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#### Review

# LIVER TRANSPLANTATION: SURGICAL ASPECTS

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Liver transplantation (LT) is now a well-accepted treatment method for end-stage liver disease and acute liver failure. It is also one of the most expensive treatments. With the advances in technical skills, management of postoperative complications and improvements in immunosuppressive drugs, liver transplantation is the standard treatment for many patients with chronic liver disease. For patients who successfully undergo LT, the probability of long-term graft and recipient survival is generally excellent, with a high likelihood of return to a relatively normal lifestyle. Indications for LT have increased over the last few years and according to the European Liver Transplant Registry, 93 634 LT were performed in Europe till 2010. Until recently Latvia was the last country in Europe, where LT was not performed. This article will review current indications, contraindications, procedure of operation and postoperative care in LT as well as give a brief insight into the first liver transplantation done in Latvia.

Key words: liver transplantation, piggy-back, primary sclerosing cholangitis, v. porta stenosis.

#### INTRODUCTION

Liver transplantation is the operation of a diseased liver with replacement of a healthy liver allograft. The most effective and commonly used technique is orthotopic liver transplantation, in which the native diseased liver is removed and replaced by the donor organ in the same anatomic location as the original liver.

The first orthotopic liver transplantation was performed in Denver (USA) by Thomas Starzl (Groth et al., 2000). The first long-term survival after liver transplantation (Biggins et al., 2006) was in 1967, but by the end of the 1970s progress was very slow and overall one-year patient survival was only 35% (Starzl et al., 1974). New advances were made in 1980s, with introduction of cyclosporine (Borel et al., 1976), progress in donor surgery (Starzl et al., 1984), organ preservation and surgery technique (Starzl et al., 1985). All these factors gave greatly improved results. For clinical transplantation, the historical beginning was Medawar's recognition that rejection is an immune reaction (Starzl, 2000). In 1983, the National Institutes of Health Consensus Development Conference made a decision that liver transplantation was no longer an experimental procedure and deserved broader application in clinical practice. This conference was the beginning of the modern era of liver transplantation and started the propagation of it around the world.

Raia of Brazil performed the first living donor liver transplantation in 1987, which was a promising method in case of organ shortage, but the result of the operation was not successful (Raia *et al.*, 1989). After this first case of living donor liver transplantation, this type of operation was started in many other countries and now has become a widely accepted method worldwide, especially in Asian countries. The one and five-year survival rates of all recipients have been reported to be 81.2% and 77%, respectively, while those for recipients less than 18 years old have reached 85.6%, and 82.6%, respectively (Abbasoglu, 2008).

# INDICATIONS FOR LIVER TRANSPLANTATION

The National Institutes of Health Consensus Conference of 1983 established orthotopic liver transplantation as the therapeutic modality of choice for certain end-stage liver diseases and the indications continue to increase. Indications for LT for adults are slightly different than those for children. The main indications for adults are:

- Chronic active hepatitis (C, B, A)
- · Primary biliary cirrhosis
- Primary sclerosing cholangitis (PSC)
- · Fulminant hepatitis
- Liver cancer (hepatocellular carcinoma, HCC)
- · Metabolic disorders
- · Autoimmune hepatitis

- Budd-Chiari syndrome
- Trauma

The main indications for children are:

- Biliary atresia or hypoplasia
- Metabolic disorders (α-1 antitrypsin deficiency, tyrosinemia, glycogen storage disease type IV, familial hypercholesterolemia, etc.)
- Neonatal hepatitis
- · Fulminant hepatitis
- Chronic active hepatitis
- Neoplasms
- Familial intrahepatic cholestasis

Indications for children differ from those of adults, because congenital and metabolic liver disorders form the main amount of indications for children.

During the last 20 years, indications for adult liver transplantation have changed. In USA cirrhosis is the main indication of LT for adults (more than 80%). The most important indications are hepatitis C (21%), alcoholic liver disease (16%), cholestatic liver disease including primary biliary cirrhosis and sclerosing cholangitis (17%). In contrast, in Korea the main indications are hepatitis B (81%) including HCC (21.5%) and fulminant hepatic failure (7%), alcoholic liver disease (4%) and hepatitis C (3%).

The main contraindications for LT are divided in two groups — absolute and relative, as follows (Starzl, 1991):

Absolute:

- · Sepsis outside the hepatobiliary system
- Metastatic disease from non-hepatic cancer
- Metastatic hepatobiliary malignancy
- · Active alcoholic disease or drug abuse
- Uncontrolled psychiatric disorder
- · Advanced cardiopulmonary disease
- Symptomatic AIDS
- Inability of the patient and/or family to understand the implications of and the commitment to LT and lifelong immunosuppression need

# Relative:

- Non-metastatic hepatobiliary malignancy
- · Extensive portal vein thrombosis
- Extensive previous abdominal surgery

- · Severe alcoholic disease
- Asymptomatic HIV-1 positive patients
- Severe renal failure
- Age over 65 (physiologic age more important then chronologic age)

# TIMING OF TRANSPLANTATION

The main aim of LT timing is to detect the period when the patient will obtain maximum benefit from receiving a new liver. If the transplantation is performed too late, the risks of the procedure can overshadow its benefits (Abbasoglu, 2008). Since the application of the Model for End-Stage Liver Disease (MELD) score (Table 1) for organ allocation in 2002 by the UNITED Network for Organ Sharing (UNOS), a cirrhotic patient has to meet minimal listing criteria for placement on the deceased donor waiting list (Child- Turcotte-Pugh score of at least 7 for most causes of cirrhosis). Once approved for listing, the patient is prioritized according to the MELD score (Koffron and Stein, 2008). The score is based on objective laboratory values (serum creatinine, bilirubin and prothrombin time (INR)), and predicts the three-month mortality of patients awaiting liver transplantation.

Table 1

THE MODEL FOR END-STAGE LIVER DISEASE SCORE

MELD score	Three-month mortality (hospitalised patients)
9	4%
10-19	27%
20–29	76%
30–39	83%
40	100%

MELD score =  $9.57 \times \log$  (Creatinine mg/dl) +  $3.78 \times \log$  (bilirubin mg/dl) +  $11.20 \times \log$  (INR) + 6.43 (Kamath and Kim, 2003).

If the MELD score is 10 or the patient has any complication of portal hypertension, it is an appropriate indication for transplant evaluation (Lopez and Martin, 2006). There are many studies and publications about MELD scoring values, in which LT is quantitatively indicated and could give the best results, but however, there is no quantitative MELD cutoff for transplant futility. The optimal time for LT is in the case when a patient has symptoms of decompensating liver or has a MELD score of 15 or greater. Patients with HCC must be referred for transplant evaluation as soon as the tumour is discovered, since LT should be performed as soon as possible in all possible HCC candidates (Thomas and Starzl, 1991). According to MELD scoring values, patients are listed in the LT waiting list and with changes of values, patients can change their place in waiting lists.

#### RECIPIENT OPERATIONS

Deceased donor whole liver transplantation consists of total (Koffron and Stein, 2008) hepatectomy of native liver, followed by implantation of the donor liver. Operation begins with bilateral subcostal incision with a midline extension to the xiphoid, extending more on the right than on the left. Then liver mobilisation from ligaments is performed, followed by skeletonisation of the hilar structures (bile duct, hepatic artery and portal vein) and vena cava inferior. The donor liver is removed with retrohepatic inferior vena cava (IVC) and prepared for implantation on the back table. Then the prepared donor liver is brought to the operation field and anastomoses are constructed between the donor liver and recipient in the following order: suprahepatic IVC, portal vein anastomosis. When these anastomoses are performed clamps are removed in sequence and the liver is perfused in portovenous inflow. Afterwards hepatic artery anastomose end-to-end is made and also end-to-end choledocho-choledochostomy is performed. In the case when the recipient bile duct technically can not be used or when the patient has PSC, a Roux-en-Y choledochojejunostomy is performed.

In cases of living donor liver transplantation to a recipient, operation is more complicated, because in the living donor a partial liver graft having much smaller-sized hepatic artery, vein and portal vein needs to be implanted. For a technically successful operation, it is important to make a large and long opening along the sides of the hepatic veins and it is important to maintain satisfactory portal, biliary and hepatic arterial sources for the reconstruction (Sugawara and Makuuchi, 2005). Anastomosis is performed in the following order: hepatic vein, PV and hepatic artery. The provision of adequate outflow is indispensable for graft function. Thus, it is necessary to obtain a wide orifice and an sufficient length of the hepatic vein for anastomosis (Lee, 2006). Bile duct reconstruction is performed last and can be done as hepaticojejunostomy or duct-to-duct anastomosis. Ductto-duct anastomosis is the better choice, as it can preserve physiologic bileo-enteric and bowel continuity and also allows for endoscopic access to the biliary tree for diagnostic and therapeutic instrumentation.

# LIVER DONORS

The principal condition for a liver donor is ABO blood type compatibility. Absolute contraindications are infectious disease and active malignancy that can cause transmission and death of the recipient. Many factors can influence the function of the donor organ, the main ones being old donor age, prolonged ischemia, hypotension and excessive inotropic support, non-heart-beating donors and steatosis (Busuttil and Tanaka, 2003). The characteristics of an ideal donor are: 50 years old or younger, no hepatobiliary disease, haemodynamic and respiratory stability, an acceptable PaO2 and haemoglobin level, no severe abdominal trauma, systemic infection or cancer, diuresis greater than 50 mL/h, normal creatinine level, and dopamine requirement less than

10  $\mu$ g/kg/min (Loinaz and Gonzalez, 2000). As in all countries there is shortage of deceased donor grafts and the number of liver recipients is increasing, it is very difficult to limit organ selection and use only ideal donor organs. The usage of liver donors with extended criteria is absolutely necessary in the current situation. Extended criteria donors (ECD) includes older donor, donation after cardiac death, grafts from individuals infected with chronic hepatitis C virus (HCV), hepatitis B, steatosis and prolonged cold ischemia time (Silberhumer *et al.*, 2007). The main goal of using ECD is to increase the number of available donors and reduce the number of deaths on the waiting list (Barshes *et al.*, 2007).

# IMMUNOSUPPRESSION AFTER LIVER TRANSPLAN-TATION

All patients after LT must receive immunosuppression to prevent liver rejection. The majority of liver transplant recipients are treated with combination of two or three immunosuppressive drugs for prevention of liver rejection. The calcineurin inhibitors Tacrolimus and Cyclosporine are the main drugs and over 95% of patients are discharged from hospital with a calcineurin inhibitor as a primary immunosuppressant (www.unos.org). Steroids are also used after liver transplantation, but the therapy is subsequently tapered and weaned in the following months. Mycophenolate mofetil (MMF), such as Azathioprine, is also used in immunosuppression to reduce the dose of calcineurin inhibitor, which can cause renal dysfunction, hypertension and hyperlipidemia in high doses. Use of modern immunosuppression therapy in recent years has led to a low rate of acute rejection - data from USA from 2003 show acute rejection in 18% of patients (www.unos.org) and chronic rejection in less than 5% of patients (Jain et al., 2001).

# LIVER TRANSPLANTATION AND HEPATOCEL-LULAR CARCINOMA

Hepatocellular carcinoma is the third most common cause of cancer-related death worldwide (Botha and Langnas, 2006). Orthotopic liver transplantation (OLT) is one of the best surgical treatment methods for early, unresectable HCC. During the last 15 years, the results of OLT have increased, because of careful patient selection according to the Conventional Milan Criteria (CMC). In 1996, the Mezzaferro group showed that a subgroup of patients with a radiologically detected single tumour 5 cm diameter or two to three tumours 3 cm in diameter had five-year and recurrence- free survival rates of 75 and 83%, respectively (Mazzaferro et al., 1996). The Milan group showed that, using CMC in treatment of HCC, ten-year overall survival surpassed 70% in 300 liver transplants. These good results were confirmed worldwide (Bruix et al., 2003). The good results of LT for HCC using Milan criteria has raised discussions of expanded criteria, i.e. bigger size of tumours. It has been proposed by a group at the University of California, San Francisco (UCSF) that single tumour size can be

up to 6.5 cm, or three or fewer tumors, the largest of which is 4.5 cm with the sum of the tumour diameters 8 cm (Yao et al., 2001). The UCSF group published results of 138 patients over a five-year period - the one- and five- year recurrence-free probabilities were 95 and 91%, and the respective probabilities for recurrence-free survival were 91 and 80% (Yao, 2006). The Barcelona Clinic Liver Cancer Group proposed to expand Milan criteria to a single tumour of 7 cm or less, or 5 tumours of 3 cm or less, in patients who showed a partial response to any treatment lasting for more than six months (Bruix and Llovet, 2002). Using any criteria for LT in case of HCC, all patient inclusion criteria are based on radiological imaging, which assess intrahepatic disease and exclude extrahepatic spread. The patient selection and also results can be improved by increasing the sensitivity of imaging studies and detection of micrometastasis (Sutcliffe et al., 2006).

During the past ten years, Milan criteria had proved that using these criteria, LT results in cases of treatment HCC, have steadily improved. Expanding of Milan criteria is still under discussion, because that includes the increased risk of vascular invasion and tumour recurrence at higher stages of HCC (Mazzaferro *et al.*, 2008). Recurrence of HCC in transplanted liver is especially common in patients with poorly differentiated liver tumours or macroscopic vascular invasion (Oton *et al.*, 2006). In case of recurrence, different kinds of treatment can be used, such as surgical resection, transarterial chemoembolisation, chemotherapy, radiotherapy and radiofrequency ablation.

# LIVER TRANSPLANTATION AND HEPATITIS C

End-stage liver disease caused by chronic HCV is the leading cause of liver transplantation in developed countries (Adam et al., 2003), including Japan (Sugawara and Makuuchi, 2006). The outcome of these liver transplantations is not very good, due to high rates of reinfection of HCV. Cirrhosis develops in approximately 25% of liver transplant recipients (range 8-44%) after 5 to 10 years and decompensated cirrhosis due to HCV is the most frequent cause of graft failure, patient death and the need for retransplantation. Although short-term graft and patient survival rates of HCV patients are comparable with other patients undergoing LT, HCV recurrence is universal and is associated with poor graft and patient survival (Johnson et al., 1996). A study by Abbasoglu et al. showed that recurrent hepatitis was the most common cause of late graft loss in patients who had undergone liver transplantation for chronic active hepatitis C (Abbasoglu et al., 1997).

Liver biopsy is the gold standard for evaluation of liver after LT and the key diagnostic criterion with which other tests are compared is assessment of fibrosis. The main strategy for improving outcome of LT in HCV patients is the eradication of the HCV virus before LT, using pretransplant antiviral treatment, eradication of HCV virus early after transplantation preemptively to prevent graft damage, and treatment for established recurrent hepatitis C in the acute or more commonly, chronic phase. Antiviral treatment with Pegylated Interferon in conjunction with Ribavirin are currently accepted as standard key drugs according to the perspectives obtained in nontransplant populations (Akamatsu and Sugawara, 2012). Better strategies including pre- and post-transplant antiviral therapy and new generation of antiviral drugs may further improve the results.

#### FIRST LIVER TRANSPLANTATION IN LATVIA

The first LT in Latvia was made in a case of liver cirrhosis caused by PSC, secondary biliary cirrhosis, mechanical jaundice and unspecific ulcerous colitis. The patient was a 46-year-old male. Due to PSC the patient has been treated in the Gastroenterology Centre of Pauls Stradiņš Clinical University Hospital since 2003. Due to mechanical jaundice, stents were placed in the bile ducts. Because of suspicion of malignant bile duct disease in 2003, biopsy of the liver was performed and cirrhosis of the liver was proved. In 2007, unspecific ulcerous colitis was diagnosed, which currently is in remission (Vilmanis *et al.*, 2012).

The donor was 62-year-old male, who had spontaneous hemorrhage in brain with determined cerebral death. Piggyback modification of LT was performed with three vascular anastomosis and CBD anastomosis with jejunum loop. Immunosuppressive therapy with Cell-Cept, Advograf and Prednisolone was started already during operation. In the first five postoperative days the patient felt quite good and on day six the patient had pain in abdomen, flatulence, signs of intoxication and leukocytosis. Ultrasound (US) and computer tomography (CT) angiography of abdomen detected 70% stenosis of v. portae anastomosis. Transcutaneous stenting of v. portae was performed and the patient was discharged from the hospital. On weekly checkups subhepatic bilioma was found and drained transcutaneously. Abdominal MRI was performed and it revealed dilated intrahepatic bile ducts with cholestasis and possible necrosis of CBD. During reoperation destructive CBD was discovered. It was resected with the subsequent anastomosis between liver and jejunum loop on stent. The further postoperative period was without complications (Vilmanis et al., 2012).

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#### AKNU TRANSPLANTĀCIJA: ĶIRURĢISKIE ASPEKTI

Aknu transplantācija (AT) mūsdienās ir kļuvusi par visā pasaulē apstiprinātu ārstēšanas metodi terminālas aknu mazspējas un akūtas aknu mazspējas gadījumā. AT ir arī viena no visdārgākajām ķirurģiskās ārstēšanas metodēm. Pilnveidojot tehniskās iemaņas, mazinot pēcoperācijas komplikācijas un uzlabojot imūnsupresijas terapiju, aknu transplantācija ir kļuvusi par standarta ārstēšanas metodi daudziem pacientiem ar hronisku aknu slimību. Pacientiem, kuri veiksmīgi pārcietuši aknu transplantāciju, ir labas iespējas transplantāta un recipienta dzīvildzei, ar lielām iespējām atgūt normālu dzīvesveidu. AT indikācijas pēdējos gados ir palielinājušās, un, pēc Eiropas Aknu Transplantācijas reģistra (ELTR) datiem, līdz 2010. gadam Eiropā ir veiktas 93 634 aknu transplantācijas. Līdz 2011. gadam Latvija bija vienīgā valsts Eiropā, kur nebija veikta AT. Rakstā apkopotas mūsdienu AT indikācijas, kontrindikācijas, operācijas veidi un pēcoperācijas aprūpe, kā arī tiks dots ieskats par Latvijā veikto pirmo aknu transplantāciju.