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Ten-year experience with liver transplantation at Queen Mary Hospital: retrospective study

瑪麗醫院過往十年的肝移植經驗：回顧研究

Objective. To report the experience with liver transplantation at the Queen Mary Hospital from 1991 to 2000.
Design. Retrospective study.
Setting. Liver transplant centre of a University teaching hospital, Hong Kong.
Patients. One hundred and forty-eight patients (127 adults and 21 children) who underwent a total of 155 liver transplants using 75 cadaver grafts (full-size, 67; reduced-size, 5; split, 3) and 80 living donor grafts (left lateral segment, 15; left lobe, 6; right lobe, 59) from October 1991 to December 2000 were reviewed.
Main outcome measures. Graft and patient survival rate.
Results. The most common disease indications for liver transplantation were chronic hepatitis B–related liver disease (n=74) in adults and biliary atresia (n=14) in children. Eighteen patients had hepatocellular carcinoma. Forty-eight (31%) liver transplants (three ABO-incompatible) were performed in high-urgency situations for patients requiring intensive care. The proportion of living donor liver transplants was 47.7% in adults and 73.9% in children. The overall 1-year and 5-year patient survival rates were 82% and 77%, respectively. The survival of high-risk recipients, such as those with fulminant hepatic failure (80%), chronic hepatitis B (81%), or hepatocellular carcinoma (94%), was not inferior to that of other patients.
Conclusion. Over the last decade, the promotion of (cadaver) organ donation through public education coupled with innovative techniques in living donor liver transplantation have enabled a liver transplantation programme to be established in Hong Kong with gratifying results.

目的：報告瑪麗醫院從 1991 年至 2000 年的肝移植經驗。
設計：回顧性研究。
安排：大學教學醫院的肝移植中心，香港。
患者：從1991年10月至2000年12月期間，接受共155次肝移植的148名患者(127名成人及21名兒童)，當中75例為屍肝移植(全肝67例；減量5例；分肝3例)，80例為活體肝移植(左外葉15例；左葉6例；右葉59例)。
主要結果測量：移植物及患者存活率。
結果：最常見的成人肝移植病因是由慢性乙型肝炎引發的肝病(74人)，兒童則為膽管閉塞(14人)。18名患者有肝細胞癌。48例(31%)肝移植(其中3例屬ABO血型不相配)是在緊急情況下為需要深切治療的患者進行的。成人和兒童接受活體肝移植的比率分別為 47.7% 和 73.9% 。患者手術後一年和五年的存活率分別為 82% 和 77%。患有暴發性肝衰竭(80%)、慢性乙型肝炎(81%)或肝細胞癌(94%)的高危病人接受肝移植的存活率並不低於其他肝病患者。
結論：在過去十年，憑著社會積極推廣器官捐贈及活體肝移植的嶄新技術，香港的肝移植計劃有令人滿意的成果。

Key words:
Liver transplantation;
Treatment outcome

關鍵詞：
肝移植；
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Introduction

The first liver transplant in Hong Kong was performed at the Queen Mary Hospital in October 1991. In its initial stages of development, the liver transplantation programme was seriously restricted by a lack of organ donors, lack of funding, and the prevalence of hepatitis B virus–related end-stage liver diseases.

The application of this life-saving procedure was limited: only a small number of operations were performed to the benefit of a few selected patients. Ironically, patients considered to be at highest risk for requiring a transplant, including those with fulminant hepatic failure, high-urgency status requiring intensive care, hepatitis B–related liver diseases, and hepatocellular carcinoma (HCC), were excluded from the programme. Over the last 10 years, however, various strategies have been adopted that have ultimately led to wider application of liver transplantation in Hong Kong. In this study, we review our experience with liver transplantation at the Queen Mary Hospital.

Subjects and methods

Data on all liver transplantations performed between October 1991 and December 2000 were reviewed. All recipients suffered from end-stage liver diseases with widely recognised indications for liver transplantation,[1] such as spontaneous bacterial peritonitis, hepatic encephalopathy, hepatorenal syndrome, intractable ascites or hydrothorax, recurrent variceal bleeding, or failure to thrive. The suitability for liver transplantation was evaluated by a multidisciplinary team consisting of surgeons, hepatologists, paediatricians, anaesthesiologists, respiratory physicians, cardiologists, and clinical psychologists, and was discussed at a monthly transplantation meeting before the recipient was accepted onto the waiting list. High-urgency patients requiring intensive care because of acute or chronic liver failure were accepted for emergency transplantation from 1994 onwards. Patients with hepatitis B–related liver diseases were accepted onto the waiting list for liver transplantation (under lamivudine prophylaxis[2]) from 1995 onwards. Selected patients with HCC of less than 5 cm in diameter and no more than three tumour nodules[3] were accepted onto the waiting list from 1997 onwards.

During the programme's 10-year period to date, the supply of cadaver donor liver grafts improved as a result of public education and relaxation of the criteria for donor acceptability. Marginal donors, such as those of advanced age, or who had adverse in-hospital events, or who had received inotropes, were frequently used and the decision for rejecting an organ was based largely on the surgeon's visual assessment of the organ at the time of the donor operation. The only absolute contraindications for donation were the presence of systemic infection, transmissible diseases, or malignancy. In addition, agreements were made to collaborate with transplantation centres in neighbouring regions, including Singapore and Taiwan, in the sharing of liver grafts.

To provide a source of organs for paediatric patients, the techniques of reduced-size liver transplantation[4] and living donor liver transplantation[5] were introduced in 1993. Living donor liver transplantation has been extended to adult recipients by pioneering surgical innovations using left lobe grafts from living donors since 1994,[6] and right lobe grafts since 1996.[7] The donor selection and technique of living donor liver transplantation have been described previously.[7-10] In brief, the primary selection criterion was the donor's voluntarism, and all potential donors were evaluated by clinical psychologists. The medical evaluation started with blood test screening for ABO blood group compatibility, transmissible diseases, liver function, and fitness for liver resection. Segmental liver volume was estimated by computed tomography scan with volumetry[11] to determine whether a left lateral segment, left lobe, or right lobe graft was appropriate. Hepatic arteriogram was also performed to evaluate the vascular anatomy. Since 1998, transplants involving living donors other than first-, second-, and third-degree relatives or spouses (with legally supporting documentation as to their status), could only be carried out after prior approval by the Human Organ Transplant Board.[12]

At the beginning, immunosuppression consisted of a triple regimen of cyclosporin, steroid, and azathioprine. Rejection episodes that were confirmed by liver biopsy were treated with steroid pulse therapy and resistant rejections were treated with orthoclone OKT_3 (muromonab CD3) or conversion to tacrolimus. Since 1997, a double regimen of tacrolimus and steroid has been adopted. The target trough level of tacrolimus was set at 15 ng/mL in the first month and 3-8 ng/mL subsequently, provided graft function remained normal. The dosage of steroid was reduced progressively with the aim of eliminating steroid use completely at 6 months after transplantation. Rejection episodes were treated with an increase in tacrolimus dosage and additional steroid pulse therapy when necessary; OKT_3 was rarely used. No patient was lost to follow-up and their status was updated to 31 March 2001.

Results

A total of 155 liver transplantations, including seven retransplants, were performed in 148 patients (127 adults and 21 children). There were 99 male and 49 female patients with a median age of 43 years (range, 6 months-68 years). The annual number of transplants increased rapidly from two in 1991 to 41 in 2000 because of an increase in both cadaver and living donor operations (Fig). There were 75 cadaver grafts (full-size, 67; reduced-size, 5; split, 3) and 80 living donors grafts (left lateral segment, 15; left lobe, 6; right lobe, 59). All cadaver grafts were harvested from various Hospital Authority hospitals with the exception of four from private hospitals (Table 1). One liver graft from the Queen Elizabeth Hospital was split into two for two adults, and one split right lobe graft was imported from Taiwan. The proportion of living donor liver transplants was 47.7% in adults and 73.9% in children. Forty-eight (31%) transplantations, three involving ABO-incompatible grafts, were performed in high-urgency situations for patients requiring intensive care, including 20 who suffered from fulminant hepatic failure. The most common disease indication for transplantation was chronic hepatitis B–related liver diseases (n=74) in adults and biliary atresia (n=14) in

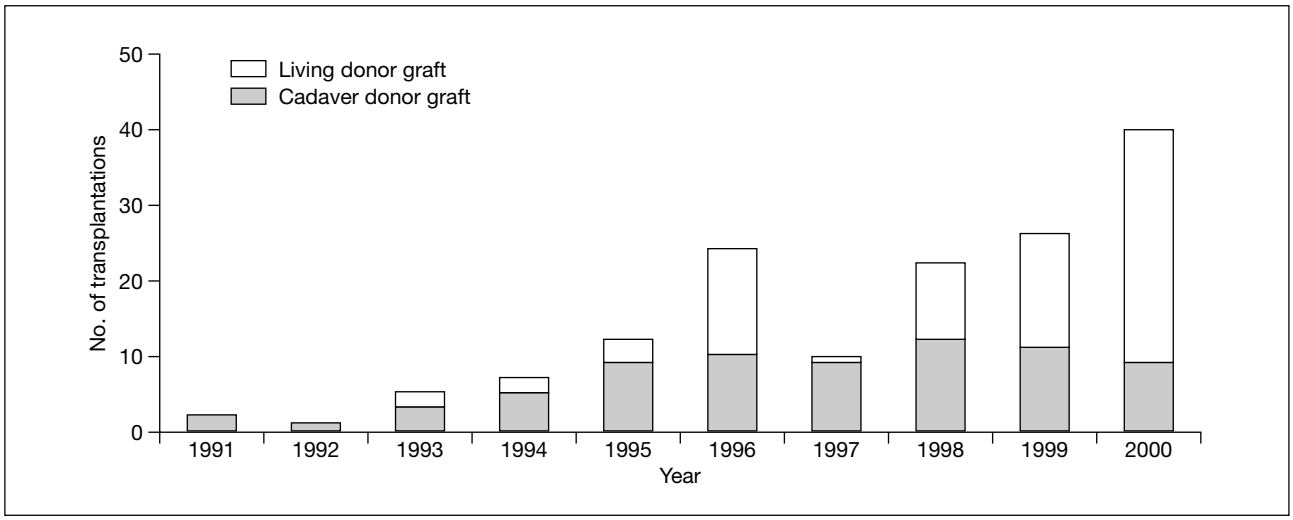

Fig. Number of liver transplantations performed at the Queen Mary Hospital each year

children (Table 2). Hepatocellular carcinoma was present in 18 patients (four with incidental tumours detected at transplantation and 14 with known tumours diagnosed before transplantation). One patient with polycystic liver and kidney disease received a combined liver and kidney transplant.

Table 1. Source of 75 cadaver donor grafts

Hospital	No. of cadaver donor grafts
Queen Elizabeth Hospital	23*
Queen Mary Hospital	22
Prince of Wales Hospital	6
Kwong Wah Hospital	6
Private hospitals	4
United Christian Hospital	3
Caritas Medical Centre	3
Pamela Youde Nethersole Eastern Hospital	2
Princess Margaret Hospital	2
Others	4†
Total	75

* Includes two split-liver grafts from one donor
† One each from Tuen Mun Hospital, Northern District Hospital, Yan Chai Hospital, and a split right lobe graft from Chang Gung Memorial Hospital, Kaohsiung, Taiwan

Table 2. Disease indications for 155 liver transplantations

Disease indication	No. of liver transplants
Cirrhosis	76 (13)*
hepatitis B	51
hepatitis C	7
alcoholic	6
primary biliary	6
crytogenic	4
secondary biliary	2
Acute-on-chronic hepatitis B	22 (4)
Fulminant hepatic failure	20
Biliary atresia	14
Re-transplantation	7
Wilson's disease	4
Autoimmune hepatitis	3 (1)
Polycystic liver	4†
Others	5‡
Total	155

* Number of patients with associated hepatocellular carcinoma is indicated in brackets
† Includes one combined liver and kidney transplant
‡ One each of Criggler-Nijjar syndrome, tyrosinaemia, familial amyloidotic polyneuropathy, ruptured hepatocellular adenoma, and Alagille syndrome

Overall survival

The overall 1-year and 5-year patient survival rates were 82% and 77%, respectively. The corresponding graft survival rates were 81% and 72%, respectively. The 5-year survival rate was 76% for adults and 81% for children.

High-risk recipients

The graft survival rate following 48 emergency transplants for high-urgency patients was 81% at 1 year and 73% at 5 years. Sixteen (80%) of 20 patients with fulminant hepatic failure, including one who received an ABO-incompatible liver graft, survived. The other two ABO-incompatible liver grafts, however, did not survive: one due to hyperacute rejection and the other following fungal infection.

Of the 74 patients who received a liver transplant for chronic hepatitis B–related liver diseases, 81% were alive at a median follow-up of 21 months (range, 5-69 months). Two (2.7%) patients had viral breakthrough due to the emergence of lamivudine-resistant tyrosine-methionine-aspartate-aspartate (YMDD) mutants. One developed graft failure at 16 months and was well with normal liver function at 28 months after re-transplantation using adefovir and hepatitis B immunoglobulin prophylaxis. The other patient was treated with adefovir and had normal graft function at 59 months.

Seventeen (94%) of 18 patients with HCC were alive at a median follow-up of 16 months (range, 6-70 months) after transplantation. The only death was caused by empyema thoracis 1 year after transplantation in a patient with no evidence of recurrence. One patient developed recurrence in the form of a solitary pulmonary metastasis, which was resected at 10 months after transplantation.

Living donor liver transplants

Table 3 shows the relationship to the recipients of the 80 living liver donors. The most common donors were a spouse for an adult and a parent for a child. The median blood loss for the donor operation was 500 mL (range, 150-2600 mL)

Table 3. Relationship to recipients of 80 living liver donors

Relationship	Adults, n=64	Children, n=16
Spouse	26	0
Parent	4	14
Offspring	14	0
Sibling	12	1
Brother-in-law	2	0
Friend	1	1
Others	5*	0

* One each from a nephew, uncle, aunt, son-in-law, and sister-in-law

and only one donor with preoperative anaemia required 1 unit of homologous packed cell transfusion. The average hospital stay was 10 days (range, 5-38 days) and the complication rate was 26.3% (Table 4). Three (3.8%) donors required further surgery, one each for incisional hernia, bile duct stricture, and small bowel obstruction from an adhesion band. All were well with normal liver function at a median follow-up of 58 months (range, 3-60 months). The 1-year and 5-year graft survival rates of living donor grafts were 78% and 76%, respectively, and were comparable to those of cadaver donor liver grafts.

Discussion

Since the first human liver transplant was performed in 1963, liver transplantation has rapidly evolved from an experimental procedure to become the most effective treatment option for almost all non-malignant end-stage liver diseases and for selected patients with hepatic malignancies. Continuous developments in organ preservation, immunosuppression, surgical technique, anaesthesiology, and intensive care medicine have refined the procedure and improved the outcome of patients after transplantation. The 1-year patient survival rate for those transplanted in recent years averaged 80% to 85%[13,14] and quality of life was good.[15,16]

At the outset, the scarcity of cadaver grafts was the most important factor limiting the application of liver transplantation in Hong Kong. Moreover, despite the increase in cadaver liver donors as a result of public education and maximal use of marginal donors over the last decade, the donor rate has remained low at less than three per million population per year. This translates into a very long waiting time of 18 to 24 months with a mortality rate on the waiting list of over 40%[17] (90% for high-urgency patients[9]).

The development of innovative techniques in living donor liver transplantation has widened the applicability of the operation so that more patients with end-stage liver disease can benefit from this life-saving procedure. The use of a liver graft from a living donor provides the unique opportunity for the patient and his or her family members to control the timing of the transplant operation together with the transplant team. The timing of a liver transplant determines the outcome after transplantation, particularly in patients with hepatic malignancy[18] and high-urgency status.[19] The risk involved to the living donor taking part is the major concern[20] and at least two donor mortalities

Table 4. Complications in 80 living liver donors

Complication	No. of living liver donors
Wound infection	9
Cholestasis	3
Bile duct stricture	1
Bleeding duodenal ulcer	1
Small bowel obstruction	1
Incisional hernia	1
Transient peroneal nerve palsy	1
Occipital pressure sore	1
Subphrenic collection	1
Urinary tract infection	1
Pleural effusion	1
Total	21

have been reported in the literature.[21,22] Nonetheless, the excellent results and the overwhelming survival benefit for the recipients, together with the safety of the donor operation in this series, justify the continuous use and expansion of this technique in Hong Kong. In fact, such favourable results have prompted an increasing number of patients and their relatives to request this treatment option; as a result, the growth in living donor grafts has outnumbered that of cadaver grafts in recent years. Currently, living donor liver transplants account for over three quarters of all liver transplants performed each year at the Queen Mary Hospital.

Other measures aimed at expanding the donor pool have had limited success. As expected, regional sharing of organs[23] has a very limited role because most transplant centres in Asia are short of organs and would not have any surplus for sharing. Although split-liver transplantation[24] offers the attractive concept of transplanting two patients with one donor liver, the logistical difficulties of mounting two simultaneous transplants and associated resource constraints seriously limit its wider application in Hong Kong at this time.

When the liver transplantation programme first began, we adopted strict selection criteria for recipients. This was particularly important given the severe shortage of organs that prevailed, and only selected patients who were most likely to benefit from the procedure were accepted onto the waiting list. Patients who required urgent liver transplantation for fulminant hepatic failure or other reasons were usually considered high-risk candidates with poor outcome. For patients with hepatitis B–related liver diseases or HCC, the concern was disease recurrence. The strict selection policy of only transplanting the fittest deprived these high-risk patients of the benefit of the procedure and severely restricted its application. With increasing experience, however, we have progressively extended the indication for transplantation to include such high-risk patients. Our results show that with aggressive medical treatment, appropriate patient selection, and advances in therapeutic modalities, the results of liver transplantation in these patients may not be inferior to those in others. In particular, the lower viral breakthrough rate and the favourable results of liver transplantation for patients with chronic hepatitis B

using lamivudine prophylaxis in our series as compared to other reports[25] contrasts sharply with earlier claims that Asians with chronic hepatitis B have poorer outcomes after transplantation.[26] We believe, therefore, that chronic hepatitis B infection, which is the most common cause of end-stage liver disease in Hong Kong, should no longer be a contraindication to liver transplantation. For HCC, which is the second most common cause of cancer death in Hong Kong, there was only one recurrence at a median follow-up of 16 months. This is an encouraging observation since recurrences tend to develop within the first year of transplantation.[27] We believe that with proper patient selection, liver transplantation may offer the best chance of long-term survival for certain individuals with HCC. In the future, it is likely that more and more patients with this disease will request this treatment option, especially as the timing of the operation can now be controlled with the advent of living donor liver transplantation.

Conclusion

The results of liver transplantation at the Queen Mary Hospital, Hong Kong, compare favourably with those of other well-established liver transplantation centres around the world. Our liver transplantation programme has developed over the last decade into an internationally reputable one, particularly in living donor liver transplantation.

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