

Compared efficacy of preservation Solutions in liver transplantation: a long-term graft outcome study from the European Liver Transplant Registry.

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and all the ELTR contributing centres www.eltr.org
and the European Liver and Intestine Transplant Association (ELITA).

Normalised intrinsic mortality risk in liver transplantation: European Liver Transplant Registry study

Lancet 2000; **356**: 621–27

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Factors	Risk ratio (95% CI)	p
Adults		
Retransplantation	2.94 (2.59–3.34)	0.0001
Cancer	2.47 (2.22–2.74)	0.0001
Acute hepatic failure	2.01 (1.77–2.27)	0.0001
Split-liver transplants in centres that do <20	1.60 (1.02–2.52)	0.04
<25 liver transplants per year	1.50 (1.29–1.74)	0.0001*
25–90 liver transplants per year	1.46 (1.31–1.62)	0.0001*
Preservation liquid ≠UW	1.34 (1.19–1.52)	0.0001
ABO compatibility	1.23 (1.07–1.40)	0.003†
ABO incompatibility	1.31 (1.00–1.73)	0.05†
Recipient age ≥60 years	1.29 (1.14–1.47)	0.0001
Cold ischaemia ≥12 h	1.17 (1.07–1.28)	0.0008
Donor age >55 years	1.14 (1.02–1.28)	0.03
Donor sex matching	1.11 (1.02–1.21)	0.02
Children		
Cancer	2.86 (1.79–4.58)	0.0001
Retransplantation	2.69 (2.20–3.28)	0.0001
ABO incompatibility vs isogroup	2.21 (1.47–3.32)	0.0001‡
ABO compatibility vs isogroup	2.06 (1.56–2.71)	0.0001‡
Acute hepatic failure	2.03 (1.62–2.55)	0.0001
Split-liver transplants in centres that do <20	1.85 (1.23–2.78)	0.003
<25 liver transplants per year	1.35 (1.07–1.71)	0.01
Cold ischaemic ≥12 h	1.33 (1.10–1.61)	0.003
Recipient age <2 years	1.22 (1.02–1.46)	0.03

Different solutions are used for organ preservation. Each substantially differs in their composition, but the purposes of each are similar:

- to prevent cellular edema,
- to delay cell destruction,
- to maximize organ function after perfusion.

TABLE 1 - Composition of the preservation solutions

	UW ³	CS ³	HTK ³	IGL-1 ³	ST* ¹¹	EC ¹²	LPD ¹²
mOsm/l	320	320	310	290	304	375	292
HES	0.25						
PEG-35				0.03			
Na ⁺	27	100	15	120		10	138
K ⁺	125	15	10	25	16	115	6
Cl ⁻			50		160	15	142
Mg ²⁺	5	13	4		32		0.8
Ca ²⁺		0.25	0.015	0.5	2.4		
HCO ₃ ⁻	5					10	
SO ₄ ⁻	4			5			0.8
PO ₄ ⁻	25			25		57.5	0.8
H ₂ PO ₄ ⁻						42.5	
Histidine		30	198				
Mannitol		60	30				
Lactobionate	105	80		100			
Raffinose	30			30			
Glutathione	3	3		3			
Adenosine	5			5			
Glutamate		20					
Glucose (g/l)						35.7	0.91
Dextran 40 (g/l)							50

Concentrations are given in mmol/l, except where otherwise indicated.
Abbreviations: HES, hydroxyethyl starch; PEG-35, polyethylene glycol 35.
* Prior to the pH correction with sodium bicarbonate.

LIVER PRESERVATION SOLUTIONS

- No large randomized study demonstrating any superiority of one solution over the others
- Clinical practice : limited retrospective studies and medico-economic factors...

The Effect of Preservation Solutions for Storage of Liver Allografts on Transplant Outcomes

A Systematic Review and Meta-analysis *Annals Surg* 2013

John M. O'Callaghan, MBBS,*† Robert D. Morgan, MBBS,* Simon R. Knight, MChir,*† and Peter J. Morris, FRS*†

16 RCT / 11 same initial flush and storage solution

TABLE 3. Primary Nonfunction Rates in Included Studies

Study	Solution 1			Solution 2			RR	P	Definition of Primary Nonfunction		
		N	n	%		N				n	%
Erhard (1994)	UW	30	1	3.33	HTK	30	1	3.33	1.00	1.00	Undefined
Brolese (2008)	UW	74	2	2.70	HTK	148	7	4.73	0.57	0.47	Undefined
Nardo (2001)	UW	90	1	1.11	Celsior	83	0	0.00	2.77	0.53	Death or retransplantation in days 1–7
Lama (2002)	UW	10	0	0.00	Celsior	10	0	0.00	1.00	1.00	Undefined
Pedotti (2004)	UW	96	0	0.00	Celsior	79	1	1.27	0.27	0.43	Undefined
García-Gil (2006)	UW	51	0	0.00	Celsior	51	0	0.00	1.00	1.00	Death or retransplantation in days 1–7
Brolese (2008)	UW	74	2	2.70	Celsior	82	0	0.00	5.53	0.46	Undefined
Lopez-Andujar (2009)	UW	103	2	1.94	Celsior	92	2	2.17	0.89	0.91	Death or retransplantation in days 1–7
Nardo (2004)	HTK	20	1	5.00	Celsior	20	0	0.00	3.00	0.49	Undefined
Brolese (2008)	HTK	148	7	4.73	Celsior	82	0	0.00	8.36	0.14	Undefined
Dondero (2010)	UW	92	4	4.35	IGL-1	48	1	2.08	2.09	0.51	Death or retransplantation in days 1–7
Schwartz (1991)	UW	32	1	3.13	Ringers	34	2	5.88	0.53	0.60	Undefined
Adam (1991)	Albumin	42	1	2.38	Ringers	41	3	7.32	0.34	0.34	Undefined
Sanchez-Urdazpal (1993)	Plasmalyte	20	0	0.00	Carolina rinse	23	0	0.00	1.14	0.95	Undefined
Bachmann (1997)	Albumin	10	0	0.00	Carolina rinse	10	0	0.00	1.00	1.00	Undefined

Studies are grouped by preservation solutions compared.

N indicates number in group; n, number with primary nonfunction; RR, relative risk of primary nonfunction, solution 1 versus solution 2.

Conclusions: Data from included studies suggest that preservation of deceased donor livers with the University of Wisconsin or Celsior solution results in equivalent outcomes.



EUROPEAN LIVER TRANSPLANT REGISTRY

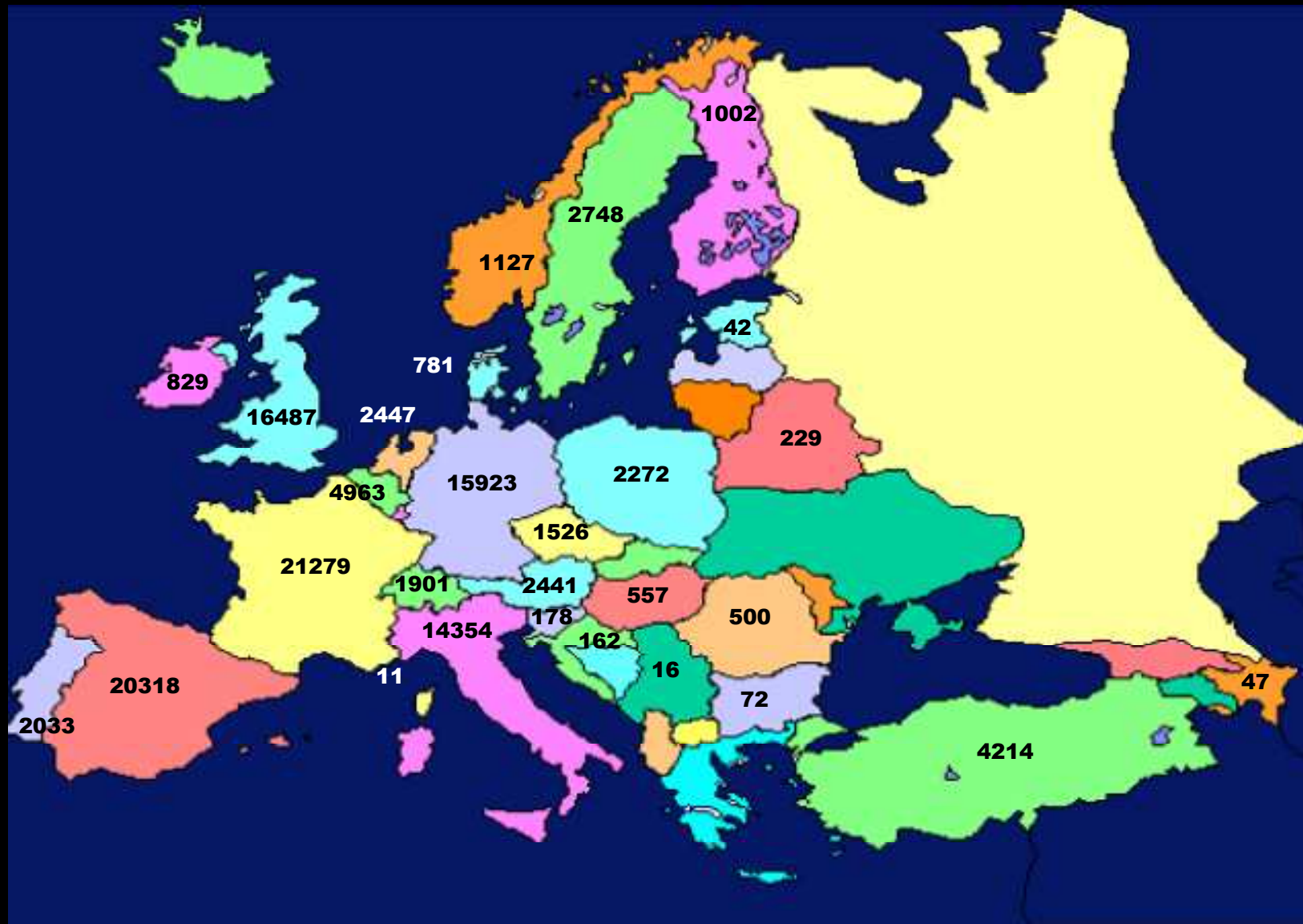
28 countries - 155 institutions

118,441 transplantations - 106,849 patients

From May 1968 to December 2013



12/2013



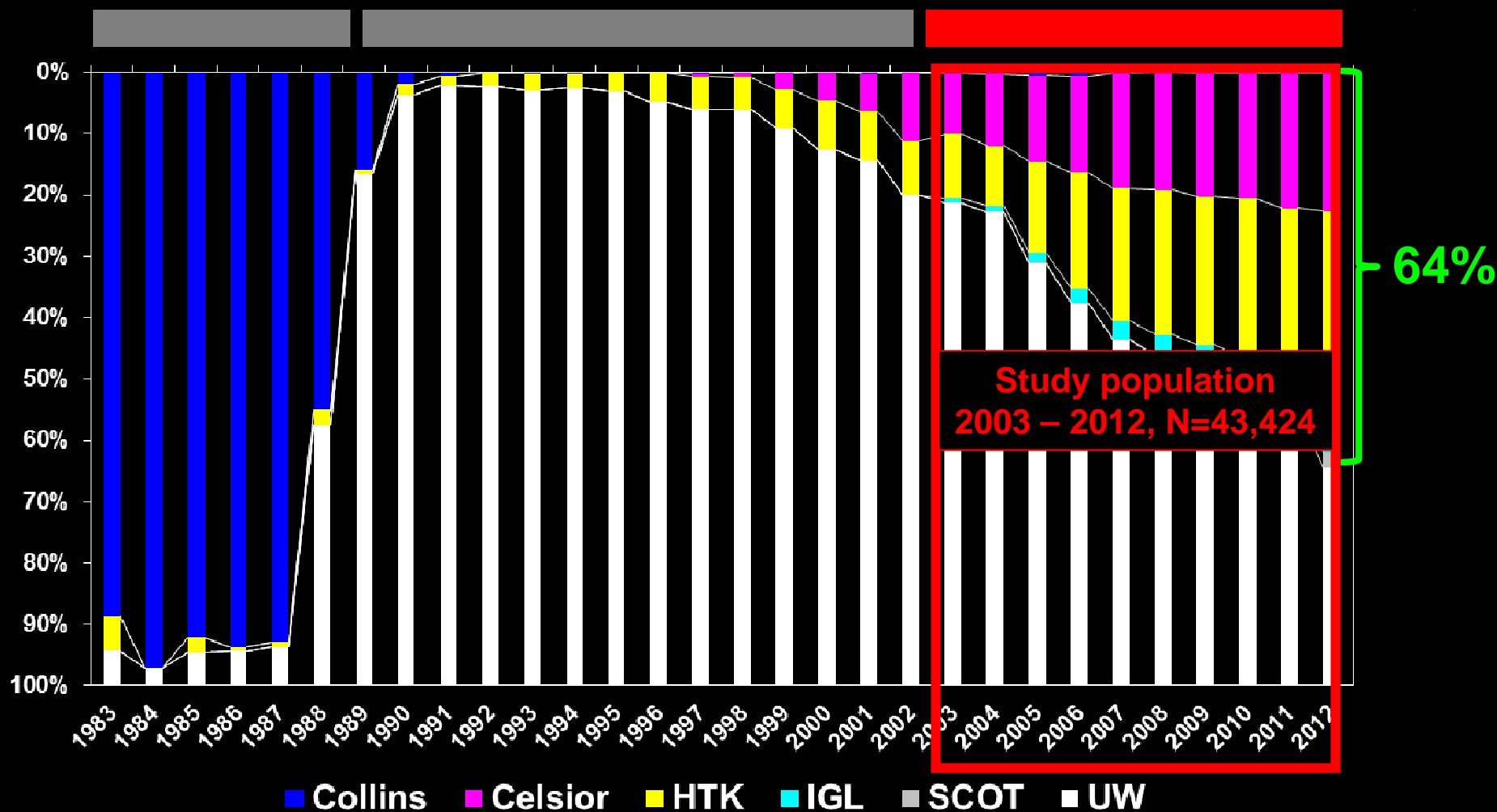
LIVER PRESERVATION IN EUROPE

Aim of the study : To compare the results of the preservation solutions used in Europe regarding Graft Survival

- 1- Evolution in the use of Preservation solutions
- 2- Definition of the study population
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Evolution of the use of Preservation Solutions in Europe

1983 – 2012, N=95,466



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Study population

106,701 1st LT
in adults (≥ 18 yrs)
1983 - 2012

43,424 1st LT
2003 - 2012

Celsior
(n=7,756)

HTK
(n=8,696)

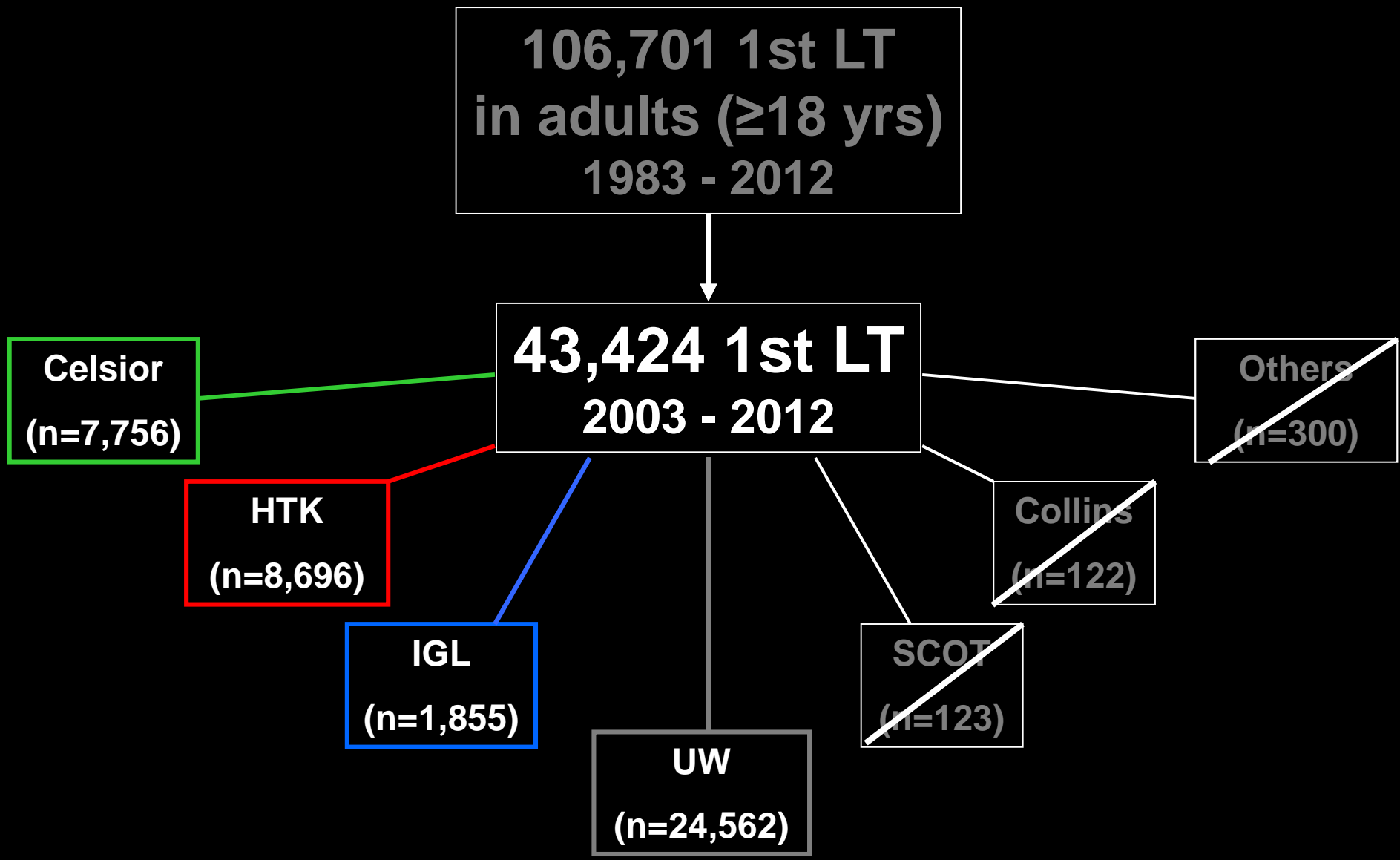
IGL
(n=1,855)

UW
(n=24,562)

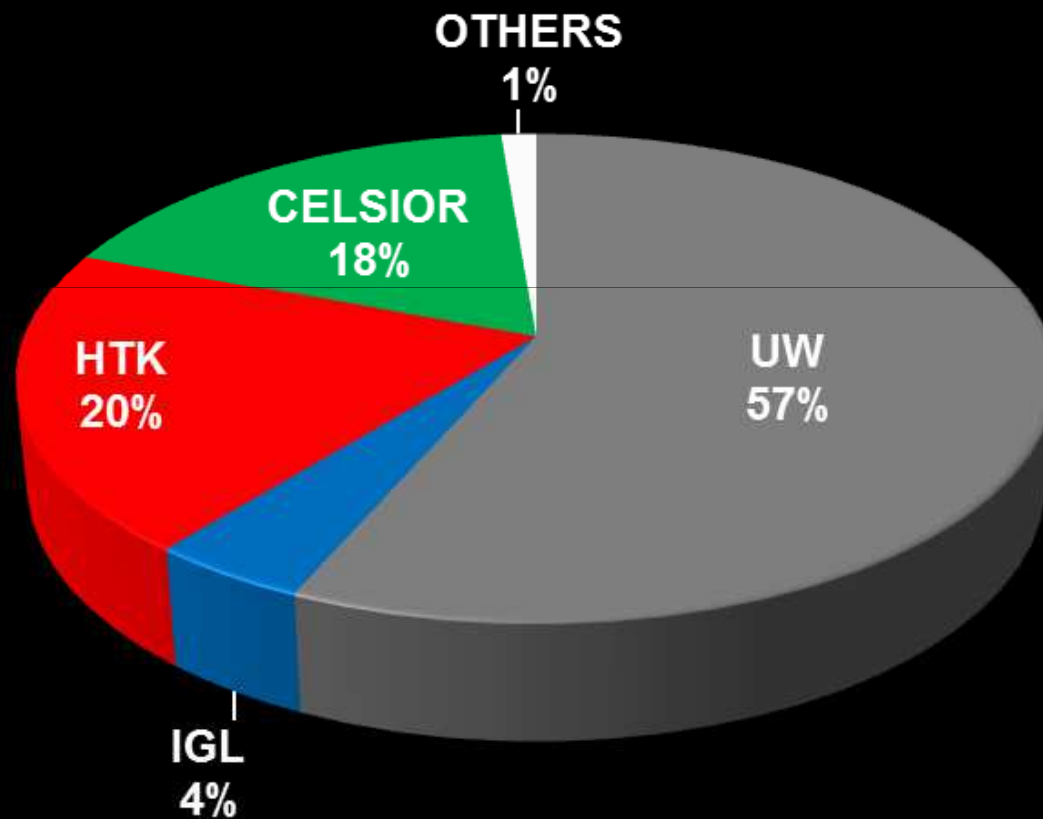
Collins
(n=122)

SCOT
(n=123)

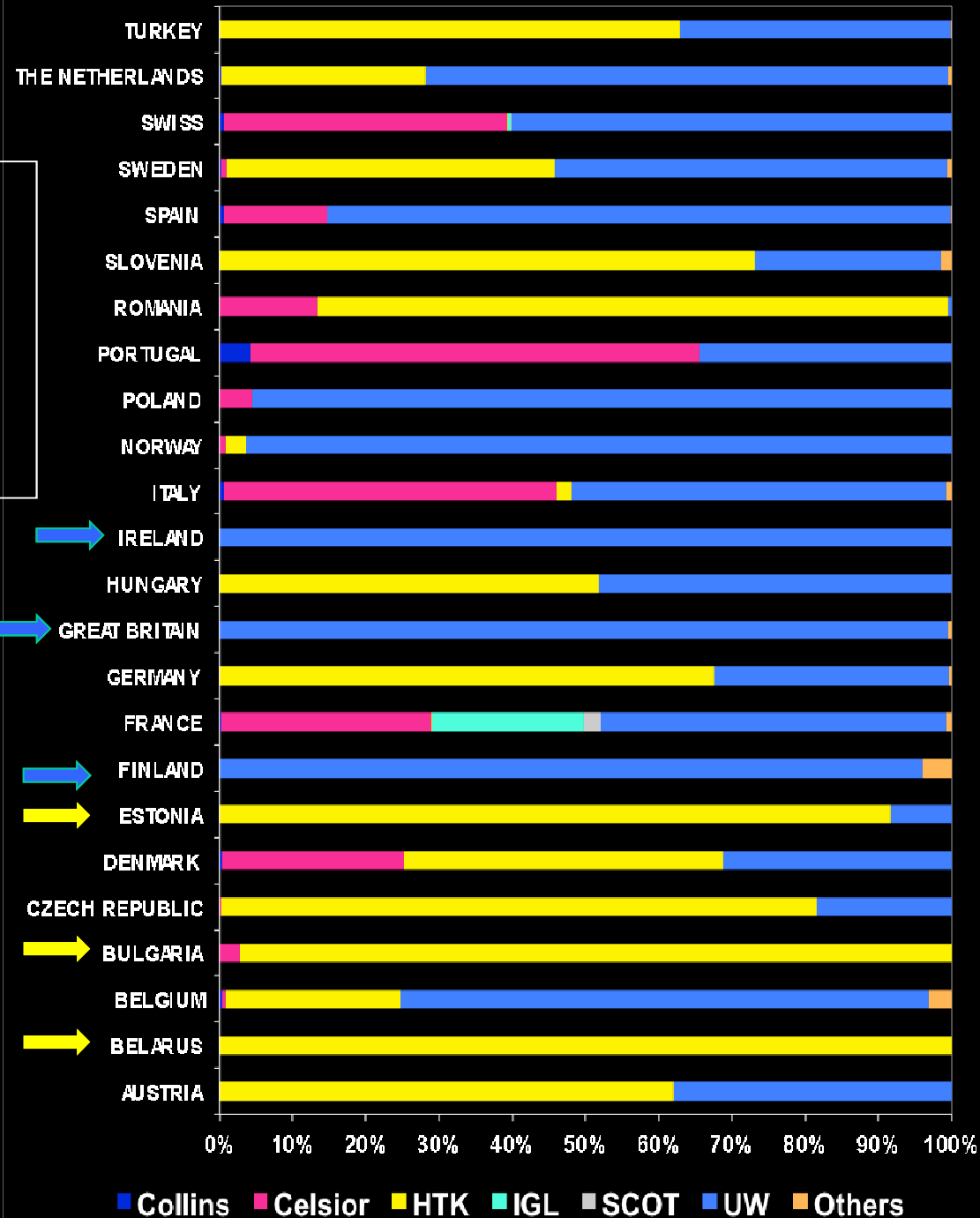
Others
(n=300)



Use of Preservation Solutions in Europe 2003 – 2012, N= 43,424



Use of Preservation Solutions in Europe



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Demographics Characteristics

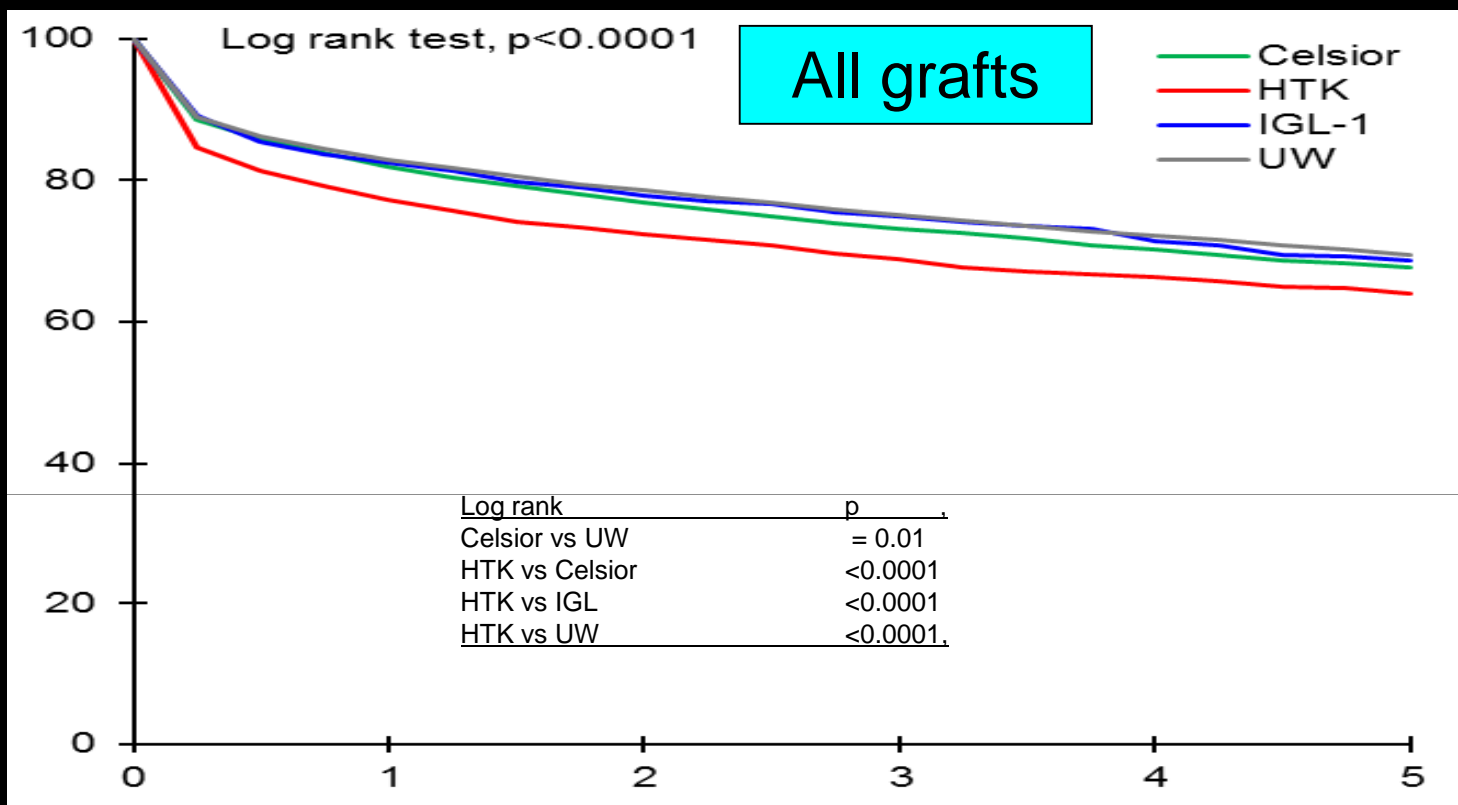
Preservation Solution	Celsior	HTK	IGL-1	UW	p
N	7,756	8,696	1,855	24,562	
Recipient characteristics					
Age (year) (mean±sd)	53±10	52±11	54±10	52±11	<0.0001
Female (%)	27%	34%	27%	33%	<0.0001
BMI (kg/m ²) (mean±sd)	25.6±6.8	26 ± 6.3	26.6 ± 18.5	26.2 ± 22.4	0.21
Disease					
Cirrhosis	54%	60%	60%	61%	<0.0001
Cancer	31%	18%	23%	17%	<0.0001
FUHE	4%	6%	6%	7%	<0.0001
Others	10%	15%	12%	15%	<0.0001
MELD score (mean±sd)	17.1±8.9	18 ± 9.2	19 ± 10.2	17.5 ± 8.7	<0.0001
INR (mean±sd)	1.8±1.3	1.7 ± 1	2.0 ± 1.6	1.7 ± 1.5	<0.0001
Bilirubin (mg/dl) (mean±sd)	5.5±8.4	6.6 ± 9.5	6.6 ± 9.5	6.2 ± 9	<0.0001
Creatinin (mg/dl) (mean±sd)	1.1±0.8	1.2 ± 1	1.2 ± 1	1.2 ± 0.9	<0.0001
Dialysis	4.9%	6.9%	7.0%	2.4%	<0.0001
UNOS status (%)					
ICU-bound	7%	8%	14%	9%	<0.0001
Continuous medical care	16%	21%	13%	14%	
Continuous hospitalization	56%	45%	50%	48%	
At home with normal function	21%	26%	22%	30%	
Tranplant characteristics					
Total ischemia time (min)	457±162	464 ± 226	477 ± 164	500 ± 180	<0.0001
Urgency (%)	6%	11%	9%	9%	<0.0001
Partial liver (split or reduced) (%)	2.8%	2.2%	5%	4.5%	<0.001
Donor Characteristics					
Age (year) (mean±sd)	54±18	48 ± 17	51 ± 18	48 ± 17	<0.0001
Female (%)	43%	44%	43%	43%	0.22
Living related	1.5%	21.1%	2.3%	2.6%	<0.0001

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Graft survival after LT in All patients 2003 – 2012, N= 42,869

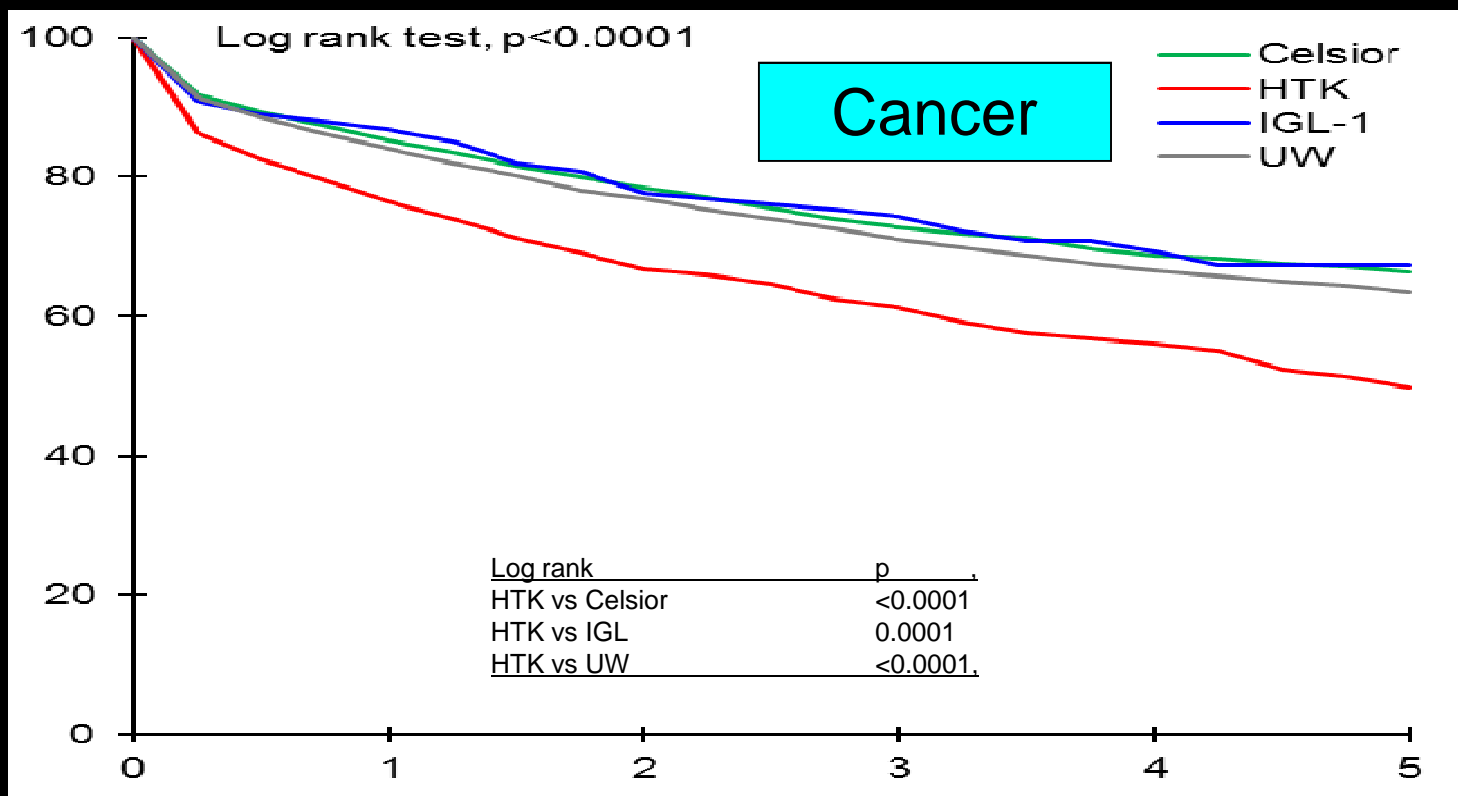


	1 yr	2 yrs	3 yrs	4 yrs	5 yrs
Celsior	82%	77%	73%	70%	68%
HTK	77%	72%	69%	66%	64%
IGL	82%	78%	75%	71%	68%
UW	83%	79%	75%	72%	69%

Exposed patients

	1 yr	2 yrs	3 yrs	4 yrs	5 yrs
Celsior	4,684	3,458	2,653	1,947	1,335
HTK	4,238	2,974	2,098	1,430	963
IGL	1,043	717	504	351	225
UW	16,588	13,889	11,470	9,286	7,225

Graft survival after LT in HCC patients 2003 – 2012, N= 42,869



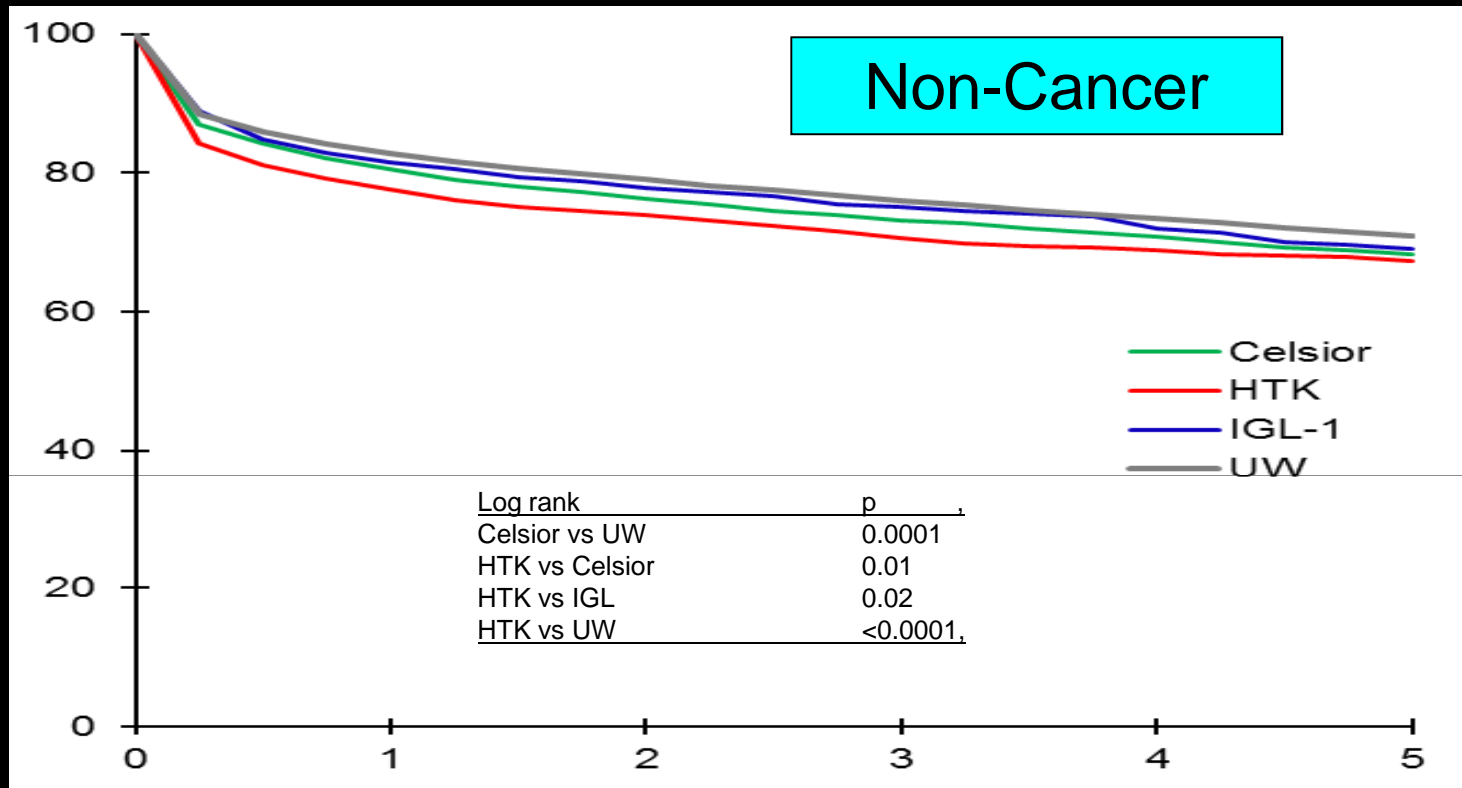
	1 yr	2 yrs	3 yrs	4 yrs	5 yrs
Celsior	85%	78%	73%	69%	66%
HTK	76%	67%	61%	56%	50%
IGL	87%	78%	74%	69%	67%
UW	84%	77%	71%	66%	63%

Exposed patients

	1 yr	2 yrs	3 yrs	4 yrs	5 yrs
Celsior	1481	1051	759	530	346
HTK	777	492	341	214	126
IGL	219	116	73	43	20
UW	2964	2379	1862	1474	1100

Graft survival after LT in Non HCC patients

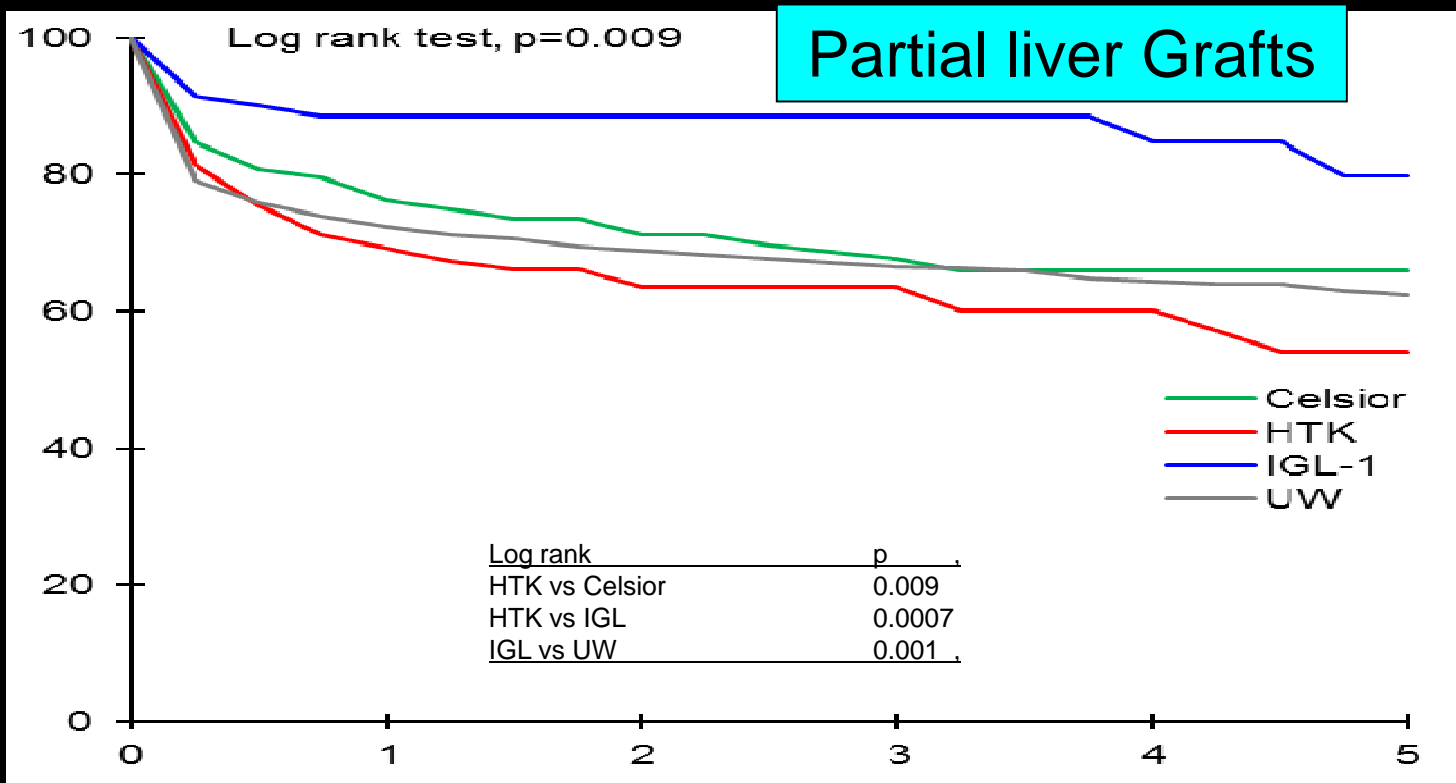
2003 – 2012, N= 42,869



	1 yr	2 yrs	3 yrs	4 yrs	5 yrs
Celsior	80%	76%	73%	71%	68%
HTK	77%	74%	70%	69%	67%
IGL	82%	78%	75%	72%	69%
UW	83%	79%	76%	73%	71%

Exposed patients	1 yr	2 yrs	3 yrs	4 yrs	5 yrs
Celsior	3184	2399	1886	1411	988
HTK	3434	2469	1748	1212	835
IGL	824	601	431	308	205
UW	13532	11448	9564	7778	6099

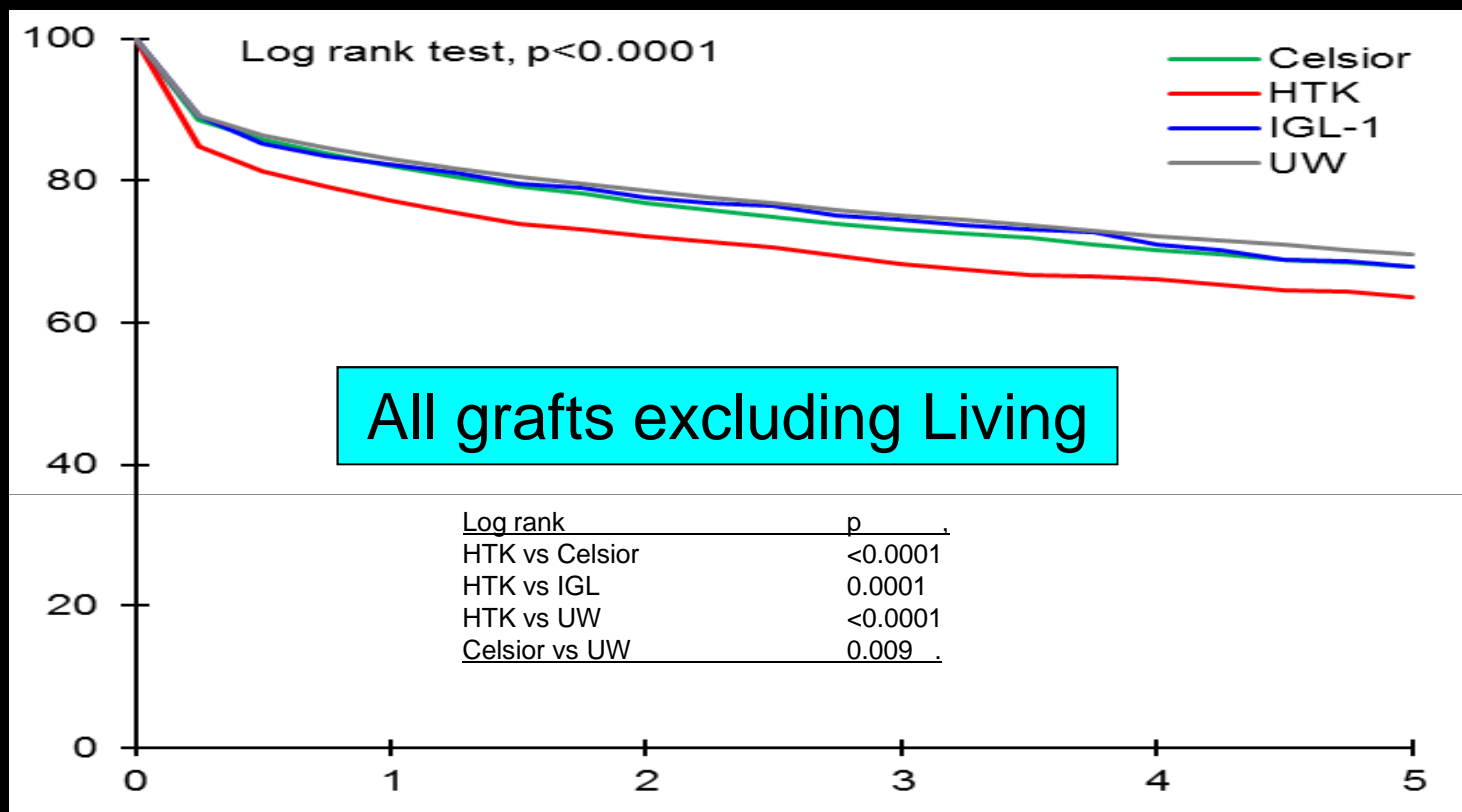
Graft survival after LT in Partial grafts (split or reduced).



	1 yr	2 yrs	3 yrs	4 yrs	5 yrs
Celsior	76%	71%	68%	66%	66%
HTK	69%	64%	64%	60%	54%
IGL	89%	89%	89%	85%	80%
UW	72%	69%	67%	64%	62%

Exposed patients	1 yr	2 yrs	3 yrs	4 yrs	5 yrs
Celsior	114	92	74	55	33
HTK	70	48	37	21	17
IGL	55	36	26	22	14
UW	581	497	431	364	294

Graft survival after LT excluding LDLT 2003 – 2012, N= 42,869

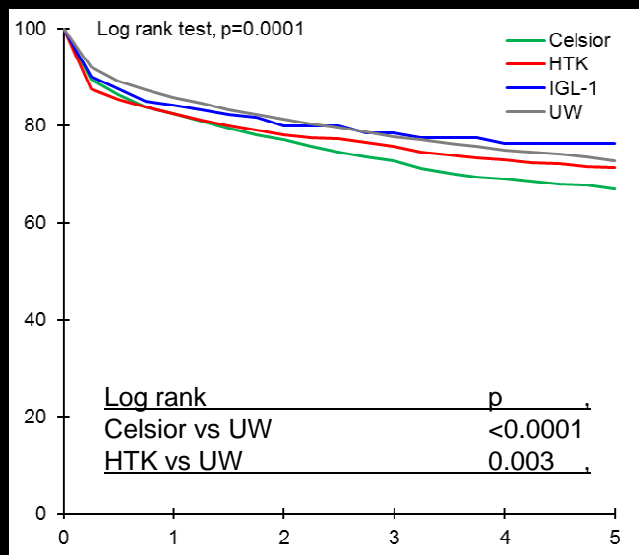


	1 yr	2 yrs	3 yrs	4 yrs	5 yrs
Celsior	82%	77%	73%	70%	68%
HTK	77%	72%	68%	66%	63%
IGL	82%	77%	74%	71%	68%
UW	83%	79%	75%	72%	70%

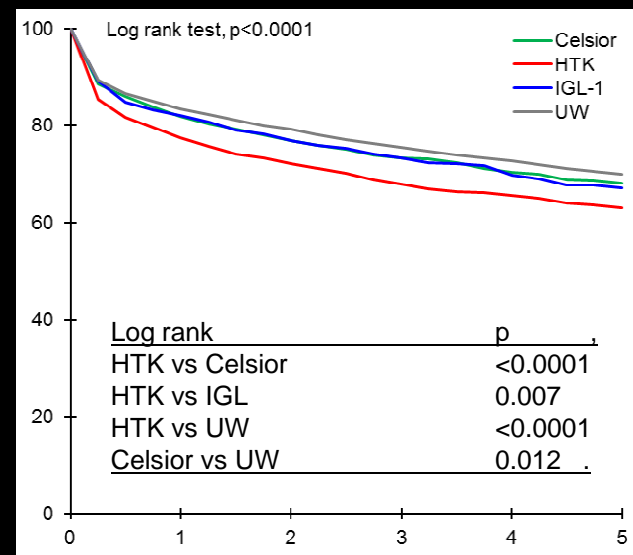
Exposed patients	1 yr	2 yrs	3 yrs	4 yrs	5 yrs
Celsior	4610	3404	2604	1909	1309
HTK	3464	2470	1739	1160	778
IGL	1012	689	480	329	204
UW	16258	13611	11245	9099	7070

Survival according to Ischemia time

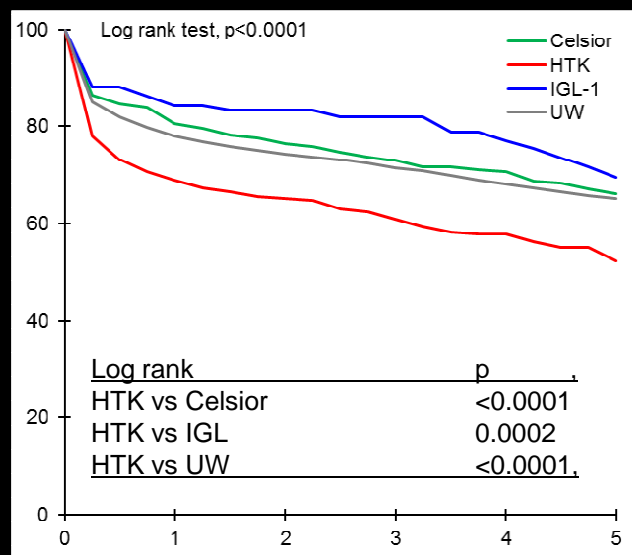
TIT < 6hrs



6hrs < TIT < 12hrs



12hrs < TIT < 18hrs



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Univariate Analysis of Graft Survival

Variable	Option	N	1 yr	3 yrs	5 yrs	8 yrs	10 yrs	p
Recipient age	15-45 yrs	9,634	83%	76%	71%	66%	63%	<0.0001
	45-60 yrs	22,106	82%	74%	69%	62%	55%	
	>=60 yrs	11,052	79%	70%	64%	56%	49%	
Recipient HBs Ag	Negative	34,441	81%	73%	68%	61%	54%	<0.0001
	Positive	5,099	85%	79%	75%	70%	68%	
Recipient anti HCV	Negative	28,179	83%	76%	71%	65%	59%	<0.0001
	Positive	11,161	81%	69%	62%	54%	46%	
Recipient HIV	Negative	31,183	82%	74%	68%	61%	53%	<0.0001
	Positive	588	77%	64%	59%	47%	-	
Urgency	No	33,659	82%	74%	68%	62%	56%	<0.0001
	Yes	3238	72%	66%	62%	59%	59%	
UNOS status*	1	3,307	69%	64%	61%	58%	57%	<0.0001
	2	5,788	76%	69%	64%	56%	52%	
	3	18,436	83%	75%	69%	63%	55%	
	4	10,242	85%	78%	72%	65%	59%	
Preservation Solution	Celsior	7,749	82%	73%	68%	59%	54%	<0.0001
	HTK	8,657	77%	69%	64%	57%	56%	
	IGL	1,855	82%	75%	68%	66%	-	
	UW	24,531	83%	75%	69%	63%	56%	

* (1) Intensive care unit-bound, (2) Continuous hospitalization, (3) Continuous medical care, (4) At home with normal function

Univariate Analysis of Graft Survival (continued)

Variable	Option	N	1 yr	3 yrs	5 yrs	8 yrs	10 yrs	p
Ischemia time	[1-6hrs[9,781	84%	76%	71%	65%	64%	<0.0001
	[6-12hrs[26,227	82%	74%	68%	61%	54%	
	[12-18hrs[4,065	76%	70%	63%	56%	48%	
	[18-36hrs[104	78%	68%	66%	66%	66%	
Type of Graft	Cad. Full siz.	37,428	82%	74%	69%	62%	55%	<0.0001
	Domino	473	81%	70%	66%	45%	42%	
	Living	2,547	79%	72%	66%	61%	59%	
	Reduced	97	68%	62%	52%	52%	-	
	Split	1,483	74%	68%	64%	56%	54%	
Main disease	AHF	2,653	72%	67%	64%	60%	60%	<0.0001
	Cancer	8,555	83%	70%	62%	54%	46%	
	Cirrhosis	25,333	82%	75%	69%	63%	57%	
	Others	5,829	82%	76%	72%	65%	59%	
Donor age >=65yrs	Yes	8,045	80%	69%	62%	54%	47%	<0.0001
	No	30,808	82%	75%	70%	63%	57%	
ABO Blood group	Compatible	2,435	77%	70%	66%	62%	58%	<0.0001
	Identical	39,170	82%	74%	68%	62%	55%	
	No identical	259	69%	62%	59%	50%	-	
Nb LT center <500	No	34,655	82%	74%	68%	61%	56%	0.008
	Yes	8,137	80%	72%	67%	62%	52%	

Prognostic Factors of Graft Survival

Recipient

- Age < 0.0001
- HBV Ag - < 0.0001
- HCV + < 0.0001
- HIV + < 0.0001
- Urgency < 0.0001
- UNOS < 0.0001
- Cause LT < 0.0001

Donor

- Age < 0.0001
- ABO Comp. < 0.0001

Transplantation

- Preservation < 0.0001
- Ischemia time < 0.0001
- Type of graft < 0.0001
- Nb LT < 500 < 0.0001

LIVER PRESERVATION IN EUROPE

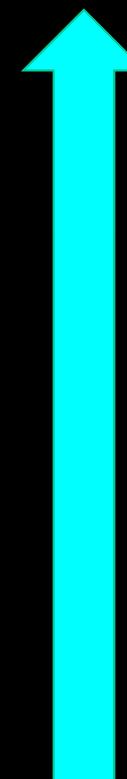
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Graft Survival

Cox model - N= 34,520

Risk factors	p	RR	CI 95%
1. Recipient HIV (+)	<.0001	1.50	[1.29;1.75]
2. Donor age ≥ 65yrs	<.0001	1.41	[1.32;1.51]
3. Recipient anti HCV (+)	<.0001	1.40	[1.34;1.47]
4. Main disease: ACHF	<.0001	1.34	[1.22;1.47]
5. Partial Liver Graft	<.0001	1.30	[1.16;1.44]
6. Recipient Age ≥ 60yrs	<.0001	1.29	[1.23;1.37]
7. Non ABO Isogroup	<.0001	1.24	[1.14;1.34]
8. Recipient HBs Ag (-)	<.0001	1.24	[1.15;1.33]
9. Ischemia time ≥ 12 hrs	<.0001	1.19	[1.11;1.27]
10. Recipient Male	<.0001	1.10	[1.05;1.15]
11. HTK solution	0.02	1.10	[1.01;1.20]
12. Main disease: not cirrhosis	0.01	1.09	[1.04;1.10]



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Cause of Death or Graft loss

2003 – 2012, N=42,869

Preservation Solution	Celsior	HTK	IGL	UW	P
N	7,756	8,696	1,855	24,562	
Infection	12.9 %	19.8 %	16.9 %	13.3 %	<0.0001
Vascular	8.7 %	5.9 %	4.9 %	9.1 %	<0.0001
Non tumoral recurrence	13.8 %	4.6 %	9.8 %	11.8 %	<0.0001
Intraoperative death	2.1 %	1.7 %	0.6 %	1.8 %	NS
Tumoral recurrence	8.1 %	10.5 %	3.7 %	9.6 %	0.0004
Others	6.8 %	6.5 %	8.3 %	7.2 %	NS
PNF or Dysfunction	8.3 %	13.7 %	7.7 %	7.1 %	<0.0001
Cardiovascular	5.6 %	7.1 %	7.9 %	5.8 %	NS
Tumor de novo	4.5 %	3.0 %	5.5 %	7.6 %	<0.0001
Rejection	4.0 %	2.3 %	3.4 %	4.7 %	0.0001
Biliary	2.8 %	6.0 %	3.1 %	4.2 %	<0.0001
Pulmonary	4.9 %	3.5 %	4.0 %	3.9 %	NS
Other hepatic	3.4 %	5.3 %	3.7 %	3.5 %	0.005
Cerebrovascular	4.2 %	2.8 %	3.7 %	2.8 %	0.04
GI	2.7 %	2.8 %	1.5 %	2.2 %	NS
Renal	0.7 %	1.2 %	1.0 %	1.0 %	NS
Hemorrhage	0.8 %	0.9 %	3.1 %	0.5 %	<0.0001
Hepatic infarction	1.3 %	0.0 %	0.6 %	0.2 %	<0.0001

Conclusion

- 1- While exclusively used in the nineties, UW solution is currently used in 36% of liver procurements in Europe
- 2- The most frequent alternative solutions are HTK, Celsior and IGL with different geographic use in relation to countries
- 3- The best results in terms of graft survival are obtained with UW, IGL and Celsior
- 4- Total ischemia time ≥ 12 h and use of HTK are independent risk factors of graft loss (+19 and +10% respectively)
- 5- PNF and Graft Dysfunction are significantly more frequently involved in Graft Loss after HTK compared to the other solutions

Adam et al, Am J Transplantation 2014 (in press)

Histidine–Tryptophan–Ketoglutarate (HTK) Is Associated with Reduced Graft Survival in Deceased Donor Livers, Especially Those Donated After Cardiac Death

Z. A. Stewart, A. M. Cameron, A. L. Singer, R. A. Montgomery and D. L. Segev*

American Journal of Transplantation 2009; 9: 288–293

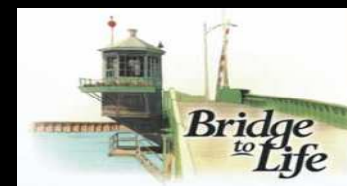
**UNOS Database (2004-2008)
HTK (n= 4755) versus UW (n= 12673)**

« After adjusting for donors, recipient and graft factors that affect graft survival, HTK preservation was associated with an **increased risk of graft loss** (HR 1.44, p= 0.002) especially with DCD allografts and those with cold ischemia time over 8 hours...

Furthermore HTK preservation was associated with a **1.2-fold higher odds of early (< 30 days) graft loss** compared to UW »

The ELTR thanks the 153 contributing centers...

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