

# 15th Seah Cheng Siang Memorial Lecture: Liver Transplantation – Lessons Learnt and Future Horizons

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## Abstract

The first clinical successes with liver transplantation by Starzl in 1967 were based on studies showing that in man, organ allografts could induce self-tolerance with the aid of immunosuppression. Overall survival figures were poor until 1983, when cyclosporine was introduced into immunosuppressive regimes, and with the introduction of tacrolimus, results improved even further. With figures for 1-year survival now up to 90%, more attention is being directed to quality of life and the side effects of immunosuppression. Nephrotoxicity along with hypertension and diabetes are of major concern, and a significant number of long-term liver transplant patients are now facing end-stage renal failure. In the majority of conditions transplanted there is also a significant chance of disease recurrence in the graft. Owing to the shortage of cadaver organs, split liver and domino techniques are increasingly utilised. Living donor liver transplantation has also come to the fore, and to minimise potential harm to the donor, new techniques are being developed which will allow greater use of left lobe grafts.

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**Key words:** Disease recurrence, Immunosuppression, Living donation, MELD, Tolerance

It is a great honour to be giving this lecture – the 15th, in memory of Professor Seah, who by all accounts was truly a great doctor, not only in the care he gave to his patients but in his dedication over many years to the advancement of medicine in Singapore.

In reflecting on some of the lessons learnt during the early days of liver transplantation, I want to take you back initially to the early 1960s. By that time it had become apparent to Starzl, working in Denver, USA, after much experimental work, that the liver was an immunologically privileged organ. For instance, dogs with liver transplants could survive for long periods after being taken off all immunosuppression, and in Cambridge, Roy Calne – the other pioneering surgeon at that time – demonstrated that in untreated outbred pigs, this tolerance extended to other donor tissues transplanted at the same time, including skin and kidney. But in referring to those early pioneering days, I can do no better than quote from Starzl,<sup>1</sup> writing in his “*History of Clinical Transplantation*”:

“It becomes apparent as the layers of history are peeled away that there were only two seminal

turning points in the evolution of clinical transplantation. One was the induction of chimerism-associated neonatal tolerance by Billingham, Brent, and Medawar in 1953. The second was the demonstration in 1962-63 that organ allografts could self-induce tolerance with the aid of immunosuppression. All subsequent developments in organ transplantation depend on exploitation of this principle, using variations of the drug strategy that had made its discovery possible.”

The demonstration that unprecedented high doses of corticosteroids could potentiate the immunosuppressive effects of azathioprine provided the basis for the first trials of human liver transplantation carried out by Starzl in 1963. But it was the preparation of anti-lymphocyte globulin in 1996 (and later OKT3 monoclonal antibody), with its greater immunosuppressive potency, that gave him his first clinical success when he restarted the programme in the summer of 1967. It was not until a decade later that we saw the next major development in drug strategy with the

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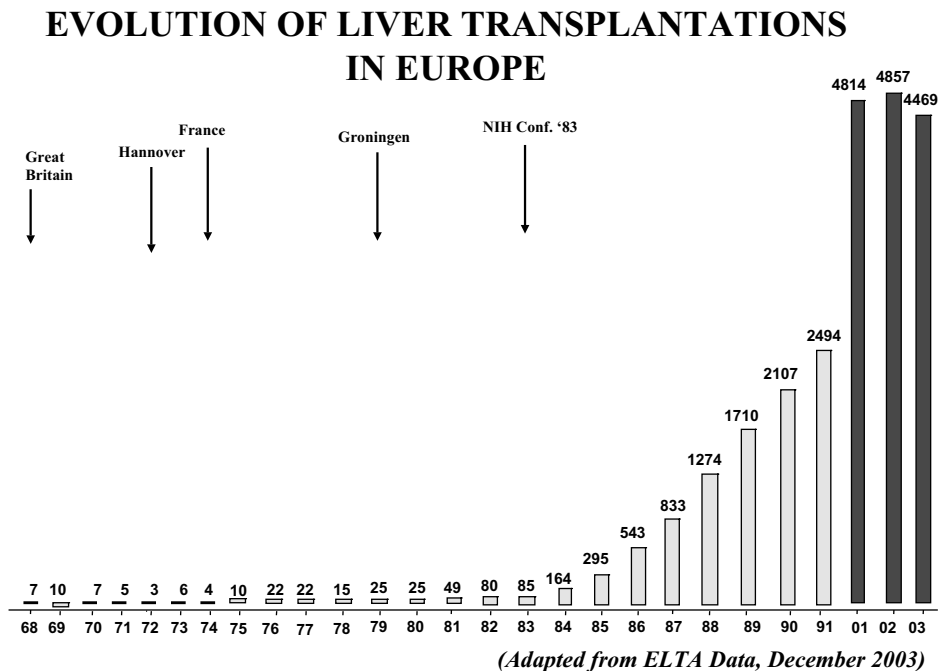


Fig. 1. Illustrating early days of liver transplantation with the few centres involved and the small number of cases each year until Consensus Development Conference in 1983. Data of European Liver Transplant Registry (ELTR), December 2003.

introduction of cyclosporine in 1979.

My involvement in liver transplantation dates back to the spring of 1968, when Professor, now Sir Roy Calne approached me to link our respective units, his in Surgery at Addenbrooke's Hospital, Cambridge and mine in Medicine at King's College Hospital, London, into what became known as the Cambridge-King's Programme.<sup>2,3</sup> Our first transplant was in October of that year but as illustrated in Figure 1, the evolution of liver transplantation in Europe was slow. Other programmes started up in hope soon ended in despair, and I have only indicated in this figure those units that stayed the course, namely, Rudolf Pichlmayr's programme in Hannover started in 1972, Henri Bismuth's in Paris in 1974, and Ruud Krom's in Groningen in 1979. Also, highlighted in Figure 1 is the year 1983, when the Consensus Development Conference was held at National Institutes of Health, Washington, USA,<sup>4</sup> where the results with cyclosporine were first presented, and as survival figures began to improve, there was a rapid increase in the numbers of cases transplanted. Annual numbers reached nearly 5000 by 2001 but have plateaued over the past 3 years due to donor organ shortage, to which I will return later.

It was certainly a rapid learning curve, with new surgical techniques particularly for the bile duct anastomosis, improved pre- and postoperative management quite apart from the immunosuppressive regimes and the susceptibility

to infection, which was the cause of so many deaths. One of the most rewarding observations to me as a hepatologist was the extent to which manifestations of chronic liver disease hitherto considered irreversible were reversible with a good functioning graft, and the extraordinary rehabilitation of the patient that this allowed. In one of our early cases severely disabled by chronic hepatic encephalopathy for some 2 years, gross electroencephalogram changes and clinical signs were completely reversed.<sup>5</sup> In another patient with Wilson's disease transplanted for end-stage liver failure from cirrhosis, there is a photograph of him after the transplant mucking out a pigsty – what better evidence of rehabilitation! With the underlying genetic defect residing in the liver, plasma ceruloplasmin levels and copper excretion became normal following the transplant.

But for most adult diseases transplanted, the grafts in time can become affected by recurrence of the primary disease. One of our earliest experiences with this was in primary biliary cirrhosis in a patient who finally died from the recurrent disease.<sup>6</sup> Usually though, this is mild and indeed for many years its existence was fiercely disputed. It occurs more frequently with FK506 than cyclosporine immunosuppression. Disease recurrence can occur with autoimmune hepatitis and primary sclerosing cholangitis, and in a number of cases may progress enough for re-transplantation to be considered. Continued immuno-

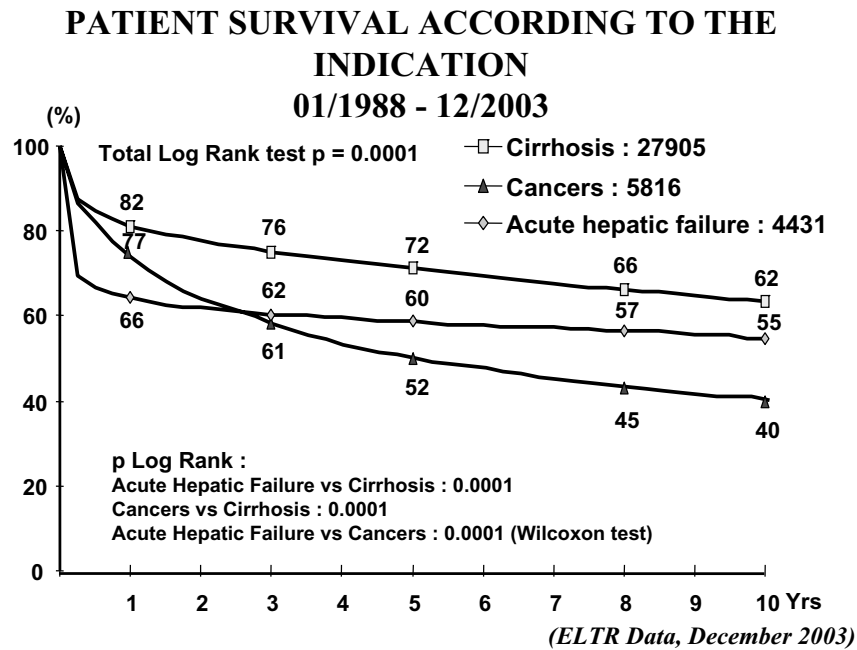


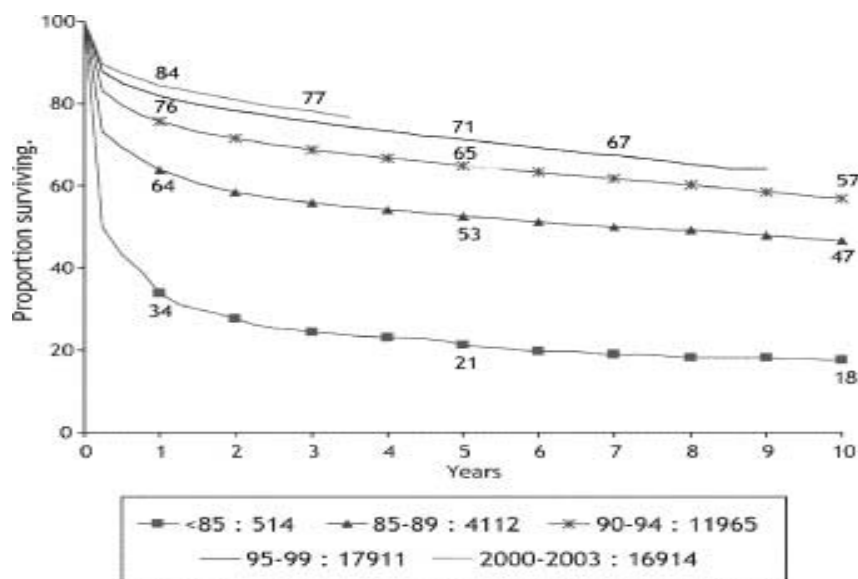
Fig. 2. Showing long-term survival curves for main disease indications of cirrhosis, liver cancers and acute hepatic failure. Data of ELTR, December 2003.

suppression with steroids is a requisite for preventing recurrence of clinically significant autoimmune hepatitis. Effective measures have also been developed to prevent recurrence of hepatitis B (HBV) infection in the graft and the occurrence of fibrosing cholestatic hepatitis, by the administration prophylactically of immunoglobulin. In those cases where HBV disease does recur, effective disease control is now obtainable with lamivudine or adefovir.

Much more difficult is the management of recurrent hepatitis C (HCV) in the graft. Not all recipients get severe disease, possibly no more than 20%, but as a result overall graft survival is reduced after 5 years. Interestingly, the severity of fibrosis appears to have worsened in recent years. This has been attributed to the use of donor livers from an older age group, in keeping with the non-transplant situation, in which the older the age of acquisition of infection, the more severe the resulting disease. In a recent series<sup>7</sup> from Burroughs's group at the Royal Free Hospital comprising 193 cases analysed retrospectively, donor age affected recipient survival only during the first 3 months. The important risk factor identified for severe fibrosis was the occurrence of acute hepatitis flares. Those patients on maintenance prednisolone and azathioprine immunosuppression had the lowest frequency of severe fibrosis and survived the longest. Turning again to the non-transplant situation, before the discovery of HCV, patients with non-A, non-B hepatitis, as they were then termed, often appeared to do well on this therapy.

Figure 2 gives long-term survival data from the European Liver Transplant Registry (ELTR) according to disease indication. The liver cancer patients, despite a 1-year survival very similar to that for cirrhosis, show a steady fall off in survival due to tumour recurrence. This contrast with the flat curve in the fulminant hepatic failure cases reflects the general lack of recurrent disease in these patients transplanted for paracetamol overdose, idiosyncratic drug hepatotoxicity or fulminant viral hepatitis. Whether recurrent tumour in the hepatocellular carcinoma cases is due to dissemination of tumour cells at the time of surgery, or whether it derives from extra hepatic deposits undetectable at the time of the transplant, has not been established. What has always been extraordinary is the very long time that may elapse before recurrence becomes evident. One of my patients went 8 years before the yearly computed tomography (CT) scan showed tumour once again in the liver.

Adoption of strict selection criteria, namely, 3 tumours  $\leq 3$  cm in diameter or 1 tumour  $\leq 5$  cm, reduced the frequency of tumour recurrence; although recent reports suggest that these criteria can be relaxed without significantly adding to the risk. Thus in a series from Busutill's group, patients with solitary tumours  $\leq 6.5$  cm or with 3 tumour nodules, the largest  $\leq 4.5$  cm in diameter, had survival rates of 90% and 75% at 1 and 5 years, compared with 50% for tumours exceeding these limits.<sup>8</sup> It is also generally accepted that in living donor liver transplantation (LDLT) the limits can be



**Patient survival according to year of LT.**

*(ELTR Data, December 2003)*

Fig. 3. Data illustrating progressive improvement in patient survival curves since start of liver transplantation but in diminishing increments. Data of ELTR, December 2003.

justifiably increased.

With the number of transplants carried out increasing after the introduction of cyclosporine,<sup>9</sup> another very important development which revolutionised the logistic of carrying out liver transplants was the introduction in 1988 of the much improved University of Wisconsin Solution.<sup>10</sup> This allowed graft preservation with subsequent excellent function for up to 24 hours after removal, which meant that the donor graft could be removed and brought back to the transplant centres rather than the team having to travel to where the donor graft organ was being removed.

Figure 3 shows the further overall improvements since those early years. The curve for the period 1985 to 1989, with an increase of 1-year survival to 64% from 34% previously, reflects the introduction of cyclosporine and the third its replacement by FK506 (mycophenolate) from 1990 onwards. Since 2000, 1-year survival in the registry has increased to 84%, although figures as high as 90% to 95% in individual series are now being reported.<sup>11</sup> The progressively smaller increments with each succeeding period would suggest that near-maximum results are being achieved. There are still some areas of management, though, that could be improved, e.g., reduction in the susceptibility to recurrent infections, which so often are the cause of prolonged hospital stays and death. In a recently published double-blind controlled trial, in which probiotics (lactic acid bacteria along with fibre) were added to an enteral

nutrition regime, versus fibre alone, the 30-day bacterial infection rate was reduced from 48% to 3%.<sup>12</sup>

There is some concern as to whether the increasing use of partial grafts, marginal organs from older donors (even in their 80s), and the use of non-heart beating donors, will reduce the upward trend in graft survival. As yet, this has not been convincingly shown. Indeed, in one series of non-heart beating donors from a single centre, 1 year graft survival was 84%.<sup>13</sup> A considerable number, 27 of the 60 organs retrieved, were considered to be less than satisfactory due to prolonged hypoxia, hypotension, or poor perfusion, and better methods for preventing the harmful effects of warm ischaemia are needed.

The advantages of tacrolimus over cyclosporine in the prevention of chronic rejection were shown against the standard drug, and not against cyclosporine formulated as Neoral, which has greater bioavailability and efficacy. The recent comparative trial carried out in the UK, which was against Neoral, showed little difference in frequency or severity of rejection, although there were patient survival benefits for tacrolimus.<sup>14</sup> It is possible that the differences would have been less if cyclosporine dosage had been based on monitoring of  $C_2$  rather than of trough blood level. In one study, the incidence of moderate to severe rejection was 13.5% with  $C_2$  monitoring compared to 23.4% with the standard  $C_0$  measurement. A switch to  $C_2$  monitoring has also been shown to allow a reduction in cyclosporine

dosage, and with this the frequency of hypertension and of a raised serum creatinine level was reduced.<sup>15</sup>

With near-maximum figures for graft survival and function being reached, increasing attention is being directed towards the quality of life in the recipient, and the adverse effects of immunosuppressive drugs. As well as hypertension, there is an increased frequency of diabetes along with hypercholesterolaemia, and increased plasma triglyceride levels. Such metabolic disturbances account for the reported increase in relative risk (2.56) of ischaemic cardiac events and of a cardiac death in long-surviving liver transplants.<sup>16</sup> The contribution of corticosteroids in maintenance regimes with tacrolimus or cyclosporine is difficult to determine. A recent study compared a conventional dual therapy regime of tacrolimus and corticosteroids with one of tacrolimus monotherapy and daclizumab induction.<sup>17</sup> Two doses of daclizumab were given – one before reperfusion and the other at day 7 to 10. Over the first 3 months after transplantation, there was a clear advantage for the latter in terms of a lower incidence of diabetes (5.7% versus 15.3%) and cytomegalovirus (CMV) infection rate (5.1% versus 11.5%), as well as in cholesterol increases (0% versus 16%). Corticosteroid-resistant acute rejection was lower in the tacrolimus-daclizumab group (2.8% versus 6.3%), although the overall rejection rate was similar.

The nephrotoxicity of the calcineurin inhibitor drugs (e.g., cyclosporine) is currently of considerable concern and only recently has the extent of this problem been documented. In a cohort study of 69,321 transplant recipients of a non-renal organ graft over the period 1999 to 2000, chronic renal failure (CRF) was documented in 11,426 (16.5%), of whom 28% required dialysis.<sup>18</sup> Other predisposing factors identified as contributing to renal impairment included age, female sex, hypertension, diabetes and postoperative renal failure. The prevalence of HCV hepatitis in the recipient group was 21.4%, with a 20% increased risk of CRF. For me as a hepatologist, there is much of interest here, for in the non-transplant setting, chronic HCV infection is known to be associated with membranoproliferative nephritis. There is also epidemiological evidence that the incidence of type II diabetes is increased in HCV infection. A recently published study<sup>19</sup> of renal histopathological changes in a series of 26 liver recipients with chronic renal failure, at a mean of 5 years after transplantation, estimated renal destruction with interstitial fibrosis and glomerular sclerosis at 45%, with severe arteriosclerosis in all. Four primary lesions were visualised: 1) cyclosporine or tacrolimus arteriopathy; 2) diabetic nephropathy; 3) thrombotic microangiopathy from cyclosporine or tacrolimus, or interferon alpha; 4) tubular lesions from starch-based plasma volume expanders. Up to 5 closely intertwined glomerular

and tubular lesions were evident within a single biopsy. By the end of the follow-up period (mean, 6.4 years), 12 of the 26 patients required dialysis. Measurements of 24-hour urine protein excretion in the various subgroups showed high levels of proteinuria, particularly in the HCV and diabetes group. Of relevance to the treatment of HCV infection post transplant is the even higher proteinuria of a small group of recipients treated with interferon which as in the non-transplant setting can occasionally induce a thrombotic micro-angiopathy.<sup>20</sup>

Fortunately with the new immunosuppressive drug, sirolimus, there is an opportunity to avoid the nephrotoxicity and other serious side effects of the calcineurin drug inhibitors. Sirolimus, a macrocyclic lactone produced by streptomyces, inhibits T lymphocyte activation and proliferation by a different mechanism and has no effect on calcineurin activity. It can be used to replace tacrolimus when the serum creatinine becomes elevated and probably should be considered for the wider group of patients developing hypertension and diabetes mellitus, although few controlled evaluations of mono or dual therapy with sirolimus have been carried out in liver transplant recipients. Of the reported side effects, hepatic artery thrombosis and wound dehiscence have been reported in the early postoperative course. Little information is available currently on the serum transaminase elevations also observed.

With the ever-increasing waiting lists for liver transplants worldwide, a number of surgical techniques are used to maximise the use of donor organs. Split liver transplantation based on the segmental anatomy of the liver, which allows its division into right and left functional lobes, was first described by Pichlmayr's group in 1988. Usually the left lobe or its lateral segments are used for a child or infant recipient and the full or extended right lobe for an adult. Overall survival figures compare favourably with whole organ grafting but attempts to produce functional grafts for 2 adults have proved less successful. In the latest series reported at the American Society of Transplantation Meeting this year,<sup>21</sup> graft survival in the 13 recipients receiving left lobe grafts were not as good as in the other 13 recipients receiving right lobes – 60% versus 92% at 24 months follow-up. Graft-to-recipient bodyweight ratios for the 2 groups were 1.1% and 0.81%, but interestingly the poorer survival with the left lobe was not due to the occurrence of primary graft non-function or the small-for-size syndrome. Unfortunately, the liver is suitable for splitting in only about 20% of donors, namely the younger age group without arterial atheroma and those with a stable circulation.

Domino transplants, using organs taken from patients being transplanted for the disease familial amyloid polyneuropathy (FAP), is another way of increasing the



## EVOLUTION OF THE NUMBER OF LIVING RELATED LIVER TRANSPLANTATIONS IN EUROPE

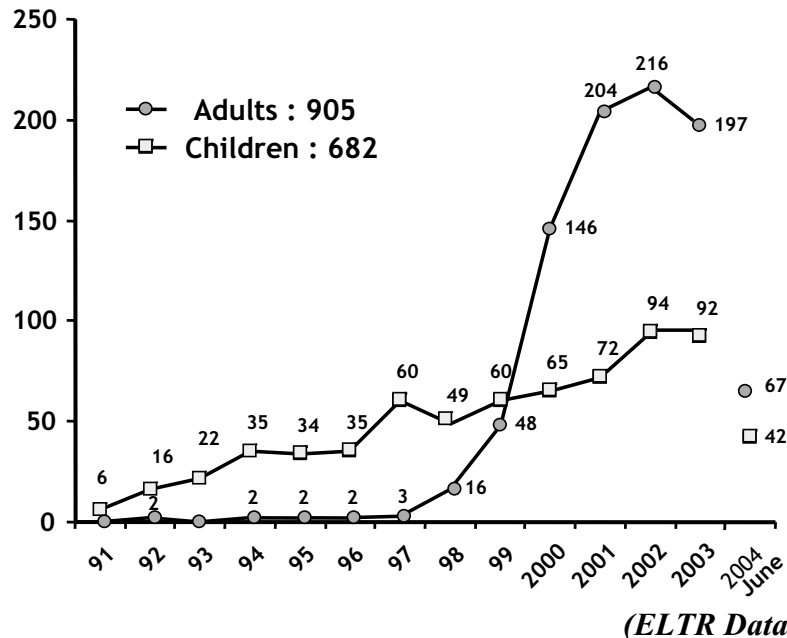


Fig. 4. Illustrating rapid rise in living donor liver transplantation for adults compared with figures for children in Europe. Data of ELTR, June 2001.



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Fig. 5. Photograph of the first patient in Cromwell Hospital LDLT Programme for overseas patients seen with her daughter who was the donor, two weeks after transplantation.

donor organ pool as such grafts are thought unlikely to give rise to the disease again at least for 15 to 20 years. The explanted FAP liver contains only microscopic deposits in hilar vessels and nerves, and since 1995, more than 300 such livers have been used as domino grafts. However, symptomatic recurrent disease may not be so delayed as recently found in one of our patients.<sup>22</sup> The recipient has HCV-positive cirrhosis and a 9-cm primary hepatocellular

cancer, well outside the limits of acceptability for a cadaver graft. The tumour has not recurred to date but at 8 years he began to notice dysaesthesias in the limbs, which progressed to an overt neuropathy. Amyloid deposits were demonstrated in nerve as well as in rectal biopsies.

The increasing number of adults being treated by LDLT in Europe is shown in Figure 4. I will never forget the first lady treated in this way in the Cromwell Hospital programme that we set up in London for overseas patients.<sup>23</sup> She had end-stage HCV cirrhosis and received the left lobe from her 21-year-old daughter. Both were doing well in the second week, when the photograph shown in Figure 5 was taken. The procedure was largely pioneered in Japan where legislation until recently prohibited the use of cadaver organs, and was initially used in infants with biliary atresia who received the left lobe or segments of it from a parent. The upper age limit was gradually extended and left lobe grafts began to be used for adult recipients with excellent results.<sup>24</sup> However, as the procedure was adopted around the world, increasing clinical experience pointed to the need for larger volume grafts in those of larger body habitus, which meant a right rather than left lobe donation.<sup>25</sup> Assessment of graft size in relation to recipient need is on the basis of the ratio of the graft volume (GV) determined by CT scanning to the calculated standard liver volume (SLV) for the recipient, or more simply by relation to

**LDLT WITH LEFT LIVER GRAFT**

- Female with end stage HCV cirrhosis aged 43 yrs (weight 68kg) received left lobe graft of 200g from 38 yr old sister (weight 63kg): GV/SLV ratio of 19%
- No small-for-size syndrome & uninterrupted recovery

Portal venous flow	377	→	190	→	145ml/100g
	reperfusion		shunt		SA ligation
Portal pressure	26	→	14	→	12mmHg

(Masetti M, et al. *Am J of Transplant.* 2004; 4(10): 1713-6)

Fig. 6. Single case study showing how restriction of portal venous inflow to a small left lobe donor graft can give excellent results.

**LK (aged 52) & NW (43) transferred from Pakistan - ascites, encephalopathy, sepsis**

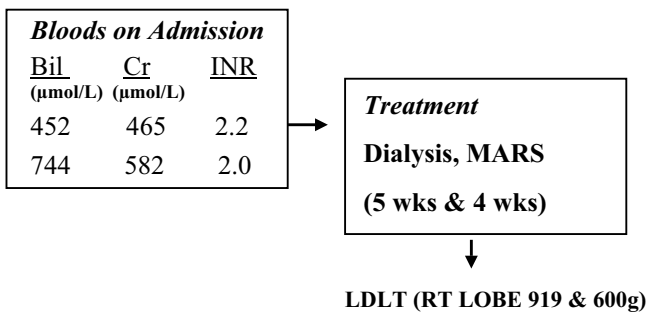


Fig. 7. Results from two patients with acute decompensation from chronic liver disease maintained for periods of weeks by use of MARS prior to LDLT.

bodyweight of the recipient. GV:SLV ratios of 30% are still considered acceptable in some centres in Japan, whereas >40% ratio is required in the Hong Kong programme, and >50% in the Western centres, the last 2 categories requiring right lobe grafts. In recipients receiving an insufficient-sized graft, the outcome is poorer with the development during the first 7 to 10 days of the so-called “small-for-size syndrome” – deteriorating graft function with deep jaundice, ascites and portal hypertension.

Regeneration of a partial graft, whether from living donor or split cadaver, is extraordinarily rapid and the majority of the growth occurs in the first 2 weeks. In one recent study,<sup>26</sup> regeneration of the remaining lobe in the donor was not complete – 79% of ideal liver weight compared with 104% in the recipient given the right lobe, a finding we have also documented. Comparative figures

for recipients of right or left lobe partial grafts from a cadaver split livers were 114% and 120%. Liver function tests in the donor, though initially markedly deranged, usually return to normal by the second week. There is undoubtedly some morbidity for the donor: 12.4% in an analysis of 1841 living donors from 46 transplant centres in Japan.<sup>27</sup> But the main concern is the potential risk to life. One donor death from liver failure occurred after the completion of a Japanese study, and there have been at least 3 other such deaths in Europe and a similar number in the USA. Some resulted from technical errors, others from insufficient remaining graft function, and in the well publicised case from New York, the donor died on the second day from a fulminating septicaemia.

Although follow-up studies of left and right lobe donors have been reassuring in terms of overall morbidity and quality of life, right lobe donation has been shown to be associated with greater operative stress and longer recovery times.<sup>28</sup> Encouragingly, some studies have now shown that it is possible to reduce the portal inflow to the liver and congestion of the graft, which is thought to be the basis for the “small-for-size syndrome,” by a portocaval shunt procedure or ligation of the splenic artery. One such example is shown in Figure 6. The GV:SLV ratio was only 19% and yet the patient made an uninterrupted recovery. The marked reduction in portal venous flow and portal pressure measurements after the shunt was carried out and then the splenic artery ligated showed how portal venous inflow into the graft can be reduced to safe levels.<sup>29</sup> The group at Ghent have also recently published convincing data<sup>30</sup> that small-for-size grafts can be used successfully in LDLT when graft hyperperfusion is prevented by graft inflow modulation (GIM) using a hemi-portocaval shunt. Of the 13 patients studied with graft to recipient body weight ratios of  $\leq 0.8\%$ , the 6 with GIM had excellent patient and graft survival figures at 1 year – 87.5% and 75% compared with 40% and 20% for those not having GIM, 3 of whom were clinically affected by the small-for-size syndrome.

With such an approach, a good outcome should be obtainable in the very sick patient with liver failure. The lesser chance of a good outcome in such cases would have an adverse effect, it is thought, on the donor, which is also the basis for the view that LDLT should not be used in the emergency situation of acute liver failure. This is a view to which I do not subscribe, if a cadaver donor organ is unlikely to be obtained and if after being fully informed the donor remains willing.<sup>31</sup> Figure 7 shows the successful use of LDLT in 2 very sick patients in our Cromwell Hospital programme, whose condition was maintained and to some extent improved by the use of liver support device known as MARS (molecular adsorbent recirculating system).

Despite very high serum bilirubin levels, the presence of renal failure and prolonged coagulation on a background of chronic liver disease, both finally had right lobe grafts performed. Although recovery was protracted, they were finally able to return home with relatively normal liver function and kidney function.

Such considerations are part of the ongoing debate on as to whether individual justice – maximum benefit for a patient, or utility – utilising organs for the benefit of the greatest number of patients, should be the basis of organ allocation. In many Western countries, cadaver organs are regarded as a public resource – a consideration which does not apply to the living donor. Whilst every effort should be made to maximise the use of donor organs, in my view much more needs to be done in countries all around the world to improve retrieval rates from those who are dying in hospital. Thus in Spain, where there is a statutory scheme based on national legislation that all those dying in hospital are considered for organ donation, retrieval rates in the year 2000 averaged 33.9 per million population, with even higher figures in some regions. This is much higher than in the other European countries and is nearly 3 times higher than the annual rate of 13.4 in the UK. Spain as a result is able to perform many more liver transplants: 24.1 compared with 11.3 per million population in the UK. Furthermore, in the UK currently, relatives refuse permission in over 40% of cases.

Meanwhile, as waiting lists grow even longer, there will continue to be difficulties in priority allocation for organs. It was to arrive at a better estimate of disease severity and likely deterioration on the waiting list that the United Network of Organ Sharing (UNOS) in America introduced the Model of End-stage Liver Disease (MELD) scoring system<sup>32</sup> as the basis for organ allocation to recipients on the waiting list. Based on objective blood measurements of serum bilirubin, serum creatinine and international normalised ratio, it has been shown to correlate closely with short-term prognosis. It can be weighted by additional points for recipients with liver cell cancers who need to be given priority for an organ and it is likely that the serum sodium will be added to provide a better indicant of prognosis in those with ascites. Scoring of disease severity does focus attention on the potential benefits of a liver transplant in a particular patient as compared with continuation of standard therapy. Only with a MELD score of above 19 is the outcome at 1 year likely to be better with a transplant.<sup>33</sup>

Finally, any consideration of future horizons in liver transplantation needs to include the use of hepatocytes for transplantation rather than whole or partial grafts. Of greatest promise for cases of inborn metabolic defects, short-lived function of cells infused into the portal vein or

transhepatically can be obtained,<sup>34</sup> although long-term engraftment in the liver in such conditions or in diseased livers represents a much bigger dimension. Primary hepatocytes currently have to be freshly isolated from cadaver donor organs not used for transplantation, and the ability to maintain the function of primary hepatocytes in culture continues to defy the best efforts of researchers. As to the use of stem cells, whether obtained from the fetus, bone marrow, or from liver primitive cells, there is as yet no evidence in man to show that their survival after implantation in the liver can enhance remodelling and repair of the damaged liver.

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