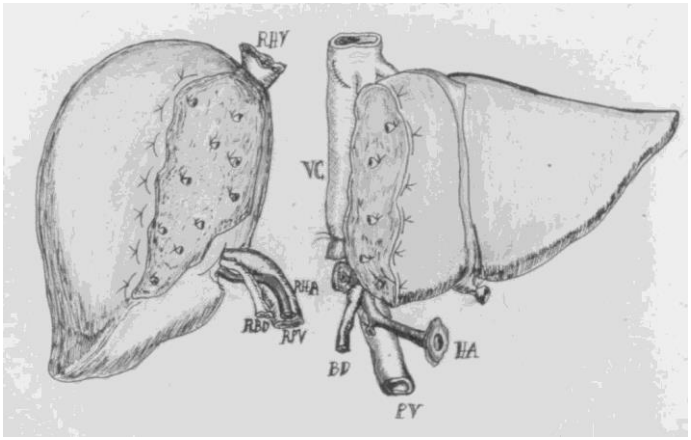
How to optimize ECD ?

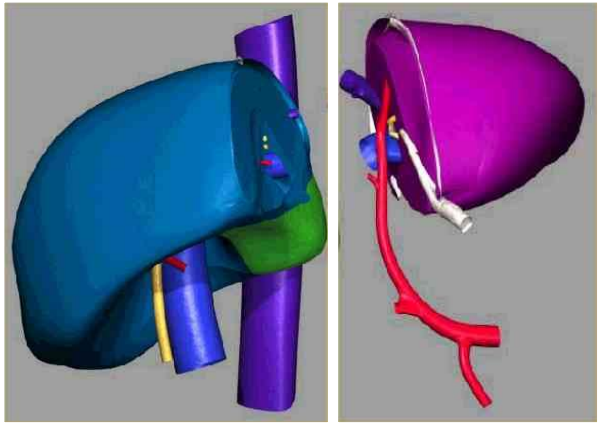




Surgical Techniques To-day and To-morrow





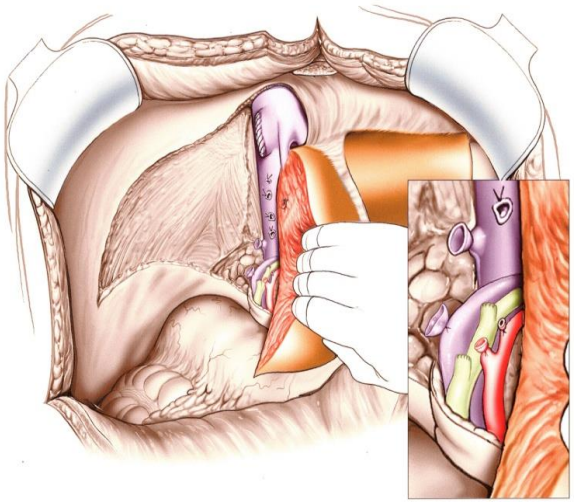


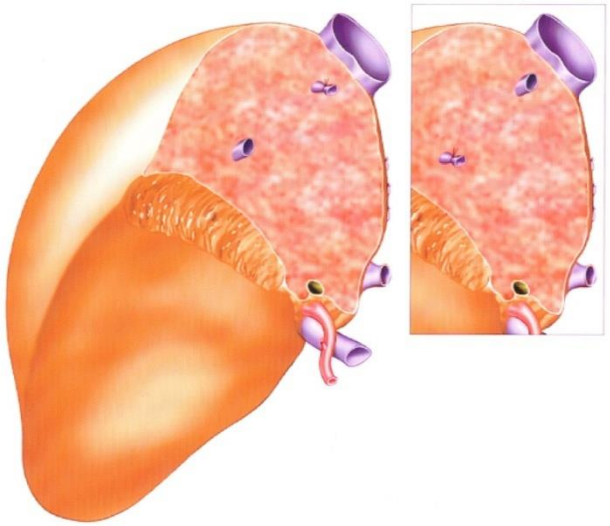
Surgical Techniques To-day and To-morrow

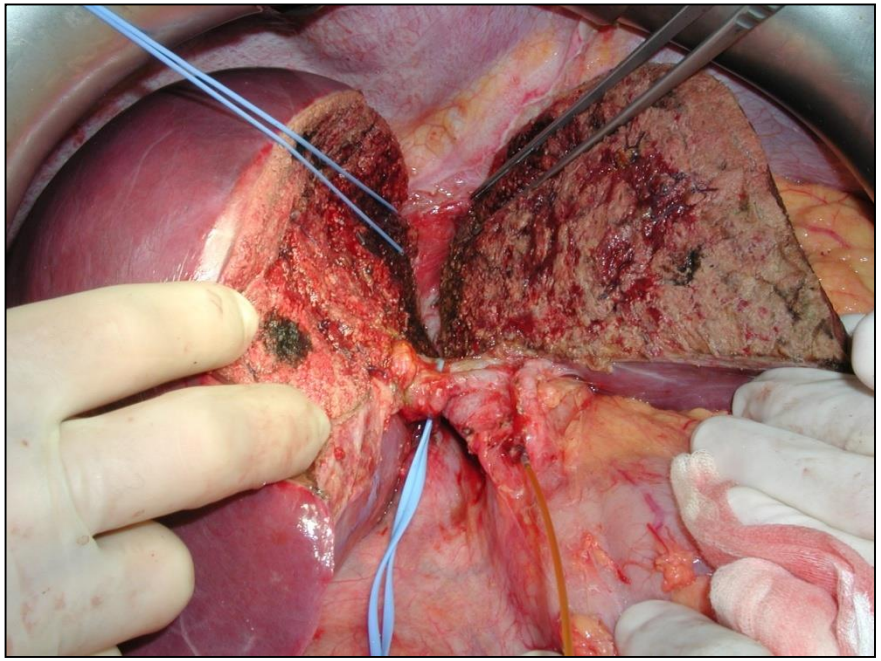
Liver Transplantation With Left Lateral Segments in Adults: A Risk or a Possibility?

Transplantation • Volume 88, Number 6, September 27, 2009

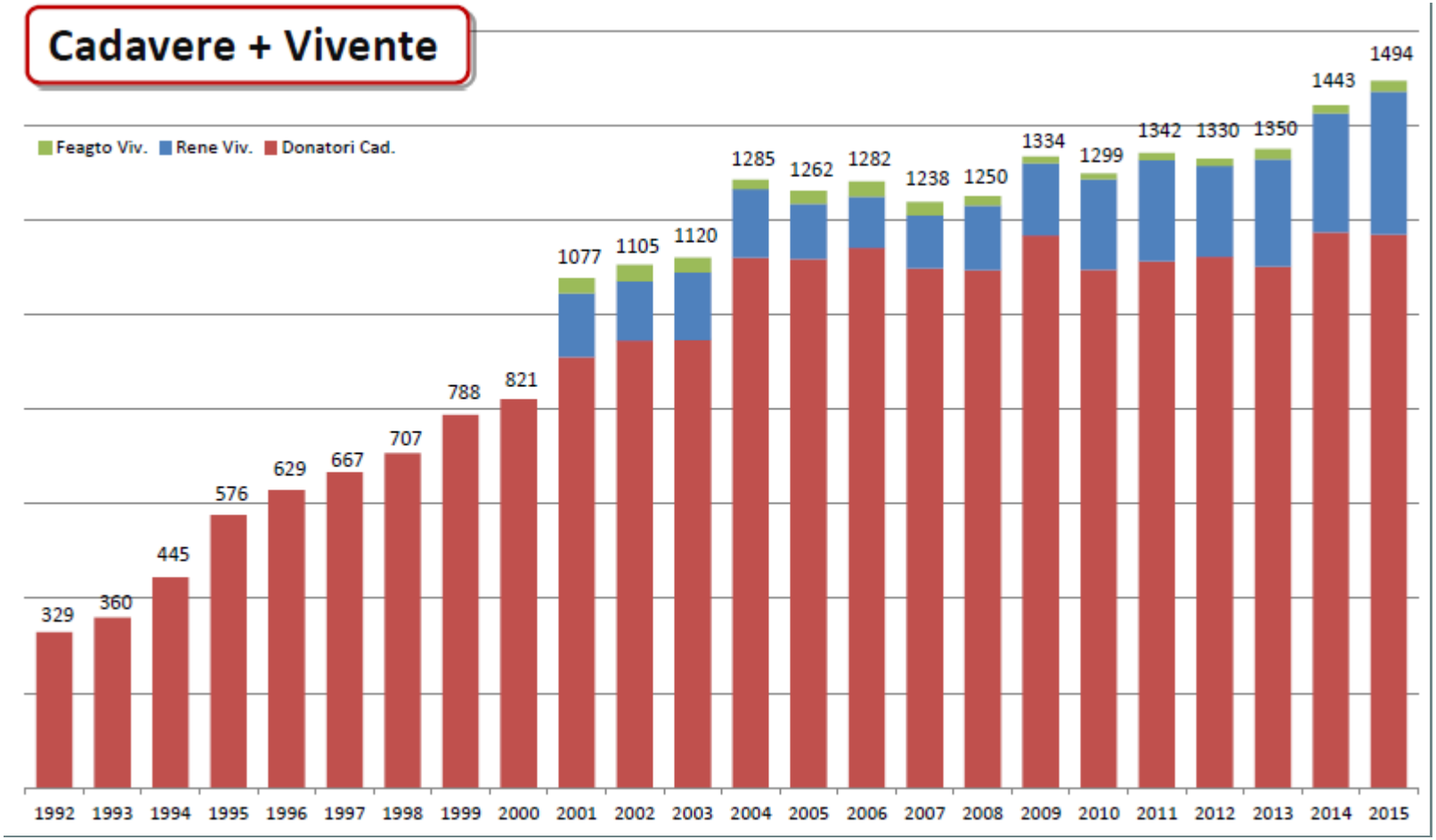
Surgical innovations: living donor







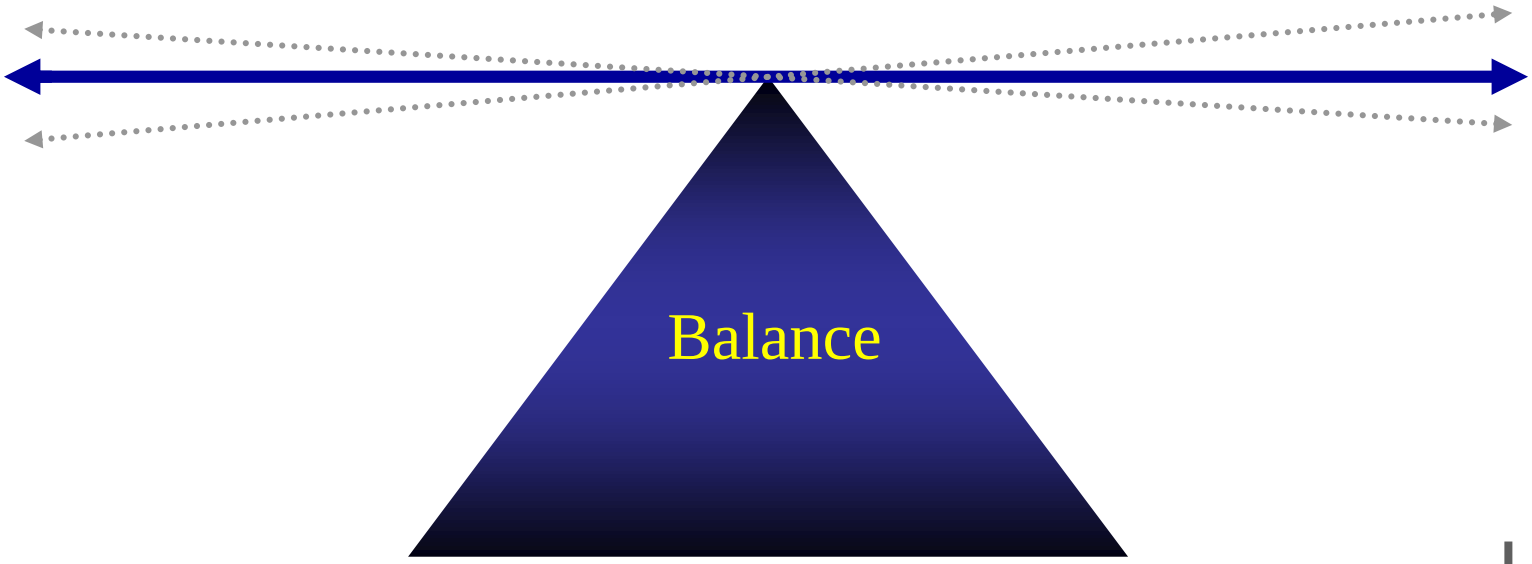
Living donors



Surgical selection, point of view

Risk donor

Recipient and graft survival



Risk of donor nephrectomy

- ***Donors Peri-operative Mortality***
- living donor mortality from three large American surveys (covering nearly 10,000 operations)
- reported death rates range from 0.03% – 0.06%
- most common causes of death pulmonary embolus, hepatitis and cardiac events (myocardial infarction and arrhythmias)
- these death rates are lower the risk in the USA of dying in a road traffic accident in one year (0.02%)

Najarian JS, Chavers BM, McHugh LE, Matas AJ. 20 years or more of follow-up living kidney donors. *Lancet* 1992

Kasiske BL, et al. The evaluation of living renal transplant donors: clinical practice guidelines. *J Am Soc Nephrol* 1996

Risk of donor nephrectomy

Nereo Rocco, in un angolo degli spogliatoi, sussurra "sapevo che sarebbe finita così. Per questo avevo chiesto il rinvio. Ma una manica di dilettanti non mi ha creduto' ‘1973

I rossoneri hanno sbagliato tutto

Determinante l'assenza di Schnellinger mal sostituito da Turone - Tutta la squadra però ha girato a vuoto - Si sono salvati soltanto Sogliano, Benetti e Rosato - I veronesi a partire dal 17' (gol di Sirena) hanno dettato legge - Una tripletta dell'ex granata Luppi

Verona 5
Milan 3

VERONA: Pizzaballa 7; Nanni 7 (dal 34' Cozzi 7), Sirena 7, Busatta 6, Batistoni 7, Mascalaito 6; Bergamaschi 7, Mazzanti 6, Luppi 7, Mascetti 8, Zigoni 7. 12° Colombo.

MILAN: Vecchi 5; Sabadini 5, Zignoli 4; Anquilletti 6, Turone 4, Rosato 6; Sogliano 6, Benetti 6, Bigon 5, Rivera 4, Chiarugi 4. 12° Belli; 13° Magherini.

Arbitro: Monti 6.

Reti: Sirena al 18', Luppi al 27' e al 30', Rosato al 35', Luppi al 70', autogol di Turone al 78', Sabadini all'83' e Bigon al 90'.

(Dal nostro inviato speciale)

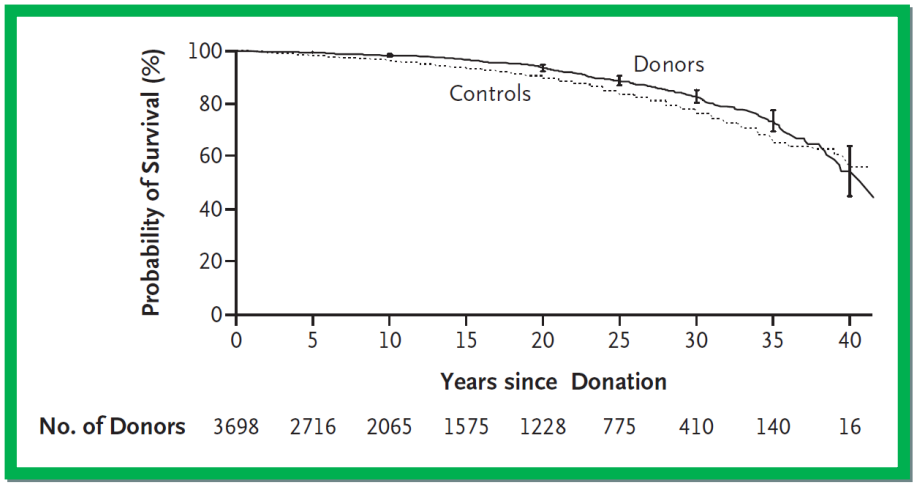
Verona, 20 maggio.

La caduta del Milan a Verona rimbomba stracciando l'alta quiete di una città che mai

FRANCO NANNI

palloni solo per obbligo, travolto dalle tenebre della più incredibile confusione. Si vede che alla squadra mancava e manca convinzione, manca la rabbia orgogliosa di gettarsi sotto nei modi dovuti. Sul campo i giallobiù sembrano Charlton, Eusebio e Netzer messi insieme. Al 27' in rapido contropiede Sirena spara da venti metri, Vecchi finge d'essere una statua ed è il cinque a uno (ma è Turone a spiazzare il proprio portiere, provocando autogol). Il Milan boccheggia disfatto, signoreggiato dal Verona che tollera alcune puntate rossonere: al 37' su corner battuto da Chiarugi, di testa Sabadini ottiene la seconda rete milanista, ma è un cerotto su una gamba di legno. Come lo è il secondo cerotto, ovvero il tocco di Bigon per il tre a cinque, mentre Monti allargando le braccia con com-

Donor nephrectomy: increased risk of end-stage renal disease



N.E.J.M. 2009

There are more than 325 living kidney donors who have developed end-stage renal disease and have been listed on the Organ Procurement and Transplantation Network

Am J Kidney Dis. 2015

Living donors

The New York Times

"... New Yorker die after surgery to give liver part to a brother..."

"Mike Hurewitz, a 57-year-old journalist, died at Mount Sinai Hospital in Manhattan on Sunday after an operation to remove part of his liver for transplant. The recipient, his younger brother, is apparently doing well. The procedure of liver-lobe transplantation, hardly more than a decade old, can save lives, but it can also lead to disaster. The case of the Hurewitz brothers illustrates both. The risk of death for a donor may be as high as 1 in 100. Yet even when the magic works, when donor and recipient survive, the procedure raises troubling questions. The death of Mike Hurewitz gives those questions a sharper edge.

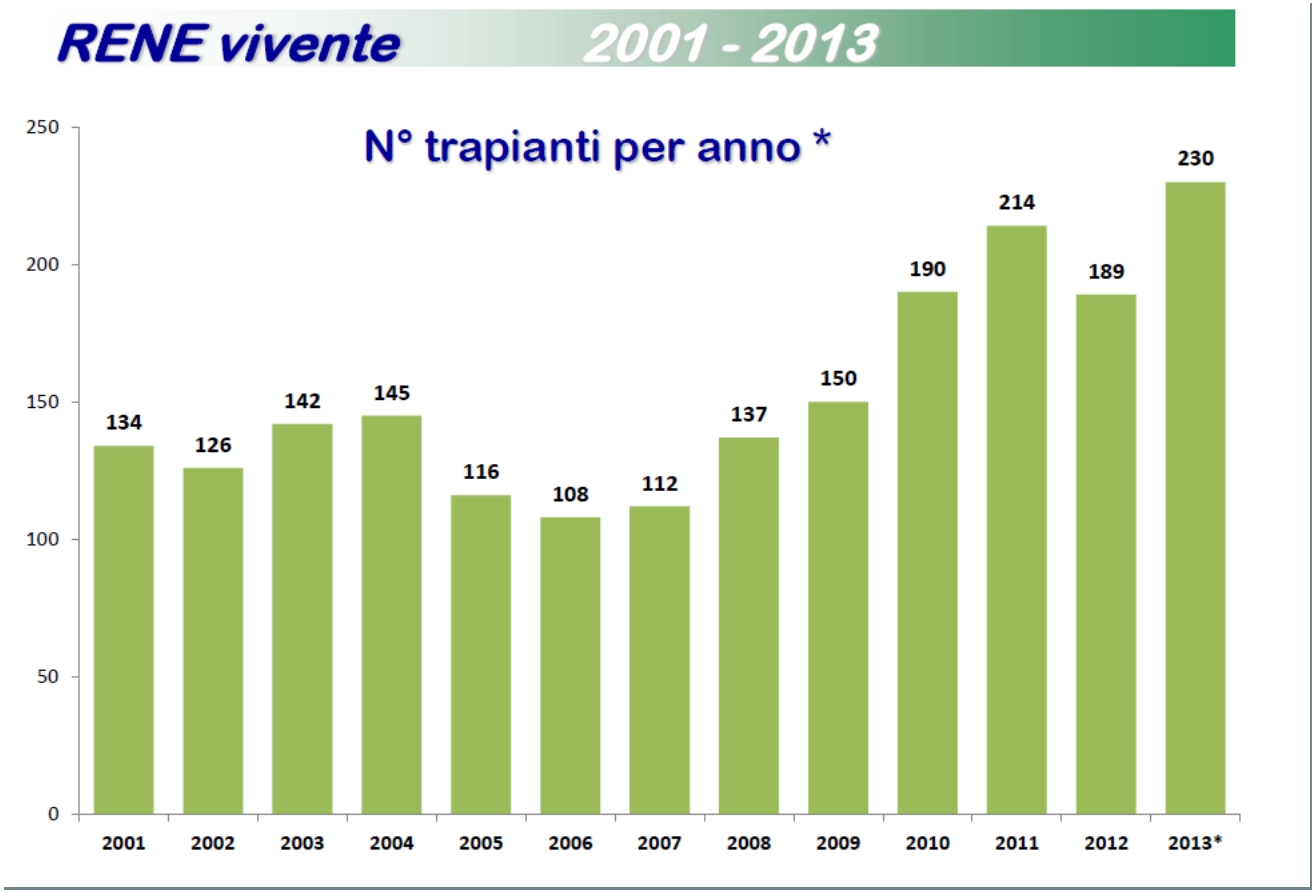
Given the risk and the potential for family pressure, should we permit people to become liver donors? Are physicians violating the "do no harm" rule by operating on healthy donors, causing them pain and risking their lives, yet bringing them no medical benefit?"

New York Times, Jannuary 12, 2002 (www.nytimes.org)

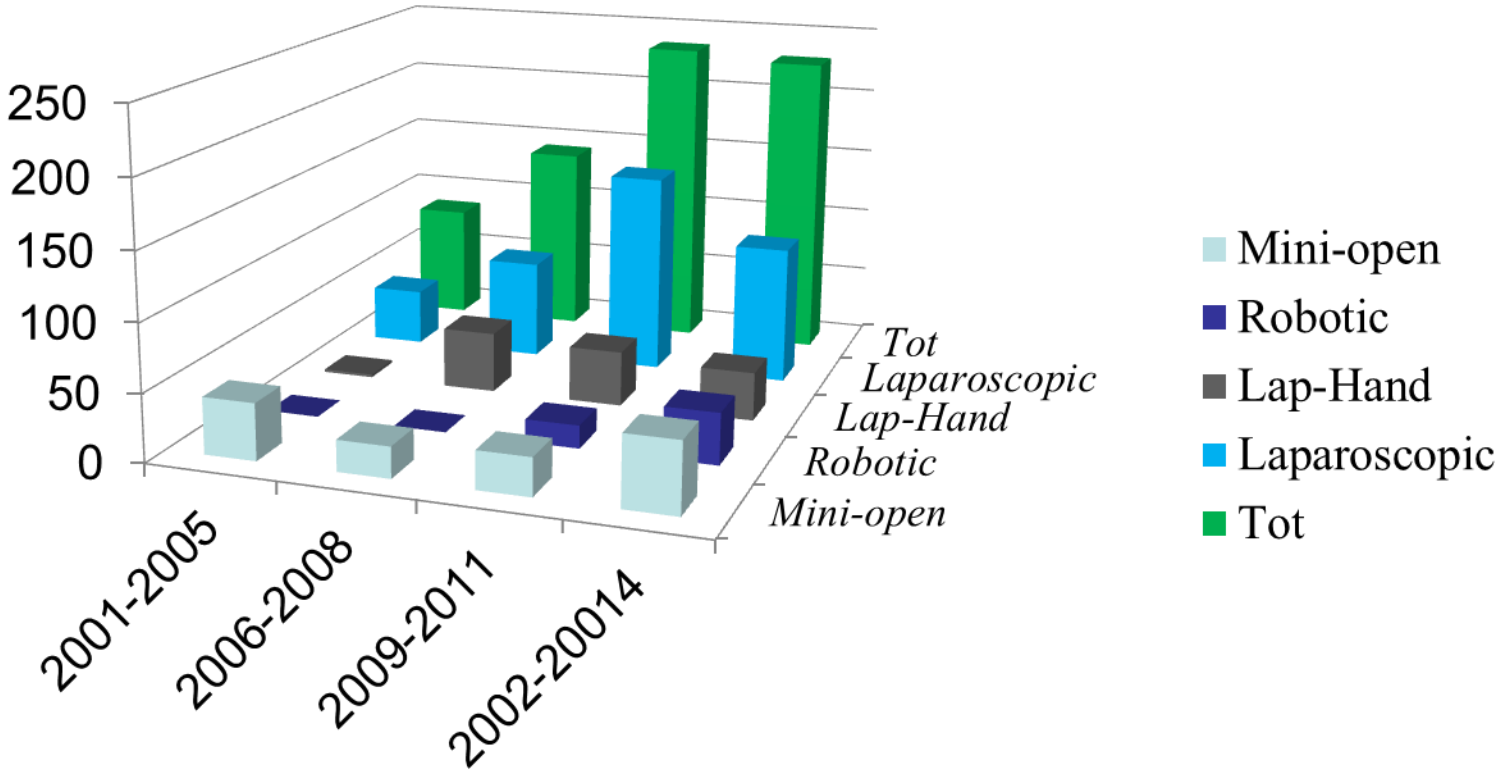
Living donor like fireman

Tecniche Mininvasive per la nefrectomia del DONatorE Vivente (MDONE): studio multicentrico italiano
Data 2001-2014

~ 600 donors among ~ 2000 Living KT



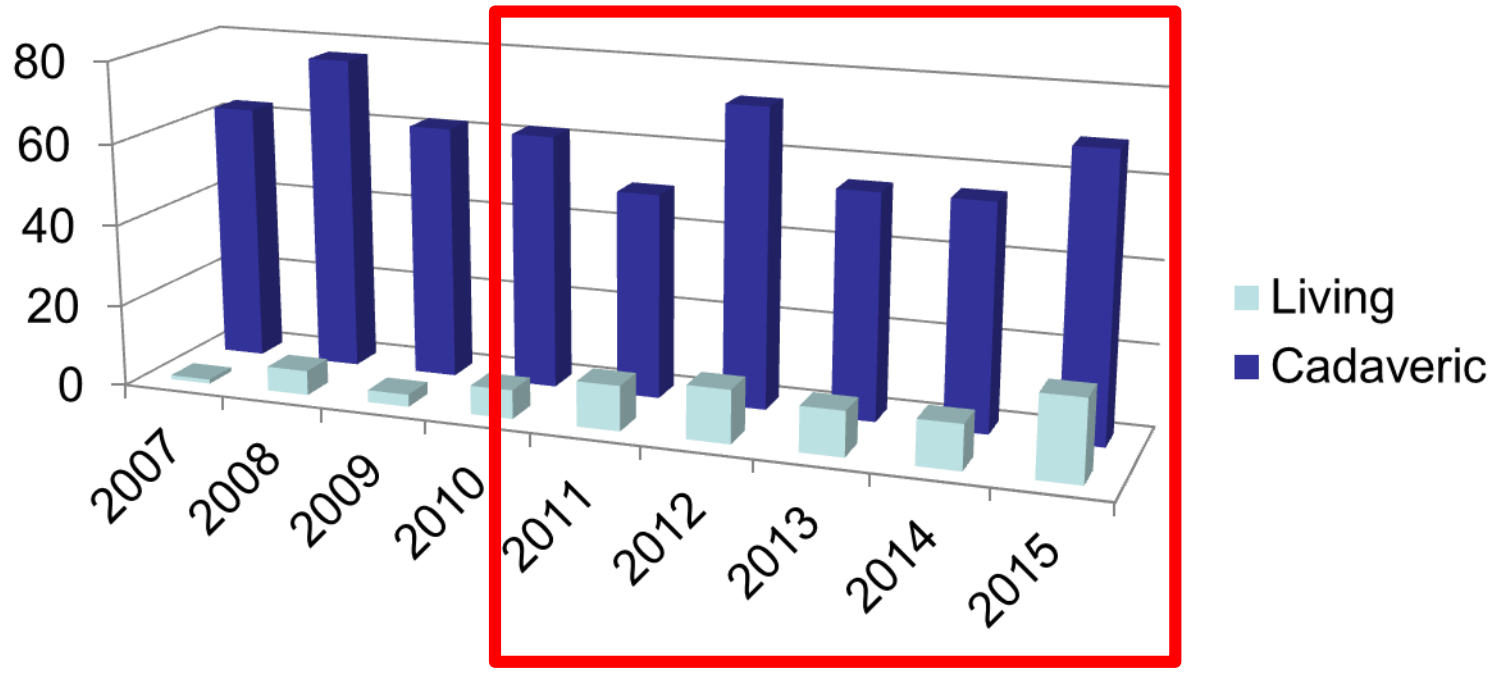
Tecniche Mininvasive per la nefrectomia del DONatorE Vivente (MDONE): studio multicentrico italiano Data 2001-2014



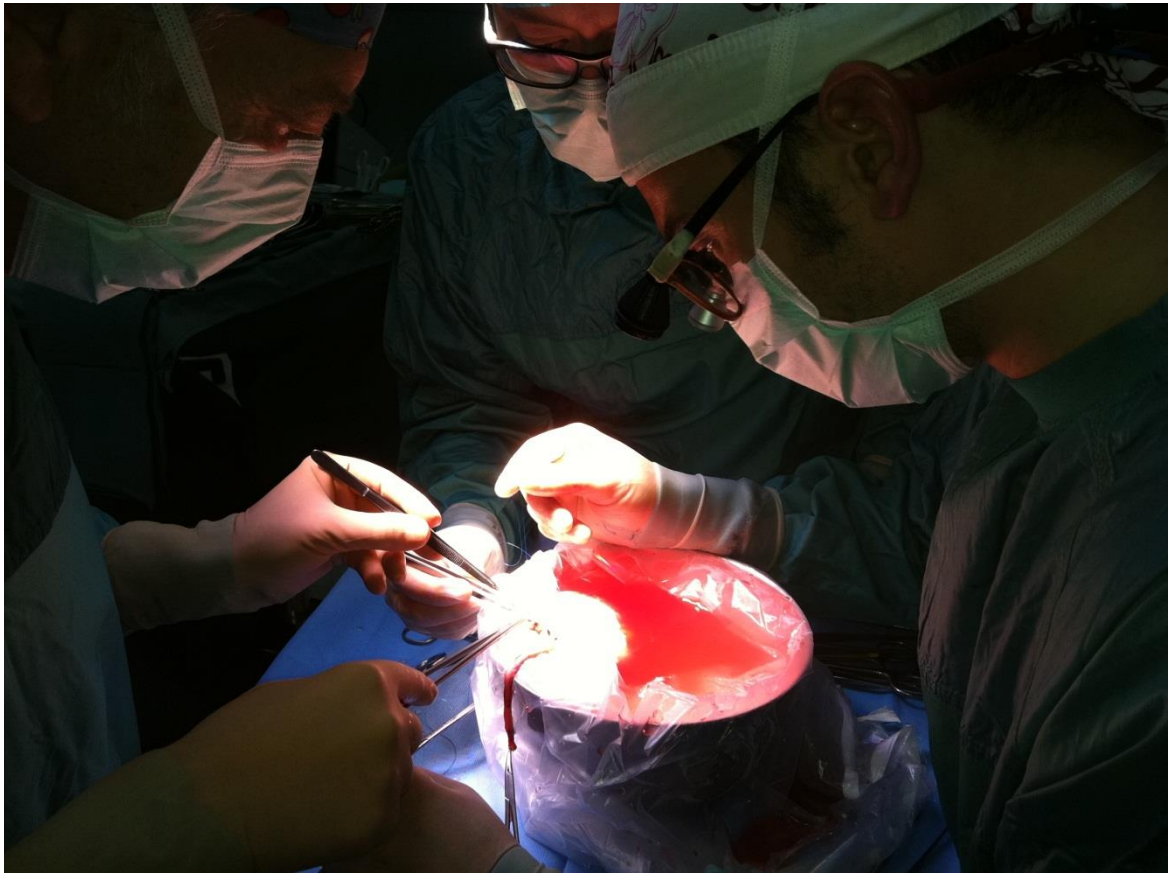
All donors had an uneventful outcome

Bologna data

1967-2010: 147 living; 2011-2015 (Pinna): 66 living



Bologna proposal for multiple arteries or vein: cryopreserved graft



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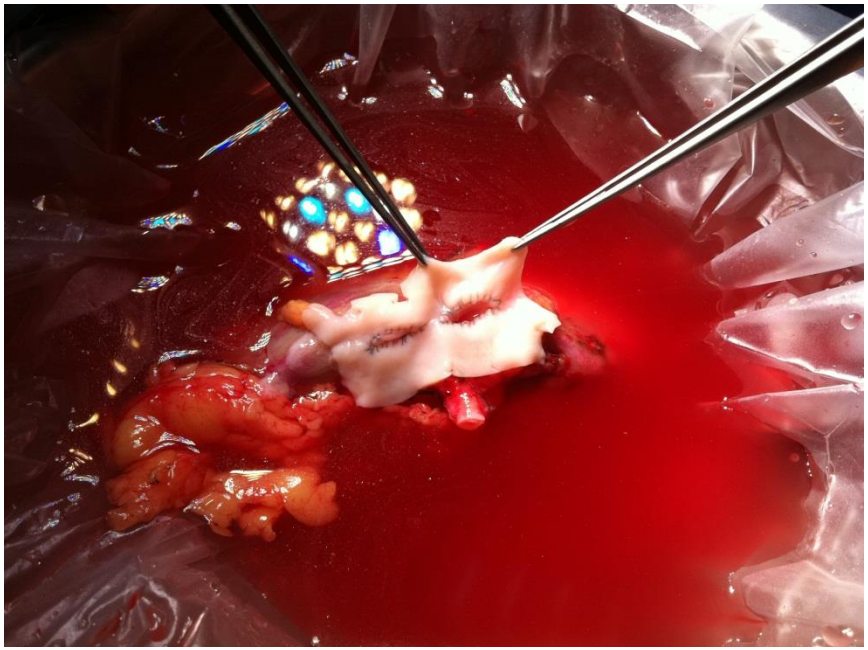

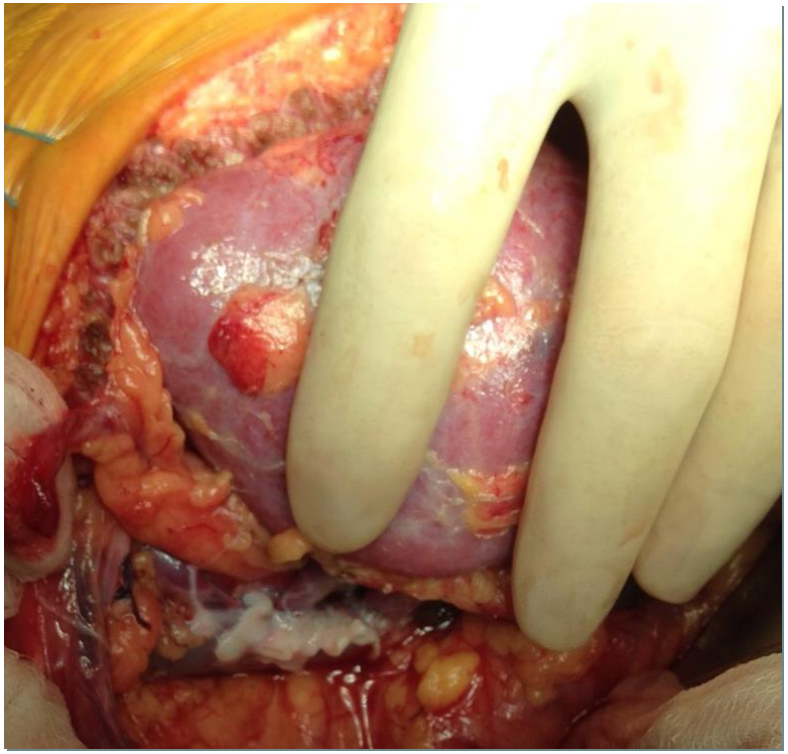

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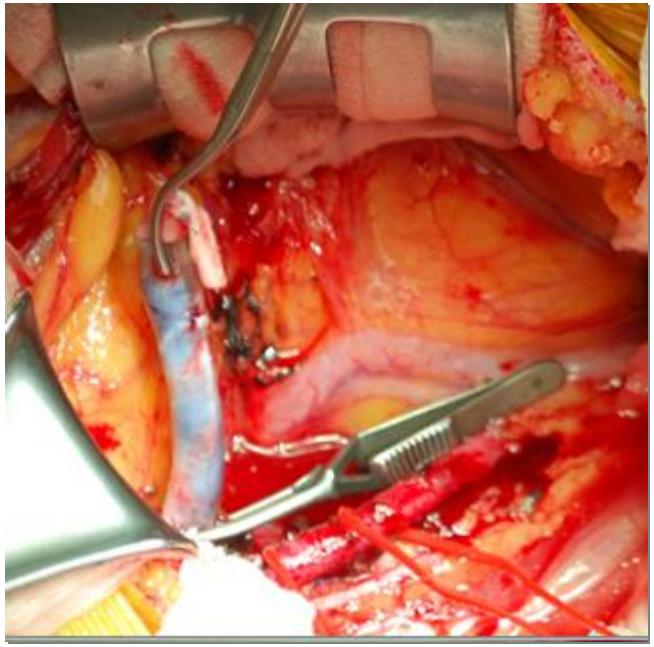
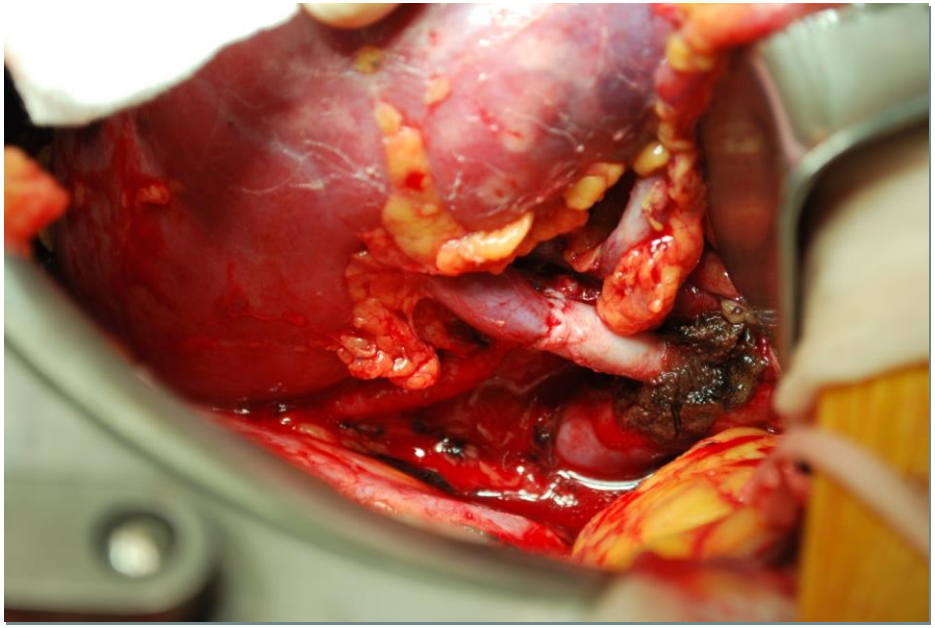




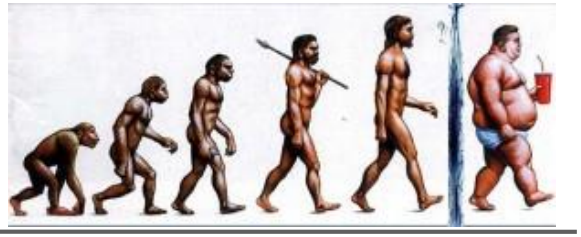
Liver transplantation

How to select? We should select? What do we measure?

What is changing?

- New indications according to population habit;
- New drug therapies (HCV+…)
- New type of donors and matching

What is changing?



In parallel to that of metabolic syndrome,
the prevalence of NAFLD is increasing
worldwide.

NASH is estimated to become the most common cause of advanced liver disease in 10-20 years.

NASH-related ESLD is likely to become
the leading indication for LT.

The prevalence of NAFLD in the general population
affects organ procurement.

Reports from different eras of liver transplantation have differed regarding the ***outcome of LT in the elderly recipients***

early 1990s:
no decrease in survival among old LT recipients[1,2]

↓

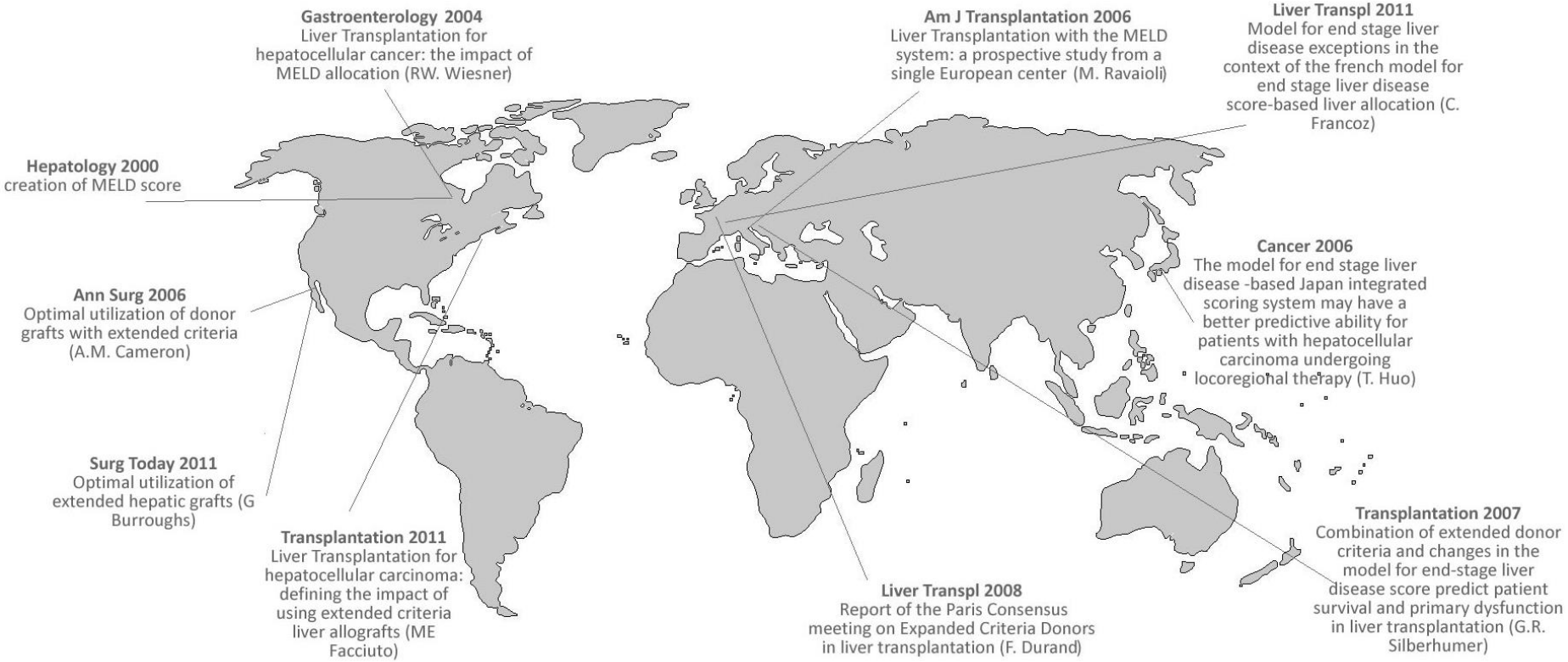
year 2000:
worse post-transplant outcomes and increased risk of graft loss[3].

↓

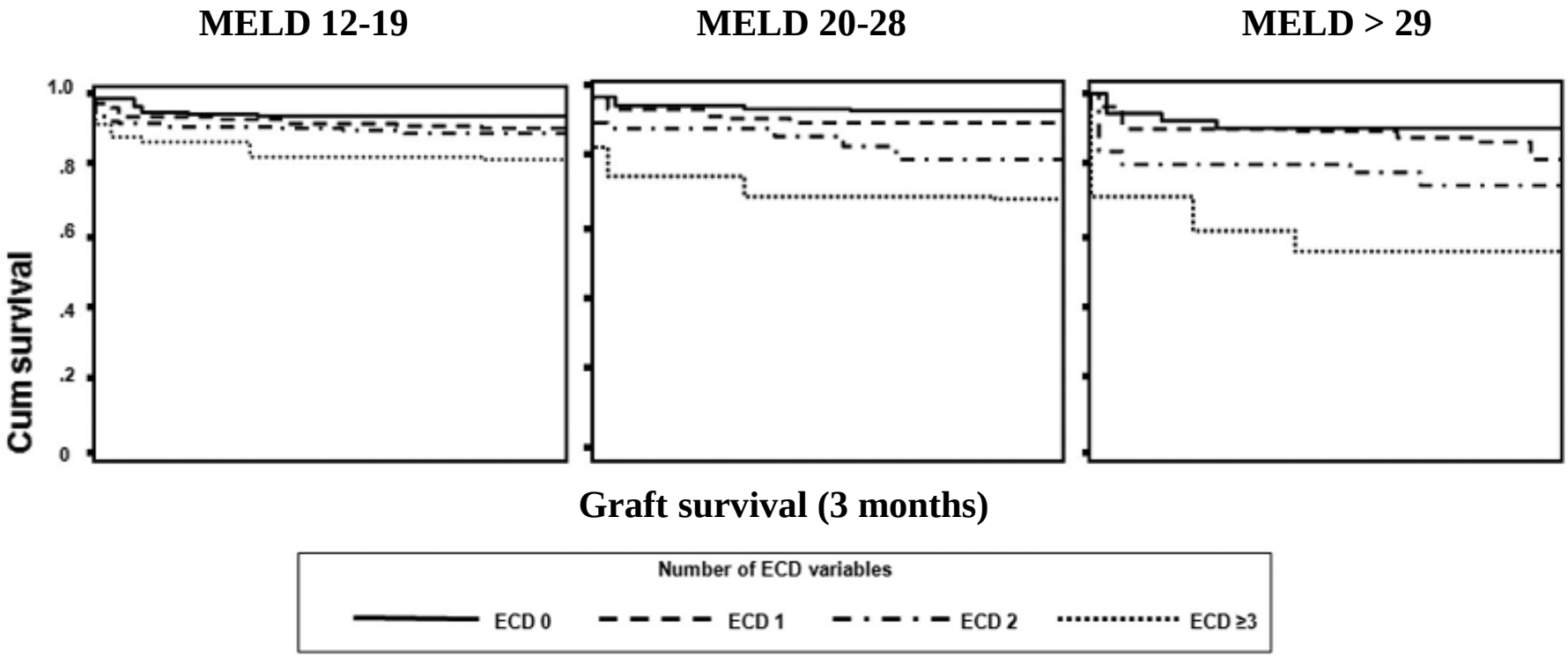
Arbitrary maximum age cutoffs

1 - Stieber AC et al. Liver transplantation in patients over sixty years of age. Transplantation 1991.
2 - Bromley PN et al. Orthotopic liver transplantation in patients over 60 years of age. Transplantation 1994.
3 - Levy MF et al. The elderly liver transplant recipient: a call for caution. Ann Surg 2001.

Decision-making process in LT changed due to: MELD and ECD



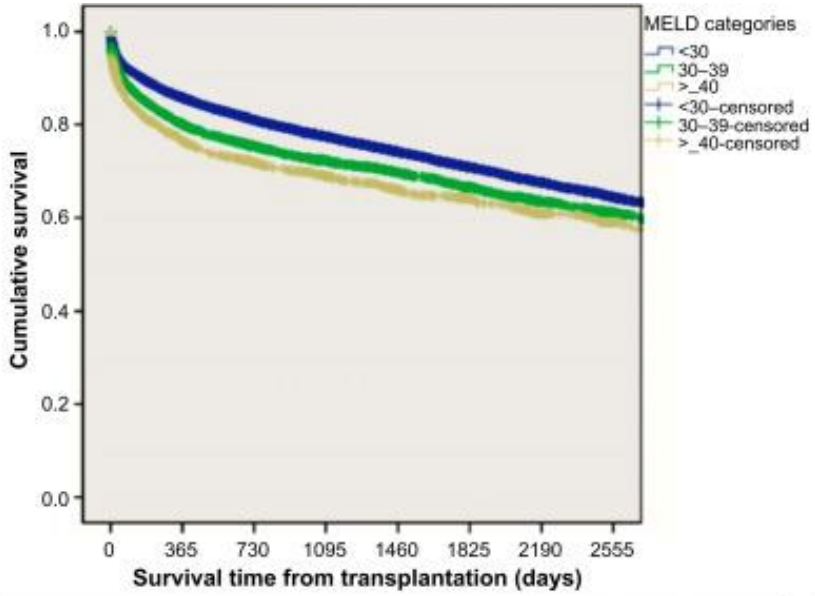
Prediction of graft dysfunction based on extended criteria donors in the MELD score era



The combination of three or more ECD variables (donor age, macrovesicular steatosis > 30% and cold ischemia time) and MELD more > 29 is the worst scenario for graft success after LT

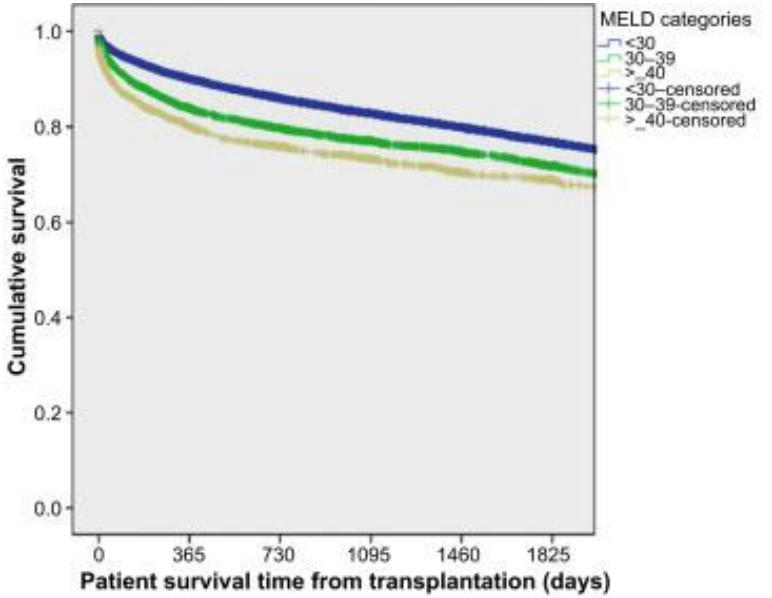
Briceño et al. Transplantation 2010

Overall patient survival correlates inversely with increasing MELD score



Graft	At TX	1 year	2 Year	3 year	4 year	5 year	6 Year	MELD
At Risk	23230	17229	13996	11151	8524	6030	3773	<30
Failed	3373	969	615	471	393	279	182	
At Risk	5398	3406	2591	1976	1454	993	599	30-39
Failed	1109	203	100	71	68	48	22	
At Risk	2336	1374	1034	774	568	397	226	>_40
Failed	573	84	42	33	16	21	7	

(a)



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Failed	573	84	42	33	16	21	7	

(b)

Panchal et al. HPB (Oxford) 2015

What happen when you limit risk?

Risk avoidance during life and LT: reduce probability of adverse events

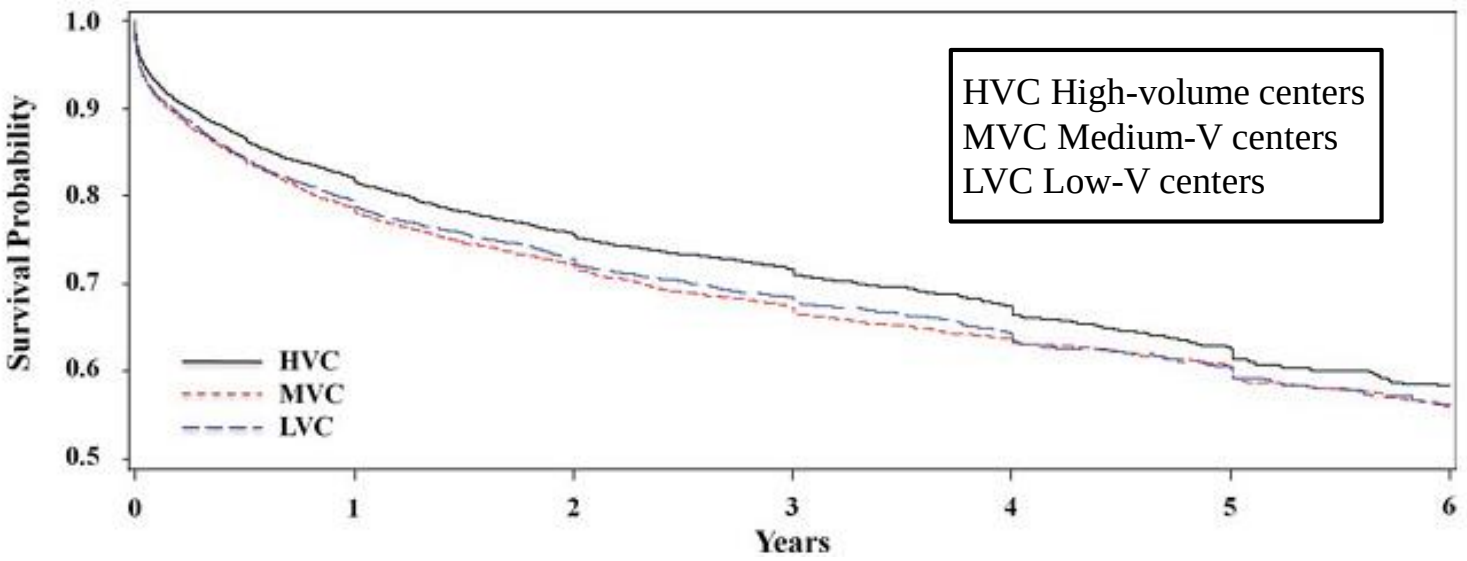
What happen limiting risks in liver transplantation

Centers that received low performance evaluations (LP) had an average decrease of 39.9 transplants ($p<0.01$) and 67.3 candidates ($p<0.01$). ***LP centers reduced the use of older donors, donations with longer cold ischemia, and donations after cardiac death*** (p-values<0.01).

Transplant characteristics	Low performing centers (n = 15 478)	Average or high performing centers (n = 34 369)	p-Value
Recipient age: mean (SD)	+2.1 (2.1)	+2.7 (1.8)	0.14
Donor age: mean (SD)	**−0.6 (2.9)**	**+1.8 (4.1)**	**0.008**
Recipient creatinine: mean (SD)	+0.4 (0.3)	+0.4 (0.2)	0.93
Cold ischemia hours: mean (SD)	**−1.6 (1.5)**	**−0.3 (1.6)**	**0.001**
Albumin: mean (SD)	+0.06 (0.22)	+0.11 (0.26)	0.39
INR: mean (SD)	+0.06 (0.31)	+0.04 (0.35)	0.77
MELD at listing: mean (SD)	+0.73 (1.76)	+0.67 (1.88)	0.88
MELD prior to transplant: mean (SD)	+0.85 (2.49)	+1.01 (2.42)	0.78
Donor risk index: mean (SD)	+0.02 (0.08)	+0.02 (0.08)	0.45
Length of stay: mean (SD)	−0.02 (0.21)	−0.02 (0.29)	0.99
Distance to center (miles): mean (SD)	−7.1 (39.7)	+4.9 (57.0)	0.32
HCV (%)	+7%	+3%	0.12
DCD (%)	**−1%**	**+3%**	**0.001**

Buccini et al. American journal of Transplantation 2014

Impact of center volume on outcomes of increased-risk liver transplants

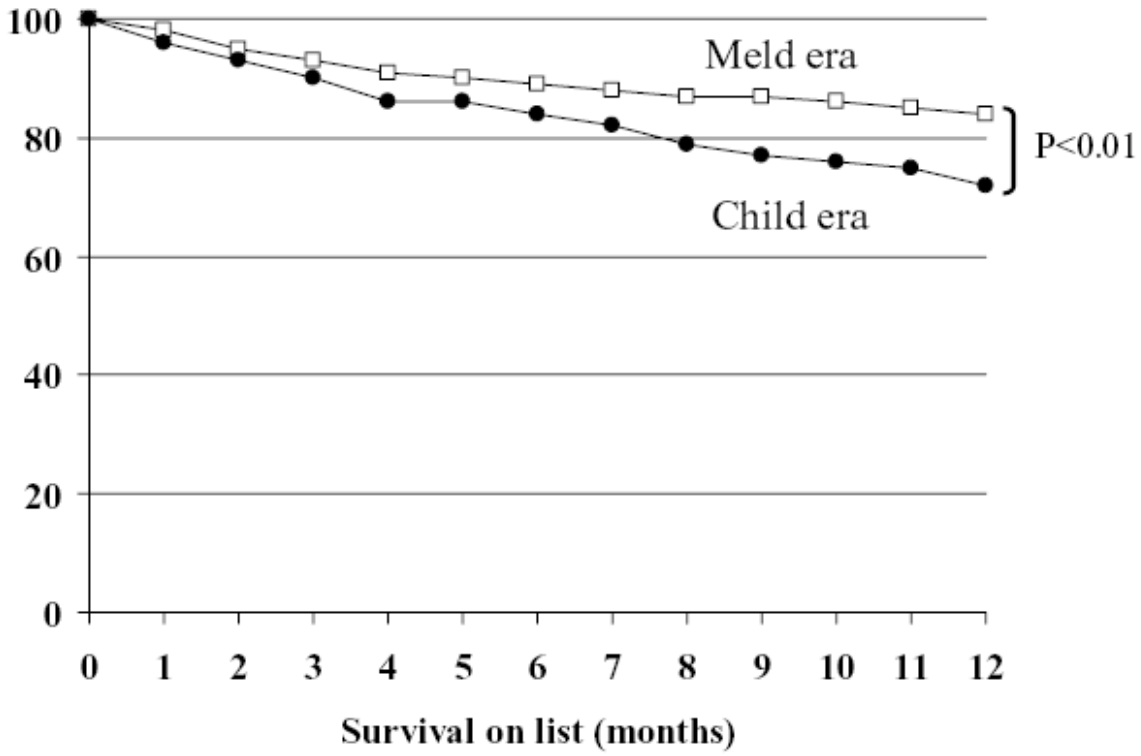


Allograft survival according to the center volume for liver transplants with DRIs > 1.90 ($P < 0.001$)

High-volume centers more frequently used higher DRI (donor risk index) livers and achieved better risk-adjusted allograft and recipient survival

Ozhathil et al. Liver Tranpl. 2011

Bologna: liver allocation according MELD since 2004



Ravaioli et al. American Journal of Transplantation 2006

Risk avoidance and liver transplantation: a single center experience in a national network

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Bologna experience 2007 – 2015 with rejected recipients and /or donors due to risk avoidance (RA)

Liver tranplantations (N. pts)	616
Recipient rejected by other centers	70 (11%)
Donor rejected by other centers	78 (12%)
Total LT in rejected donor and / or recipient	142 (23%)

**6 pts rejected received a rejected liver*

Principal causes for the **rejection of candidate** to LT by other transplant center (**n = 70**)

Comorbidity, n (%)	**13 (18.5)**
**CCI – OLT = 1, n (%)*	*7 (54.8)*
**CCI – OLT > 1, n (%)*	*6 (46.2)*
Portal vein thrombosis, n (%)	**11 (15.7)**
Partial / Complete PVT, n (%)	*5 (45) / 6 (55)*
Severity of disease, n (%)	**7 (10.0)**
Previous surgery, n (%)	**6 (8.6)**
Liver resection	*33.3*
Cholecystectomy and biliary surgery	*33.3*
Kidney transplantation	*16.7*
Small bowel resection	*16.7*
Obesity, n (%)	**6 (8.6)**
Multifocal HCC, n (%)	**4 (5.7)**
Previous tumor, n (%)	**4 (5.7)**
Depression, n (%)	**3 (4.3)**
Age, n (%)	**3 (4.3)**
Alcohol use < 6 months, n (%)	**2 (2.9)**
Combination of cause, n (%)	**11 (15.7)**

**CCI-OLT: Charlson Comorbidity Index -orthotopic LT*

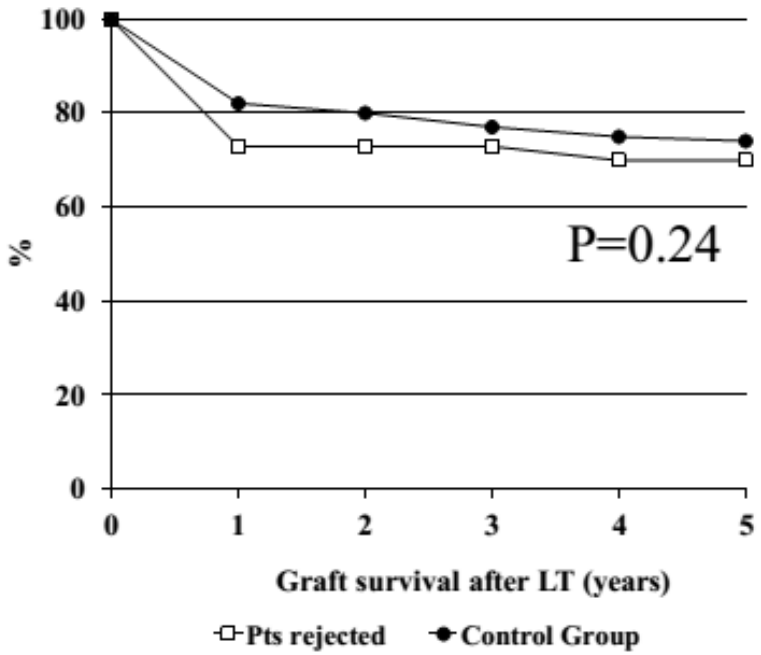
Principal causes for the **rejection of the liver graft** by other transplant center (**n = 78**)

HBcAb +, n (%) *(among extended criteria grafts)*	**26 (33.3%)**
HCV +, n (%) (genotype 1, 9 cases; genotype 2, 2 cases; genotype 3, 3 cases)	**14 (17.9%)**
HBsAg +, n (%)	**5 (6.4%)**
Moderate-severe hepatic steatosis, n (%) (macro-vescicular steatosis 30% 6 cases; 35 % 1 case)	**7 (9.0%)**
Neoplastic risk, n (%)	**5 (6.4%)**
Infective risk, n (%)	**4 (5.1%)**
Age, n (%)	**3 (3.9%)**
Drug use, n (%)	**1 (1.3%)**
Obesity, n (%)	**1 (1.3%)**
Deficit F XI, n (%)	**1 (1.3%)**
Combinations of cause, n (%)	**11 (14.1%)**

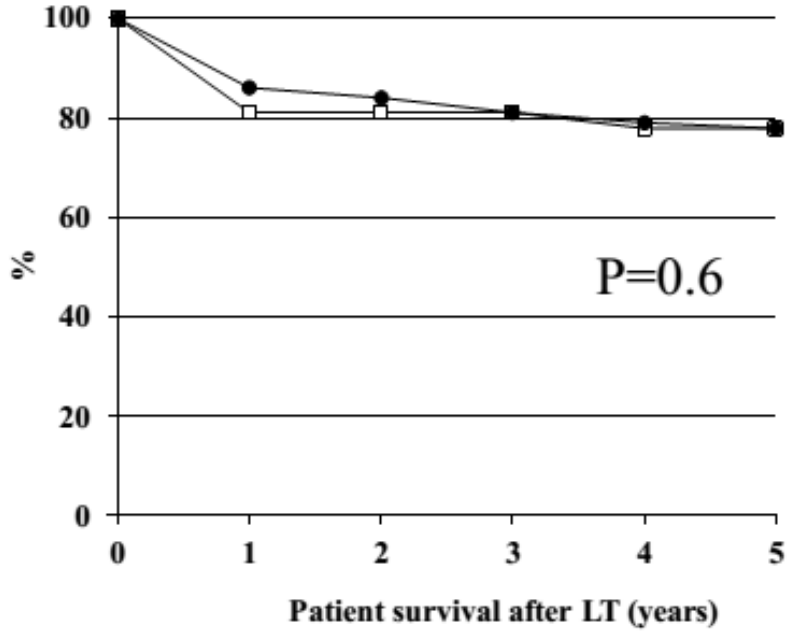
Recipient and donor features: study group vs. control group

	Group A (n = 142)	Group B (n = 474)	P
MELD, median	21	21	ns
MELD 25-29, n (%)	30 (21.1)	84 (17.7)	ns
MELD ≥ 30, n (%)	17 (11.9)	76 (16.0)	ns
Partial/Complete PVT, n (%)	12 (8.4) / 11 (7.7)	44 (9.3) / 18 (3.8)	ns
Pre-LT ICU stay, n (%)	6 (4.2)	41 (8.6)	
Mechanical ventilation pre-LT	3 (2.1)	11 (2.3)	
Donor age, median years	60	61	ns
Donor age > 70 years, n (%)	53 (37)	153 (32)	ns
BMI donor median	25	25	ns
HBsAg+	6 (4.3)	3 (0.6)	<0.01
HBcAb+	37 (26)	83 (17.5)	<0.05
HCV+	15 (10.6)	17 (3.6)	<0.01
Donor macro-steatosis, any grade, n (%)	40	45	ns
Extended criteria donor, n (%)	43 (30.3)	128 (27.0)	ns
Ischemia time, median minutes	420	380	< 0.001

Rejected recipients vs. control group

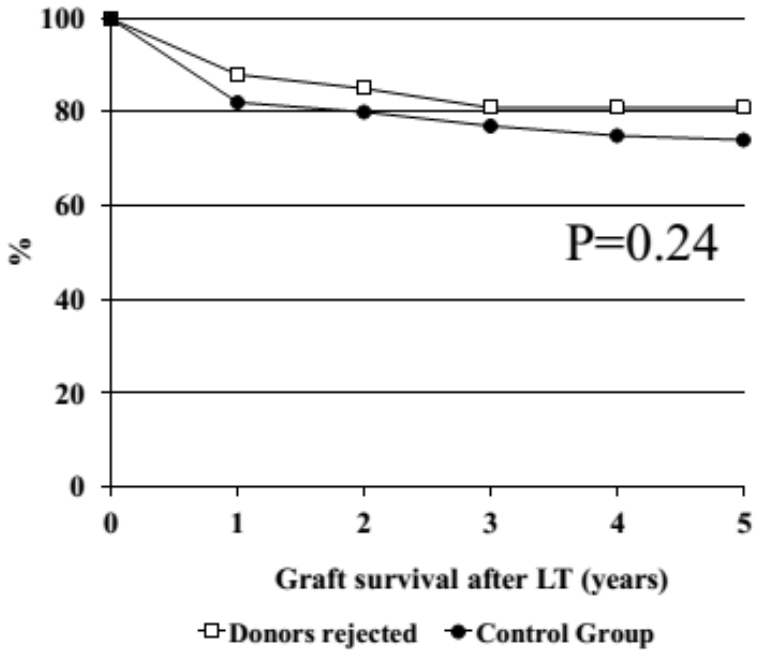


At risk grafts					
Pts rejected	43	36	29	20	10
Control group	337	272	230	190	152

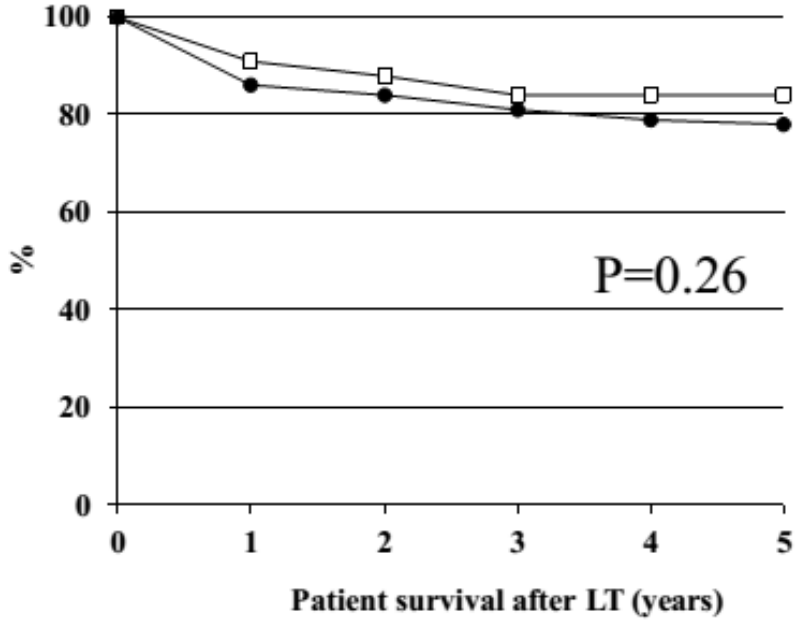


At risk patients					
Pts rejected	47	39	32	21	11
Control group	355	290	245	204	163

Rejected donors vs. control group



At risk grafts					
Donors rejected	59	51	40	34	25
Control group	337	272	230	190	152



At risk patients					
Donors rejected	62	52	41	35	26
Control group	355	290	245	204	163

Propensity score analysis of the study group population and transplantations from the national database

	Initial cohorts				Propensity score matched cohorts			
	Bologna (n=474)	National Data (n=3020)	p	Effect size	Bologna (n=411)	National Data (n=411)	p	Effect size
Recipient age	51.9 ± 11.1	53.2 ± 9.1	0.004	-0.128	52.2 ± 10.8	52.2 ± 9.8	0.971	0.002
Recipient male	332 (70.0%)	2301 (76.2%)	0.005	-0.140	295 (71.8%)	289 (70.3%)	0.701	0.033
HCV-Ab positivity	207 (43.7%)	1425 (47.2%)	0.166	-0.070	181 (44.0%)	177 (43.1%)	0.833	0.018
HCC	142 (30.0%)	656 (21.7%)	0.001	0.190	110 (26.8%)	119 (29.0%)	0.534	-0.049
MELD	20.2 ± 8.9	16.2 ± 7.5	0.001	0.486	18.9 ± 8.5	18.7 ± 8.2	0.667	0.024
Donor age	57.7 ± 18.8	55.0 ± 18.5	0.003	0.145	56.8 ± 18.9	56.4 ± 18.0	0.751	0.022
Patient survival			0.686				0.319	
1-year	86.3%	88.4%		-0.063	87.5%	87.1%		0.012
3-year	80.6%	80.6%		0.000	81.3%	78.8%		0.063
5-year	77.7%	75.5%		0.052	78.1%	74.0%		0.096

The results of the graft and the patient survival were comparable with national data on 11,517 LTs performed in the period from 2000 to 2012. The propensity score analysis confirmed a similar outcome between the two groups

For the propensity match the variables recipient age, sex, HCV positivity, HCC, MELD and donor age were entered into logistic regression.

Liver transplantation

How to select? We should select? What we measure to select?

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Meeting Report

A Multistep, Consensus-Based Approach to Organ Allocation in Liver Transplantation: Toward a "Blended Principle Model"

BENEFIT STATEMENTS

Benefit

1. Transplant benefit of at least 5 years after transplantation is the best available indicator for maximizing the life-saving potential of procured livers.
2. Transplant benefit should be regulated according to minimal acceptable posttransplant results (UTILITY), and take into account the risk of dropout from the waiting list (URGENCY).
3. When measuring transplant benefit, the gain in life years is equivalent to the difference in the mortality ratio of patients with or without LT. The measure of gain in life expectancy is more understandable than the difference in mortality ratio with or without transplant.
4. Most studies on transplant benefit calculation are based on waiting list populations.
5. However, the implementation of a national registry to sample prospective cohorts of cirrhotic patients potentially eligible for LT based on the ITT principle is strongly recommended.
6. Quality-adjusted life years (QALYs) should be included in the transplant benefit estimation as a relevant endpoint. Cost effectiveness should also be evaluated, though neither evidence nor data are available in the transplant benefit estimation.
7. Evaluation of potential harm to individuals and waiting-list populations should be included in the transplant benefit estimation.

Liver transplantation

How to select? We should select? What we measure to select?

Priority and sharing	LT indication
P1 (Macro area sharing after serving those with MELD>30)*	Rendu–Osler–Weber
	Hepatoblastoma (young adult)
	Hemangioma (if Kasabach Merritt syndrome)
	Acute late ReLT
	FAP (if domino)
P2 (Sharing at regional level)	Hepato-pulmonary syndrome
	PPH
	Refractory hydrothorax
	Chronic late ReLT
	Hepato-renal syndrome (if not automatically equated to MELD)
	Previous severe infections
P3 (Sharing at regional level)	Refractory ascites
	FAP
	Wilson's (with compensated cirrhosis and initial neurological symptoms)
	NET metastases
	Hemangioendotheliomas
P4 (Sharing at regional level)	PSC or PBC with intractable pruritus
	Polycystic disease
	Complicated adenoma
	Hemangiomas
P Multidisciplinary (Center-based)	Hepatic encephalopathy
	Fibrolamellar HCC
	Liver adenomatosis (not complicated)
	Hilar cholangiocarcinoma
	CRC metastases

Thanks who help us to avoid risk avoidance

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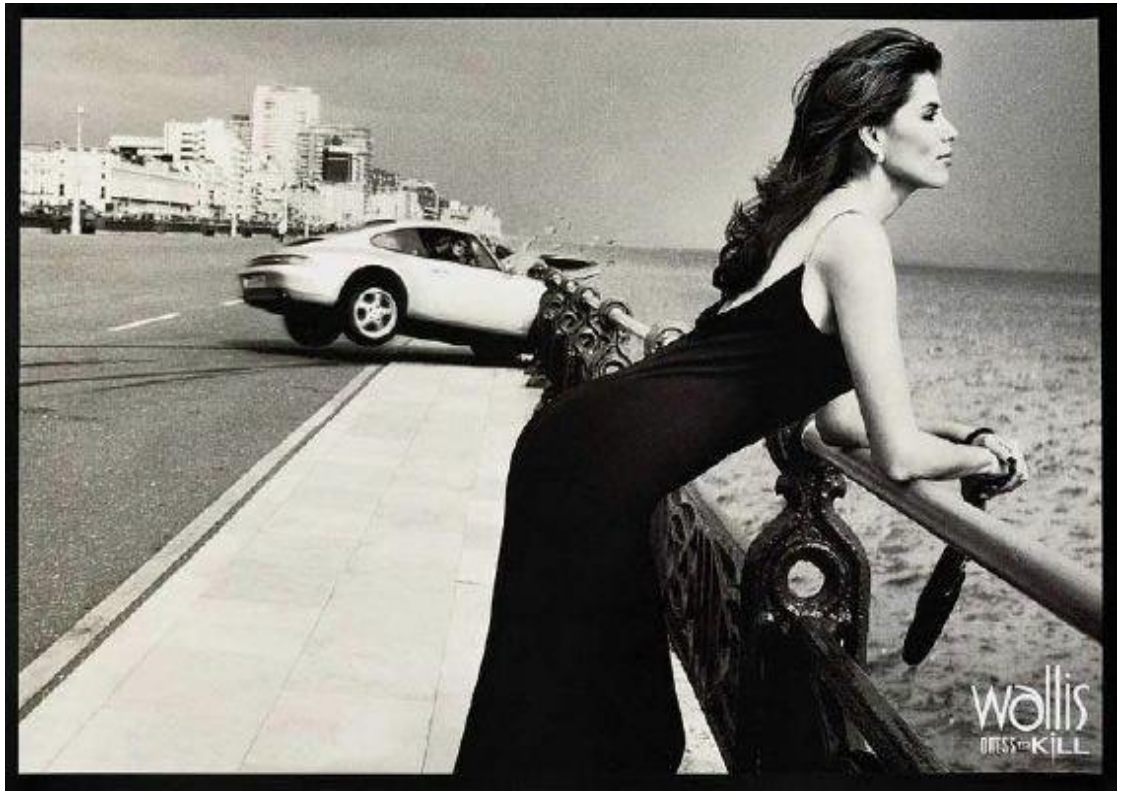
Past, present and future



LT has changed perspectives of pts, but also of doctors and surgeons, who needed to change their life.

Some were limited by this experience and others were excited, but none remained as before.

Scientific meeting focus to understand the work of these people, but many secrets remain in our minds and experience.

Conclusions: support donation and living donors