Editorial Commentary

Liver transplantation for primary sclerosing cholangitis—morbidities including disease recurrence

Nobuhisa Akamatsu^

Artificial Organ and Transplantation Surgery Division, Department of Surgery, University of Tokyo, Tokyo, Japan

Correspondence to: Nobuhisa Akamatsu, MD, PhD. Artificial Organ and Transplantation Surgery Division, Department of Surgery, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. Email: nakamats-tky@umin.ac.jp.

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Primary sclerosing cholangitis (PSC) is one of the major diseases indicated for liver transplantation (LTx). There are some important points to be considered when discussing LTx for PSC, which makes it a unique etiology among liver transplant physicians. PSC often coexists with inflammatory bowel disease (IBD), mainly ulcerative colitis (UC), and patients with PSC are prone to develop colorectal cancer and cholangiocarcinoma both before and after LTx. While the surgical techniques in LTx for PSC are similar to those in other diseases, choledochoenterostomy is usually required for PSC recipients since severe cholangitis often damages the common bile duct. This leads to the high incidence of biliary complications among PSC recipients. Because the background of the development of PSC is supposed to be autoimmune disease, the postoperative immunosuppressive regimen should be considered and planned not only for the inhibition of rejection but for the control of autoimmunity. Most importantly, the recurrent PSC among recipients who underwent LTx for PSC definitely impairs the graft and patient survival after LTx, which has resulted in the significantly poor outcomes of LTx for PSC (1). Most recent European registry study of 6,463 primary LTx for PSC patient reported the survival rate at 1, 5, 10, 15, 20, and 30 years of 89.7%, 79.8%, 70.7%, 58.3%, 43.8%, and 20.4%, respectively (2). The recent article by Vannas *et al.* (3) well investigated these unique issues in LTx for PSC recipients among their single center experience which represents the national records of LTx for PSC in Finland.

Vannas *et al.* focused on the Comprehensive Complication Index (CCI), recently proposed calculation index reflecting the gravity of overall complication burden on the patient on a scale from 0 (no complication) to 100 (death). They found that CCI >42 can predict the significantly poorer survival after LTx for PSC. In addition, transplant at an earlier era, higher model for end-stage liver disease (MELD) score, and high/low body mass index were associated with higher CCI. Since CCI is an aggregation score of post-transplant complications according to the severity stratified by Clavien-Dindo classification (4), it is quite reasonable that the higher the CCI score the poorer the patient outcome. The fact that there was no difference in CCI between cirrhotic PSC recipients and non-cirrhotic PSC recipients was quite interesting. In addition, it was noteworthy that the way of biliary reconstruction (duct-to-duct *vs.* choledochoenterostomy) was not associated with CCI score. These facts may represent that the complications developing among PSC recipients are more affected by disease specific causes such as cholangitis, recurrent PSC, and infections (5). It was regretful that the details of biliary complications including anastomotic biliary stricture,

^ ORCID: 0000-0003-1603-5147.

biliary leakage, and non-anastomotic biliary stricture were not presented in the article. With regard to the long-term survival of PSC recipients and disease recurrence, the development of these biliary complications is significantly associated with patient outcomes. As Hildebrand *et al.* (6). reported, biliary strictures, especially anastomotic strictures with or without biliary leakage, are closely linked with PSC recurrence and it is difficult to completely distinguish between them despite the attempts of investigators to exclude anastomotic strictures from the recurrent disease. They concluded that both biliary stricture and recurrent disease affect long-term graft and patient survival after LTx for PSC, and that donor age, IBD, and prothrombin time-international normalized ratio (PT-INR) at LTx are independent risk factors for biliary stricture and recurrent disease and allow for risk estimation depending on the recipient-donor constellation.

LTx for PSC is unique in view of its close relation to the development of cholangiocarcinoma and colorectal cancer (7,8). The exclusion of pre-transplant coexistence of malignancy and the monitoring for the development of *de novo* malignancy is utmost important for all LTx recipients, however, much more caution should be paid for PSC recipients regarding cholangiocarcinoma and colorectal cancer. Cholangiocarcinoma is the most common malignancy in patients with PSC, accounting for 2–8% of cases and being the leading cause of death in these patients (7). In this aspect, Finnish approach for LTx for PSC patients including those with increased risk of cholangiocarcinoma, defined as repeated suspicious dysplasia or aneuploidy DNA, detected with flow cytometry and biliary brush cytology as candidates for LTx, seems acceptable and appropriate given the large donor pool. It may prevent developing cholangiocarcinoma during both pre-transplant and post-transplant period among PSC patients, which definitely leads to the improvement of outcome of this disease. With this approach, Vannas *et al.* did not find any post-transplant development of cholangiocarcinoma among their cohort, describing only four cholangiocarcinoma cases (2%) in the explanted livers. About 70% of PSC cases are accompanied by IBD among which UC comprises the most common subtype (>75%), and the disease control of IBD itself and development of colorectal cancer both before and after LTx is significantly associated with the graft and patient survival after LTx for PSC. It is well recognized that the severity (activity) of IBD is closely related with the progression of PSC, and a lower risk of LTx or death was observed when colectomy is performed before PSC diagnosis (8). This is the case after LTx for PSC, meaning that those with active IBD after LTx are at higher risk of recurrent PSC which leads to the graft failure and colectomy for IBD before LTx was proved to be a significant protective factor for the development of recurrent PSC after LTx by many authors (9,10). Unfortunately, there was no description regarding the coexistence of IBD nor IBD activity after LTx in Vannas's study. Since concurrent IBD and its activity is well-recognized prognostic factor among PSC recipients, this should always be incorporated as an important variable affecting the outcomes of this population. The development of colorectal cancer after LTx for PSC was reported to be 3% in this Finnish study. The annual incidence rate of colorectal cancer in PSC patients is less than 0.5%, with a 30-year cumulative risk of 13%, while IBD patients have a 2% chance of colorectal cancer which is 5 to 15 times greater than the normal population over the course of 30 years. PSC/IBD patients have a higher chance of developing colorectal cancer, up to 30% at 20 years after diagnosis. Although PSC/IBC patients are at greater risk of colorectal cancer, there is a debate about whether LTx alters the progression of colorectal neoplasia in these patients or not. The risk of colorectal cancer in PSC/IBD patients was reported to increase after LT, around 7% within a few years after LTx for PSC (8).

Although it was not discussed in this Finnish study, recurrent disease is the most important issue in LTx for PSC (11). The incidence of recurrent PSC varies widely among transplant centers, which may reflect differences in the diagnostic criteria, length and type of follow-up, and inclusion of protocol biopsies. Recent systematic reviews of 22 and 14 publications reported average recurrence rates of 18.5% (5.7–59.1%) and 17.7% (10.1–27.1%), respectively, with the critically high incidence of graft loss among recurrent recipients, around 50% (11,12). Regarding reported factors associated with PSC recurrence, cholangiocarcinoma before LTx, co-existence of active IBD, older donor age, higher MELD score, and episode of acute cellular rejection were risk factors, while colectomy before LTx and good control of IBD activity was protective. Consistent with other autoimmune liver diseases, disease recurrence as well as rejection is more common after LTx for PSC. Whether the modification of immunosuppression is protective or not for the development of recurrent PSC is a matter of debate. Vannas *et al.* found that azathioprine was associated with a higher morbidity rate, while mycophenolate mofetil acted as a protective for

morbidity and mortality, however, these findings were strongly confounded by an era effect as authors mentioned. Azathioprine is rarely used in LTx today, however, the protective effect of mycophenolate mofetil seems promising among PSC recipients. A recent Japanese nationwide study (13) revealed that cyclosporine use as a calcineurin inhibitor and mono or no immunosuppressive regimen during the maintenance phase were risk factors for recurrent PSC, the latter being an independent risk factor. Japanese transplant clinicians have tended to use a triple regimen (tacrolimus, steroid, and mycophenolate mofetil) or to increase the maintenance dose of tacrolimus and steroid among PSC recipients. Actually, double (tacrolimus and mycophenolate mofetil) or triple therapy accounted for 91% of PSC during the maintenance phase among recent cases, in contrast to the high proportion of those receiving only calcineurin inhibitor (56%) among old cases.

In conclusion, there is still plenty of unsolved problems in LTx for PSC including prevention of surgical complications and disease recurrence, immunosuppressive regimens, and monitoring for IBD, colorectal cancer and cholangiocarcinoma, all of which will be improved along with the accumulation of experiences and latest knowledge for the better prognosis of this disease entity.

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