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Liver Transplantation in Rigshospitalet, Denmark：—Our experience of 37 cases—

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Abstract：Background：Liver transplantation has become an established treatment for patients with end-stage liver disease. The aim of this study is to analyze the results of liver transplantation and also describe the current state of liver transplantation in Denmark.

Patients：All patients receiving liver transplantation in Denmark between May 2002 and February 2003 were included.

Results：A total of 47 cases had been placed on a list to undergo liver transplantation from May 2002 to February 2003. Of these 2 patients died while on the waiting list. Thirty-seven liver transplantations have been performed. Twenty-nine (78.4%) cases were cases of elective transplantation. Eight (21.6%) patients underwent an urgent transplantation due to acute hepatic failure and coma. Thirty-five patients received transplantation using a cadaveric donor liver, and 2 cases were living-donor liver transplantations. The median waiting time for electively listed patients was 62 days. Thirty-one patients received a first liver allograft. The mean age of these patients was 40.6 years (range：0-64). Four of the patients were children (range：10 months-2 years old). One patient was older than 60 years. The male-to-female ratio was 20：11. The three most frequent diagnoses indicating the need for liver transplantation were alcoholic liver cirrhosis (25.8%), acute hepatic failure (12.9%), and cryptogenic liver cirrhosis (9.7%). Six of 37 patients underwent second-time transplantations due to hepatic artery thrombosis, primary non-function, and disease recurrence. The survival rate at 30 days was 94.6%. Sixteen patients (43.2%) had postoperative complications following liver transplantation. The main postoperative complications were pneumonia (18.9%), acute renal failure (16.2%), hepatic artery thrombosis (10.8%), and biliary complications (10.8%).

Conclusion：The waiting times for liver transplantation were short, and the death rates while awaiting a donor liver were low. The results of liver transplantation in Denmark are comparable to the results from other centers. The therapeutic system of liver transplantation in Denmark was thus found to work efficiently.

Key words：Liver transplantation, Transplantation activity, Organ procurement

Introduction

Liver transplantation has become an established treatment for patients with end-stage liver disease. More than 4,000 liver transplantations a year have been carried out in 120 institutions in Europe.[1] For Nordic countries, including Finland, Sweden, Norway, Iceland, and Denmark, liver transplantation started in Helsinki, Finland, in 1982. In Denmark, liver transplantation has been performed since October 1990, and a total of 427

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transplantations were performed during the period from October 5, 1990 to February 28, 2003. The population of each Nordic country is small. In 2002, the population of Denmark, including Iceland, Greenland, and the Faroe Islands, was 5, 767, 931, and thus the number of people benefiting from the 5 Scandiatransplant countries was 24, 440, 494. The Scandiatransplant association was established according to the bylaws legally adopted, and includes 5 Nordic countries. All candidates for transplant are registered on the Scandiatransplant waiting list. The five liver transplant centers have established rules for the substitution of a liver in patients whose c linical condition is highly urgent. Highly urgent patients have priority in receiving a suitable liver when it becomes available, and the liver is transferred between the centers. If a patient registered as highly urgent does not receive a transplant within 72 hours, the patient is taken off the high urgency waiting list.[2)]

We present the profile of the patients receiving liver transplantation in the overall experience of Rigshospitalet, Denmark.

Materials and methods

We collected and analyzed the data of patients who received liver transplantation between May, 2002 and February, 2003. Thirty–seven liver transplantations, in 33 patients, were performed in Denmark. The donor data were obtained by a chart review.

We analyzed 1) organ procurement, 2) transplantation activity, 3) indications and operations, 4) survival rate, and 5) postoperative complications.

Results

Organ procurement

In 35 cases, there was a cadaveric donor, and in 2 cases a living donor. The most frequent of cause of donor death was spontaneous cerebral hemorrhage (54.3%), while traffic accidents were responsible for 34.3% of the deaths. The majority of donors (51.4%) were 40–59 years of age. One donor was older than 60. Twenty－eight donors (80.0%) were operated on in Denmark and 7 donors (20.0%) in other countries. When looking only at urgent liver transplantation, in 28.6 % cases an organ from an outside country was used. Thirty－six donors were in the Scandiatransplant organization and one child donor was in the Euro－transplant organization. One recipient received a liver transplantation with an ABO－incompatible allograft.

Transplantation activity

A total of 47 cases were listed for liver transplantation from May 2002 to February 2003 (Table 1). Thirty－seven cases (78.8%) received liver allograft. Of these, 31 received their first liver allograft, and 6 received their second liver allograft. Two patients died while on the waiting list. One patient was permanently withdrawn from the waiting list because the condition of the patient improved. Seven patients were still on the waiting list as of February 28, 2003. The median waiting time was 62 days (2－388).

Thirty－seven patients underwent cadaveric liver transplantation (Table 2). Living－donor liver-transplantation was performed in 2 patients. One patient received a reduced－size graft. One patient

Table 1. Liver transplant activity in Denmark (May, 2002－Feb, 2003)

	cases (%)
Total number of registry patients	47
Receiving transplantation	37 (78.7)
Deaths on waiting list	2 (4.3)
Withdrawn because of improved condition	1 (2.1)
On the waiting list	7 (14.9)
Mean waiting time	62 days
Overall transplant rate*1	6.94 pmp*2

*1：Quotation from Scandiatransplant Registry in 2002
*2：pmp；per million population

Table 2. Surgical procedures in patients (May, 2002－Feb, 2003)

Surgical Procedure	cases (%)
Cadaveric	35 (94.6%)
Living－donor	2 (5.4%)
Elective	29 (78.4%)
Urgent	8 (21.6%)
First liver transplantation	31 (83.8%)
Second time liver transplantation	2 (5.4%)
Retransplantation	4 (10.8%)

underwent liver and kidney transplantation concurrently. Twenty-nine patients received elective transplantations. Eight patients underwent emergency liver transplantation. One of these patients received a left lateral segment from a living donor.

The median follow up time was 12.7 months.

First liver transplantations

The mean age of the 31 patients receiving their first liver allograft was 40.6 years (range : 0-64). Four children (range:10 months-2 years old) were included. One patient was older than 60 years. The male-to-female ratios in the adults and the children were 17:10 and 3:1, respectively. The indications for liver transplantation in 31 patients receiving the first graft transplantations are listed in Table 3. The three most frequent diagnoses indicating the need for liver transplantation were alcoholic liver cirrhosis (25.8%), acute hepatic failure (12.9%) and cryptogenic liver cirrhosis (9.7%).

Second-time transplantations

Table 4 shows the patient profiles for second-time transplantation. The causes of operation were hepatic artery thrombosis in 3 cases, primary non-function in 1, multiple biliary stones in 1, and secondary portal hypertension in 1. Four patients, with hepatic artery thrombosis and primary non-function, underwent retransplantation. Two patients underwent a second-time transplantation due to disease recurrence.

Survival rate and complication

The perioperative mortality rate (30 days) was 5.4% (2 patients). The causes of death were cerebral edema and cardiac arrest. The cause of the cardiac arrest was unknown. Seventeen patients (45.9%) had postoperative complications following liver transplantation. The complications related to surgical procedure were hepatic artery thrombosis in 4 cases and biliary complications in 4 (Table 5). Three of 4 patients with hepatic artery thrombosis underwent retransplantation. One patient underwent a removal of thrombosis with a Fogaty-catheter and a re-anastomosis of the artery. All 4 patients are still alive. Biliary complications included leakage in 3 cases and bleeding of the biliary duct in 1. Two patients died due to multiple-organ failure more than 30 days after transplantation. General postoperative complications included pneumonia in 7 cases and acute renal failure in 6. In addition, seven cases (18.9%) had acute rejection.

Table 3. The indications for first-liver transplantation in 31 patients

Diagnosis	Number of cases
Alcoholic liver cirrhosis	8 (25.8%)
Acute hepatic failure	4 (12.9%)
Cryptogenic liver cirrhosis	3 (9.7%)
Primary biliary cirrhosis	2 (6.5%)
Primary sclerosing cholangitis	2
Posthepatitis C cirrhosis	2
Biliary atresia	2
Polycystic liver disease	1
Cystic fibrosis	1
Alpha 1-antitrypsin deficiency	1
Hemochromatosis	1
Primary hypoxidase type I	1
Caroli's deasease	1
Carcinoid tumor	1
Hemangio-endothelioma	1

Table 5. Postoperative complications

Complications	Number of cases
Acute rejection	7 (18.9%)
Pneumonia	7 (18.9%)
Acute renal failure	6 (16.2%)
Hepatic artery thrombosis	4 (10.8%)
Biliary complications	4 (10.8%)

Table 4. The patient profiles of retransplantations

age (at the second time)	gender	primary diagnosis	first transplantation	cause of retransplantation
30	M	cholestatic hepatitis	elective	arterial thrombosis
52	M	acute liver failure	urgent	primary non-function
53	M	Caroli's disease	elective	arterial thrombosis
58	F	acute liver failure	urgent	arterial thrombosis

Discussion

In patients with acute or chronic liver failure a timely referral is necessary if a successful outcome is to be achieved.[3)4)] The ability to intervene before any major deterioration occurs depends on the recognition of early indicators of disease progression. In addition, it is important that a timely graft is available before the condition of the patient deteriorates further to multiple organ failure. The most serious issue facing liver transplantation is the shortage of donor organs needed to meet demand. Living－donor liver transplantation, split–liver transplantation, and domino transplantation have diminished the death of patients who were on the waiting list. In Asian countries, living－donor liver transplantation is frequently used to save the patients because cadaveric grafts are scarce due to social and political reasons.[5)]

In our data, of the 47 patients on the waiting list, thirty–seven (78.7%) received transplants during the specified period and 7 patients were still waiting at the end point of our study. Although 2 patients died while on the waiting list, the median waiting time of electively patients was 62 days, and which is thus considered to be short. Two patients underwent living－donor liver transplantation. The outcome of a liver transplantation with reduced size grafts is generally inferior to the results of a liver transplantation with full－size grafts.[6)] One patient received a reduced－size liver graft. Because Denmark's small population, it is difficult to find size－matching grafts for children who need a transplant within a limited period of time. We have used reduced－size liver grafts in these patients.[7)] We have taken advantage of the organ exchange in Scandiatransplant in order to get the liver in time. Seven grafts (20%) came from outside countries.

Bjoro et al. summarized the results and developments in liver transplantation in Nordic countries from 1982 to 98 in their report.[8)] The median waiting time of electively patients was 42 days, and thus shorter than at UK transplant and UNOS.[9)] The survival rate following liver transplantation is still increasing, and for the last 3－year period, the 1－year patient survival rate is above 85% . According to the Scandiatransplant Registry, the overall transplant rate is 6.76 per million population in 2002. Neubergen commented that the therapeutic system of liver transplantation worked efficiency in Nordic countries although the greater concern was the possibility that patients who would be suitable candidates are either not being referred as transplant candidates or are not accepted for transplantation.[10)] In addition, he also commented that poor donation rates may also explain the lower liver transplant rate in the patients of Nordic countries'.

Many Japanese children have gone abroad and received new livers in America, Australia and other countries. The causes of the scarcity of cadaveric grafts are due to religious beliefs, social customs and law. In Japan, under the law, cadaveric grafts are regulated to be taken only from brain death patients over 16 years of age. A change in the liver transplantation system may be needed in order to resolve the donor shortage.

One characteristic of liver transplantation in Denmark is that the most common cause of chronic liver failure is alcoholic liver cirrhosis, and acute liver failure is also a frequent indication. The major argument against the widespread use of liver transplantation for patients with alcoholic liver cirrhosis has been the fear of a high rate of recidivism. According to the 1993 Paris consensus conference on the indications for liver transplantation, liver transplantation in those patients was indicated only in the case of those "patients whose liver disease remains serious despite alcohol withdrawal, without any consensus on the ideal period of abstinence：3 to 6 months or more".[11)] Pageaux et al. reported that most recent studies had clearly shown that the mortality rate after liver transplantation of those patients did not differ from that of non－alcoholic recipients. In addition, only 10.6% of the patients returned to excessive alcohol use. Alcoholic cirrhosis, under the above consensus, is a good indication for liver transplantation.[12)] The patients with alcohol cirrhosis are expected to increase the number of candidates for liver transplantation, because alcohol cirrhosis is the leading cause of end－stage liver disease in Europe and USA.

Among all European countries, Denmark had the

second highest rate of acute liver failure (14.9%) next to Finland (26.0%).[1] Acetaminophen is the most common cause of acute liver failure in Denmark.[13] The survival rate of those patients was lower than that related to other causes. The predictors of poor outcome after fulminant hepatic failure include abnormal CT scan, mechanical ventilation, and a requirement for hemofiltration.[14] In our cases of death due to acute liver failure, mechanical ventilation and hemofiltration were carried out before operation, and the patients died due to cerebral edema.

Viral liver disease is one of the indications for liver transplantation. Patients with viral liver disease present with acute hepatic failure, subacute hepatic failure and end-stage cirrhosis. The advent of new antiviral agents, hepatitis B immune globulin and lamivudine, and strict adherence transplant indications significantly reduce the risk for hepatitis B virus recurrence and increases the survival rate.[15] On the other hand, recurrent hepatitis C virus infection after transplantation is nearly universal, and hepatitis C virus allograft cirrhosis is associated with a high rate of decompensation and mortality.[16] Early recurrence, particularly within the first year after transplantation, was associated with significantly poor patient and graft survival rates.[17] The prevention of recurrence after transplantation and strict criteria for transplantation for patients with hepatitis C are therefore required. According to our data, only 2 patients had post-hepatitis C cirrhosis. Although the proportion of patients with viral hepatitis infection in Europe is low, some immigrants from countries with a high prevalence of viral infection may be brought in for clinical treatment.[8]

A limited number of patients with hepatocellular carcinoma are currently offered liver transplantations because of the strict criteria introduced in the past to avoid recurrence.[18] Although there was no patient with hepatocellular carcinoma in the period for which data were collected, 7 patients received liver transplantations from 1990 to 2002 in Denmark (data not shown).

The most prominent surgical complications are hepatic artery thrombosis, stenosis of or leakage from biliary anastomosis, portal vein thrombosis, and intraabdominal bleeding. Hepatic artery thrombosis is the most common vascular complication after liver transplantation, and its rate was from 5 to 20%.[19] Hepatic artery thrombosis has traditionally been managed through retransplantation. Some reports have shown that urgent revascularization is an effective means to salvage grafts. One of a total of 4 patients with hepatic artery thrombosis was treated without retransplantation, and the graft was salvaged. In our series, 10.8% of 37 liver transplants required retransplantation. Hepatic artery thrombosis accounted for 75% of retransplantations. In addition, acute liver failure in the primary diagnosis accounted for 50%. Higher preoperative serum creatinine and serum bilirubin levels were associated with a higher postoperative mortality.[20] Because the incidence of hepatic artery thrombosis and other complications leading to graft failure was relatively high in patients in a poor preoperative condition such as acute liver failure, the grafts of those patients needed to be checked carefully for early diagnosis. Biliary tract complications have always been common after liver transplantation and the overall incidence ranges from 9% to 15%.[21] Rasmussen et al reported that the lowest complication rate was found in patients where the biliary system was reconstructed with a choledoch-ocholedochostomy without a stent.[22] End-to-end biliary duct anasto-mosis was routine at Rigshospitalet. Biliary complications were observed in 4 cases (10.8%). This complication rate is comparable to the results from other centers.

Conclusion

We herein described the current state of liver transplantation in Denmark. The therapeutic system of liver transplantation in Denmark works efficiency. Although the survival rate data can not be made available too soon after transplantation, the rate of major surgical complications was comparable to the results from other centers. In addition, liver transplantation is now accepted at Rigshospitalet as a routine procedure.

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References

1) European Liver Transplant Registry. Report 1997. Updated on September 2002. Paris : The Registry ; 2002.
2) Grunnet, N., Asmundsson, P., Bentdal, O., Madsen, M., Persson, N. H., Salmela, K., Tufveson, G.: Organ donation, allocation, and transplanta-tion in the Nordic countries : Scandiatransplant, 1999. Transpl. Proc., 33 : 2505－2510, 2001.
3) Bramhall, S. R., Minford, E., Gunson, B., Buckels, J. A. C. : Liver transplantation in the UK. World J. Gastroenterol., 7 : 602－611, 2001.
4) Rosen, H. R., Shackleton, C. R., Martin, P. : Indications for and timing of liver transplantation. Med. Clin. North. Am., 80 : 1069－1102, 1996.
5) Lo, C. M. : Complications and long－term outcome of living liver donors : a survey of 1,508 cases in five Asian centers. Transplantation, 75 : S12－S15, 2003.
6) Langnas, A. N., Marujo, W. C., Inagaki, M., Stratta, R. J., Wood, R. P., Shaw, B. W. Jr.: The results of reduced－size liver transplantation, including split livers, in patients with end－stage liver disease. Transplantation, 53 : 387－91, 1992.
7) Kirkegaard, P., Hjortrup, A., Larsen, P. N., Rasmussen, A. : The use of reduced－size liver grafts in elective nonurgent recipients. Transpl. Proc., 26: 1784－1785, 1994.
8) Bjoro, K., Friman, S., Hockerstedt, K., Kirkegaard, P., Keiding, S., Schrumpf, E., Olausson, M., Oksanen, A., Isoniemi, H., Hjortrup, A., Bergan, A., Ericzon, B. G. : Liver transplantation in the Nordic countries, 1982－1998 : changes of indications and improving results. Scand. J. Gastroenterol., 34 : 714－722, 1999.
9) Harper, A. M., Edwards, E. B., Ellison, M. D. : The OPTN waiting list, 1988－2000. Clin. Transpl., : 73－85, 2001.
10) Neubergen, J. : Liver transplantation: Lessons from the Nordic experience. Scand. J. Gastroenterol., 34 : 642－643, 1999.
11) Consensus statement on indication for liver transplantation. Hepatology, 20 : Suppl 1 : 63－68, 1994.
12) Pageaux, G－P, Michel, J., Coste, V., Perney, P., Possoz, P., Perrigault, P－F, Navarro, F., Fabre, J－M., Domergue, J., Blanc, P., Larrey, D. : Alcoholic cirrhosis is a good indication for liver transplantation, even for cases of recidivism. Gut, 45 : 421－426, 1995.
13) Larsen, F. S., Ranek, L., Hjortrup, A., Kirkegaard, P., Clemmesen, J. O., Hansen, B. A. : Fulminant liver failure before and after introduction of liver transplantation at Rigshospitalet. Ugeskr. Laeger, 157 : 885－888, 1995.
14) Lu, A., Monge, H., Drazan, K., Millan, M., Esquvel, C. O. : Liver transplantation for fulminant hepatitis at Stanford University. J. Gastroen-terol., 13 : 82－87, 2002.
15) Villamil, F. G. : Hepatitis B : progress in the last 15 years. Liver Transpl., 8 : S59－66, 2002.
16) Rosen, H. R. : Hepatitis B and C in the liver transplant recipient : current understanding and treatment. Liver transpl., 7 : S87－98, 2001.
17) Ghobrial, R. M., Steadman, R., Gornbein, J., Lassman, C., Holt, C. D., Chen, P., Farmer, D. G., Yersiz, H., Danino, N., Collisson, E., Baquarizo, A., Han, S. S., Saab, S., Goldstein, L. I., Donovan, J. A., Esrason, K., Busutti, R. W. : A 10－year experience of liver transplantation for hepatitis C: Ananlysis of factors determining outcome in over 500 patients. Ann Surg, 234 : 384－394, 2001.
18) Mazzaferro, V., Regalia, E., Doci, R., Andreola, S., Pulvirenti, A., Bozzetti, F., Montalto, F., Ammatuna, M., Morabito, A., Gennari, L. : Liver transplantaion for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N. Engl. J. Med., 334 : 639－699, 1996.
19) Cavallari, A., Vivarelli, M., Bellusci, R., Jovine, E., Mazziotti, A., Rossi, C. : Treatment of vascular complications following liver transplantation : multidisciplinary approach. Hepatogastroenterology, 48 (37) : 179－183, 2001.
20) Deshpande, R. R., Rela, M., Girlanda, R., Boweles, M. J., Muiesan, P., Dhawan, A., Mieli－Vergani, G., Heaton, N. D. : Long－term outcome of liver retransplantation in children. Transplantation, 74 : 1124－1130, 2002.
21) Moser, M. A., Wall, W. J. : Management of biliary problems after liver transplantation. Liver Transpl., 7 : S46－52, 2001.
22) Rasmussen, A., Braidley, P., Jamieson, N. V., Friend, P. J., Calne, R. Y. : Biliary complications in orthotopic liver transplantation. Transpl. Proc., 26: 1792, 1994.

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