Liver transplantation in Singapore 1990-2004

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ABSTRACT

Introduction: Liver transplantation is the accepted standard of care for patients with hepatocellular carcinoma, decompensated liver cirrhosis, and acute liver failure. Since the first liver transplant done in Singapore in 1990, results have been improving. We review the overall results of liver transplantation over the last 15 years.

Methods: All transplant cases from 1990 to 2004 were reviewed retrospectively.

Results: 100 liver transplants were performed over the last 15 years; four in the first five years and 96 in the subsequent ten years. Overall one- and five-year survival rates were 80 percent and 78 percent, respectively. 44 were paediatric transplants, of which biliary atresia was the commonest indication for paediatric transplant. 56 were adult transplants of which hepatocellular carcinoma and decompensated hepatitis B cirrhosis were the commonest indications for adult transplant. Infection remained the commonest cause of mortality.

Conclusion: The number of transplants carried out per year was small due to the low cadaveric donation rate, but the survival of liver transplant patients was comparable to well-established liver transplant centres.

Keywords: chronic hepatitis B, cirrhosis, hepatocellular carcinoma, liver failure, liver transplantation

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INTRODUCTION

Liver transplantation has revolutionised the care of patients with end-stage liver disease[1,2]. Improving results of liver transplantation has given hope to patients with end-stage liver diseases. After the first successful liver transplant performed by Starzl in 1963, results of liver transplantation have been improving with a reported five-year survival rate of up to 70%[3,4]. Liver transplantation was first started at the National University Hospital (NUH), and the first successful liver transplant in Singapore was performed in 1990. However, initial results were poor, with high mortality[5,6]. In 1995, the programme was revamped with the formation of a new team. A new director was appointed, together with collaboration from various medical and para-medical disciplines from both the public and private hospitals. This paper aims to review the overall results of liver transplantation in Singapore over the last 15 years.

METHODS

Though the NUH Liver Transplant Programme was physically located at NUH, the members were from all public restructured hospitals as well as the private sector. The transplant team met twice a week to discuss its patients and transplant-related issues. The programme ran on an "open" concept, i.e., any medical healthcare workers were welcome to join and present their patients for discussion for listing for transplantation. Decisions were made on a consensus basis. Patients who were listed were placed on the waiting or pending list and were followed up at the Transplant Clinic at regular intervals, and their progress was updated regularly during the rest of the programme. Patients who were rejected for liver transplantation were usually discharged back to the referring doctor for further follow-up. Patients who were initially considered unsuitable for transplantation may be referred and discussed at a later date when their liver diseases progressed.

In general, all patients with decompensated cirrhosis, i.e., development of ascites, hepatic encephalopathy or variceal bleeding, were considered for transplantation. However, due to the long waiting time and the shortage of cadaveric donors locally, only patients with advanced decompensated disease were listed for transplant; for instance, patients with severe ascites resistant to all medical therapy, recurrent variceal bleeding despite medical and endoscopic therapy, or recurrent encephalopathy despite

Table I. Indications (n=47) and cause of death (n=8) for paediatric liver transplant recipients.

Indications for transplant	**No.**	
Biliary atresia and hypoplastic bile duct syndrome	32	
Glycogen storage disease	3	
Alagille syndrome	3	
Hepatic artery thrombosis (re-transplant)	2	
Acute Wilson's disease	1	
Hepatic vein thrombosis (re-transplant)	1	
Byler disease	1	
Idiopathic subfulminant liver failure	1	
Cause of death	**No.**	**Time post-transplant (days)**
Bacterial infection	2	26, 44
Portal vein thrombosis with gastrointestinal bleeding	2	952, 1,393
Cytomegalovirus infection	1	166
Chronic rejection	1	75
Primary non-function	1	2
Post-transplant lymphoproliferative disorders	1	76

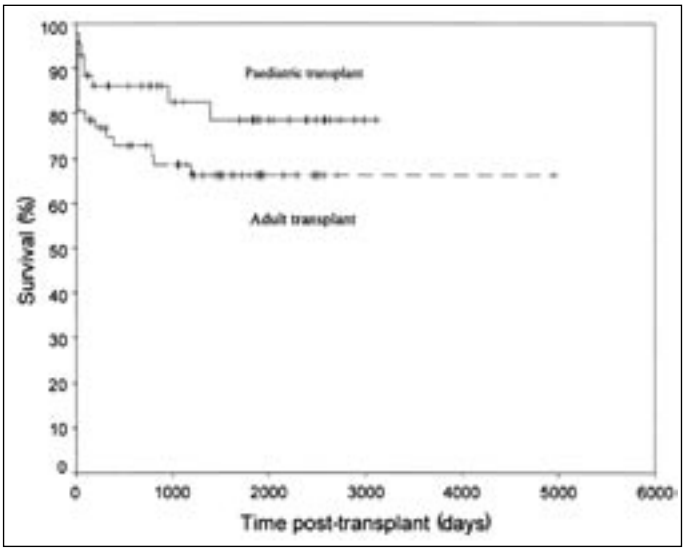

Fig. 1 Survival analysis of adult and paediatric transplant.

maximised laxative therapy. Patients with "early" decompensated cirrhosis were monitored further before being listed for liver transplant. Indication for hepatocellular carcinoma (HCC) followed the Milan criteria[7]. Briefly, patients with HCC were considered for transplant if they have one nodule less than 5 cm in diameter, or maximum of three nodules with each maximum of 3 cm, and with no evidence of regional or systemic spread. Since November 2003, the liver transplant team implemented the model for end-stage liver disease (MELD) scoring system as a measure for prioritising potential recipients who were on the waiting list, with priority given to those having the highest MELD scores[8]. This is in line with the practices of established international centres such as UNOS[9].

All liver transplant patients performed in the NUH Liver Transplant Programme from January 1990 to July 2004 were included in the study. Their diagnosis, demographics, and outcome are presented. Data was analysed using the Statistical Package for Social Sciences (SPSS) version 10.0 (Chicago, IL, USA). Actuarial survival was estimated with Kaplan-Meier analysis.

RESULTS

100 liver transplants were performed in 96 patients (with four re-transplants) over the 15-year period, where 56 were performed in adults and 44 in paediatric patients. Four were performed from 1990 to 1994, and 96 were performed after 1994. While only one out of four recipients in the first five years survived, 69 (72%) out of 96 recipients in the subsequent ten-year period survived (p=0.028). Median follow-up was 176 ± 15 (range 1-707) weeks. 68 subjects were male. Four (4%) had re-transplants, 70 (72%) were alive and 26 (26%) died. Overall one-, three-, and five-year actuarial survival rates were 80%, 78%, and 71%, respectively.

There were 44 paediatric transplants, with a mean age of 3.5 ± 0.6 (range 1-16) years. 21 (48%) were male. Indications for the 31 paediatric liver transplants are listed in Table I. Biliary atresia was the commonest indication for paediatric liver transplants. 18 (41%) had cadaveric transplant, while 26 (59%) had living-related left lobe transplant. There was no difference in survival between the cadaveric and living-related left lobe transplant (20/26 versus 13/18, p=0.50). Mean follow-up period was 186 ± 22 (0.3-445) weeks. 33 (75%) were alive at last follow-up, eight (18%) died, and three (7%) had re-transplant. 14 (45.2%) had cadaveric liver transplant, while 17 (54.8%) had left lobe living-related liver transplant. Overall, the one-, three-, and five-year actuarial survival rates were 86%, 82%, and 78%, respectively (Fig. 1). Infection and vascular complications were important causes for mortality and morbidity (Table I).

There were 56 adult liver transplants. Mean age was 49.8 ± 1.4 (16-66) years, of which 47 (84%) were male. At follow-up at 33 (1-135) months, 37 (66%) were alive, 18 (32%) died, and one (2%) underwent re-transplant. Indications of the 56 adult liver transplants are listed in Table II. Median (range) MELD score among the patients at time of transplant was 17 (7-42).

HCC was the commonest indication for adult liver transplant. Patients with HCC had to fulfill the Milan's criteria (i.e. maximum three lesions, each lesion less than 5 cm, total diameter less than 8 cm, and with no regional or systemic metastasis) before being put on the waiting list[10,11]. Decompensated hepatitis B cirrhosis was the second commonest indication. Patients with chronic hepatitis B were given lamivudine prior to the transplant and their serum hepatitis B virus DNA titre had to be less than 100,000 copies/ml (Digene®, Digene Corp, USA) before the transplant for fear of hepatitis B viral breakthrough post-transplant.

Hepatitis B immunoglobulin (HBIG) were not routinely administered post-transplant for patients with chronic hepatitis B. One patient had re-transplantation for ischaemic cholangitis from the first transplant but died shortly after the re-transplantation due to infection. Overall, the one-, three-, and five-year actuarial survival rates were 75%, 68%, and 66%, respectively. Infection and vascular complications were also the main causes of mortality in adult transplant recipients.

Table II. Indications for transplant (n=56) and cause of death (n=18) for adult liver transplant recipients.

Indications for transplant	**No.**	
Hepatocellular carcinoma	19	
Related to chronic hepatitis B	11	
Related to chronic hepatitis C	6	
Related to alcoholic liver cirrhosis	1	
Related to citrullinaemia	1	
Decompensated hepatitis B cirrhosis	14	
Drug-induced hepatitis with liver failure	5	
Cryptogenic cirrhosis	5	
Decompensated hepatitis C cirrhosis	3	
Primary biliary cirrhosis	3	
Autoimmune hepatitis with decompensated cirrhosis	2	
Alcoholic liver disease	1	
Primary sclerosing cholangitis	1	
Familial amyloid polyneuropathy	1	
Acute Wilson's disease	1	
Ischaemic cholangitis (re-transplant)	1	
Cause of death	**No.**	**Time post-transplant (days)**
Infection	4	
Bacterial	3	11, 18, 98
Asperigillosis	1	9
Non-compliance	2	
Leading to chronic rejection	1	797
Leading to Hepatitis B flare	1	1,198
Hepatocellular carcinoma recurrence	2	196, 785
Hepatic artery thrombosis	2	14, 18
Graft ischaemia	2	12, 20
Primary non-function	2	3, 10
Post-operative bleeding	1	1
Cerebrovascular accident	1	390
Congestive heart failure	1	15

DISCUSSION

The results of adult liver transplantation in Singapore have improved since the first four years in 1990-1994. The current overall first- and third-year actuarial survival rates of our patients (80% and 78%, respectively) compares favourably with results of the United Network of Organ Sharing (85.6% and 75.9%, respectively) and the European Liver Transplant Registry (76% and 69%, respectively)[12,13].

In terms of the number of transplants, only four cases were performed from 1990 to 1994, and 96 cases were done from 1995 to 2004. While only one of the four recipients (25%) in the first five years survived the transplant, 69 of the 96 recipients (72%) in the subsequent period survived. There was an improvement in terms of number of transplants done, as well as survival post-transplant. These improvements were likely to be due to many reasons. Firstly, there had been better publicity of the transplant programme and relatives of potential liver donors are more open to organ donation. Secondly, there have been improvements in surgical techniques, immunosuppression regimens and peri-transplant intensive medical care. For instance, risk of graft reinfection from hepatitis B after transplantation has now been minimised with the use of lamivudine[14].

Thirdly, an important aspect of our successful transplant programme is the formation of a closely-knit multidisciplinary team comprising transplant surgeons, hepatologists, anaesthetists, intensivists, dieticians, medical social workers and transplant coordinators, who meet regularly to evaluate patients and discuss on management. This team is truly a national team that draws expertise from all the government-restructured hospitals. Finally, with the improvement in the survival rate of transplant patients in the late 1990s, more gastroenterologists and hepatologists appreciated that this was a genuine option for patients with end-stage liver disease, resulting in an increase in number of patients referred to the programme. Liver transplantation is currently the only real option for patients with end-stage liver disease, and is an established treatment

alternative not only in Western countries, but in many Asian countries as well[15].

Due to the low availability of cadaveric liver grafts and the relatively long waiting time for cadaveric liver grafts, other options have been employed to increase the liver transplant rate. Left lobe living-related transplantation technique was used successfully in paediatric patients. It helped increase the pool of available liver grafts to paediatric patients. This type of transplantation operation can thus be performed in a semi-elective setting so recipients can be optimised medically prior to the transplant. Survival of left lobe living-related transplants was similar to that of cadaveric transplants in paediatric recipients. Left lobe living-related transplants will continue to be an important source of liver grafts for paediatric patients with end-stage liver diseases.

Recently, right lobe living-related liver transplants for adult patients have gained momentum in the transplant community. A right lobe graft will have sufficient liver mass for proper post-transplant graft function. Centres in the West, Japan and Hong Kong have reported good results with survival rates of up to 87%[16-18]. However, donor morbidity, mainly due to postoperative biliary complications, infection and pain, has been reported to be up to 20% of cases[19]. In addition, at least three deaths among the donors have been reported[20]. Careful recipient and donor selection are imperative for the success of right lobe living-related transplants. Our centre is currently planning to perform right lobe transplants.

In conclusion, the overall results of liver transplantation have improved. Liver transplantation in Singapore can no longer be considered experimental, as our results clearly match those of our more eminent colleagues in the US and Europe. As liver transplantation is the only treatment available for patients with end-stage liver disease, all such patients should have the opportunity to be considered for transplantation. However, the most significant obstacle to liver transplantation in Singapore, as in other countries worldwide, is the availability of liver donors. Unless this substantially increases, liver transplantation will remain a treatment available only to a small number of patients. It remains to be seen whether the changes in the Human Organ Transplant Act will substantially increase the pool of cadaveric organs available[21].

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