EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR)

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Introduction

Background of the European Liver Transplant Registry

Since 1968 the European Liver Transplant Registry (ELTR) collects prospectively the data of liver transplantation (LT) in 145 centers all over Europe. It represents more than 95% of the overall European data compared to the published official figures [1]. This collection is made prospectively through a standardized questionnaire. The first part of the questionnaire includes items regarding date and indication for LT, donor and recipient data, surgical technique of LT, and the immediate postoperative immunosuppression therapy. The second part concerns graft and patient outcome, and immunosuppressive regimen follow-up. Participation in the ELTR is voluntary and a standard computerized database is provided to contributing centers with detailed instructions for the collection of accurate and uniform information [2].

Along with reports concerning LT for specific hepatic diseases [3–12], ELTR has allowed the development of risk models for liver-transplantation mortality according to the characteristics of the donor and recipient, and of the transplant procedure [13,14].

Quality of the data is assessed routinely. A regular auditing process is conducted each year to ensure the reliability of the scientific analysis of the data, a control of the good adequacy between ELTR questionnaire and patient charts is performed by randomly conducted audit visits. Results of these audit visits have indicated that ELTR data were reliable and the scientific results of ELTR can be considered credible and representative of LT in Europe [15–18]. In addition, a control quality program has been developed internally. The data are subjected to checks for completeness, consistency, and range. Comprehensive logical intra- and inter-updates are performed. Moreover, the ELTR has established agreements with the European Organ Sharing Organizations (OSO): United Kingdom Transplant Service Support Authority (UKTransplant), Spanish Organizaciòn Nacional de Transplantes (ONT), Scandinavian Scanditransplant (SKT), Dutch Transplant Foundation (NTS), Eurotransplant (ET), French Agence de la Biomédecine (ABM) to exchange data collected from European Centers and to cross check common data between OSO and ELTR.

Patients and methods

We have first considered all data since 1968 to show the evolution of results of LT in Europe since its initial development. The rest of the analysis has been undertaken during two different periods: (a) from January 1988 to December 2009 (89,865 LT – 80,347 patients), where the date from January 1988 was chosen

Keywords: Liver transplantation; Registry; Outcome.
Received 18 August 2011; received in revised form 4 April 2012; accepted 5 April 2012
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† The order of the sixteen co-authors was determined according to the decreasing number of liver transplants recorded in the ELTR. The list with all the centers is available at the following link: www.eltr.org/spip.php?page=centers-tous.
Abbreviations: ELTR, European Liver Transplant Registry; ELITA, European Liver and Intestine Transplant Association; ESOT, European Society of Organ Transplantation; LT, liver transplantation; HCV, hepatitis C virus; HBV, hepatitis B virus; ALD, alcoholic liver disease; Retx, Retransplantation.

	Overall	LRLT
AUSTRIA	2193	38
BELARUS	34	0
BELGIUM	4316	341
BULGARIA	30	15
CZECH REPUBLIC	1089	1
DENMARK	734	8
ESTONIA	12	0
FINLAND	801	0
FRANCE	16,366	409
GERMANY	14,116	715
GREAT BRITAIN	13,684	138
HUNGARY	425	3
IRELAND	653	0
ITALY	11,697	212
MONACO	11	0
NORWAY	734	1
POLAND	1462	135
PORTUGAL	1645	26
ROMANIA	206	47
SLOVENIA	140	0
SPAIN	15,714	189
SWEDEN	2163	54
SWITZERLAND	1475	59
THE NETHERLANDS	1972	14
TURKEY	1946	1217
EX-YUGOSLAVIA	16	1
TOTAL	93,634	3622

Fig. 1. Number of LTs performed in each country, overall and living related liver transplantation (LRLT) (May 1968–December 2009).

as corresponding to the diffusion of cyclosporine-based immunosuppression and to the standardization of the surgical procedure, (b) the last 10-year period data from January 2000 to December 2009 (54,088 LT – 48,218 patients) to give a more recent evaluation of LT results in Europe.

Data were analyzed as a whole without distinction of pediatric transplants that represent 10% of LTs in Europe.

Data are analyzed with Statistical Analysis System (SAS). The dynamics of data control are continued during the statistical analyzes. Calculation of survival rates are determined by the actuarial method.

Results

From May 1968 to December 2009, the ELTR collected data concerning 93,634 liver transplantations (LTs) in 83,816 patients from 145 centers of 26 countries (Fig. 1). These data give a comprehensive overview of the status and evolution of LT in Europe. Both the number of transplant centers and the annual number of LTs performed in Europe have gradually increased since the creation of ELTR (Fig. 2). However, after an exponential increase from the eighties, a plateau has become to be reached in recent years with about 5800 LTs performed all over Europe.

Main indications for LT in Europe

Main indications for LT in Europe with the corresponding graft and patient survival rates at 1, 5 and 10 years are listed in Table 1. Cirrhosis is the most frequent indication (52%), mainly related to either viral infection (21% with 13% of hepatitis C virus infection (HCV) and 7% of hepatitis B virus infection (HBV)), or alcohol abuse (19%). Combined viral and alcoholic (ALD) cirrhosis represents 3% of cases, with 2% of HCV–ALD. Cirrhosis is followed by three major indications: primary liver tumors (14% with 12.1% of hepatocellular carcinoma), cholestatic disease (11%), and acute hepatic failure (8%, 2% of which are virus-related). Cholestatic disease includes primary biliary cirrhosis (6%) and extra-hepatic biliary atresia (4%). Primary sclerosing cholangitis represents 4% of cases. Biliary atresia is the most frequent indication (57%) in the pediatric population, followed by metabolic disease (19%). Metabolic disease represents 6% of indications with familial amyloïdotic polyneuropathy as the major indication (2%), followed by three indications of equal frequency (1%): Wilson

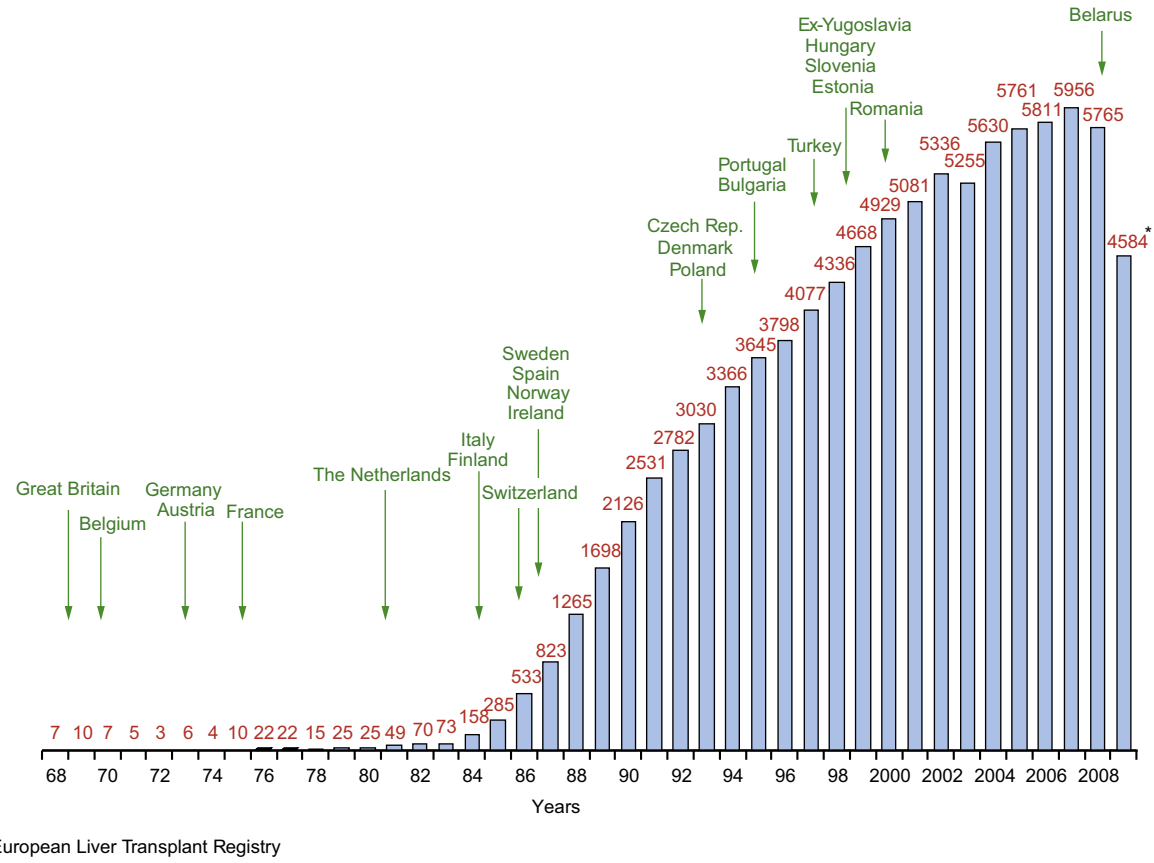


Fig. 2. Evolution of 93,634 LTs performed in Europe since May 1968. Arrows indicate the year the first LT was performed in indicated countries. *This decrease is owed to the fact that some centers did not yet send their updating further to the recent changes of the questionnaire.

disease, alpha-1-antitrypsin deficiency and hemochromatosis. Secondary tumors (mainly carcinoid), Budd Chiari and benign liver tumors (mainly polycystic disease) represent only 1% of indications in Europe.

The percentage of main indications for LT has significantly changed with time. While cancers represented 50% of indications before 1980, they dramatically decreased during the nineties (10%) before resuming a linear increase since 2000, to currently represent more than 20%. Conversely, acute hepatic failure that led anecdotally to LT before 1986 has since become a recognized indication for LT. (Fig. 3).

In the 10 recent years, two groups of indication have shown an increase: primary liver tumors (16%), mainly related to HCC, and cirrhosis (53%), mainly alcoholic (20%). Drug-related fulminant hepatitis is henceforth the leading disease in the group of acute hepatic failures. In the same way, primary sclerosing cholangitis is the main indication in the group of cholestatic diseases. Patient and graft survival of this 10-recent-year population are summarized in Table 1.

Mortality of LT

One, 3 and 6-month patient's survivals were 90%, 85% and 82% before 2000. Survival rates dramatically increased to reach 94%, 91% and 88%, respectively. The critical period for post-LT outcome is the first 6 months: 46% of deaths and 65% of re-LT occurs within 6 months after LT (Fig. 4). In 49% of cases, re-LT is indicated in the month after primary LT, and one quarter of deaths occurs within the first month after LT.

Data represented in Tables 2 and 3 correspond to main cause of death or graft failure. Main causes of death in the 18,186 patients (about 23%) who died after primary LT or re-LT were, by decreasing order: (1) general causes as multiple organ failure and cerebrovascular, cardiovascular, pulmonary, and renal complications (29%); (2) recurrence of primary disease (20%), mostly cancer (11%); (3) sepsis (18%) mostly bacterial (9%); (4) technical complications (5%), mostly hemorrhage and vascular (3%); and (5) rejection (4%) mostly chronic (3%) (Table 2). Intra-operative deaths and primary non-function represented 3% of all deaths. When we consider only the patients who survive beyond 6 months (Fig. 5), there are less technical complications, infection and general complications (cerebrovascular, cardiovascular, pulmonary, and renal), but more tumoral and non-tumoral recurrences, *de novo* tumor and rejection.

The data of the last 10 years show a decrease in overall mortality (16%) with the same distribution of the causes of death observed in the population from 1988.

Overall patient survival

When all indications are considered during the entire study period, patient survival rates are 82% at 1 year, 71% at 5 years, 61% at

Table 1. Primary indications for LT in Europe and the corresponding survival.

	From 1988 to 2009													Last 10 years [1999-2009]						
	Percentage			Survival rate (%) yr										Percentage			Survival rate (%) yr			
	No. patients	of the disease (%)	of the total (%)	1		5		10		15		20		No. patients	of the disease (%)	of the total (%)	1		5	
Indication for LT				Graft (%)	Patient	Graft (%)	Patient	Graft (%)	Patient	Graft (%)	Patient	Graft (%)	Patient				Graft (%)	Patient	Graft (%)	Patient
Acute hepatic failure	6507		8	64	70	56	64	51	58	44	53	38	47	3449		7	70	76	62	69
Virus	1251	19	2	67	73	57	65	50	58	41	52	35	46	645	19	1	75	80	65	72
Drug	1187	18	1	66	71	57	63	49	55	42	48	39	45	728	21	2	70	75	61	66
Toxic	242	4	0.3	67	71	63	68	58	64	54	61	40	61	164	5	0.3	69	73	64	69
Postoperative/traumatic	178	3	0.2	40	50	35	45	33	44	26	44	-	-	120	3	0.2	47	57	43	55
Unknown/others	3649	56	5	63	69	56	64	52	59	46	55	39	49	1792	52	4	69	76	63	70
Cholestatic disease	9114		11	79	87	70	78	62	70	45	59	30	44	4675		10	83	89	74	81
Primary biliary cirrhosis	4515	50	6	81	86	75	80	66	71	53	59	43	48	1929	41	4	85	90	78	83
Primary sclerosing cholangitis	3582	39	4	80	87	69	78	57	70	45	59	30	44	2170	46	5	83	90	72	82
Secondary biliary cirrhosis	550	6	1	70	75	60	65	50	57	47	54	47	54	307	7	1	71	76	61	65
Others	467	5	1	77	83	69	77	61	71	51	60	30	60	269	6	1	74	81	62	73
Congenital biliary disease	4152		5	79	86	74	83	70	80	65	77	59	73	2167		4	84	90	79	87
Extrahepatic biliary atresia	3346	81	4	79	87	74	83	71	81	68	79	62	75	1662	77	3	85	91	80	88
Alagille syndrom	228	5	0.3	79	84	73	81	69	77	54	73	54	73	147	7	0.3	83	88	79	85
Congenital biliary fibrosis	193	5	0.2	81	87	76	81	68	75	63	70	-	60	98	5	0.2	88	92	84	91
Caroli disease	196	5	0.2	78	87	69	81	63	78	40	60	-	-	138	6	0.3	77	86	67	83
Choledocal cyst	37	1	0.05	86	86	75	86	52	73	20	49	-	-	17	1	0.04	74	74	46	74
Others	152	4	0.2	82	86	76	81	70	80	61	72	-	-	105	5	0.2	85	88	80	84
Cirrhosis	41,593		52	79	83	67	72	56	61	46	51	37	42	25,424		53	81	85	69	73
Virus related cirrhosis	18,348	44	23	78	82	64	69	54	59	46	51	38	43	11,030	43	23	80	88	65	74
Virus B	4187	10	5	79	83	69	74	63	68	56	61	46	49	2400	9	5	84	87	75	79
Virus C	10,753	26	13	76	80	60	65	48	53	38	43	29	33	6590	26	14	77	81	59	64
Virus BD	1382	3	2	87	92	82	87	77	84	71	79	66	76	835	3	2	89	93	83	88
Virus BC	683	2	1	76	81	64	71	54	60	49	54	43	54	407	2	1	77	82	67	74
Virus BCD	165	0	0.2	89	91	80	82	63	66	50	53	37	40	106	0.4	0.2	90	91	82	83
Other viruses	1178	3	1.5	81	84	64	69	53	59	45	50	36	40	692	3	1.4	83	87	63	69
Alcoholic cirrhosis	15,019	36	19	81	86	69	73	55	59	44	48	33	36	9555	38	20	83	86	71	75
Combined viral and alcoholic	2244	5	3	82	87	67	72	51	56	38	41	33	35	1531	6	3	84	88	70	74
Viral C and alcoholic	1790	4	2	81	85	65	69	50	54	37	40	30	31	1228	5	3	84	86	69	73
Viral B and alcoholic	454	1	1	85	89	74	79	59	62	41	45	41	45	303	1	1	88	92	76	80
Cryptogenic (unknown)	3443	8	4	76	81	66	72	57	63	48	54	34	42	1892	7	4	79	83	69	74
Autoimmune cirrhosis	1892	5	2	80	85	69	76	59	67	48	57	46	55	1069	4	2	84	88	72	80
Drug-related	68	0.2	0	74	77	68	72	62	66	-	-	-	-	31	0.1	0.06	75	77	70	77
Others	579	1	1	68	73	58	63	49	54	41	46	26	20	316	1	0.7	83	87	63	65

Indication for LT	From 1988 to 2009													Last 10 years [1999-2009]							
	No. patients	Percentage		Survival rate (%) yr										No. patients	Percentage		Survival rate (%) yr				
		of the disease (%)	of the total (%)l	1		5		10		15		20			of the disease (%)	of the total (%)	1		5		
				Graft (%)	Patient	Graft (%)	Patient	Graft (%)	Patient	Graft (%)	Patient	Graft (%)	Patient				Graft (%)	Patient	Graft (%)	Patient	
Primary liver tumors	10,991		14	72	76	49	52	40	40	34	37	24	27	7640		16	81	83	61	64	
Hepatocellular carcinoma and cirrhosis	9122	83	11	80	83	58	62	46	49	37	40	25	29	6874	90	14	82	86	62	66	
Hepatocellular carcinoma and non-cirrhotic liver	638	6	1	67	71	40	43	29	31	24	26	20	23	215	3	0.4	78	84	57	61	
Hepatic cholangiocellular carcinoma	332	3	0.4	62	66	28	31	19	21	14	17	-	-	142	2	0.3	73	79	33	37	
Biliary tract carcinoma (Klatskin)	252	2	0.3	64	66	30	32	22	24	14	16	12	13	79	1	0.2	65	68	32	37	
Hepatoblastoma	180	2	0.2	81	84	69	74	61	69	58	66	-	-	127	2	0.3	82	86	70	76	
Epithelioid hemangioendothelioma	159	1	0.2	81	88	71	77	67	72	58	67	58	67	96	1	0.2	81	90	76	84	
Hepatocellular carcinoma-fibrolamellar	50	0.5	0.1	65	70	32	36	27	33	27	33	-	-	18	0.2	0.04	65	71	30	38	
Angiosarcoma	21	0.2	0.03	27	33	7	13	-	-	-	-	-	-	5	0.1	0.01	56	56	-	-	
Other liver malignancies	237	2	0.3	67	71	41	43	36	38	29	31	-	-	84	1	0.2	81	87	49	53	
Secondary liver tumors	516		1	74	79	43	50	29	32	24	25	15	15	361		1	77	83	50	55	
Carcinoid	196	38	0.2	81	86	55	58	33	34	24	24	16	16	109	30	0.2	85	90	63	66	
Other neuroendocrine	160	31	0.2	69	74	44	49	27	30	26	26	-	-	108	30	0.2	70	76	46	59	
Colorectal	47	9	0.1	70	79	31	33	14	14	-	-	-	-	25	7	0.1	78	86	33	37	
GI non-colorectal	15	3	0.02	72	72	36	36	29	29	29	29	-	-	5	1	0.01	80	85	-	-	
Non-gastrointestinal	18	3	0.02	64	64	24	24	-	-	-	-	-	-	6	2	0.01	75	80	-	-	
Others	80	16	0.1	61	65	28	32	18	22	15	19	-	-	108	30	0.2	-	-	-	-	
Metabolic diseases	4855		6	80	86	72	78	63	70	57	65	48	59	2866		6	82	87	72	79	
Familial amyloïdotic polyneuropathy	1280	26	2	81	87	69	76	56	62	43	50	-	-	873	30	2	82	88	68	76	
Wilson disease	812	17	1	81	88	76	84	68	79	62	75	56	70	514	18	1	84	90	78	85	
Alpha-1-antitrypsin deficiency	542	11	1	84	89	77	83	68	75	63	69	37	63	293	10	1	88	91	83	87	
Hemochromatosis	468	10	1	73	76	63	66	49	53	38	39	-	-	269	9	1	75	78	62	66	
Cystic fibrosis	225	5	0.3	79	84	65	71	53	59	53	56	-	-	155	5	0.3	80	86	62	67	
Byler disease	212	4	0.3	83	93	80	92	77	87	72	83	72	83	101	4	0.2	85	94	79	92	
Primary hyperoxaluria	230	5	0.3	79	85	71	78	65	71	60	67	60	67	148	5	0.3	77	85	70	78	
Tyrosinemia	98	2	0.1	84	91	73	85	72	83	69	83	69	83	35	1	0.1	87	90	67	84	
Glycogen storage disease	95	2	0.1	83	90	79	86	79	86	68	73	59	62	66	2	0.1	84	91	76	82	
Non-alcoholic steatohepatitis	86	2	0.1	85	87	83	84	62	63	-	-	-	-	84	3	0.2	85	86	83	84	
Crigler-Najjar	59	1	0.1	88	97	79	92	79	92	79	92	-	-	31	1	0.1	86	100	76	95	
Homozygous hypercholesterolemia	21	0.4	0.0	83	83	74	74	50	74	50	74	-	-	15	1	0.03	83	83	64	64	

Table 1 (*continued*)

Indication for LT	From 1988 to 2009													Last 10 years [1999-2009]						
		Percentage		Survival rate (%) yr											Percentage			Survival rate (%) yr			
	No. patients	of the disease (%)	of the total (%)l	1		5		10		15		20		No. patients	of the disease (%)	of the total (%)	1		5	
				Graft (%)	Patient	Graft (%)	Patient	Graft (%)	Patient	Graft (%)	Patient	Graft (%)	Patient				Graft (%)	Patient	Graft (%)	Patient
Protoporphyria	19	0.4	0.0	78	84	72	72	66	66	57	57	57	57	7	0.2	0.01	68	68	48	48
Others	708	15	1	79	84	69	75	62	69	60	67	58	62	275	10	1	-	-	-	-
Budd-Chiari	712		1	72	78	64	71	55	64	49	59	40	49	400		1	76	81	66	73
Benign liver tumors or polycystic disease	1015		1	83	86	77	82	71	75	64	68	61	65	733		2	85	89	79	85
Polycystic disease	732	72	1	86	89	80	85	73	77	66	69	66	69	548	75	1	88	91	81	87
Hemangioma	99	10	0.1	80	85	78	84	73	80	66	72	-	-	60	8	0.1	79	84	75	82
Adenomatosis	38	4	0.05	83	83	74	74	74	74	74	74	-	-	27	4	0.06	85	85	85	85
Nodular regenerative hyperplasia	33	3	0.04	81	81	63	63	63	63	52	52	-	-	19	3	0.04	88	88	68	68
Hepatic adenoma	27	3	0.03	60	71	50	61	33	61	33	61	-	-	19	3	0.04	71	77	55	61
Focal nodular hyperplasia	16	2	0.02	74	93	66	93	45	51	-	-	-	-	12	2	0.02	74	91	74	91
Others	70	7	0.1	71	79	63	73	57	57	57	62	-	-	48	7	0.1	68	73	63	70
Parasitic disease	68		0.1	75	77	67	68	56	57	52	53	26	27	31		0.1	81	81	55	55
Alveolar echinococcosis	47	69	0.1	77	79	67	69	55	57	49	52	30	31	23	74	0.05	89	89	62	62
Cystic hydatidosis	7	10	0.01	57	57	43	43	43	43	43	43	-	-	4	13	0.01	-	-	-	-
Schistosomiasis (Belharzia)	4	6	0.005	75	75	-	-	-	-	-	-	-	-	2	6	0.004	-	-	-	-
Others	10	15	0.01	80	80	80	80	-	-	-	-	-	-	2	6	0.004	-	-	-	-
Other liver diseases	824		1	71	74	61	66	52	57	47	53	44	51	472		1	74	79	66	71
Total	80,347		100	75	82	63	71	53	61	44	51	36	43	48,218		100	79	85	66	73

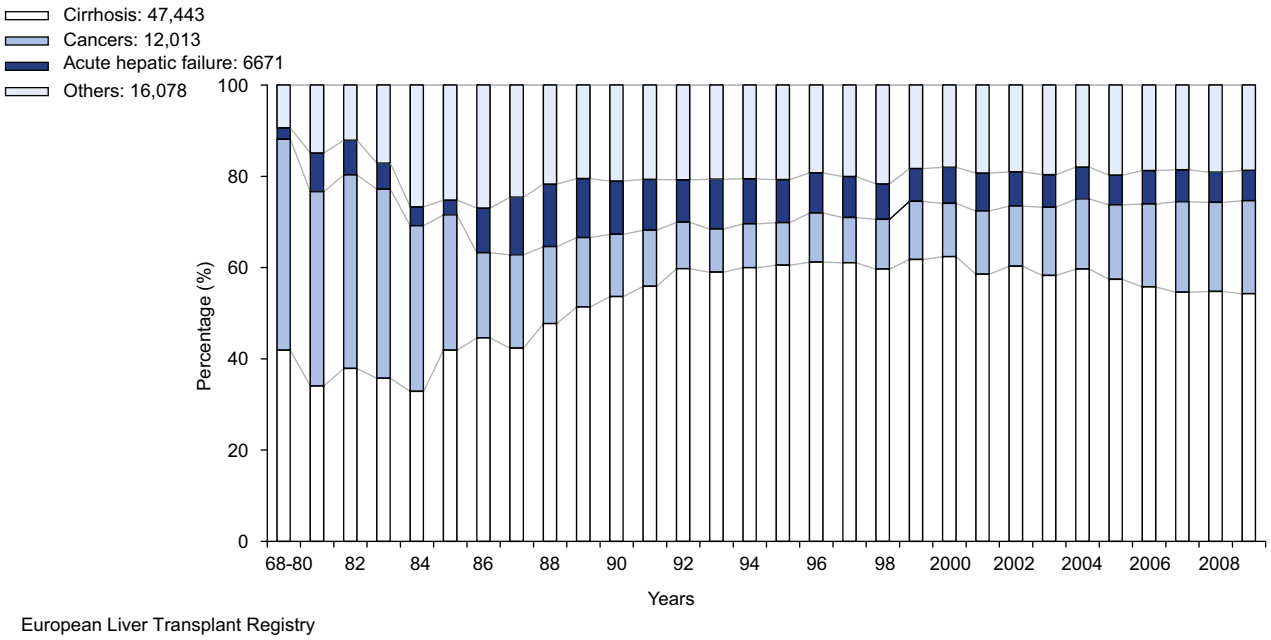
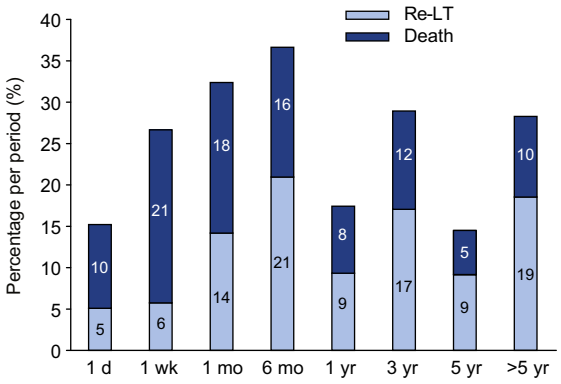


Fig. 3. Evolution of primary indications for LT in Europe (05.1968–12.2009).



Cumulative proportions (%)	1 d	1 wk	1 mo	6 mo	1 yr	3 yr	5 yr	>5 yr
Ret-LT	10	31	49	65	73	85	90	100
Death	5	11	25	46	55	72	81	100

European Liver Transplant Registry

Fig. 4. Mortality and re-LT. Percentage per period and cumulative proportions (01.1988–12.2009).

10 years, 51% at 15 years and 43% at 20 years. When we consider only the patients who survive beyond 6 months, patient survival rates are dramatically higher (96% at 1 year, 83% at 5 years, 71% at 10 years, 61% at 15 years and 52% at 20 years). After an improvement between 1988 and 2000, the survival of these patients appears to be relatively steady since 2000 (Fig. 6).

Survival has improved regularly year after year, reaching 85% at 1 year after 2004 compared with 76% in 1990–1994 and only 33% before 1985 (Fig. 7). The improvement concerns all the indications but particularly LT for cancers (Fig. 8).

When we consider the last 10-year period, survival of patients transplanted in the recent 10 years has improved to reach 85% at 1 year and 73% at 5 years.

Survival of pediatric versus adult liver transplant recipients

Ten percent of LTs have been performed in pediatric patients (<15 years), with 3.4% of children younger than 2 years. Five-year survival in children is significantly better than in adults (79% *vs.* 70%, p <0.0001). In the pediatric population, 5-year survival rate is identical for children under 2 years and for those aged 3 to 15 years (79%).

In the 10 last years, the rate of pediatric LT has decreased to 8% and the corresponding 5 year-survival is still better than in adults (82% *vs.* 72%, p <0.0001).

Survival according to the indication for LT

The 5-year patient survival rate is significantly better for cirrhosis (72%) than for primary liver tumors (52%, p <0.001) and acute hepatic failure (64%, p <0.001). In viral cirrhosis, HBV and HCV co-infection have a better 5-year survival (82%) than mono-infection with HCV (65%) or HBV (74%). The greater survival rates obtained in metabolic diseases (78%), cholestatic disease (78%) and congenital biliary disease (83%), occur partly because of the high percentage of children in these groups. Details of survival rates at 1, 5 and 10, 15 and 20 years according to the primary indication are listed in Table 1.

Although 5-year survival in the last 10-year population was improved in all indications, the most important gain in survival was observed in LTs for primary liver tumors, which is presently 64%, liver metastases (55%) and acute hepatic failure (69%).

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Table 2. Post-LT mortality after first LT in Europe. Complications correspond to first declared cause of death according to date of occurrence.

Cause of death	Date of the mortality occurence								Total	Percentage of	
	1 d	1 wk	1 mo	6 mo	1 yr	3 yr	5 yr	>5 yr		the complication (%)	of the total (%)
Intra-operative death	508	0	0	0	0	0	0	0	508	100	3
Primary non-function	115	229	172	0	0	0	0	0	516	100	3
Technical	91	114	257	246	82	111	30	55	986	100	5
Haemorrhage	67	42	69	46	10	8	5	3	250	25	1
Vascular complications	21	59	157	96	35	35	9	20	432	44	2
Biliary complications	0	3	17	95	36	60	13	31	255	26	1
Hepatic infarction	3	10	14	9	1	8	3	1	49	5	0.3
Sepsis	22	142	801	1346	281	295	133	267	3287	100	18
Bacterial infection	13	81	390	633	139	154	74	181	1665	51	9
Fungal infection	1	9	125	181	24	24	11	10	385	12	2
Viral infection	0	4	23	121	21	19	4	11	203	6	1
Sepsis not designated	8	48	263	411	97	98	44	65	1034	31	6
Rejection	6	17	85	113	125	164	55	82	647	100	4
Chronic rejection	0	0	0	67	109	153	50	80	459	71	3
Acute rejection	6	16	82	43	13	10	5	1	176	27	1
Not designated	0	1	3	3	3	1	0	1	12	2	0.1
Recurrence of initial disease	0	1	10	362	616	1383	599	712	3683	249	20
Tumoral	0	0	1	214	382	850	338	267	2052	56	11
Non-tumoral	0	1	9	148	234	533	261	445	1631	44	9
Tumor *de novo*	1	0	5	76	149	450	381	731	1793	100	10
General causes	333	495	1055	1208	321	530	324	987	5253	100	29
Cardiovascular	181	155	232	230	77	152	115	369	1511	29	8
Cerebrovascular	55	144	185	198	64	113	43	164	966	18	5
Pulmonary	26	54	216	305	72	105	53	172	1003	19	6
Gastrointestinal	26	37	122	140	33	68	47	90	563	11	3
Renal	3	11	47	58	20	27	35	119	320	6	2
Mutiple organ failure	42	94	253	277	55	65	31	73	890	17	5
Other liver causes	7	32	68	54	25	40	27	62	315	100	2
Other or unknown causes	69	82	165	225	89	186	110	272	1198	100	7
Total	1152	1112	2618	3630	1688	3159	1659	3168	18,186	100	100

Table 3. Recipient graft survival according to the type of LT in Europe.

Type of LT/graft	From 1988 to 2009						Last 10 years [1999-2009]		
	No. grafts	Survival rate (%)					No. grafts	Survival rate (%)	
		1 yr	5 yr	10 yr	15 yr	20 yr		1 yr	5 yr
Cadaveric full size	68,728	78	65	55	46	36	40,268	81	68
Split liver	3919	73	65	56	50	50	2983	76	67
Right	1728	76	66	52	43	-	1327	77	67
Left	1738	72	65	59	51	-	1323	75	66
Living donor	3481	80	69	61	60	-	3099	80	68
Right	2113	79	64	51	51	-	2051	79	65
Left	1191	81	76	71	69	-	880	81	76
Reduced liver	1988	69	62	58	54	51	711	74	68
Domino (sequential)	665	81	59	41	-	-	590	83	62

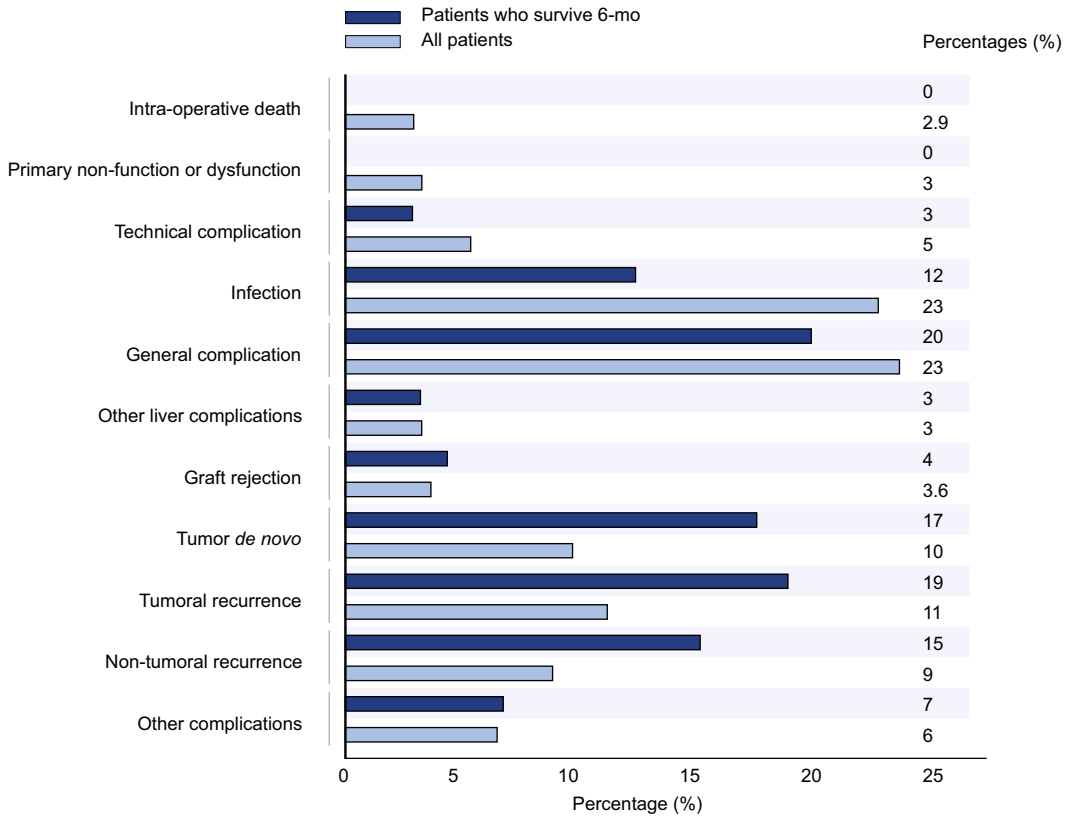

Fig. 5. Cause of death after LT of patients who survive beyond 6 months.

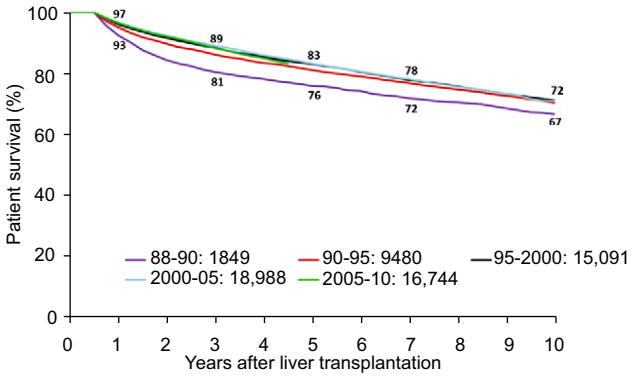

Fig. 6. Evolution of patient survival in patients who survive beyond 6 months.

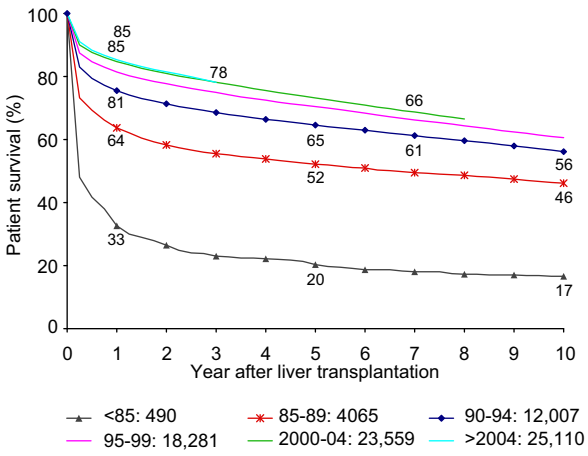

Fig. 7. Patient survival according to year of LT.

Survival according to donor and recipient characteristics

Donor characteristics

The majority of donors were male (59%). Seventy-six percent were younger than 55 years, whereas 11% were older than 65 years. An increasing percentage of livers are coming from donors older than 60 years (1% in 1989, 15% in 1999 and 29% in 2009), in relation to the increasing gap between a growing waiting list and a relatively stable donor pool (Fig. 9). Graft survival when organs were procured from donors younger than 55 years was significantly higher than that with organs from donors older than 65 years (65% *vs.* 57% at 5 years, p <0.0001). With 71% at 1-year and 50% 5-year graft survival, there is no argument to discard octogenarian grafts among aged subjects without associated risk factors (Fig. 10).

When we consider the last 10-year period, 5-year graft survival was 69% with donors younger than 55 years and 59% with donor older than 65 years. However, aged grafts are more frequently transplanted to aged recipients (33% of grafts older than 60 years were used in recipients older than 70 years, and only 21% were used in recipients younger than 70 years, p <0.0001), explaining at least in part, the difference in survival.

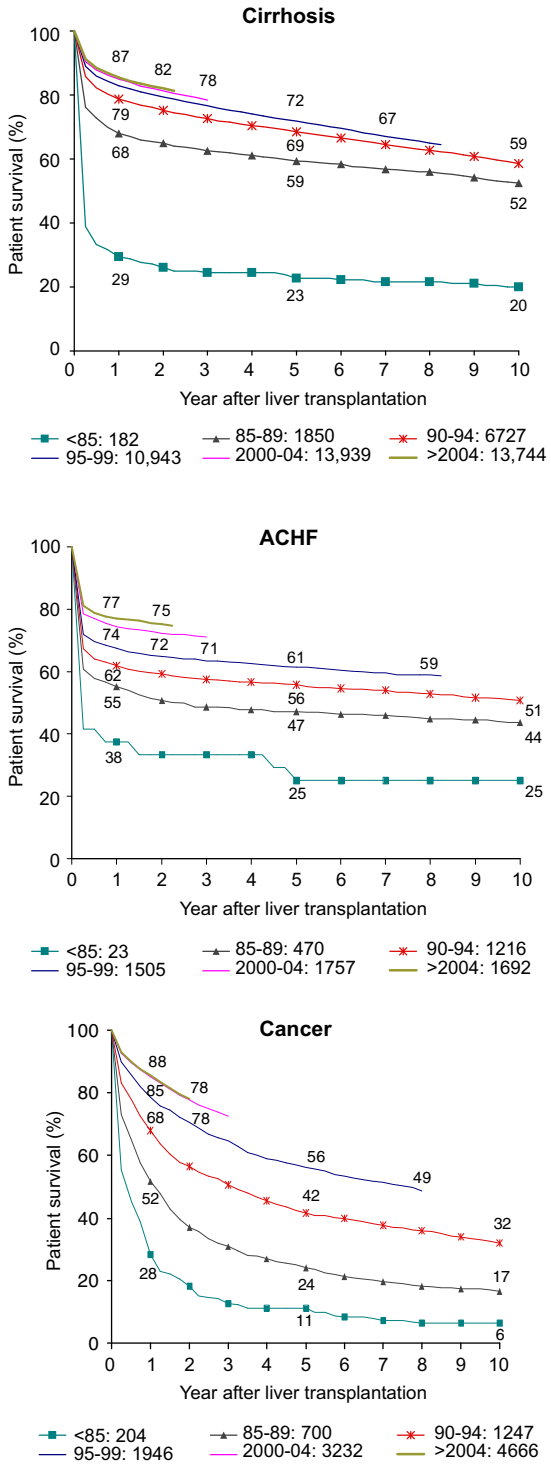

Fig. 8. Patient survival according to indication for and year of LT.

Recipient age

In addition to the already mentioned better 5-year survival of pediatric *vs.* adult LT recipients, an influence of recipient age is observed for adults. Survival rates are 74% for adults aged 16–45 years, 70% for those aged 46–60 years, and 64% for those older than 60 years. However, average age of transplanted recipients has increased steadily during the last decade, and patients older than 60 years, who represented less than 5% in the 1980s, represented approximately 25% of transplant recipients in 2009 (Fig. 11).

When we consider the last 10-year period, 5-year survival has increased in all the subgroups of adult recipients to reach 77% for adults of 16–45 years, 73% for 46–60 years and 66% over 60 years.

Blood group type matching

Ninety-two percent of LTs were isogroup, and 7.6% were compatible. Only 0.6% were incompatible and restricted to urgent procedures. In emergencies, isogroup and compatible LTs have similar survival. In elective conditions, isogroup LTs have a better 5-year survival than compatible LTs (66% *vs.* 60%, p <0.0001). Incompatible LTs have a decreased 5-year graft survival rate as compared to isogroup and compatible LTs (27% *vs.* 53%, p <0.0001). However, use of these incompatible grafts in emergency indications allows around 50% survival rate in patients otherwise destined to a fatal outcome.

Although 5 year-survival in the last 10-year population was improved in all the groups of type matching, the most important gain in survival was observed in incompatible matching (+41%). However, only 0.3% of LTs were incompatible.

Survival according to surgical technique

More than 99% LTs were done orthotopically, and 87% of grafts were full size. Alternative procedures to full size LTs have been used increasingly in recent years (9% before 2000 *vs.* 16% after 2000). In the 2000s, alternative procedures were represented by reduced livers (2%), split livers (6%) living donors (6%), and domino transplants (1%). 1, 5, 10, 15 and 20-year graft survivals of each type of graft are summarized in Table 3. Survival at 5 years was similar between split liver and cadaveric full size grafts (65%), but lower than that of living donors (69%) and higher than that of reduced and domino grafts (62% and 59%, respectively). Auxiliary grafts represented 0.8% of overall LTs with a lower graft survival as compared to non-auxiliary grafts in urgent indications (5-year survival rates: 45% *vs.* 52%), and in elective indications (60% *vs.* 66%, p <0.0001). Graft survival was better when cold ischemia time was less than 12 h and University of Wisconsin solution was used for preservation (p <0.001).

When we consider the last 10-year period, 5-year graft survival has increased in all types of graft to reach 68% for reduced grafts, 67% for split and 62% for domino.

Living related LT in Europe

The ELTR has cumulated data concerning 3622 living related LTs (LRLTs) performed in 78 centers from 20 countries from October 1991 to December 2009 (Fig. 1). The results of this technique will be published elsewhere. In summary, adults represented 65% of LRLTs. Since 2001 adult LRLTs largely exceeded pediatric LTs. The donor surgical mortality rate was 0.18%. Overall 5-year graft survival of LRLT was 69%, better for children than for adults (78% *vs.* 63%, p <0.001). Whereas graft survival of LRLT was better than cadaveric LT for children (78% *vs.* 72%, p <0.001), it was similar for adults (64% *vs.* 63%). Overall, graft loss included more technical complications (26% *vs.* 14%), more infection (23% *vs.* 18%), more rejection (8% *vs.* 4%), more tumor recurrence (12% *vs.* 9%), but less

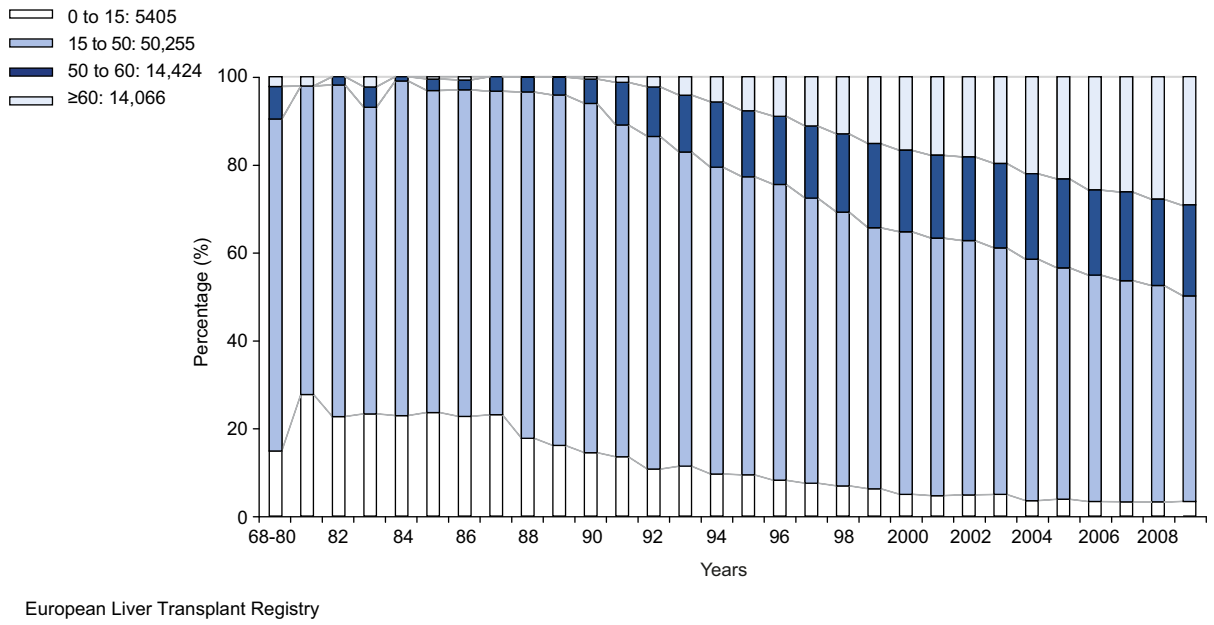

Fig. 9. Evolution of donor age in Europe (05.1968–12.2009).

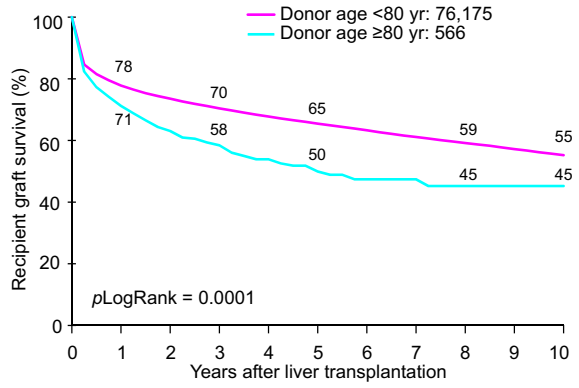

Fig. 10. Recipient graft survival according to donor age.

general complications (20% *vs.* 27%) and less non-tumor disease recurrence (4% *vs.*12%) after LRLT than after cadaveric LT (all p <0.05).

Re-LT

Main causes of re-LT

Re-LT was indicated in 5596 cases (7%) mainly for technical complications (37%) (mostly vascular (27%) and biliary (10%)), for primary non-function (25%) and for rejection (19%), mainly chronic (14%). Recurrence of primary disease (mostly non-tumoral) was concerned in only 11% of cases (Table 4).

Survival

Five-year graft survival rates for the second and third LTs were 42% and 37%, respectively, significantly lower than those for primary LT (65% – p <0.0001) (Fig. 12).

The data of the last 10 years show a decrease in the use of re-LT (5%) with an increase of technical complications (41%) and a decrease of rejection (10%). Moreover, 5-year graft survival was increased in all the ranks of re-LT and the gap between primary LT (68%) and 2nd LT (52%) has been reduced.

Discussion

With more than 90,000-recorded LTs, the ELTR is a unique source to evaluate the evolution and results of LT in Europe. It is representative of LT in Europe (95% of LTs performed). Owing to a routine control of data including audit visits to randomly selected centers, its scientific value has been recently emphasized [15–18].

Almost 6000 LTs per year are currently performed in Europe, a number similar to that of the United States (US). However, donation rates in Europe vary much more than in United Network for Organ Sharing (UNOS) regions. Spain has by far the highest donation rate in Europe (34.2 per million inhabitants in 2008) followed by most of the other European countries with a rate of organ donation between 20 and 25 per million inhabitants, similar to that of Region 8 in the US (Colorado, Kansas, Nebraska and Wyoming) which has the highest donation rate (24 per million inhabitants in 2008) [19]. To cope with a donor shortage that presently represents the most important limiting factor of LT, alternatives to cadaveric LT such as split, domino, or living related LTs are increasingly used accounting for 15% of all procedures. Although more technically demanding, these techniques give results similar to that for cadaveric LT and allow a larger number of patients to undergo LT. Nevertheless, they need high expertise from the centers [13,14]. This expertise is also likely to minimize the risk for donors in case of LRLT, although no relationship has been clearly demonstrated between the centre's expertise and the diminution of the risk of donor mortality and morbidity.

In terms of indications, two main issues emerge from the European experience: (1) as expected, cirrhosis continues to represent the main indication of LT with more than half of the

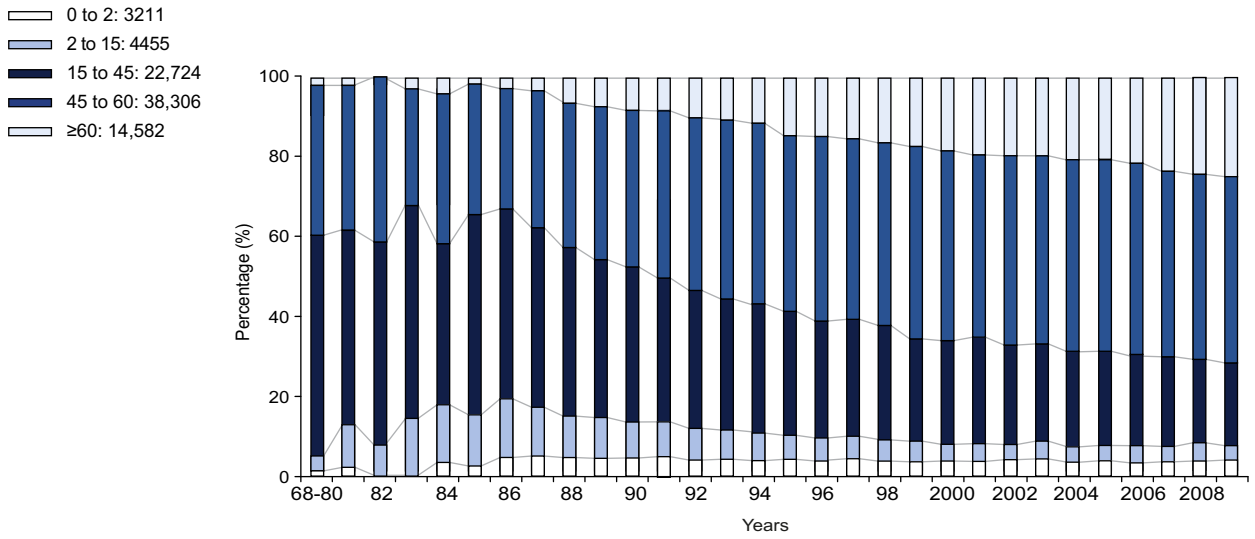

Fig. 11. Evolution of recipient age in Europe (05.1968–12.2009).

Table 4. Cause of re-LT after the first LT in Europe. The complications correspond to the first cause of failure declared according to time of occurrence.

Cause of retransplantation	Date of retransplantation occurrence								Total	Percentage of	
	1 d	1 wk	1 mo	6 mo	1 yr	3 yr	5 yr	>5 yr		the complication (%)	the total (%)
Primary non-function	152	952	309	0	0	0	0	0	1413	100	25
Technical	39	381	584	474	169	245	88	111	2091	100	37
Vascular complications	37	362	525	320	76	95	35	47	1497	72	27
Biliary complications	1	5	34	141	93	146	53	63	536	26	10
Hepatic infarction	0	9	20	11	0	3	0	0	43	2	1
Haemorrhage	1	5	5	2	0	1	0	1	15	1	0.3
Sepsis	5	31	26	23	17	17	7	15	141	100	3
Bacterial infection	5	26	16	15	7	10	3	8	90	64	2
Viral infection	0	0	2	2	4	3	2	4	17	12	0.3
Fungal infection	0	3	3	3	3	1	0	0	13	9	0.2
Not designated	0	2	5	3	3	3	2	3	21	15	0.4
Rejection	4	42	139	215	200	242	91	117	1050	100	19
Chronic rejection	0	0	0	167	186	229	88	114	784	75	14
Acute rejection	3	38	129	37	10	9	3	3	232	22	4
Not designated	1	4	10	11	4	4	0	0	34	3	1
Recurrence of initial disease	1	9	7	57	73	196	93	190	626	100	11
Non-tumoral	1	9	7	56	70	190	89	185	607	97	11
Tumoral	0	0	0	1	3	6	4	5	19	3	0.3
Tumor *de novo*	2	3	3	6	2	1	3	2	22	100	0.4
Other liver causes	41	53	89	137	49	87	48	99	603	100	11
Other or unknown causes	15	41	58	56	25	27	9	22	1413	100	25
Total	218	1459	1126	831	486	728	291	457	5596	100	100

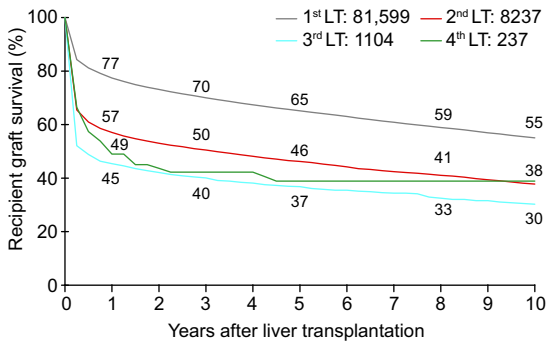

Fig. 12. Graft survival according to the number of LTs (01.1988–12.2009).

patients, and a large predominance within this group of patients with alcoholic (20%) and virus C related cirrhosis, (2) the major change is occurring for cancer, mainly HCC, which represents currently 20% of all indications, after a significant decrease from 50% in the eighties to only 10% in the nineties. The better selection of patients within the Milan criteria [20] with consequently equivalent results of survival between HCC and benign hepatic disease obviously explains this evolution.

One of the most important findings in the evolution of LT is the significant improvement of results with time, leading presently to a 1-year survival rate of 85%, all indications confounded. This results probably from a greater surgical expertise, a better selection of patients and an improved post-LT management of complications and immunosuppressive therapy. The improvement is particularly significant for cancers, mainly hepatocellular carcinoma as previously mentioned, with a gain of 36% in 1-year survival rates from 1990 to 2004. This gain was confirmed with the data of the last 10 years with an improved 5-year survival of 66%.

Donor and recipient age influence the quality of the results, as shown by a previous analysis of ELTR data focused on mortality after LT [13,14]. However, they are not prominent factors of mortality. Despite the fact that donor age >55 has been demonstrated as an independent risk factor of post-transplant outcome [13], the evolution shows that older donors are increasingly used to augment the donor pool. Similarly, recipient age has been considered as independently associated with higher post-transplant mortality, the but older recipients increasingly undergo LT owing to improved results and better selection of patients.

What has not changed with time is the critical period of the first 6 months and, more generally, the first year to determine the final outcome of the transplanted recipients. More than a half of the deaths and three quarters of re-LTs occurred within the first year after LT. That means that when patients have successfully reached the first year after LT, they have an optimal chance to survive at long-term.

When required (in approximately 7% of patients), re-LT is associated with much less optimal results than the first LT. However, there is no team that would consider this result a reason to exclude a new LT suggesting that a sort of moral contract exists with the patient, in addition to strict consideration of the optimal use of organs. Interestingly, the gap of survival is observed between first and second LT while third and fourth LTs are not associated with results much worse than those of second LTs.

One of the prominent features of recent years has been the development of LRLT, performed by almost half of the centers. As with split LT, LRLT aims to provide more patients with transplants, but with special attention to decrease as much as possible risks for the donor, now estimated to be of 0.18% for mortality and 23% for postoperative morbidity. However, LRLT has tended to decrease in recent years in Europe mirroring the trend in the US, where it has actually decreased [21]. Potential living liver donors are best served by accurate information about donor mortality. Access to such data is difficult and these individuals benefit from living liver donor registries and peer-reviewed publication of donor mortality. That may provide an impetus for centers with unreported deaths to submit these outcomes to the liver transplantation community [22,23].

In conclusion, LT is definitely a validated therapy of end-stage liver disease, acute liver failure and HCC. It is becoming relatively safe as compared to the initial years. Indications are oriented to more optimal use of the limited donor pool. Survival is increasing gradually in relation to greater expertise in the surgical procedure and management of immunosuppressive therapy. Alternatives to conventional use of cadaveric full size liver grafts are expanding to palliate the organ shortage. This latter development including the increasing use of non-heart beating donors, the long-term evaluation of the MELD allocation policy now used in the majority of countries will probably represent a key issue in the near future. To increase the donor pool, to avoid patient death on the waiting list, and to offer equal access to good indications of LT have become the main challenges of a treatment that presently allows 70–80% of patients to survive at 5 years.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Acknowledgments

The authors are indebted to all the 145 contributing centers listed at the following link www.eltr.org/spip.php?page=centers-tous. The registry is supported by a grant from Astellas, Novartis and a logistic support of the Paul Brousse Hospital (Assistance Publique – Hôpitaux de Paris). ELTR is a service of the European Liver and Intestine Transplant Association (ELITA).

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