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Liver Transplantation for Cholestatic Liver Diseases in Adults

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Synopsis

Liver transplantation (LT) is an established lifesaving therapy for patients with cholestatic liver diseases, including primary cholestatic diseases, namely primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC), as well as secondary forms of cholestatic liver disease, including those with cholestatic complications of LT needing a re-transplant. Patients with cholestatic liver diseases can be transplanted for either complications of end stage liver disease or for disease-specific symptoms prior to the onset of end stage liver disease. Patients with cholestatic liver disease need to be regularly assessed for symptoms, lab parameters, development of hepatobiliary tumors, and the status of concomitant IBD if present, including colon cancer screening. Patient survival after liver transplantation for cholestatic liver diseases is generally better than for other indications.¹

Keywords

MELD exceptions; living donor transplantation; cholestatic liver disease; waitlist mortality

Introduction

Liver transplantation (LT) is a lifesaving therapy for patients with primary cholestatic liver disease, including primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC), as well as secondary forms of cholestatic liver disease, including those with cholestatic complications of LT needing a re-transplant. These three processes will be the focus for the purposes of this review as they are the most common forms of cholestatic liver disease necessitating LT. Patients with cholestatic liver disease can be transplanted for either complications of end-stage liver disease or for cholestatic disease-specific symptoms prior to the onset of endstage liver disease. Patients with cholestatic liver diseases face unique

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complications compared to patients with other chronic liver diseases, and need to be regularly assessed for symptoms of cholestasis (i.e., pruritus), lab abnormalities due to cholestasis (most notable fat-soluble vitamins), and for patients with PSC, development of hepatobiliary tumors, and complications of concomitant inflammatory bowel disease (IBD) including colon cancer. Patient survival after liver transplantation for cholestatic liver diseases is generally better than for other indications, as will be discussed.¹ Although a liver transplantation can be lifesaving for cholestatic liver diseases, one of the main challenges is the potential for recurrent disease which may necessitate re-transplantation. Other cholestatic diseases that may necessitate LT include total parenteral nutrition (TPN) induced cholestasis, biliary atresia, Alagille syndrome, progressive familial intrahepatic cholestasis, sarcoidosis, cystic-fibrosis associated liver disease, secondary sclerosing cholangitis, and fibropolycystic disease of the liver, which are rare outside of the pediatric setting, and will not be covered in this review.

Primary Biliary Cirrhosis

Identifying patients most likely to need a liver transplant

Several mathematical models have been developed to estimate projected survival in PBC in order to determine optimal timing for LT. The Mayo risk score was developed in an attempt to predict time to transplant in patients with PBC. This model incorporates: age, bilirubin, albumin, prothrombin time, peripheral edema, and presence or absence of diuretic therapy. When the score is >7.8 it is thought that patients benefit from LT¹. Two studies found that pre-transplant disease severity as measured by the Mayo PBC risk score appeared to have a direct effect on survival following LT for PBC. Patients with higher risk scores had a tendency for worse outcomes regardless of the era of transplantation^{2,3}. As expected, patients who were malnourished or chronically ill preoperatively were found to have less favorable short-term outcomes after LT². These data suggest that predictive risk models such as the Mayo PBC risk score may be able to predict the probability of poor outcomes following LT for PBC.

Indications for transplantation

PBC has gone from the leading indication for liver transplantation in the 1980s to the sixth most common indication in 2006 due to effective medical therapy with UDCA⁴. It still remains the indication for LT in up to 5% of patients receiving an LT in the US each year. Despite the effectiveness of UDCA, 30% of patients will be incomplete responders and face the greatest risk of progressing to cirrhosis. Furthermore, due to the disease being asymptomatic in some patients, PBC can be diagnosed at such a late stage that even effective medical therapy cannot stave off the need for LT.

Most patients with PBC who require an evaluation for LT have developed decompensation from cirrhosis and portal hypertension, including ascites, hepatic encephalopathy, variceal bleeding, or hepatocellular carcinoma (HCC). Patients with more-preserved liver function can also be considered for LT if they suffer from intractable symptoms of PBC including pruritus, chronic fatigue, or severe metabolic bone disease⁵. These indications are controversial because the current system of LT follows an 'urgency-based' model that

prioritizes patients using the Model for End Stage Liver Disease (MELD) score. Unless a living donor is available, patients with PBC without complications from portal hypertension will have difficulty obtaining deceased donors due to their low MELD scores and the disparity in available deceased donors compared to the number of patients on the waiting list⁶⁻⁸. The other alternative is to apply for exception points for these patients, but these are not standard indications for exception points, and practices related to exception points vary from region to region⁹. Importantly, even though LT may be lifesaving for patients with decompensated cirrhosis from PBC, for those with symptoms such as fatigue from PBC, there is the potential that fatigue attributable to PBC may not resolve with LT.¹⁰

Waiting list mortality for patients with PBC

Until recently, information on the waiting list mortality among PBC patients in the US relied on small case series or older data. However, a recent study evaluated the waitlist outcomes for these patients by analyzing United Network for Organ Sharing (UNOS) data for all adults on the waitlist between 2002 and 2014. During this time period, 16.5% of waitlisted patients with PBC died on the waiting list without receiving an LT, as compared to 12.4% with hepatitis C virus (HCV) and 8.5% with PSC. Importantly, the risk of waitlist mortality varied across the US, but despite this, PBC patients had higher waitlist mortality than PSC patients in the first three months after being waitlisted, and 40% higher overall. Compared to patients with PSC, PBC patients died more often from cardiovascular causes.¹¹

MELD score in PBC and MELD exceptions

As referenced above, since 2002, patients on the LT waitlist have been prioritized using the MELD score, an objective score to prioritize the 'sickest first.' The MELD score is a good predictor of survival in patients with all forms of liver disease, although the Mayo PBC risk performs similarly to the MELD score in predicting survival in PBC patients⁸. The MELD score is based on three parameters (serum creatinine, bilirubin, and INR), and does not account for symptoms of liver disease that do not affect laboratory tests. For patients with PBC, this most commonly manifests as intractable pruritus. There are no standardized policies for granting exception points for patients with pruritus. Transplant centers may submit an application to their regional review board (RRB; there is 1 RRB within each of the 11 UNOS regions), to have the case reviewed on a case-by-case basis. There is variability among centers and regions in the utilization of such exceptions, however, given that they are related to quality-of-life, and not mortality, they are being approved less frequently, and in the future, may be eliminated. As one example of geographic variability in exception points, a study published in 2011 by Argo et al examined regional differences in utilization of "symptom-based" MELD exceptions, which specifically excludes those for hepatocellular carcinoma. This would include exceptions for symptoms such as pruritus and fatigue commonly seen in patients with PBC. In this study, the authors reviewed OPTN data for waiting list registrants during the MELD allocation from February 27, 2002 to November 22, 2006. Interestingly, although utilization of system-based exception varied widely across UNOS regions, it did not correlate with organ availability as estimated by the regional mean physiologic MELD at transplantation. There were no statistical differences between PSC and PBC, and cholestatic diseases were treated as one group in this analysis.⁹

Living Donor Liver Transplantation for PBC

Because the symptoms of PBC are not captured by the MELD score, living donor liver transplant (LDLT) is an attractive option for patients with PBC. Post-LDLT outcomes in PBC are excellent, with reported 5-year survival rates of 80%. No significant difference is seen in survival for deceased donor versus living donor transplants in patients with PBC.¹²

Post transplant outcomes in PBC

Outcomes of LT in patients with PBC are excellent and in general better than for other indications for LT. In Western populations (US and UK), 1-, 3-, 5-, and 10- year survival rates post-transplantation were 93–94%, 90–91%, 82–86%, and 67% respectively. Graft survival in patients with PBC at 1, 3, 5, and 10 years was 85%, 83%, 57–81%, and 61%, respectively.^{13,12} Patients with PBC, as with other autoimmune diseases, may need longer courses of steroid therapy or higher doses. Some patients are even kept on low doses of prednisone chronically. Interestingly, those who received a LDLT were more likely to have corticosteroid withdrawal than those who received deceased donor transplants for PBC in a study of 1032 patients.¹⁴ Nevertheless, there are no controlled trials that have identified the optimal immunosuppression regimen in these patients.

Recurrence rates of PBC post-transplant are estimated at 21–23% at 10 years and >43% at 15 years.¹⁵ Median time to recurrence is 3–5.5 years, although it can be as rapid as less than 1 year after transplant. Diagnosing recurrent PBC after LT can be difficult as anti-mitochondrial antibodies can remain positive after transplant without recurrent disease. Anti-parietal cell antibodies may be useful in the diagnosis of post-transplant PBC recurrence, but are not yet a definitive tool.¹⁶ The diagnosis requires a liver biopsy with histologic features of portal inflammatory infiltrates, lymphoid aggregates, epithelioid granulomas, and bile duct damage. To date, no predictors of disease recurrence have been identified, but HLA mismatch and choice of immunosuppression may have an impact on recurrence rates. The treatment of post-transplant recurrent PBC is also unclear. Biochemical improvement can be seen with ursodeoxycholic acid but there is no clear evidence that it improves patient or graft survival or alters the natural history of disease recurrence.¹⁷ Despite a high rate of post-transplant recurrence, graft loss due to recurrent PBC occurs at a rate of 1–5.4%.¹⁸

While patient and graft survival are often used as outcomes for LT, an important multicenter study by Gross et al answered the question of what the quality-of-life before and after liver transplantation for cholestatic liver disease is.¹⁹ Using the National Institute of Diabetes and Digestive and Kidney Diseases Liver Transplant Database Quality of Life Questionnaire (NIDDK LTD-QOL), a validated and reliable instrument, four areas were assessed: liver – related symptoms, physical functioning, health satisfaction, and overall wellbeing. An increase in disease severity led to a worsened quality of life, but this was reversible with LT. Patients with PBC were compared to those with PSC and there were no significant differences in the following measures of QOL before LT or at 1 year follow up: Symptoms Composite Score, pain rating, Function Composite Score, Karnofsky score, sick days, employment status, health rating, health satisfaction, life satisfaction, or happiness. All results were reported as composites for the 157 adult patients with PSC and PBC. Results

were remarkable for significantly improved health-related quality of life ratings after LT compared to scores before LT, with improvements in symptoms, function, health satisfaction, and overall quality of life. Importantly, the HRQOL at 1 year after LT was not associated with pre-LT clinical factors, suggesting that a remarkable recovery can be made even by those who are very ill prior to transplant.^{19,20}

Secondary cholestatic disease post-transplantation

Cholestasis post-transplantation is a common occurrence; it can be extrahepatic due to mechanical obstruction of the main bile ducts or intrahepatic, due to a variety of causes. Cholestasis in the post-LT period usually remains subclinical, but when severe, it is associated with irreversible liver damage, necessitating retransplantation.

The causes of cholestasis are best categorized by time of occurrence: early (within 6 months of LT) or late (after 6 months post LT). Common causes of intrahepatic cholestasis include ischemia/reperfusion injury, bacterial infection, acute cellular rejection, cytomegalovirus infection, small for size grafts, medication injury, intrahepatic biliary strictures, chronic rejection, hepatic artery thrombosis or stenosis, ABO blood group incompatibility, biliary cast syndrome, fibrosing cholestatic hepatitis C, cholangiopathy post-donation after cardiac death (DCD) donation, and recurrent disease (Table 1).

By contrast, extrahepatic cholestasis, is usually related to biliary stones or anastomotic strictures. Extrahepatic cholestasis due to anastomotic strictures typically require interventions to reverse, which can be endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiogram (PTC) depending on the location, presence of a duct-to-duct anastomosis versus Roux-en-Y, and accessibility of the biliary tract.

There has been a continued emphasis on increasing the utilization of DCD livers, which can provide good posttransplant graft and patient survival, but are frequently associated with biliary complications, most commonly ischemic cholangiopathy (diffuse intra-hepatic strictures). These patients need to be relisted, and the challenge is obtaining high enough priority for re-transplantation. A recent analysis of OPTN/UNOS data from 2002 to 2011 revealed that due to the use of MELD exception points, DCD patients relisted for LT underwent retransplantation 71.4% of the times. Of those with an approved MELD exception, 85.2% underwent retransplantation, compared to 57% of those with an exception denied, and 69.4% of those not applying for an exception. Patients with an approved exception were 3.3 times more likely to undergo retransplantation. Clearly, standardization of exception points for DCD recipients requiring retransplantation is required.²¹

Primary Sclerosing Cholangitis

Indications for transplantation

Primary sclerosing cholangitis (PSC) is a chronic disease that leads to progressive fibrosis and stricturing of the biliary tract and the hepatic parenchyma, and frequently develops into biliary cirrhosis. Similar to other forms of chronic disease, liver transplantation is indicated for patients with PSC who develop complications of portal hypertension, which include

ascites, hepatic encephalopathy, variceal hemorrhage, and/or spontaneous bacterial peritonitis.²² Additionally, patients with PSC who develop cirrhosis are at risk for developing hepatocellular carcinoma (HCC), although at a much lower rates than others forms of chronic liver disease (e.g., hepatitis C, non-alcoholic steatohepatitis).²³ In the small subset of patients with PSC who do develop HCC, indications for transplantation and increased waitlist priority (exception points) are based on the Milan criteria: 1 tumor $\leq$ 5cm, or 2 or 3 tumors $\leq$ 3cm.²⁴

In contrast to other etiologies of chronic disease that almost uniformly require transplantation when complications of portal hypertension and/or HCC develop, PSC has two unique indications for liver transplantation: cholangiocarcinoma (CCA) and recurrent bacterial cholangitis. Although nearly all patients with chronic liver disease who are placed on a transplant waitlist have underlying cirrhosis, this is not a requirement for listing for liver transplantation. It is estimated that among patients with PSC, anywhere from 25–50% of patients waitlisted for a liver transplant do not have radiographic and/or histologic evidence of cirrhosis²⁵ and/or complications of portal hypertension (e.g., ascites).²⁶

The incidence of CCA is dramatically higher in patients with PSC when compared to patients with other etiologies of liver disease, and/or the general population. Depending on the means of diagnosis (e.g., radiographic diagnosis, post-mortem), the lifetime risk of developing CCA in the setting of PSC ranges from 10–40% in patients with PSC.^{27–30} Historically CCA was deemed a contraindication to liver transplantation, yet in a subset of patients with CCA (hilar CCA occurring most commonly, but not exclusively in PSC), the post-transplant outcomes are quite good. Among patients with hilar CCA who undergo neo-adjuvant chemo-radiation and survive to undergo a liver transplant, the 5-year recurrence free survival is 65%.³¹ But hilar CCA, with or without PSC, should only be considered an indication for liver transplantation among patients who undergo the Mayo Clinic PSC protocol (discussed in detail in exceptions section).^{28–30}

The second indication for transplantation that is unique to patients with PSC (or rarely in patients with biliary strictures from diseases such as autoimmune cholangiopathy or congenital or acquired structural biliary anomalies) is recurrent bacterial cholangitis. Longstanding biliary inflammation leads to the development of biliary strictures and subsequent stasis, which places patients with PSC at an increased risk of recurrent bacterial cholangitis. Although the risk of bacterial cholangitis is influenced by the severity of disease, presence of a dominant stricture, and history of prior biliary manipulation (i.e., endoscopic retrograde cholangiopancreatography with sphincterotomy), it is a common complication of PSC. Available data suggest that nearly 40% of patients with PSC waitlisted for a liver transplant in the US have a history of at least one episode of bacterial cholangitis prior to waitlisting, with almost 30% of patients developing at least one subsequent episode while on the waitlist.²⁵ Recurrent cholangitis has been considered an indication for liver transplantation due to the potential for morbidity (e.g., frequent hospitalizations, impaired quality of life), and hypothesized risk of mortality.

Patients with PSC may also develop complications from longstanding cholestasis including refractory pruritus, weight loss, and metabolic bone diseases resulting. These complications

may lead to significant morbidity, utilization of medical care, and frequent hospitalizations. Although these complications impair a patient's quality of life, under the current urgency-based (sickest-first) system of liver transplantation, such patients have low waitlist priority in the absence of concomitant severe liver dysfunction, and thus would only be considered for liver transplantation under extenuating circumstances and/or if a potential living liver donor were available.

Waiting list mortality for patients with PSC

In the United States, a patient's rank on the liver transplant waitlist is based on his/her Model for End-Stage Liver Disease (MELD) score. This score is a calculated value based on a patient's serum bilirubin, creatinine, and international normalized ratio (INR). The weighting of each of these lab values varies and depends on the scale of each lab value, such that small increases in a patient's serum creatinine yields greater increases in MELD scores than small changes in the serum bilirubin.³²⁻²⁵ Because the vast majority of patients with PSC on the liver transplant waitlist, especially those without cirrhosis and portal hypertension, manifest their disease with greater elevations in their serum bilirubin, rather than the serum creatinine, many had speculated that under the MELD system, patients with PSC would have less access to transplantation. Despite these concerns, since 2002, this has not been the case.^{25,26} When compared to waitlisted patients in the US from 2002–2009 with all other etiologies of liver disease, the adjusted risk of dying on the waitlist was significantly lower for patients with PSC: HR for waitlist mortality: 0.72, 95% CI: 0.66–0.79, $p < 0.001$.²⁶ Several hypotheses exist to explain this phenomena: 1) preferential use of living donor liver transplants (LDLTs)³⁶ in patients with PSC; 2) increased prioritization among the patients with recurrent bacterial cholangitis granted increased priority in the form of MELD exception points³⁷; 3) cirrhosis and portal hypertension being less prevalent among waitlisted patients with PSC^{25,26,38}; and 4) the low attributable risk of mortality due to bacterial cholangitis among patients with PSC who develop this complication.²⁵

Between 2/2002–3/2011, transplanted centers applied for MELD exception points in order to gain increased waitlist priority for over 320 patients with PSC suffering from bacterial cholangitis. This was based on the concern that bacterial cholangitis in patients with PSC increased a patient's risk of mortality, despite limited data to support this contention, until recently. In a 10-year study from two large liver transplant centers, there were 171 patients waitlisted for a liver transplant with PSC, of whom 39% had a history of bacterial cholangitis prior to listing, and 28% had at least one episode of bacterial cholangitis while on the waitlist. Despite this highly prevalent condition, the waitlist mortality was not significantly different for patients with a history of recurrent bacterial cholangitis, and over this 10-year period, no patients were removed from the waitlist for death or clinical deterioration due to bacterial cholangitis.²⁵

MELD exception points for patients with PSC

As mentioned in the previous section, in select circumstances, CCA can be an indication for transplantation and increased waitlist priority, rather than a contraindication to transplantation. Due to the excellent post-transplant results displayed at the Mayo Clinic in Rochester, among patients with hilar CCA (with and without PSC), patients meeting specific

criteria are eligible for exception points and increased waitlist priority. To be eligible for liver transplantation, patients must meet specific inclusion and exclusion criteria (Table 2), including the presence of peri-hilar CCA ≤ 3 cm without metastatic disease, and then must undergo neo-adjuvant chemo-radiation and staging to ensure absence of extra-hepatic disease.³¹ Patients who meet all of these criteria and undergo the protocol at a transplant center with a formalized treatment protocol that mirrors that derived at the Mayo Clinic, may then be eligible for exception points upon successful chemo-radiation and tumor staging.³¹

Unlike CCA, there are no formalized protocols for awarding exception points for patients with PSC who experience recurrent bacterial cholangitis. These exception applications have been reviewed on a case-by-case basis, and, excluding UNOS Region 9 that had a regional policy for awarding exception points, were at the discretion of members of each UNOS region's regional review board. A consensus conference convened in 2006 recommended that exception points for recurrent cholangitis be restricted to patients with recurrent cholangitis complicated by bacteremia or other septic complications⁴¹, however the criteria used in practice to award exception points has not been stringent.³⁷ Since publications of these guidelines, 158 patients had at least one exception approved for recurrent cholangitis, with 70% of such patients never having an episode of bacteremia or sepsis, or having only a single episode of cholangitis.³⁷ Importantly, three-quarters of patients receiving a MELD exception were transplanted.³⁷ The increased access to transplant for patients receiving exception points, with data lacking on the risk of mortality as a result of cholangitis, has led UNOS to develop more stringent criteria for awarding exception points to such patients.

Post-transplant outcomes

Approximately 5% of all adult transplant recipients in the US each year have PSC as the primary etiology of liver disease necessitating a liver transplant. Despite this, approximately 14% of transplant recipients with PSC receive a living donor liver transplant, compared to 3.5–4% of transplant recipients with other forms of chronic liver disease.³⁶ When considering all liver transplant recipients (deceased-donor or living-donor), patients with PSC have post-transplant graft and patient survival that is not different than other transplant recipients; in the era prior to direct-acting antiviral therapies for hepatitis C, patients with PSC had superior post-transplant survival compared to these patients.⁴² However, when considering only recipients of a living donor allograft in the US from 2002–2013, patients with PSC transplanted at an 'experienced' center (defined as having performed >15 living donor liver transplants) had superior post-transplant graft and patient survival even after adjusting for other factors.⁴³

Although patients with PSC have excellent post-transplant survival, they are at risk for recurrent PSC, which is estimated to occur in the range of 15–35% of transplant recipients.⁴⁴ The wide range of the estimated risk of recurrent PSC rests in part on the challenges in diagnosing recurrent PSC, as it is considered a diagnosis of exclusion. Recurrent PSC has the similar radiographic, endoscopic, and/or histologic appearance to PSC prior to transplantation, yet the features characteristic of PSC can also be seen in patients who have developed a hepatic artery stenosis/thrombosis, chronic ductopenic rejection,

cytomegalovirus infections of the biliary tract, and/or received a transplant from a donor with an incompatible blood type or from a donation after cardiac death donor. For these reasons, the diagnosis of recurrent PSC is one of exclusion, and requires exclusion of conditions that can mimic recurrent PSC (Table 3).⁴⁴

Management of immunosuppression in liver transplant recipients with PSC, unlike non-immune etiologies, is more complex due to the increased risk of acute cellular rejection in patients with PSC. However, despite this increased risk there are no data demonstrating the optimal regimen, in terms of the backbone of the immunosuppression regimen or the number of immunosuppressant medications that are needed. Furthermore, there are no data that have demonstrated an association between a patient's post-transplant immunosuppression regimen and the risk of recurrent PSC, and whether long-term combination immunosuppression is needed.^{45–47} In contrast to the lack of data on the relationship between post-transplant immunosuppression and rejection or recurrent PSC, there are data that suggest that choice of immunosuppression impact post-transplant activity of inflammatory bowel disease (IBD) in patients with PSC. Specifically, combination therapy with tacrolimus and mycophenolate mofetil has been associated with a significantly increased risk of worsening of IBD post-transplantation, while combination cyclosporine and azathioprine was associated with fewer IBD flares.⁴⁸ In spite of these data, one-third of patients with PSC and IBD will have worsening of IBD symptoms post-liver transplantation.^{49–51}

Lastly, with regards to post-transplant outcomes and management in transplant recipients with PSC, is the issue of management of post-transplant IBD. The basic underlying premise of medical management of IBD post-transplantation does not differ from IBD in other settings, with the goals of therapy focused on managing a patient's symptoms, and when present, endoscopic abnormalities. However, one additional consideration is the potential for an increased risk of infections when biologic therapy (e.g., infliximab) is added to standard post-transplant immunosuppression.^{48–51} For this reason, some experts consider azathioprine as the preferred treatment option for patients with moderate to severe IBD, especially as azathioprine has been used in transplant recipients for over 20 years, in combination with other immunosuppressant medications (e.g., tacrolimus). Nevertheless, for patients who do not respond to azathioprine, and/or severe IBD (e.g., fistulizing Crohn's disease), biologic therapy should be considered, with close monitoring for infectious complications. The risk of developing colorectal cancer in patients with PSC and IBD persists after liver transplantation, thus continued colorectal surveillance every 1–2 years for patients transplanted with PSC and IBD should continue post-liver transplantation.^{49,52,53}

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Key Points

- Cholestatic liver diseases are the indication for liver transplantation in 10% of patients in the US.
- Post-transplant outcomes in patients with cholestatic liver diseases are as good, if not better, than other forms of liver disease.
- Primary biliary cirrhosis and primary sclerosing cholangitis can recur after liver transplantation, and potentially impact long-term graft outcomes.

Table 1

Causes of post transplant cholestasis

Early (6 months)	Late (>6 months)
Extrahepatic:	Extrahepatic:
Stricture – anastomotic, compressive	Stricture – anastomotic
Multiple strictures – HAT or ischemic	Multiple strictures – HAT, ischemic, recurrent
Bile leak	PSC
Cholangitis	Choledocholithiasis
Intrahepatic:	Intrahepatic:
Ischemia/reperfusion injury	Intrahepatic biliary strictures
ABO incompatibility	ABO incompatibility
Hepatic artery thrombosis/stenosis	Chronic rejection
Acute cellular	Recurrent disease (PBC, PSC, HCV)
Sepsis	Drug induced
Drug induced	Acute cellular rejection
Small-for-size	De novo AIH
Post transplant infections – bacterial, fungal, CMV, HCV, HBV	De novo viral hepatitis

Abbreviations: HAT = hepatic artery thrombosis, PSC = primary sclerosing cholangitis, CMV = cytomegalovirus, HCV = hepatitis C virus, HBV = hepatitis B virus, PBC = primary biliary cirrhosis, AIH = autoimmune hepatitis

Table 2

Inclusion and exclusion criteria for patients with cholangiocarcinoma being considered for the Mayo treatment protocol and MELD exception points

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> Intraluminal brush or biopsy showing evidence of positive tumor cells or cells strongly suspicious for CCA, OR Radiographic malignant appearing stricture, and one of the following criteria: <ul style="list-style-type: none"> Ca 19-9 > 100 U/mL in the absence of acute bacterial cholangitis Polysomy on fluorescence in-situ hybridization (FISH) Well-defined mass on cross-sectional imaging 	<ul style="list-style-type: none"> Evidence of extrahepatic disease or regional lymph node involvement Previous malignancy (excluding skin or cervical cancer) within the 5 years prior to diagnosis of CCA Previous abdominal radiotherapy Uncontrolled infection prior to treatment Prior attempt at surgical resection of the tumor leading to violation of the tumor plane Any medical condition precluding transplantation Any transperitoneal biopsy, including percutaneous and/or endoscopic ultrasound guided FNA

Abbreviations: MELD=Model for End-Stage Liver Disease; CCA=cholangiocarcinoma; Ca=cancer antigen; FNA=fine-needle aspiration

Table 3Diagnostic criteria for recurrent primary sclerosing cholangitis following liver transplantation²³

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> Confirmed diagnosis of PSC prior to liver transplantation Cholangiography (MRCP or ERCP) performed 90 days after transplantation demonstrating intrahepatic and/or extrahepatic biliary structuring, beading, and/or irregularity, OR Liver biopsy demonstrating fibrous cholangitis and/or fibro-obliterative lesions, with or without biliary fibrosis or cirrhosis, and/or ductopenia 	<ul style="list-style-type: none"> Hepatic artery stenosis or thrombosis on radiographic imaging or angiography Chronic ductopenic rejection on histologic evaluation of liver biopsy Isolated extrahepatic anastomotic strictures Donor and recipient ABO incompatibility Non-anastomotic strictures occurring prior to day 90 post-transplantation

Abbreviations: PSC=primary sclerosing cholangitis; MRCP=magnetic resonance cholangiopancreatography; ERCP=endoscopic retrograde cholangiopancreatography

Adapted from Zenouzi R, Weismuller TJ, Hubener P, et al. Low risk of hepatocellular carcinoma in patients with primary sclerosing cholangitis with cirrhosis. *Clinical gastroenterology and hepatology*. 2014;12(10):1733–1738, with permission.