

Examination of factors influencing survival of liver transplantation for hepatocellular carcinoma - Summary of dr. Piros Laszlo's PhD thesis

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death worldwide. In addition to hepatitis C (HCV), HCC is a leading indication for orthotopic liver transplantation (OLT), which is the best therapy of choice for early, unresectable HCC. However OLT for HCC is limited by graft shortage and the need for appropriate patient selection. Until the late 1980s – early 1990s, the results after OLT for HCC were poor with high early tumor recurrence and low 5-year patient survival. These discouraging observations and the shortage of deceased donor liver grafts disposed the transplant community to establish stringent and careful selection criteria. Recognizing that patients with small, incidentally found tumors had survival rates after liver transplantation equivalent to those after transplantation for benign disease, Mazzaferro et al. in Milan established criteria for OLT published in 1996. They showed that patients with radiologic evidence of a single tumor ≤ 5 cm in diameter, or two to three tumors ≤ 3 cm in diameter had 5-year and recurrence-free survival rates of 75 and 83%, respectively. The successful Milan criteria are still accepted worldwide, as the gold standard to select recipients, but the growing problem of donor shortage led to the need for expanding the criteria for OLT to include larger tumors, as shown by the group from the University of California, San Francisco (UCSF).

The Hungarian Liver Transplantation Program launched in 1995 in the Department of Transplantation and Surgery, Semmelweis University, Budapest. From that time more than 60 patients underwent OLT for hepatic tumor, which were HCC in most of the cases. The overall 5-year survival after OLT is more than 80% among our patients. However it is a general observation worldwide, that in the case of HCC the OLT survivals are in some degree lower. Immunosuppression, which is mandatory to avoid acute rejection episodes, also increase the incidence of malignancies – including recurrence of HCC itself. The present study was undertaken to examine outcomes for our series of patients who received OLT for HCC in a single institution in Hungary. One of the goal is to determine whether expansion of Milan criteria, based on our datas from preoperative imaging and explant pathology, could be justified by post-transplant survival of at least 50% at 5 years. The study analyzes the possible influential factors of outcome of OLT for HCC. The secondary aim is to find the possible ways with the help of our findings to improve patient survival by refining recipient selection and tailoring individual immunosuppressive therapy.

Material and methods. Using a partly prospectively and partly retrospectively collected transplant database, we performed a review of all patients who underwent OLT for HCC at our Department from 1996 to October 1, 2013. Disease extent was determined by preoperative computed tomography (CT) or magnetic resonance (MRI) images. Pretransplant adjuvant treatments included chemotherapy, radiofrequency ablation (RFA), transarterial chemoembolization (TACE), and liver resection in selected patients. When imaging studies were unable to differentiate between treatment defects and residual tumors for patients who had received RFA or TACE, dimensions of the radiologic defect were used for analysis. All explants were examined and categorized based on tumor number, size, distribution, HCC histologic grade and vascular invasion. Patients with HCC were classified as having tumors either meeting Milan criteria, beyond Milan criteria but within UCSF criteria, or exceeding UCSF criteria. Patients were

listed for OLT based on UNOS (United Network for Organ Sharing) criteria from 1995 to 2005 and according to the MELD system after 2005. Hungary has been a full member of Eurotransplant since July 1, 2013. Since then ET Liver Allocation System (ELAS) has been operative for livergraft allocation in Hungary. Liver transplantation was performed using standard techniques including orthotopic implantation with removal of the retrohepatic vena cava with cross-clamp technique or with reservation of the vena cava with the piggyback technique. Postoperative immunosuppression included a triple drug regimen of cyclosporine, azathioprine and prednisone from 1995 to 1999. Use of tacrolimus was begun in 1999 and mycophenolate mofetil started in 1997. Sirolimus and another mTOR-inhibitor, the everolimus have been available from 2004 and 2010 respectively.

Results. In our liver transplant population most of the liver tumors (n=49, 80,32%) were HCC. 42,85% of the recipients with HCC were between 55-60 years old and it seems that our recipients getting older by the time goes on. The male to female ratio is 3:2 among our patients. Our HCC-OLT population was homogenous by race, 98% of the patients were Caucasian and there was just one Asian patient (2%). HCC most commonly occurs in the presence of cirrhosis as a result of long standing chronic liver disease. The most of our patients who underwent OLT for HCC are in the 56-60 years old group, and mainly they had underlying HCV cirrhosis too. The average MELD score was 9,51 (6-25). Until October 1, 2013 totally 21 of 49 (42,85%) patients died after OLT for HCC. The main cause was the recurrence of the HCC in 38%, followed by sepsis in 33% and HCV recurrence in 19%. Sporadically primary non function of the graft (PNF), acute myocardial infarct and de novo malignancy occurred each in 1 case (4,7%) respectively. Overall survival for the entire group at 1, 3, and 5 years after transplantation was 73,48%, 65,2%, and 50.08% respectively. Using pretransplant imaging, 33 tumors (67%) were within Milan criteria, 8 (16%) were beyond Milan but within UCSF criteria, and 7 (14%) exceeded UCSF criteria. Preoperative treatments (TACE, RFA, chemotherapy, resection) were used in 28 patients (57%). New onset, non-HCC malignant tumour developed in 2 cases (4%). Two main techniques were performed during OLT for HCC in our Department: standard cross-clamp in 41 patients (84%) and piggyback method in 8 patient (16%). There was no significant difference between the two techniques. All of the patients got immunosuppression starting with a CNI, MMF and prednisolone combination. 20 of our patients were converted to either Sirolimus or Everolimus (40,8%).

Conclusions. According to our findings Milan criterias are still the safest criteria system, however slightly expanded criterias don't have significantly worse result. Preoperative imaging methods sometimes show less or smaller tumours, and the explant histology reports the exact staging of HCC at the time of OLT. Bridging and down-staging therapies, such as TACE, RFA are adviseable to maintain or decrease the tumor within or below the Milan criterias. Histological examination especially of the lymphovascular invasion is mandatory to assess the estimated prognosis. Extremely high levels of AFP mean higher risk. HCC recurrence is an important factor on the outcome, therefore continous oncological screening is mandatory beside the transplant follow-up. Immunosuppressant agents are chiefly responsible not just for higher risk of recurrence but for higher risk to develop de novo malignancies. Viral serology must be done periodically to catch HCV recurrency in time and start the adequate antiviral therapy. Potentially mTOR inhibitors could be a potent immunosuppressive agents after OLT for HCC due to this antiproliferative effect. In our Department we started to investigate CYP 3A4 metabolizer attribute

of donor livers and mTOR activity in the HCC, normal and cirrhotic liver biopsies to evaluate the potential efficacy of the immunosuppressive strategy. The key of succes is to find a better and individualized immunosuppressive protocol, wich is not only protective against acute rejection of the transplanted organ, but also protective against recurrency or de novo manifestation of malignancy. Development in living donor liver transplantation for HCC is desired because of shortening the waiting time to avoid progression of the malignant disease. One of our most important efforts is to expand the liver donor pool by developing the living donor liver transplant program.