1000 LIVER TRANSPLANTATIONS AT THE DEPARTMENT OF GENERAL, TRANSPLANT AND LIVER SURGERY, MEDICAL UNIVERSITY OF WARSAW – ANALYSIS OF INDICATIONS AND RESULTS

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The aim of the study was to analyze indications and results of the first one thousand liver transplantations at Chair and Clinic of General, Transplantation and Liver Surgery, Medical University of Warsaw.

Material and methods. Data from 1000 transplantations (944 patients) performed at Chair and Clinic of General, Transplantation and Liver Surgery between 1994 and 2011 were analyzed retrospectively. These included 943 first transplantations and 55 retransplantations and 2 re-retransplan-
Liver transplantation is the only effective and acceptable treatment method of patients with end-stage liver failure. We have witnessed enormous progress in the patient qualification and perioperative management over the recent decades. This in combination with new regimens of immunosuppressive treatment resulted in marked improvement of short- and long-term results of transplantation (1-5). The history of liver transplantation began in 1950’s and 1960’s from the series of animal experiments conducted at institutions in the United States (6, 7, 8). First successful liver transplantation worldwide was performed in Denver by Thomas Starzl in 1967 (9), and one year later Roy Calne at Cambridge performed the first successful transplantation in Europe (10).

Until 1980’s, one-year patient survival was approximately 30% (11). It largely resulted from lack of successful immunosuppression, which was then based on combination of glucocorticosteroids, azathioprine and antilymphocytic globulin. Breakthrough was the result of introduction of cyclosporine to clinical practice in 1979 (12). Multiple cornerstones in the history of liver transplantation also included launching of tacrolimus (13) and first successful transplantation from a live donor in 1989 (14).

Due to multitude of conditions that potentially result in liver failure, the list of indications to liver transplantation is extensive. Commonly accepted indications worldwide clearly include liver failure caused by hepatitis C virus (HCV) and hepatitis B virus (HBV) infection, alcoholic liver disease, autoimmune liver diseases, secondary biliary liver cirrhosis, Budd-Chiari syndrome, liver cysts, biliary duct cysts, Amanita phalloides poisoning, paracetamol overdose, congenital metabolic defects and others (1, 15, 16). The second group of indications includes liver tumors: hepatocellular carcinoma, metastases of neuroendocrine tumors, hemangioendothelioma epitheliodes and hepatoblastoma (17, 18). Isolated cases of liver transplantation were reported in patients with benign, unresectable liver neoplasms that resulted in failure of this organ due to the extent of involvement of healthy liver parenchyma, caused Kasabach-Merritt syndrome (hemangiomas) or posed a risk of malignant transformation (adenoma) (19, 20). Also unresectable cases of alveococcosis are accepted indications to transplantation, with their clinical course resembling a malignancy (21).

Liver retransplantations are usually classified according to timing of their performance in relation to the first transplantation as early or late; an arbitrary time period to divide the two is 6 months. Early retransplantations are usually performed due to hepatic artery thrombosis, primary graft non-function and chronic or acute rejection process, while indications to late transplantations include predominantly recurrence of the underlying disease and chronic organ rejection (22).

The aim of this study was to analyze indications to first transplantations and retransplantations as well as analysis of results of transplantations with regard to postoperative mortality and 5-year patient and graft survival rate in the material composed of first
1000 liver transplantations performed at the Department of General, Transplant and Liver Surgery, Medical University of Warsaw.

MATERIAL AND METHODS

The liver transplantation program at the Department of General, Transplant and Liver Surgery was started with first successful transplantation in 1994. One thousandth transplantation took place on 27 October 2011. A total of 1076 transplantations were performed until 30 March 2012. Figure 1 demonstrates a clear increasing trend in the number of liver transplantations over the years, from 16 in 1999 to 141 in 2011. Data related to the first one thousand of liver transplantations in 944 patients were analyzed retrospectively. These included 943 first transplantations, 55 retransplantations and 2 re-retransplantations. Median patient age was 46 years (range 17-74) male to female ratio was 6:5.

Right liver segments recovered from living donors were transplanted to 4 recipients. Two liver fragments were collected from mothers, one from a father and on from a sister of a recipient. The other patients received organs recovered from deceased donors (fig. 2). Before the transplantations the organs were prepared during back-table procedures (Images 1 and 2).

The transplantations were performed using one of 2 surgical techniques: piggyback (70.7%) or conventional (29.3%). Piggyback technique that was made popular in 1989 by Tzakis et al. (23), was based on hepatectomy with preservation of retrohepatic part of the inferior vena cava of the recipient. Images 3 and 4 present examples of explanted organs. Despite the fact that literature reports other possible types of anastomoses of the inferior venae cavae during piggyback transplantation (24, 25), they were routinely performed using “side-to-side” technique (fig. 3). Conventional trans-
plantation involved excision of extrahepatic part of the inferior vena cava of the recipient and subsequent performance of two anastomoses during the procedure of implantation: in the supra- and intrahepatic segment (fig. 4). It must be emphasized that occlusion of the inferior vena cava in this method, results in greater hemodynamic abnormalities than in the piggyback technique, in which blood flow is maintained. This fact is related to requirement of temporary use of veno-venous extracorporeal circulation (fig. 5) in vast majority of classical transplantations. After completion of anastomoses of the inferior vena cava, subsequent anastomoses of the portal vein, hepatic artery and biliary ducts were done. Images 5 and 6 illustrate images of a graft before its implantation and after reperfusion, respectively.

Immunosuppressive therapy was based on glicocorticosteroids, one of calcineurin inhibitors (tacrolimus or cyclosporine) and mofetil mycophenolate. Chimeric antibody anti-CD25 (basiliximab) was used for induction. Immunosuppressive regimen in patients with hepatocellular carcinoma also included an additional mTOR inhibitor (rapamycin).

Perioperative mortality was defined as death within 30 days after the transplantation. Long-term patient and graft survival were defined as time to death and time to retransplantation or death, respectively. Observations
were censored at year 5 after the transplantation in both these cases. Kaplan-Meier survival analysis was used to estimate patient and graft survival. Reverse version of this method was used to calculate the median follow-up. The survival analysis was done using STATISTICA v. 9 software (StatSOFT).

RESULTS

The most common indications for the liver transplantation included liver failure caused by HCV (27.8) and HBV (18%) infection and alcoholic liver disease (17.7%). Other indications, listed in the order of frequency, included: hepatic neoplasms, primary sclerosing cholangitis, primary biliary cirrhosis, autoimmune hepatitis, Wilson’s disease, Budd-Chiari’s syndrome, secondary biliary cirrhosis, polycystic liver disease, alveococosis and acute liver failure caused by Amanita phalloides poisoning (fig. 6). Etiology of liver failure was unknown in 57 (6%) of patients. Rare indications included: hemochromatosis (n = 7), intrahepatic bile duct cysts (Carolí’s syndrome) or intra- and extra hepatic bile duct cysts (n = 7), and liver failure caused by paracetamol intoxication (n = 6), cystic fibrosis (n = 2), alpha-1-antitrypsin deficiency (n = 1), Dubin-Johnson syndrome (n=1), idiopathic liver rupture (n = 1), HELLP syndrome (n = 1), Alagille’s syndrome (n = 1), amyloidosis (n = 1), liver trauma (n = 1), and liver failure after resection of colorectal cancer metastases (n = 1).

Classic hepatocellular carcinoma was the most common indication for transplantation...
among liver neoplasms (93/125, 74.4%). Final histopathological examination of an explanted liver due to suspected hepatocellular carcinoma, did not support the preliminary diagnosis and demonstrated presence of other malignancies. These included lymphoma, papillary adenocarcinoma and primary cholangiocellular cancer. Atypical types of hepatocellular carcinoma were found in 4 patients: a mixed tumor containing components of hepatocellular and cholangiocellular carcinoma (combined HCC/CCC) in 3 patients and carcinosarcoma in 1 patient. Furthermore, transplantations were performed in 3 patients with fibrolamellar type of hepatocellular carcinoma in a healthy liver. Incidental nodules of hepatocellular morphology were found in 13 explanted livers. The other cases included transplantations due to metastases of neuroendocrine cancer (n = 8), hemangioendothelioma epithelioides (n=6), hepatoblastoma (n = 2),metastases of renal cancer (n=2), cystadenocarcinoma (n=2), giant hemangioma (n = 1) and adenoma (n = 1). Biliary duct cancer was accidentally detected in 5 patients with primary sclerosing cholangitis and 1 in Caroli’s syndrome.

Thirty five retransplantations were performed within up to 6 months after the first transplantation (early retransplantations, 63.6%) and 20 retransplantations in the later phase (late retransplantations, 36.4%). Median time from the first transplantation to retransplantation in an early phase was 8 days (range 1 – 101 days) and for retransplantation in a late phase was 2.6 years (range: 8 months – 12 years). Indications for early retransplantations included: hepatic artery occlusion caused by thrombosis (n = 19) or kinking of arterial anastomosis (n = 1), primary non-function (n = 5), graft failure due to cholestasis (n = 3), venous outflow obstruction (n = 3), acute rejection (n = 2), portal vein thrombosis (n =1) and graft rupture after reperfusion (n = 1). Graft failure caused by recurrence of the underlying disease was the cause of 9 of 20 (45%) late retransplantations. Primary sclerosing cholangitis recurred in 4 patients, recurrent hepatitis C in 3 patients and recurrent primary biliary hepatic cirrhosis in 2 patients in this group. Other late retransplantations were performed due to graft failure caused by impaired bile outflow (n = 4), de novo hepatitis C infection (n = 3), chronic rejection (n = 2) and late hepatic artery thrombosis (n = 1). A dominant cause of graft injury was not established in 1 case.

Postoperative mortality rate after the first transplantation was 8.9%, including 0.9% intraoperative deaths. Postoperative mortality rate was significantly reduced over the years and fell from 31.3% in 1994 – 1997 to 6.6% in 2010 – 2011. Similar decreasing trend was found for the intraoperative mortality rate (fig. 7).

Median follow-up was 4.5 years. Patient survival 1, 3 and 5 years after the first transplantation was 85.5, 78.2, and 74.3%, respectively (fig. 8). Lower survival rates were found...
for patients after retransplantation (1 year: 57.6%; 3- and 5-year: 54.7%; fig. 9). One, 3- and 5-year graft survival rate after the first transplantation was 82.5, 75.1, and 71% (fig. 8), while after retransplantation it was 55.8, 52.9, and 52.9% (fig. 9).

**DISCUSSION**

The presented results illustrate evolution of the liver transplantation program at the Department of General, Transplant and Liver Surgery over 18 years of its existence. Previous results of this program were reported in 2000 (26). Number of transplantations performed each year increased from under 20 in the 1990’s, to 50 in 2001 and 141 in 2011, resulting in a total of more than 1000 surgical procedures. We must emphasize that such high volume of transplantation procedures is characteristic for the largest liver transplantations centers worldwide (27-30).

Cirrhosis related to viral hepatitis, in particular by hepatitis C virus infection, remains the most common indication for first liver transplantation. These observations are consistent with data published by European Liver Transplant Registry, ELTR, www.eltr.org based on data from more than 100,000 surgical procedures at the European centers. The rate of patients undergoing liver transplantation due to alcoholic hepatic cirrhosis (17.7% versus 21.5% according to ELTR) is also similar. In summary, general structure of indications in the studied material is not significantly different from that reported in official reports of this registry.

Incidental liver malignancies were found in 19 patients (2%). Incidental diagnosis of hepatocellular carcinoma in an explanted liver has no significant effect on long term results of transplantation because these malignancies are usually characterized by low stage and low recurrence rate (31, 32). However, the presence of incidental cholangiocarcinoma poses a significant problem, since they are associated with high malignancy recurrence rate after the transplantation (33). Despite the fact that other centers perform liver transplantations in highly selected patients with low stage cholangiocarcinoma, after intensive chemo- and radiotherapy (34), this is still not a routine management. Detailed results of liver transplantation due to primary sclerosing cholangitis, including cases of accidental cholangiocarcinoma, in our own material were reported in a previous paper (35).

First liver retransplantation was reported by authors from Department of General, Transplant and Liver Surgery in 1998 (36). In contrast to results reported by other authors (22, 29, 37), both acute and chronic rejection of this organ was not a common indication to retransplantation. Early retransplantations were usually performed due to complications of the first transplantation, i.e. hepatic artery thrombosis and primary graft non-function. We must emphasize that recently methods of interventional radiology have played an important role in the treatment of patients with the hepatic artery thrombosis (38). Late re-

![Fig. 8. Patient and the transplanted organ (graft) survival rate up to 5 years after the first transplantation](image1)

![Fig. 9. Patient and the transplanted organ (graft) survival rate up to 5 years after the retransplantation](image2)
transplantations were most commonly caused by a recurrence of the disease that was the indication for the first transplantation.

Perioperative mortality rate was significantly reduced versus the initial years of the program. Increased experience of the surgical team (39) and progress in perioperative management probably significantly contributed to this observation. Recently the perioperative mortality rate was 6.6%, which was consistent with the literature data (40).

Five-year patient and graft survival according to the European Liver Transplant Registry is 59-72% and 9-55%, respectively. Similar results are reported by the authors from the USA. In a paper published in 2005, Busuttil et al. (a center in Los Angeles, USA), based on data from 3200 surgical procedures, 5-year patient and grafts survival was 72 and 64%, respectively (41). Levi et al. (a center in Miami, USA) analyzed data from 2000 surgical procedures in one of the most 6 recent reports and found that patient and graft survival rates were 69.3-73.8% and 62.3-71.2%, respectively (depending on the year when the transplantation was performed) (42). Therefore, our results: 74.3% (5-year patient survival rate) and 71% (5-year graft survival rate) are not different and even higher that the data reported in the literature. Analysis of factors affecting patient survival after the transplantation at our Department was presented in one of the recent reports (43). Retransplantations were associated with markedly poorer results as compared to first transplantations, which was supported by observations by other authors (44).

In conclusion, development of liver transplantation program at the Department of General, Transplant and Liver Surgery of Medical University of Warsaw over the last 18 years resulted in achievement of results at the level of the largest centers worldwide. Liver failure caused by HCV and HBV infections and alcoholic liver disease remain the most common indications for the transplantation. The structure of other indications is consistent with European data.

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