Transpl Int (2000) 13: 122–128
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ORIGINAL ARTICLE

Lauri E. J. Kyllönen
Kaija T. Salmela
Björn H. Eklund
Leena E. H. Halme
Krister A. V. Höckerstedt
Helena M. Isoniemi
Heikki J. Mäkisalo
Juhani Ahonen

Long-term results of 1047 cadaveric kidney transplantations with special emphasis on initial graft function and rejection

Received: 4 May 1999
Revised: 9 December 1999
Accepted: 15 December 1999

L.E.J. Kyllönen (✉) · K.T. Salmela
B.H. Eklund · L.E.H. Halme
K.A.V. Höckerstedt · H.M. Isoniemi
H.J. Mäkisalo · J. Ahonen
Division of Transplantation,
Department of Surgery,
Helsinki University Central Hospital,
Kasarmikatu 11, 00130 Helsinki, Finland
e-mail: lauri.kyllonen@huch.fi
Tel.: + 358-9-4719-8188-470
Fax: + 358–9–17–4975

Abstract We studied the effect of initial graft function and acute rejection on graft survival in 1047 cadaveric renal transplantations during 1991–1997 with a constant policy of donor selection, graft allocation, and immunosuppression. The overall 1- and 5-year patient survival rates were 96% and 88%, and the 1- and 5-year graft survival (GS) rates were 92% and 78%. Delayed graft function (DGF) occurred in 31% and there were 1.2% never-functioning grafts. One-year GS in transplantations with early graft function (EGF) was 95% compared to 87% in DGF ($P < 0.001$). Donor age and cause of death, type of graft perfusion and cold ischemia time, and type and length of dialysis treatment were significant factors in determining the onset of graft function. These factors did not have a significant direct effect on GS. Early (< 100 days) acute rejection occurred in 25%. In transplantations without rejection, the 1 and 5-year GS was 93.3% and 80.8%. In acute rejection responding to steroids, the GS was equal to that up to 3 years, but after that a significantly worse survival rate was observed (1- and 5-year GS: 93.6% and 73.4%). DGF was detrimental to GS both in transplantations without rejection and in all rejection types.

Key words Kidney transplantation · Delayed graft function · Acute rejection · Long-term results

Abbreviations *ARR* Acute steroid-reversible rejection · *AVR* Acute vascular rejection · *CIT* Cold ischemia time · *EGF* Early graft function · *DGF* Delayed graft function · *GS* Graft survival · *HD* Hemodialysis · *NOR* No rejection · *PD* Peritoneal dialysis · *PS* Patient survival · *SRR* Steroid-resistant rejection

Introduction

The quality of initial graft function has been seen as predictive for later graft survival (GS) after renal transplantation [9, 18]. There is much discussion on whether delayed onset of kidney graft function (DGF) as such is a risk factor for GS. In some studies, an association between DGF and GS has only been found in combination with acute rejection [5, 12, 28], whereas others have postulated that DGF by itself has a detrimental effect on GS and that both immunological and nonimmunological factors are involved in DGF [8, 10, 16, 17, 25]. The causes leading to DGF include a variety of donor and recipient factors, of which one of the most studied is the length of graft preservation time [21, 27].

Evolution of the transplantation process demands continuous evaluation of the results. This is particularly important now, as the era of a more or less uniform immunosuppression seems to be approaching its end. Registry studies with large numbers of patients are vital in evaluation of the results of transplantation, but as they comprise varying patient populations and policies, they may hide important information.

From 1991 to 1997 we performed 1,047 cadaveric kidney transplantations, and during that period our donor selection criteria, principles of allocation of kidney grafts, and the choice of immunosuppression remained essentially the same. We report here the results of analyses of these transplantations.

Patients and methods

Patients and the transplant procedure

From January 1991 to December 1997, all adult patients who underwent a cadaveric kidney transplantation at our institution, except for two patients with simultaneous liver and kidney transplantation, were included in this study. Thus, this study comprises altogether 1,047 kidney transplantations performed on 1,017 patients with a minimum follow-up of 1 year.

Our pretransplant workup included a blood transfusion program unless the patient had been pregnant or had undergone transfusion earlier. The general requirements for transplantation were a sharing of at least two antigens in the HLA-AB and one in the HLA-DR loci, a negative T-cell crossmatch test against donor spleen cells, and avoidance of repeated HLA-class I mismatches. The transplant operation itself remained essentially unmodified, with preferably an end-to-end arterial anastomosis to the hypogastric artery and with an open ureteroneocystostomy [24].

In 618 transplantations the recipient was male (59.0%). The mean age of recipients was 44.7 years (range 15–72 years). The diseases causing the uremia are shown in Table 1. All patients were on maintenance dialysis before transplantation and had been on dialysis an average of 18.6 months (range 0–215 months). The number of recipients on peritoneal dialysis was 468 (44.7%). Of the transplantations, 170 (16.2%) were retransplantations (137 second, 29 third, and 4 fourth transplantations).

In addition to the clinical and follow-up data prospectively collected in a computer database, data for the determination of the onset of graft function and for re-evaluation and classification of all acute rejection episodes were collected from patient journals.

Donors and organ retrieval

All donors were heart-beating donors. Forty (3.8%) of all grafts were imported within the Scandiatransplant organ exchange program. The mean age of donors was 38.8 years (range 1–66 years). The donors were male in 62.8% of the 1047 transplantations. Donor death was caused by intracranial bleeding in 60.0%, trauma in 31.6%, and other factors in 8.4%. During the 7-year period of this study, the proportion of multiorgan donors increased steadily, and our transplant team increasingly took responsibility for kidney-only donors as well. The proportion of kidneys retrieved from multiorgan donors was 52.7%. The kidneys were perfused either in situ or on the backbench immediately after removal, depending on the surgical team. The proportion of in situ-perfused kidneys was 55.6%.

Immunosuppression

Induction immunosuppression consisted of a combination of cyclosporine, methylprednisolone, and azathioprine. Oral cyclosporine was started preoperatively and continued after the transplant operation with a dose of 5 mg/kg every 12 h. The dose was later adjusted according to blood trough levels. Methylprednisolone was initially given at 1 mg/kg per day and tapered to 0.2 mg/kg per day by 3–4 weeks after transplantation. Azathioprine was administered at 50 mg thrice daily and tapered to 25 mg thrice daily at day 14 after transplantation.

In acute rejection of the allograft, first-line therapy consisted of oral methylprednisolone (3 mg/kg per day for 5 days). In rejection not responding to steroids, the rejection treatment was augmented with mono- or polyclonal (Orthoclone OKT3, Ortho Pharmaceutical, Corp., Raritan, N.J. and ATG, Fresenius, Munich, Germany) T-cell antibodies. In vascular rejection, in particular when the crossmatch test against the kidney donor converted to positive, we carried out a series of plasma exchanges.

Table 1 Cause of uremia in 1,047 adult cadaveric renal transplantations in 1991–1997 in Helsinki

	n	Male (%)	% of all diagnoses
Glomerulonephritis	322	69.3	30.8
Diabetes	257	59.1	24.5
Polycystic disease	155	54.2	14.8
Pyelonephritis	118	34.7	11.3
Systemic disease[a]	39	43.6	3.7
Nephrosclerosis	37	86.5	3.5
Malformation	36	83.9	3.4
Amyloidosis	28	32.1	2.7
Syndrome[b]	16	75.0	1.5
Other	39	64.1	3.7
All	1047	59.0	100.0

[a] The group of systemic disease comprises SLE ($n = 17$), Wegener's granulomatosis ($n = 8$), Henoch-Schönlein Purpura ($n = 5$), Sjögren's Syndrome ($n = 3$), Polyarteritis nodosa ($n = 2$), and one each of Renal tubular acidosis, Trombangitis obliterans, and Goodpasture's syndrome

[b] Alport's syndrome ($n = 12$) and Nail-Patella syndrome ($n = 3$)

Graft function

DGF was defined as described by Halloran et al. [9]: plasma creatinine concentration higher than 500 μmol/l throughout the first post-transplant week, or the need of more than one dialysis session in the first week, or oliguria of less than 1 l/24 h for more than 2 days. The day of onset of graft function was defined as the first day of spontaneous decrease of plasma creatinine concentration. The graft was considered as having failed when the patient returned to maintenance dialysis, the graft was removed, or the patient died with a functioning graft.

Rejection

A clinical suspicion of rejection was further investigated with ultrasound and Doppler flowmetry and confirmed with fine-needle aspiration biopsy or histological biopsies. Ultrasound-guided histological biopsies were routinely taken in suspected rejections, in rejections not responding to steroids, and in prolonged (usually > 14 days) primary nonfunction of the graft to exclude rejection as the cause of nonfunction. Clinical classification of rejections was done prospectively, and data were collected into the patient database. For this study, each rejection episode was re-evaluated from patient records as well. The effect of early rejection (during the first 100 days after transplantation) on GS was analyzed.

Table 2 Occurrence of delayed graft function *(DGF)* in 1,047 cadaveric renal transplantation in 1991–1997, according to pre-transplant parameters. The 13 never-functioning grafts were excluded from the table

		n	DGF%
Donor type (N.S.)	Multiorgan	547	28.3
	Kidney only	487	33.5
Donor age, in years ($P < 0.01$)	1–9	37	28.2
	10–19	97	20.6
	20–29	128	16.3
	30–39	173	30.1
	40–49	327	34.0
	50–59	235	38.4
	60–66	37	35.1
Cause of donor death ($P < 0.025$)	Bleeding	622	33.0
	Trauma	327	24.5
	Other	85	38.6
Graft perfusion ($P < 0.01$)	Backbench	456	35.3
	In situ	578	27.1
Dialysis mode ($P < 0.005$)	Peritoneal	460	21.2
	Hemodialysis	574	38.5
Time on dialysis ($P < 0.001$)	< 6 months	157	22.9
	6 months–1 year	295	27.1
	1–2 years	340	29.4
	2–3 years	126	34.1
	> 3 years	116	54.3

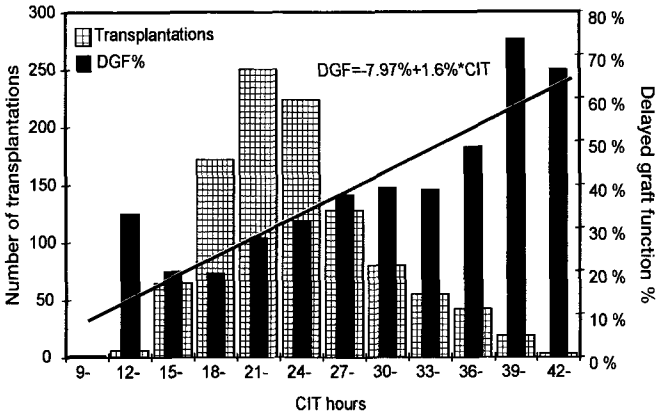

Fig. 1 Delayed graft function by cold ischemia time *(CIT)* in 1,047 cadaveric renal transplantations. The line shows the trend line calculated by weighted least squares

The transplantations were divided into groups according to occurrence of rejection, its clinical response to therapy, and biopsy findings: no rejection (NOR), acute steroid-reversible rejection (ARR), and steroid resistant rejection (SRR). Within the SRRs, a subgroup of acute vascular rejection (AVR) was defined according to vascular changes in histology. Histological changes seen in the biopsies, except for the first years of the study period, were scored according to the Banff classification (26].

Statistics

The chi-squared test was used with contingency tables and when actual 1-year-survival data were evaluated. The survival curves were calculated by means of an actuarial life-table analysis using the Kaplan-Meier product-limit method for censored data. Comparisons of survival curves were made using a log-rank analysis and Cox's F-test. Graft half-life estimates were calculated as described by Cho [3].

Results

Onset of graft function

In 712 (69%) transplantations the onset of graft function was early, and in 322 (31%) transplantations it was delayed. The graft never started to function in 13 (1.2%) transplantations. In transplantations with DGF, the onset of graft function occurred on average on day 14 after transplantation (ranging up to 91 days).

We found that donor age, cause of death, type of graft perfusion, and patient time on dialysis were significant parameters contributing to DGF, whereas the type of donor was not (Table 2). Furthermore, in patients on peritoneal dialysis (PD) the frequency of DGF was lower than in patients on hemodialysis (HD). The frequency of DGF was linearly correlated to the length of cold ischemia time (CIT) as shown in Fig. 1.

Acute rejection

Early rejections occurred in 248 (24.6%) of the 1047 transplantations. The mean time from transplantation to onset of rejection was 21 days (range 2–99 days), and 81.5% of the episodes occurred during the first

Table 3 Comparison of renal transplantations with early *(EGF)* and delayed graft function *(DGF)*. (*CIT* Cold ischemia time, *GS* graft survival, *S-Crea* serum creatinine)

	DGF	EGF
n	322	712
Mean CIT (SD), in h	26.8 (6.1)	24.5 (5.3) $P < 0.0001$
Mean CyA trough level on day 21, in µg/l	266	304 $P = 0.004$
Acute rejections	29.8%	21.2% $P < 0.008$
1-year GS	87.5%	94.5%
5-year GS	71.0%	80.9%
Mean S-Crea at 1 year, in µmol/l	140	122 $P = 0.00003$
Graft half-life (SE), in years	13.0 (2.0)	19.0 (2.3)

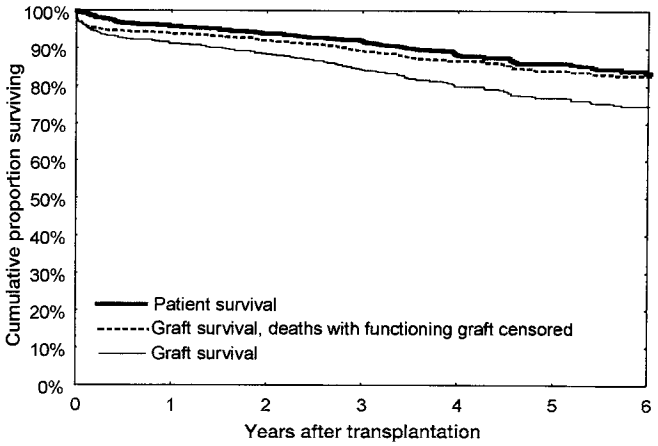

Fig. 2 Patient survival, graft survival, and graft survival with deaths with functioning graft censored in 1,047 cadaveric renal transplantations in 1991–1997

Table 4 Mean serum creatinine and creatinine clearance at day 21 after transplantation, according to onset of graft function and rejection type in 1,047 cadaveric renal transplantations. All differences were statistically significant except in delayed graft function *(DGF)* between acute steroid-reversible rejection *(ARR)* and steroid-resistant rejection *(SRR)*. (*EGF* Early graft function, *NOR* no rejection)

	Serum creatinine, in µmol/l		Creatinine clearance, in ml/min per 1.72 m^2	
	EGF	DGF	EGF	DGF
NOR	127.2	255.8	59.6	34.9
ARR	162.6	380.6	46.6	27.5
SRR	240.6	418.9	38.3	24.0
All	139.6	295.0	56.1	23.6

Table 5 Patient survival *(PS)* after 1,047 renal transplantations in Helsinki, 1991–1997

PS (%)	1-year	3-year	5-year	
Overall	95.9	91.9	86.0	
Recipient age < 50 years	98.5	94.6	89.1	$P < 0.005$
Recipient age 50–70 years	92.1	87.7	80.9	
Primary kidney disease	96.0	94.3	89.2	$P = 0.06$
Diabetics	98.0	90.0	80.3	

month after transplantation. The rejection rate was 22.9% in first transplantations and 33.5% in retransplantations.

ARR occurred in 180 (17.2%) and SRR in 78 (7.5%) transplantations. Of the SRRs, 31 (3.0% of all transplantations) were classified as AVR. There were significantly more rejections in DGF than in early graft function (EGF) to EGF (Table 3).

Graft function

The quality of graft function early after transplantation was defined by mean serum creatinine and creatinine clearance values at 3 weeks after transplantation (Table 4). The values followed a logical order: highest creatinine and lowest clearance in SRR, lowest creatinine and best clearance in NOR. In all groups, DGF significantly worsened the results.

Patient survival

The operative mortality within 1 month of renal transplantation was 0.76%. The overall patient survival is depicted in Fig. 2. Patient survival (PS) was analyzed by patient age and underlying kidney disease (Table 5). Of the seven patients over 70 years of age at the time of transplantation, three died within 6 months. In diabetics, the initially good PS later fell well below that of patients with primary kidney disease.

Altogether 102 recipients died during the follow-up time of this study. The most common causes of death in both diabetic and nondiabetic patients were cardio- and cerebrovascular diseases, which accounted for 58% of the deaths in diabetic and 43% of the deaths in nondiabetic patients.

Factors affecting graft survival

The overall GS rates at 1, 3 and 5 years were 91.3%, 84.1%, and 76.8%. When deaths with functioning graft were censored, the respective GS rates were 93.9%, 89.3%, and 84.0% (Fig. 2).

Age, cause of death, or type of donor did not significantly influence GS. The long-term GS in transplanta-

Table 6 Graft survival *(GS)* after 1,047 renal transplantations in Helsinki, 1991–1997. (*HD* Hemodialysis, *PD* peritoneal dialysis)

GS (%)	1-year	3-year	5-year
Overall	91.3	84.1	76.8
Primary kidney disease	91.8	85.3	77.1
Diabetics	92.2	82.8	76.0
Amyloidosis	78.2	65.4	58.1
Patients on HD	90.9	85.1	78.9
Patients on PD	92.1	84.7	76.5
First transplantations	91.7	85.8	78.2
Retransplantations	90.9	78.7	74.5
Recipient age < 50 years	92.5	84.3	76.7
Recipient age 50–70 years	89.7	84.6	77.6

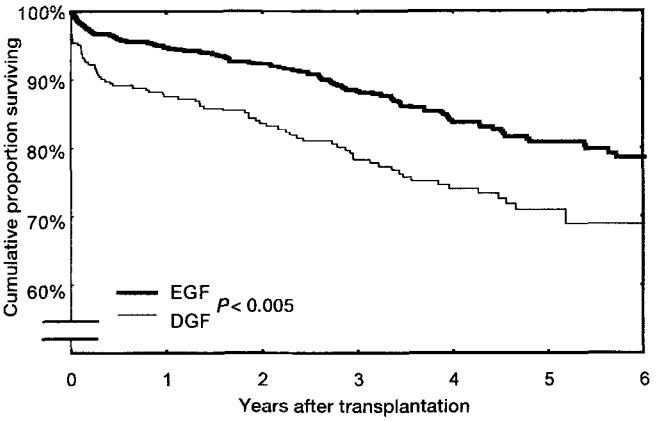

Fig. 3 Onset of graft function and graft survival in 1,047 cadaveric renal transplantations in 1991–1997. [*EGF* Early graft function (n = 712), *DGF* delayed graft function (n = 322)]

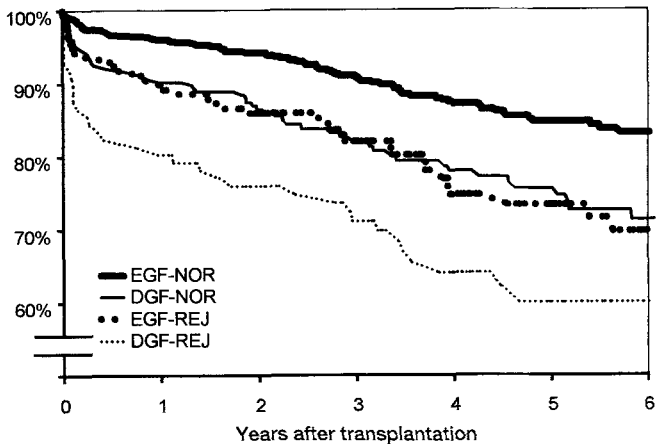

Fig. 4 The combined effect of early (*EGF*) and delayed graft function (*DGF*) and rejection on graft survival in 1,047 cadaveric renal transplantations in 1991–1997. (*NOR* No rejections, *REJ* rejection)

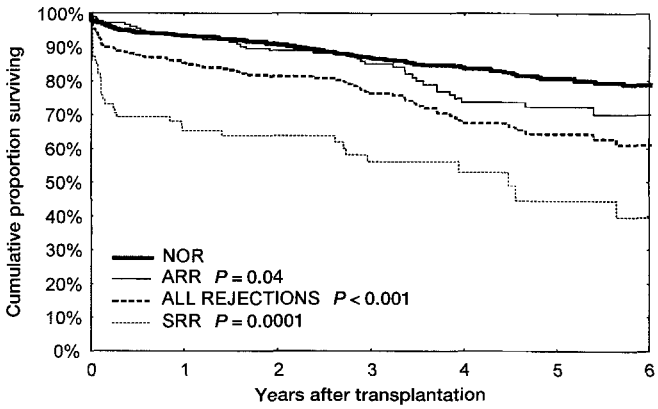

Fig. 5 Graft survival in 1,047 cadaveric renal transplantations in 1991–1997, according to occurrence and type of rejection. (*NOR* No rejections, *ARR* acute steroid-reversible rejection, *SRR* steroid-resistant rejection). *P* values given: ARR vs NOR, All Rejections vs NOR, SRR vs ARR

tions with in situ-perfused grafts was 3% better than transplantations with backbench-perfused grafts (P = 0.004).

The GS rates in diabetics were not significantly different from the rates in patients with primary kidney disease (Table 6). When deaths with functioning graft were censored, the GS in all diagnosis groups was very similar; even the difference in GS between amyloidosis and the other diagnosis groups disappeared. Pretransplant type of dialysis, number of transplantation, or recipient age group did not significantly affect GS.

The impact of DGF on GS is shown in Fig. 3. The GS rates for the 322 recipients with DGF were significantly worse than those for the 712 recipients with EGF. The graft half-life estimate after 1 year was significantly better in EGF than in DGF (Table 3).

The deleterious effect of DGF on GS was evident both in transplantations without rejection (P = 0.00048) and in transplantations with rejection (P = 0.036) (Fig. 4)

GS in transplantations with rejection was significantly worse than in transplantations without rejection (Fig. 5). This also applied to the mild steroid-reversible rejections. Among the ten patients with late rejection (> 100 days after transplantation), the estimated GS at 5 years was 37%.

Discussion

Three major issues adversely contributing to long-term survival of renal allografts were identified in this study: delayed onset of graft function, acute rejections, and patient death with functioning graft.

The true annual graft loss is well-demonstrated in the middle curve of Fig. 2, where deaths with functioning graft have been censored. After the first year, the rate of graft loss remained rather constant at around 3% during the 8 years of follow-up.

The impact of death with functioning graft was prominent, particularly in patients with diabetes or amyloidosis. Earlier studies have shown patient mortality to be the main obstacle to success of transplantation in diabetics, who constitute a large proportion of renal transplant recipients in the Nordic countries [7, 13]. The results in diabetic recipients have improved in the 1990s compared to our earlier experience [24]. Although they still have a much higher mortality with respect to cardiovascular and cerebrovascular diseases than nondiabetics, diabetics meet these complications only later in the post-transplant period, as their 1-year PS was excellent. This may be a favorable result of improved dialysis technique and assessment of risk factors before the transplant operation. However, the natural course of the primary disease takes its toll in later years. We noticed a similar divergence of PS in diabetics after the third post-transplant year as reported by Corwin et al. [4].

Our rate of DGF was higher than rates reported from other centers [8, 21, 22]. As in the study by Peters et al. [21], we could very clearly show that within the time frame of 16–40 hours of CIT the incidence of DGF increased linearly. Other factors significantly affecting DGF were donor age and cause of death as well as type of graft perfusion. Of the recipient factors, the type of dialysis affected DGF strongly in favor of patients on PD, whose frequency of DGF was only half of that of patients on HD. This is in accordance with two recent studies [2, 29].

In addition to the shorter CIT in the group of PD, there are probably other factors, e.g., differences in the perioperative hemodynamic status, which need to be examined further. All our patients had a somewhat high level of cyclosporine at 3 weeks after transplantation. This, however, did not explain the high proportion of DGF. The same protocol, including preoperative institution of cyclosporine treatment, was administered to all recipients irrespective of the primary function of the graft. In patients with EGF, the cyclosporine trough level was even slightly higher than in patients with DGF.

A very interesting finding in our study was that although DGF strongly correlated with GS, factors affecting DGF did not directly affect GS themselves. These factors were age and cause of death of donor, CIT, and type of pretransplant dialysis. Individually, none of these factors had a significant effect on GS. In another recent single-center study on 586 transplantations, Pfaff et al. [22] showed this to be true of CIT as well as age and cause of death of donor, whereas Moreso et al. have reported a significant deleterious effect of donor age (> 50 years) on GS [17].

The effect of acute rejection on long-term GS has been widely discussed [1, 8, 12, 15, 23]. In our study, for up to 3 years the GS of patients with a reversible rejection was very similar to the GS of patients without any rejection. Thereafter the survival curves apparently diverge.

When analyzed separately, both DGF and acute rejection were risk factors for long-term GS in our patients, and thus it is not surprising that their combined effect on long-term GS was conspicuous. In all rejection types and in NOR, GS was significantly better in EGF than in DGF. The increased graft failure rate in DGF may partly be explained by the association of DGF with rejection, as reported by some authors who deny the effect of DGF on GS in the absence of rejection [7, 14, 27]. Our results do not support this assumption but show that, in addition to the association of DGF with a high frequency of more severe rejections, DGF also brings a poorer long-term GS into transplantations without any rejection. These results suggest that other mechanisms besides rejection must be involved. The connection between DGF and poor long-term survival may be explained by reperfusion injury as demonstrated earlier [10].

On the basis of the results of this study, some clinical considerations can be made: cardiovascular and cerebrovascular complications are the major cause of patient and graft loss after renal transplantation. It is difficult to know to what extent these complications are aggravated by the immunosuppressive therapy or to which amount they are due to sequels of the underlying disease. Often, the waiting time for transplantation is too long, and many patients would certainly benefit from an earlier transplantation. Organ shortage is an undeniably limiting factor, and a fair allocation policy does not always meet the needs of the individual patients.

Another issue concerns the attempt to influence the factors causing DGF. The donor-dependent factors cannot be affected, but one may try to avoid too long waiting times by proper managing of the waiting lists and too long graft preservation times by practical measures. It is an interesting feature that patients on PD have a significantly lower rate of DGF than patients on HD but still show similar GS rates. This latter finding confirms the earlier experience of our center [11] and of others [2, 6, 19, 20, 29] and requires further study to determine what changes in dialysis policies might be of value.

In summary, we have found that DGF is a significant factor affecting long-term GS, both through and independent of acute rejection. These results also seem to indicate a long-term effect of by acute reversible rejection on GS. Death with functioning graft is a major cause of graft loss.

Acknowledgements This study was supported by grants from the Kurt and Doris Palander Foundation and Einar and Karin Stroehm Foundation.

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