Editorial

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The improved results of liver transplantation

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For far too long liver transplantation represented a high-risk procedure in a few experimental centres. With the introduction of technical innovation, cyclosporine and improved donor organisation, an increased awareness and appreciation of the benefits were realised. Spurred on by the National Institutes of Health Consensus Conference of 1984, other groups began to look again at liver grafting as a modality of treatment in end-stage hepatic failure. Such activity has continued to expand in recent years: whereas in Europe by 1985 only 535 transplantations had been performed, over 7000 patients have now been grafted in some 72 centres in 13 European countries; in 1990 alone more than 1800 liver transplants were performed [8]. The major European activity has been in France, the United Kingdom and Germany, with recently rapid expansion in Spain and Italy.

This increased activity has been mirrored by a progressive improvement in overall results. Whereas prior to 1984 in some 510 European patients a 1-year survival of only 33% was recorded, in 1989 1418 patients were grafted with a 1-year survival of 71.3%, and of the 1635 patients transplanted in 1990 an actuarial survival of 74.6% is anticipated [8]. Thus it may be anticipated that nearly three-quarters of all patients will make a full and complete recovery. However, those transplanted for cancer run the risk of recurrence, and emergency grafts performed in desperately ill patients have a significantly inferior outcome, with 1-year survival under 60%. If such categories are excluded, even more impressive results can now be recorded. Within our own unit, taking cases grafted in the last 3 years, over 90% 1-year survival has been recorded in children and primary biliary cirrhotic patients. It is gratifying to see that the increasing activity is mirrored by significantly improved results.

Why has there been such a significant improvement? While it is frequently said that the introduction of cyclosporine has revolutionised organ grafting and is largely responsible for the improved result, this is undoubtedly an over-simplification. Many factors have contributed to our increased ability to graft patients successfully.

One possible reason for improved results could be the elimination of high-risk patients, with better recognition of those who will benefit. In point of fact, however, increasingly difficult cases are being addressed. While in the early 1980s it was frequent to exclude patients from transplantation programmes if they had portal vein thrombosis, impaired renal function, diabetes or major previous surgery, all such patients would now be accepted. Fulminant hepatic failure requiring emergency grafting, previously excluded, is now considered a prime indication for transplantation, and increasingly complex procedures are considered for those with multi-system failure. For instance, patients with primary hyperoxaluria undergo combined liver and renal grafting [10, 29], and for those with cystic fibrosis and liver failure, triple grafting with heart, lung and liver has been undertaken. Thus, there is no clear indication that simpler cases are being selected – if anything, the opposite. However, there has been a change in the categories of selection: fewer tumour patients as a proportion of the overall number and an increasing number of children and adolescents are now being accepted.

Nor perhaps has timing of surgery yet made a significant impact in the improved results. Taking bilirubin as a marker of the degree of severity of disease at the time of referral in conditions such as primary biliary cirrhosis, we found no reduction in overall bilirubin levels at the time of referral during the last decade [17]. There thus seems little indication that patients are being referred earlier. At this time, we would normally try to avoid grafting in cachectic patients with overwhelming sepsis and hepatorenal failure whose life expectation can be counted in days rather than months, since it is increasingly clear that "poor candidates are mainly responsible for poor results"! Nevertheless, as many as a third of patients waiting for grafting will be in a high urgency category where death can be anticipated within weeks, and it is difficult to deny a graft to a patient in the agonal phase who has been waiting for a suitable organ. We and others continue to offer liver grafts to such patients, although intensive

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effort is made to improve their general condition before grafting.

Similarly, in fulminant hepatic failure, the recent establishment of early prognosis criteria [20] should allow transplantation before the onset of brain damage, acute renal failure or haemodynamic instability and thus, perhaps, increase the post-transplant survival. There is now a general agreement between physicians and transplant surgeons on the liver diseases eligible for transplantation and, moreover, on the appropriate timing for patient referral. Primary biliary cirrhosis is a chronic cholestatic disease with a predictable course corresponding to the bilirubin level, and for which transplantation can be offered with excellent results before the onset of severe hepatic insufficiency. In primary sclerosing cholangitis, the picture of a symptomatic patient with advanced liver disease is a primary indication for liver transplantation, and any attempt at repair, surgically or by stenting a biliary stricture, may considerably complicate the transplant procedure and therefore compromise the outcome, even though the patient's condition may be temporarily improved. Similarly, in biliary atresia, the failure of a Kasai procedure, resulting in early symptomatic cholestatic cirrhosis, should lead to transplantation before liver decompensation without further surgical intervention, as re-establishment of bile-flow is rare. For the same reasons, in case of variceal bleed, surgeons should remember that any abdominal procedure may significantly alter the outcome of a subsequent liver transplant. However, if sclerotherapy fails in controlling the haemorrhage, mesocaval shunt should be preferred, as it avoids porta hepatis dissection and can easily be taken down during transplantation [2].

The timing for transplantation is much less clearly defined for non-cholestatic cirrhosis, such as post-necrotic cirrhosis or auto-immune cirrhosis, since these usually do not follow a predictable course. In these situations we recommend transplantation to be considered in patients who present with recurrent variceal bleeding, intractable ascites or encephalopathy in spite of adequate treatment, with a poor quality of life and an estimated length of survival of less than 1 year. Moreover, there is still a strong reluctance to consider transplantation for alcoholic cirrhosis, for many reasons, among which are the frequent psychological inabilities of these patients to face the important constraints of treatment and follow-up, the risk that they will return to their previous drinking habits, and the frequent association of serious alcohol-related complications such as cerebral disease, chronic pancreatitis, neuropathy and malnutrition. Nevertheless, it is likely that alcoholic cirrhosis will increasingly become an indication for liver transplantation in the near future. In addition to the former criteria for non-cholestatic cirrhosis, an abstinence of at least 6 months and a psychiatric evaluation should be weighed up before patients with alcoholic liver disease are considered as suitable candidates for a new liver [15].

Transplantation for liver malignancies has been disappointing, with a 2-year survival of about 30%, mainly due to tumour recurrence [19, 24]. For this reason, liver transplantation for cancer is usually only considered if full evaluation including laparoscopic assessment shows the tumour to be confined to the liver. If there is any doubt of extra-hepatic spread, we perform histological frozen sections during liver transplantation, and if spread is present, the procedure is aborted. The long-term results of major cluster excision for liver malignancies are still awaited [27]. Finally, the rising demand for livers, resulting in increased time on the waiting list, may lead to a certain reconsideration of indications with well-established poor prognosis, such as tumours or hopeless transplantation in final end-stage cirrhosis. In the future this may lead to controversy as to who should be given priority of claim to a compatible liver: the sickest patient, or the one who could benefit the most from the graft.

Undoubtedly, a major advance in liver transplantation in the past 3 years was the development of the University of Wisconsin (UW) solution for organ preservation, which allows an increase of cold ischaemic time up to 20 h without adversely affecting the quality of organ storage in terms of early liver function or graft survival [13]. The beneficial effects of an extended preservation time are multiple, since it allows liver retrieval from greater distances and better sharing of organs, longer "back-table" preparation for reduced-size liver grafts, split-liver grafts, or ex-vivo separation of pancreas and liver after combined procurement. Furthermore, surgeons can arrange for a second candidate to be available, in case the recipient proves to be inoperable, thus avoiding organ wastage. Frequently, liver replacement can be performed as a semi-elective procedure during daylight hours, simplifying the difficult hospital logistics of co-ordinating donor and recipient procedures.

Undoubtedly one of the most significant factors resulting in improved survival was the ability to re-graft a patient in whom graft failure has occurred. In adults, approximately 5% of liver grafts will not function due to damage in the donor, preservation injury or reperfusion damage, and hepatic artery thrombosis requires a further 5–8% of adults to be re-grafted in emergency situations. More than half of such re-grafted adults will ultimately make a full and complete recovery. The option of re-grafting for children has been even more important. Primary non-function combined with technical difficulties in very small infants has required a re-grafting rate of between 15% and 25% in many major programmes, and the increased availability of organs has made it possible to provide these grafts. Thus, for the first time in recent years, primary graft failure of the liver has not been synonymous with patient death, and the majority of these patients can be salvaged.

In some ways, advances in surgical technique have only contributed to a limited extent to the improved results of liver grafting; they have, however, helped to alleviate the scarcity of donors. In children, the introduction of the segmental graft has meant that for the first time infants can be successfully grafted. Segments two and three taken from adult livers can be transplanted in children when the donor-to-recipient weight ratio is as high as ten to one [1, 3]. Although these transplantations are associated with a higher complication rate (infection and morbidity), the majority of the children in these cases now make a full recovery. Similarly, patients requiring emergency grafting

have benefited from split-liver grafting, allowing the use of one liver for two recipients [7]. Recently, "living related liver transplants", using the left lateral segment from a parent, have been achieved, although the substantial morbidity both in donor and in recipient raise the question of the ethics of single-organ donation from living donors [3].

Nevertheless, increasing familiarity with the technical problems, anatomical variations and options for dealing with portal vein thrombosis, porto-systemic shunt and previous surgery have contributed to a reduction of intra-operative blood loss and transfusion needs. In our own institution the median blood requirement in adults in the last 100 cases was 5.1 units, and in children it was 2.6; the "disasters" requiring 30–50 units of blood are now rare. The introduction of veno-venous bypass during the anhepatic phase has also contributed significantly to the care of the critically ill patients, with the maintenance of cardiac output and renal function, thus minimising fluid support at a risk of post-operative fluid overload [26]. While the cell saver and auto-transfusion were used frequently in earlier years [6], they are rarely nowadays employed in our own unit. Fewer patients leave theatre in an uncontrolled condition, and our greater appreciation of fibrinolysis and reperfusion coagulopathy with improved monitoring using thrombo-elastograms and intensive laboratory monitoring undoubtedly has helped further to control the peri-operative phase [23]. Nevertheless, nearly half of all deaths still occur within 7 days of surgery, from a combination of reasons which include technical problems and primary non-function.

Increased awareness about these intra-operative difficulties has been matched by improved post-operative care [14]. The recognition of the risks of over-transfusion and pulmonary oedema combined with the growing recognition that organ loss from rejection is uncommon, whereas sepsis accounts for the majority of deaths after 1 week, have lead to progressive adjustments of immunosuppressive protocols. The introduction of triple therapy, allowing reduction in cyclosporine, together with closer monitoring of whole blood levels and reduced steroids and with earlier recognition of viral infection and prompt treatment, has also been a major factor. The development of specialist post-transplant care units gaining increasing familiarity with problems peculiar to immunosuppressed patients may also have helped.

Greater efforts are now being directed towards the long-term outcome after liver transplantation. The rising number of long-term survivors is now entering a new area in which the monitoring of late complications will be needed. Disease recurrence is well established for tumours [19, 24], liver disease related to hepatitis B virus (HBV) [25], and Budd-Chiari syndrome [11], and has been reported in primary biliary cirrhosis [22] and chronic active auto-immune hepatitis [16]. The recent identification of hepatitis C virus will probably lead to the recognition of graft viral re-infestation [4]. In tumours, except for incidental carcinoma discovered on pathological examination of native livers [12], neither a rigorous pre-transplant assessment nor the use of chemotherapy have been able to avoid recurrence entirely. However, new chemotherapy schedules may in future improve the long-term outcome in selected patients when transplantation is for cancer. In B-virus-related liver disease, the immunoprophylaxis using anti-HBV immunoglobulins tends to protect the graft only transiently, not preventing viral reinfestation in a significant number of cases [25]. The combination of long-term immunoprophylaxis using human anti-HBV monoclonal antibodies and new anti-viral agents might decrease the rate of viral recurrence in infected recipients and has to be evaluated in prospective trials [18]. In Budd-Chiari syndrome, unless there is a well-established cirrhosis, we still advocate performance of a meso-systemic shunt in most patients. Nevertheless, in case of liver transplantation, anticoagulation therapy should be pursued indefinitely to prevent re-thrombosis.

In addition to disease recurrence, the need for permanent immunosuppression in long-term survivors will surely become the greatest concern not only in regard to long-term function of the graft but also in regard to quality of life. Thus, transplant patients remain exposed to late infections and to adverse side effects of cyclosporine such as hypertrichosis, hypertension and nephrotoxicity, since most protocols now discontinue the steroids after 3–12 months.

Furthermore, the increased risk of de novo malignancies in long-term immunosuppressed patients, which has been mainly reported in association with kidney transplantation, is likely to extend to liver recipients with prolonged follow-up [21]. Therefore, the recent arrival of a new generation of immunosuppressors has brought large expectations. A murine monoclonal antibody (OKT3), targeted against the T-cell receptors, has been shown to treat refractory rejection episodes efficiently, but also induces an adverse humoral immune response with substantial side effects and is consequently not appropriate for long-term immunosuppression [5]. A new immunosuppressive agent, FK 506, has been reported to be suitable for prophylactic immunosuppression while reducing the incidence of early acute rejection and being potentially able to reverse ongoing chronic rejection without serious side effects [9, 29]. Nevertheless, these enthusiastic preliminary results have yet to be confirmed in larger series of patients in controlled prospective trials against cyclosporine currently running in both Europe and the United States.

Conclusion

Although liver transplantation still cannot be considered as a routine therapy, the initial phase of development has now been reached and results are encouraging. The benefits to the patient from the liver transplant "revolution" are clear, since it represents the only therapeutic option for patients with advanced liver disease. In return, it has brought unexpected problems to the fore. A vast increase in potential candidates is now confronting the transplant teams, bringing the problem of organ shortage and with it the need to clarify selection and timing in order to avoid potential organ wastage in "hopeless" cases. Since more than three-quarters of transplant patients will make a complete medical recovery, the long-term effects of im-

munosuppression and quality of life become all-important. Our goal now must be effective utilisation of all potential livers and further improvement of results in critical groups of candidates.

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