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Abstract At present, it is frequently accepted to expand the organ pool for liver transplantation (LTx) by including livers from critical donors. From 1990 to June 2002 a total of 1,208 LTx were performed. Of those, 67 livers from donors older than 60 years were transplanted to 66 patients, including re-LTx in eight patients. Fourteen patients had malignant diseases (21%). Ten patients had a high urgency status (15%). Median donor age was 65 years (range 61–80 years). Primary graft function was observed in 84%. Patient survival rate at 1 and 5 years was 79% and 62%, and graft survival was 68% and 53%, respectively. No difference was observed in LTx with livers from donors younger than 60 years. Fifteen graft losses occurred during the study. Surgical complications were observed in 23 patients (34%). The outcome of LTx with livers from donors older than 60 years is satisfactory and is comparable to results of LTx with livers from donors younger than 60 years. The frequency of vascular complications and cholestasis syndrome is not increased.

Keywords Liver transplantation · Donor age · Surgical technique · Outcome · Patient survival

Despite great efforts, the shortage of organ donors has not been solved in many European countries. In fact, the number of critical organ donors, such as donors older than 60 years of age, has increased constantly. To overcome the high mortality of patients with end-stage liver disease on the waiting list, certain transplant centres have recently accepted liver grafts from these critical donors.

Thomas E. Starzl and his co-workers were the first to describe that livers from older donors (>50 years) could be used successfully for liver transplantation (LTx) [1]. Since then, numerous studies have shown that livers from older donors can be transplanted as successfully as livers from younger donors [2, 3, 4, 5, 6], while others have presented a significant influence of the donors' older age on the outcome of the recipients' LTx [7, 8, 9, 10, 11, 12, 13]. In studies published in the early 1990s, donors older than 50 years were considered old [2, 3, 7, 10, 12]. More recent reports presented results of LTx with livers from donors older than 60 years [8, 9, 11] or even older than 70 years [4, 6, 13]. However, the number of patients enrolled in most single-centre studies was very low, rarely exceeding 30 patients who underwent LTx [2, 3, 7, 8, 11, 13].

In this study we have retrospectively analysed 67 patients who underwent LTx with livers from donors older than 60 years in the last decade with a mean follow-up time of 29.8 months (range 4.1–129.6 months). We studied early and late graft function of liver grafts from donors older than 60 years. The incidence of vascular and bile-duct complications were of particular interest.

Patients and methods

Recipients

From 1 January 1990 to 30 June 2002 a total of 1,208 liver transplant surgeries were performed at our centre, including first LTx in 1,018 patients, second LTx in 173 patients, third LTx in 16 patients and fourth LTx in one patient. The inclusion criterion for the study was a donor age of more than 60 years. During the study period, 67 livers from donors who were older than 60 years were transplanted to 66 recipients. Fifty-nine patients received their first liver graft, and eight patients their second. Thus, one recipient received two grafts from donors who were older than 60 years. Figure 1 shows the frequency of LTx from donors older than 60 years. Details of recipients receiving grafts from donors who were older and younger than 60 years are shown in Table 1.

The study was reviewed by the local ethics committee and carried out in accordance with the Declaration of Helsinki.

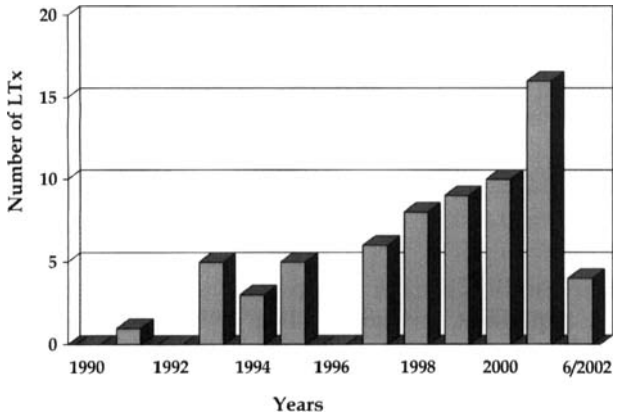

Fig. 1 Frequency, at yearly intervals, of LTx from donors who were older than 60 years

Donors

In 35 cases liver grafts were procured by local harvesting teams, while 32 grafts were harvested and shipped from other centres. The median age of organ donors was 65 years (range 61–80 years). The mean stay in the intensive care unit (ICU) was 4.3 ± 3.8 days (1–18 days). Additional demographic details of donors older than 60 years and younger than 60 years are listed in Table 2.

Anatomical variations were observed in 13 grafts from donors older than 60 years (18%). An accessory left hepatic artery was present in eight patients, and an accessory right hepatic artery in five. Organs where preserved with University of Wisconsin Solution (Via-Span, Bristol-Myers Squibb) in 28 cases and HTK (Custodiol, Dr. Franz Koehler Chemie) in 39 cases, respectively.

Table 1 Details of transplant recipients (*BMI* body mass index, *HCC* hepatocellular carcinoma, *NS* not significant)

Details	Donors ≤ 60 years (n = 1,141)	Donors > 60 years (n = 67)	$P^{a,b}$
Age (mean ± SD)	36 ± 20 years	49 ± 11 years	< 0.001
BMI (mean ± SD)	23 ± 4 kg/m^2	24 ± 5 kg/m^2	NS
Child score (mean ± SD)	10 ± 3	10 ± 2	NS
Malignancy (n)	182 (16%)	15 (22%)	NS
HCC (n)	122 (11%)	14 (21%)	< 0.05
Other malignancy (n)	60 (5%)	1 (1%)	NS
Hepatitis B (n)	160 (14%)	19 (28%)	< 0.005
Hepatitis C (n)	153 (13%)	16 (24%)	< 0.05
High urgency status (n)	247 (22%)	10 (15%)	NS
1. LTx (n)	959 (84%)	59 (88%)	NS
2. LTx (n)	165 (14%)	8 (12%)	NS
≥3. LTx (n)	17 (2%)	–	NS
Underlying disease (n)[c]			
Post-hepatitic cirrhosis (viral)	203 (21%)	24 (41%)	< 0.001
Cholestatic disease	263 (27%)	15 (25%)	NS
Cryptogenic cirrhosis	104 (11%)	8 (14%)	NS
Acute hepatic failure	102 (11%)	4 (6%)	NS
Malignancy without cirrhosis	60 (6%)	1 (2%)	NS
Enzyme deficiency	54 (6%)	–	NS
Budd–Chiari syndrome	36 (4%)	1 (2%)	NS
Cystic liver disease	33 (3%)	–	NS
Autoimmune hepatitis	32 (3%)	2 (3%)	NS
Alcohol-induced cirrhosis	30 (3%)	3 (5%)	NS
Storage disease	29 (3%)	1 (2%)	NS
Others	13 (1%)	–	NS
CIT (mean ± SD)	10.6 ± 4.3 h	10.3 ± 4.4 h	NS

[a]Chi quadrate test
[b]Student's t test
[c]Diagnosis is given only for primary transplant candidates

Table 2 Details of organ donors (*BMI* body mass index, *NS* not significant)

Donor details	Donors ≤ 60 years ($n=1,141$)	Donors > 60 years ($n=67$)	$P^{a,b}$
Age (mean ± SD)	32 ± 15 years	66 ± 5 years	< 0.001
Gender (*n*male)	669 (59%)	30 (45%)	< 0.05
BMI (mean ± SD)	23 ± 4 kg/m^2	26 ± 3 kg/m^2	< 0.001
Donor type (*n*)			
Cadaveric	1,089 (95%)	66 (99%)	NS
Domino	8 (1%)	1 (1%)	NS
Living related	44 (4%)	0	NS
Cause of death (*n*)[c]			
Cerebral bleeding	435 (40%)	46 (70%)	< 0.001
Cerebral trauma	487 (45%)	6 (9%)	< 0.001
Cerebral gunshot	46 (4%)	3 (5%)	NS
Cerebral tumour	17 (2%)	1 (2%)	NS
Intoxication	16 (1%)	0	NS
Others	88 (8%)	10 (15%)	NS
ICU stay (mean ± SD)[c]	3.2 ± 3.3 days	4.3 ± 3.8 days	< 0.05
Vasopressors (*n*)[c]	538 (54%)	35 (53%)	NS
Cardiac arrest (*n*)[c]	96 (9%)	3 (5%)	NS
Sodium (mean ± SD)[c]	147 ± 10 (mmol/l)	147 ± 9 (mmol/l)	NS
AST (mean ± SD)[c]	31 ± 39 (U/l)	19 ± 13 (U/l)	< 0.05
ALT (mean ± SD)[c]	24 ± 36 (U/l)	21 ± 23 (U/l)	NS

[a]Chi quadrate test
[b]Student's *t* test
[c]Cadaveric donors only

Operating procedure

For donors older than 60 years, full-size liver grafts were transplanted orthotopically in all patients. Until 1995 veno-venous bypass was used in ten of 14 patients (71%). Since 1996 all transplants have been performed without veno-venous bypass. Mean operation time was 4.6 ± 1.5 h (range 1.4–8.8 h). The hepatic artery was anastomosed to the abdominal aorta in eight patients. In one case of severe arteriosclerosis, interposition of an iliac allograft was primarily required. Arterial anastomosis was performed between donor and recipient hepatic artery, using the branch patch technique, in all other patients ($n=59$). In all cases in which accessory arteries of the liver graft were present, arteries were anastomosed separately by branch patch technique as well. Before 1997 the bile duct was reconstructed as side-to-side in 12 patients and as end-to-end anastomosis in four, respectively. Since 1998 the bile duct has been routinely anastomosed by end-to-end technique. Primary hepatico-jejunostomy was performed in 14 patients.

Immunosuppressive protocols

Standard primary immunosuppression consisted of calcineurin inhibitors and prednisolone (Decortin H, Merck) and was administered to 50 patients (75%). Of those, 45 patients were treated with cyclosporin A (Sandimmun Optoral, Novartis Pharma) and five with tacrolimus (Prograf, Fujisawa). Calcineurin inhibitors were primarily combined with mycophenolate mofetil (CellCept, Roche) ($n=15$) or with azathioprine (Imurek, Glaxo Smith Kline) ($n=2$) to avoid steroids in patients with hepatitis C cirrhosis. Since 1999 basiliximab, an anti-IL2 monoclonal antibody, (Simulect, Novartis Pharma; two single doses on days 0 and 4) was given routinely ($n=35$). Rejection was treated with methylprednisolone (Urbason, Aventis Pharma) at doses of 500 mg for three consecutive days, or the patient was switched to a tacrolimus-based immunosuppressive regimen.

Statistics

We retrospectively analysed the perioperative courses of patients by reviewing patient charts. Follow-up until 30 September 2002 was studied based on data collected at our transplant outpatient clinic. Mean follow-up time was 29.8 months (range 4.1–129.6 months). We compared recipient and donor details for older and younger donors, using the chi-quadrate test or Student's *t*-test as indicated (Tables 1 and 2). Transplant and patient survival rate was calculated by Kaplan–Meier analysis (Fig. 2). For comparison of subgroups the log-rank test was used. Prognostic factors associated with long-term graft survival were analysed by Cox regression (univariate analysis) or stepwise Cox regression (multivariate analysis). For prognostic factors associated with graft loss within 30 days, statistical analysis was done by university logistic regression and multivariate stepwise logistic regression. A *P* value of less than 0.05 was considered statistically significant. We used the SPSS software package (SPSS, Chicago, Ill., USA) for statistical analyses.

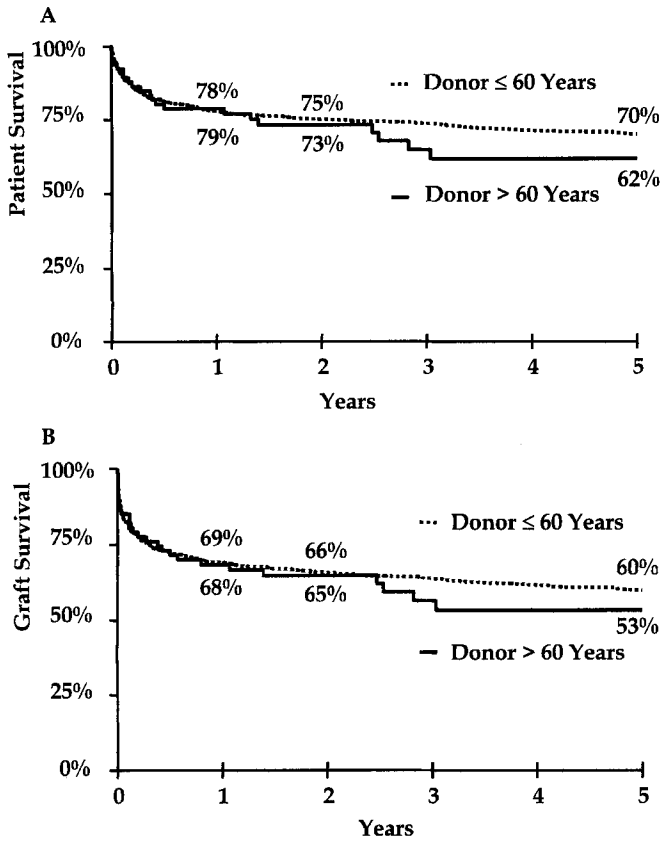

Fig. 2 Patient and graft survival after LTx using liver grafts from donors who were older than 60 years versus donors who were younger than 60 years

Results

Patient and graft survival

Between 1 January 1990 and 30 June 2002, 67 LTx were performed in 66 recipients, and included eight re-LTx. Overall patient survival rates were 79%, 73% and 62% at 1, 2 and 5 years, respectively. The 1-, 2- and 5-year graft survival rates were 68%, 65% and 53% (Fig. 2). Within the same period 1,141 liver grafts from donors younger than 60 years were transplanted to 965 recipients. A comparison of both groups showed no statistically significant difference in patient and graft survival rates.

Causes of death

Within the follow-up period 21 patients died 0.1 to 36.6 months after LTx. Of those, 13 patients died within the first 6 months after LTx. Five deaths occurred within the first 30 days after LTx, representing 7.6% of all patients. Early deaths were caused by septic complications, such as septic multi-organ failure, in 11 patients or by primary non-function (PNF) of liver grafts in two patients. Another eight patients died 6.1 to 36.6 months after LTx. Causes of death were tumour recurrence in four patients, cardiac arrest in two and pneumonia in one. Those seven patients were not directly associated with LTx since all patients had functioning liver grafts at the time of death. One patient died from chronic graft failure.

Causes of graft loss

A total of 15 graft losses occurred during the study. The time of graft loss ranged from 1 day to 8.1 years after transplantation (median 10 days). Ten grafts were lost in the early postoperative course. The causes of graft loss were PNF in eight patients and necrosis of the bile duct in two patients. Of those, seven patients received a second liver graft. Late graft losses were observed in five patients and were caused by chronic rejection ($n=2$), hepatitis re-infection ($n=2$) and recurrent cholangitis ($n=1$). Successful re-transplantation was carried out in three patients.

Postoperative liver function

Of the 67 LTx studied, 56 grafts showed primary graft function (PGF) (84%). Delayed function was observed in three patients (4%) and PNF in eight (12%). Laboratory data from recipients that received grafts from donors who were older than 60 years, at 3, 6 and 12 months after LTx, are shown (Fig. 3). Cytoplasmatic liver enzymes such as AST and ALT were within normal range after LTx. Values for cholinesterase (CHE) were also normal and even showed a slight increase over time, demonstrating stabilised liver function. Persistently elevated mean values were recognised for γGT, alkaline phosphatase and total bilirubin. However, those values decreased continuously, returning to almost normal activity at 12 months after LTx. In addition, creatinine and urea returned to normal values at 6 months.

Surgical complications

Complications requiring surgical revision were observed in 23 patients. Most frequently, postoperative bleeding required re-laparotomy (11 patients). Necrosis of the extrahepatic bile duct, leading to bile leakage, was observed in five patients. Of those, two patients received a second liver graft, while three patients underwent hepatico-jejunostomy. Another four patients developed wound ruptures requiring surgical revision. In one patient toxic mega-colon occurred and had to be treated by subtotal colectomy. Vascular complications were

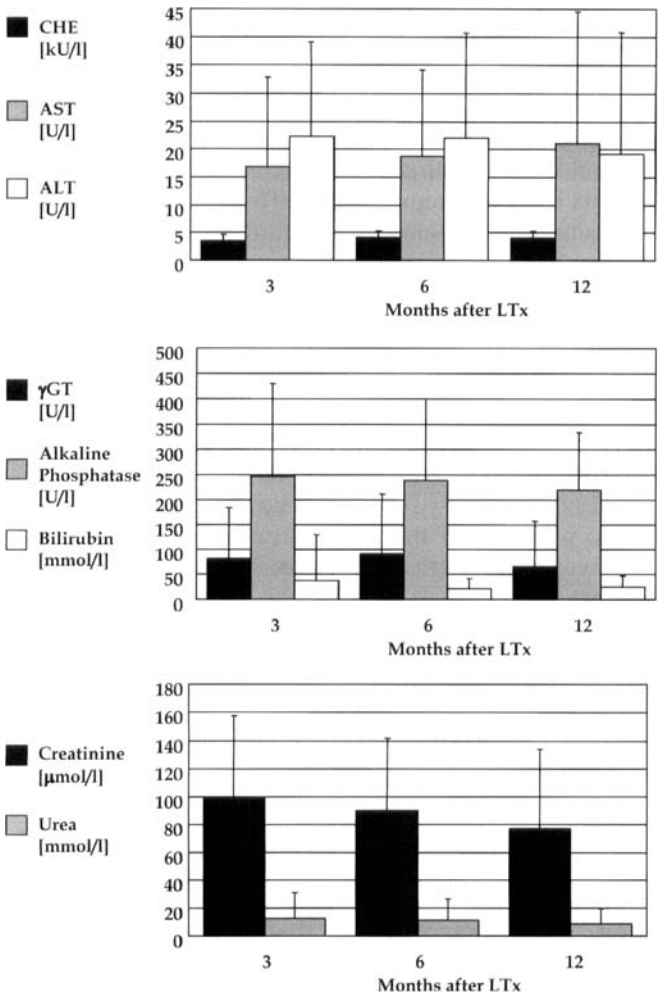

Fig. 3 Laboratory data presenting liver and kidney function 3, 6 and 12 months after LTx from donors who were more than 60 years of age

observed in two patients (3%). Thrombosis of the hepatic artery required interposition of an iliac venous allograft, while thrombosis of the portal vein was treated by thrombectomy.

Cholestasis

Cholestasis syndromes occurred in seven patients (10%) 15 days to 36 months after LTx (median 17 months). Strictures of the extrahepatic bile duct were treated successfully by repeated endoscopies and stent implantation in two patients. In another patient with a primary hepatico-jejunostomy, percutaneous trans-hepatic bile duct drainage was required. This patient is now free of symptoms 27 months after primary intervention without any further drainage. Chronic cholestasis syndromes had to be treated surgically in three patients. One patient required a hepatico-jejunostomy. The other two patients received open bile duct revision with dilatation of the extrahepatic bile duct and temporary implantation of a T-tube. All three patients are now free of symptoms. One patient with severe recurrent cholangitis underwent successful re-transplantation 10 months after primary LTx.

Acute rejection

Twenty-three patients (34%) experienced one or more biopsy-proven rejection episodes. Patients suffering acute rejection episodes were treated with a steroid bolus for three consecutive days ($n=12$), switched to tacrolimus-based immunosuppressive regimen ($n=4$), a combination of steroid bolus and switched to tacrolimus ($n=6$) or increased cyclosporin ($n=1$). Of these 23 patients, one required re-transplantation due to hepatitis C re-infection, while there were also histological findings indicating chronic rejection in the explanted liver graft.

Hospital stay

Median postoperative stay in the ICU was 10 days (range 2–155 days; mean 25 days) for patients receiving liver grafts from donors who were older than 60 years. Median total hospital stay (excluding patients who died in the ICU) was 28 days (range 8–96 days; mean 41 days). In comparison, patients who underwent LTx with livers from donors younger than 60 years had a median stay in the ICU of 11 days (range: 1–302 days, mean: 24 days). Median total hospital stay for those patients was 38 days (range 7–177 days; mean 45 days). There was no statistical difference for stay in the ICU or for total hospital stay in either groups.

Prognostic factors influencing outcome after LTx

Prognostic factors potentially influencing outcome after LTx were studied by univariate and multivariate analysis for all 1,208 patients who underwent LTx. Prognostic factors associated with 30-day graft survival were analysed (Table 3). Recipients receiving their liver graft in a high urgency situation had a significant higher incidence of graft loss within 30 days. In addition, higher cold ischaemia time (CIT) was significantly correlated with early graft loss. When prognostic factors associated with long-term graft survival were tested by multivariate analysis, recipient age, malignant disease, high urgency procedures and CIT showed a highly significant influence on graft survival (Table 4). None of the donor factors tested showed a significant influence on long-term graft survival.

Table 3 Prognostic factors associated with 30-day graft survival (*BMI* body mass index)

Risk factors	Univariate[a]		Multivariate[b]	
	Score	*P*	Score	*P*
Recipient data				
Age	0.5	0.480	–	
Malignancy	0.9	0.334	–	
Hepatitis B	0.1	0.742	–	
Hepatitis C	0.1	0.900	–	
High urgency	12.8	0.000	12.4	0.000
CIT	8.1	0.004	13.2	0.000
Donor data				
Age	0.7	0.405	–	
Donor >60 years	0.2	0.645	–	
Gender	1.8	0.179	–	
BMI	3.6	0.058	–	
ICU stay	0.1	0.914	–	
Cardiac arrest	0.0	1.000	–	
Vasopressors	3.9	0.049	2.7	0.101
AST	0.1	0.743	–	
ALT	0.8	0.377	–	
Sodium	0.1	0.871	–	

[a]Logistic regression
[b]Multivariate stepwise logistic regression

Discussion

In the early phase of clinical LTx, donors more than 50 years of age were considered unsuitable for transplantation. Since then, the limit of donor age that is acceptable for transplantation has been constantly expanded. In the early 1990s Wall et al. compared outcome after LTx from donors older than 50 years and younger than 50 years. They reported similar 1-year patient (71% vs 76%) and graft survival rates (65% vs 69%) for organs from older and younger donors [2]. However, of the 23 older donors, only three were above 60 years of age [2]. Alexander and Vaughn, reviewing results from the UNOS of the late 1980s, confirmed these results. However, out of 2,913 liver grafts, as few as 11 were from donors older than 55 years [7]. In contrast, other studies presented a significant influence of donor age on the outcome of LTx. In a multi-centre analysis from France 1,947 patients who had undergone LTx were studied. Of those 1,947 livers, 18 came from donors over 60 years of age. The 1-year graft survival rate was as low as 33%, compared with 61% from donors who were 6 to 59 years of age [8]. At the same time, the Pittsburgh group presented their single-centre experience with 54 liver grafts from donors who were between 60 and 79 years old [14]. After 2 years, patient and graft survival rates were 71% and 43%, respectively. In contrast, patient (78%) and graft (71%) survival rates were significantly higher after LTx from donors younger than 60 years [14]. Washburn et al. reviewed the data from 29 liver transplant recipients who had received grafts from donors older than 60 years. The observed 1-year patient and graft survival rates were significantly lower for this patient group than that of patients who had received grafts from donors younger than 60 years (59% vs 79% and 45% vs 75%). Some authors have even presented results of LTx with livers from donors of over 70 years of age [4, 6]. Both studies showed excellent patient survival as high as 91% and graft survival as high as 85% after 1 year. However, in the study by Grazi et al. patients of re-LTx and emergency procedures were excluded [6].

Table 4 Prognostic factors associated with long-term graft survival (*BMI*body mass index, *HCC* hepatocellular carcinoma)

Risk factors	Univariate[a]		Multivariate[b]	
	Score	*P*	Score	*P*
Recipient data				
Age	12.0	0.001	6.8	0.009
Malignancy	11.1	0.001	8.8	0.003
Alcoholic	0.1	0.770	–	
Hepatitis B	0.1	0.779	–	
Hepatitis C	6.1	0.013	1.5	0.226
High urgency	7.9	0.005	16.3	0.000
CIT	10.9	0.001	10.5	0.001
Donor data				
Age	7.8	0.005	2.8	0.092
Donor >60 years	1.9	0.170	–	
Gender	3.1	0.080	–	
BMI	0.6	0.452	–	
ICU stay	0.6	0.444	–	
Cardiac arrest	1.51	0.219	–	
Vasopressors	0.4	0.545	–	
AST	0.1	0.883	–	
ALT	1.2	0.279	–	
Sodium	0.2	0.692	–	

[a]Cox regression
[b]Multivariate stepwise Cox regression

We report on our single-centre experience of 67 LTx from donors older than 60 years in the last decade. Included were four patients with acute liver failure and eight patients who underwent re-LTx. In fact, as many as ten patients underwent transplantation with a high urgency status (15%), including the above-mentioned four patients with acute liver failure and six patients with PNF after LTx. At our centre no distinction between allocation of livers from younger and older donors was made. The 1-, 2- and 5-year patient survival rates were 79%, 73% and 62%, respectively, after LTx with livers from donors older than 60 years, while 1-, 2- and 5-year graft survival rates were 68%, 65% and 53%. Those results were comparable to those of LTx with livers from donors who were younger than 60 years.

There are major concerns that, due to arteriosclerosis of the hepatic artery, the frequency of vascular complications might be increased when livers from

older donors are used routinely. In the study by Grazi et al., seven vascular complications were observed in 36 patients who underwent LTx (19%) using livers from donors who were older than 70 years [6]. In all patients, vascular complications were related to hepatic artery reconstruction. In a more recent study, the same group showed an unchanged frequency of arterial complications (19%) in 68 patients who underwent LTx with livers from donors who were older than 70 years [15]. Another study reports a higher incidence of graft failure as a result of ischaemic injury in livers from donors older than 60 years than from younger donors [9]. However, no further explanation was given as to what mechanisms were related to the ischaemic injuries. In the study by Washburn et al. the frequency of arterial complications (3.4%) did not increase when organs from donors over 60 years of age were used [11].

In our own patient population 13 out of 67 liver grafts from donors older than 60 years showed multiple arteries (19%). However, as few as one arterial complication (1.5%) was observed. This patient was successfully treated by reconstruction using a venous vessel graft. Our policy for arterial reconstruction is to perform arterial anastomosis to the recipient's common hepatic artery at the junction of the gastroduodenal artery, using a branch patch technique. This is of particular importance when arteriosclerosis of the aorta and truncus is present at the donor site. In fact only in eight of the 67 patients was arterial anastomosis performed to the abdominal aorta. In one case, in which severe arteriosclerosis of the donor hepatic artery was present, interposition of an iliac vessel graft was primarily used for reconstruction. Since 1998 the branch patch technique has been performed routinely (47 of 67 patients).

Another disadvantage in transplantation of livers from old donors might be irreversible damage of the bile duct system, causing chronic cholestasis syndrome. The frequency of impaired biliary drainage after LTx in the presence of an obviously normal vascular situation ranges from 4% to 24% [16, 17, 18, 19, 20]. Cholestasis is caused mainly by strictures of the extrahepatic bile duct localised at the site of the bile duct anastomosis as a result of technical problems or proximity to the anastomosis site. Numerous mechanisms are discussed that might be responsible for the observed phenomenon, including ischaemic damage of the biliary epithelium in the absence of obvious arterial problems. In our study cholestasis syndromes occurred in seven of the 67 patients (10%) who underwent LTx with livers from donors who were over 60 years of age. Strictures of the extrahepatic bile duct at the site of the anastomosis could be successfully treated in three patients without further surgical revision. One patient received a second LTx due to severe recurrent cholangitis. The remaining three patients presented with multiple strictures of the extrahepatic bile system and were treated successfully by open bile duct revision (two patients) or hepatico-jejunostomy (one patient). Thus, the older age of organ donors had no influence on the occurrence of cholestasis syndromes.

The most important question in the use of liver grafts from older donors is whether there are clear variables that might influence the outcome after LTx. In a multivariate analysis Hoofnagle et al. studied the relationship between donor age and 3-month graft survival after LTx with grafts from donors who were older than 50 years [12]. The only significant factor for the prediction of graft survival was the assessment of the liver quality by the harvesting surgeon. No other features accounted for the observed poor graft survival of livers from older donors [12]. This correlates with the experience of others, who could not point out the relation between risk factors and function of liver grafts or graft survival within the group of older organ donors [4, 9]. However, limited numbers of patients might have made it difficult for those authors to observe a clear or even significant difference for the donor factors analysed.

In our study, we analysed numerous relevant donor factors that might correlate with the outcome after LTx. However, none of the donor factors tested by multivariate analysis showed a significant influence on 30-day or long-term graft survival. The experience of the harvesting team is of critical importance for the outcome of LTx when livers from critical donors are used. Specific liver tests, such as MEGX [21] or standard liver biopsies [22], might help to clarify the quality of donated livers and predict the outcome after LTx. However, at our centre, liver biopsies were not performed on a routine basis.

In conclusion, livers from donors who are older than 60 years can be safely used for transplantation. Within our patient population the incidence of vascular complications is very low. This might be a result of a consequent technique for arterial reconstruction to the recipient's common hepatic artery instead of aortal anastomosis. The frequency of cholestatic syndromes is within the range of that observed in LTx from younger donors. The duration of treatment in the ICU and total hospital stay are not prolonged for recipients of liver grafts from donors who are older than 60 years. The age of organ donors per se should no longer be considered as a contradiction for the use of liver grafts.

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