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Liver transplantation: Current status in British Columbia

While the number of liver transplants performed across North America has increased, there has been an even greater increase in the number of patients who are on a liver transplant wait list.

ABSTRACT: Orthotopic liver transplantation has become an accepted treatment for patients with acute or chronic decompensated liver disease of various causes. In British Columbia, liver transplantation has been performed since 1989. Today up to 35% of all transplantations are done in patients with hepatitis C. While there are few absolute contraindications to transplantation, there are some relative ones, including age and certain comorbidities. After transplantation, the primary care provider has an important role to play in surveillance and treatment of the patient's global health needs. Although post-transplant survival has been excellent, a tragic disparity exists between organ availability and need, which results in a 30% mortality rate on the liver transplant wait list in BC. Careful patient selection and optimal organ allocation is critical given the scarcity of this life-saving resource.

The first successful human liver transplant was performed by Dr Thomas Starzl and his colleagues in 1968 in Colorado on an 18-month-old child who survived 400 days. Despite improved technical aspects of transplant surgery, the 1-year survival rates were not above 35% in the 1960s and 1970s, mainly because of graft failure due to allograft rejection. A major breakthrough in the field was the development of calcineurin inhibitors, with a landmark paper reporting 11 of 12 patients alive 1 year post-transplant on cyclosporine-based immunosuppresion.[1] The availability of tacrolimus as an alternative to cyclosporine[2] and the introduction of other immunosuppressive agents, including biologicals and mycophenolate mofetil, as well as refinements of surgical techniques, intensive care, and diagnostic modalities, have led to current 1-year survival rates of 85% to 95% and 5-year survival rates of 75% after liver transplantation in BC (**Figure 1**).[3] In contrast, the expected survival of a patient with Child class C cirrhosis is in the order of 20% to 30% at 1 year. In addition to the survival benefit, liver transplantation provides patients with a distinct improvement in quality of life.[4]

Today orthotopic liver transplantation (OLT) has become an accepted treatment for patients with acute or chronic decompensated liver disease of various causes, as well as a form of gene replacement therapy for several systemic metabolic diseases in the absence of structural liver disease. In BC this most notably takes the form of urea cycle defects in adolescence.[5] Approximately 400 liver transplants are performed in Canada every year. In British Columbia liver transplantation has been available since 1989. The number of transplants performed increased from 3 in 1989 to 47 in 2008.

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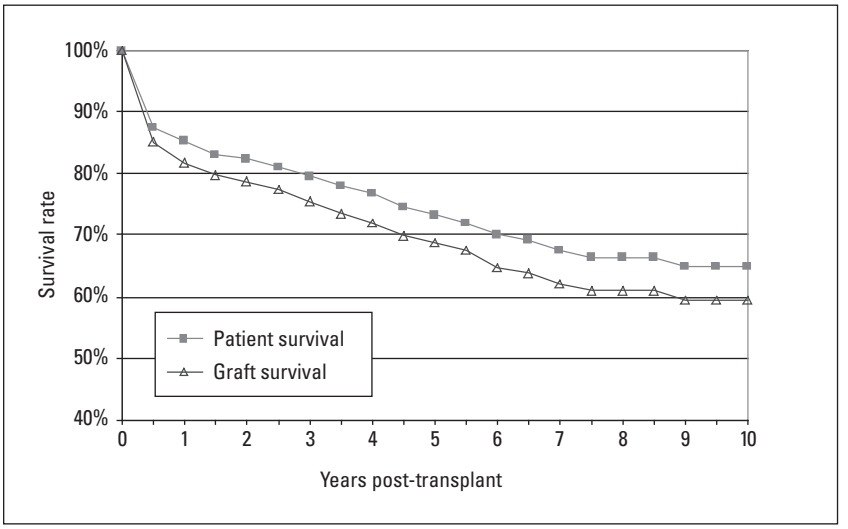

Figure 1. Patient and graft survival for first liver transplants in BC, 1995–2004.

Source: BC Transplant

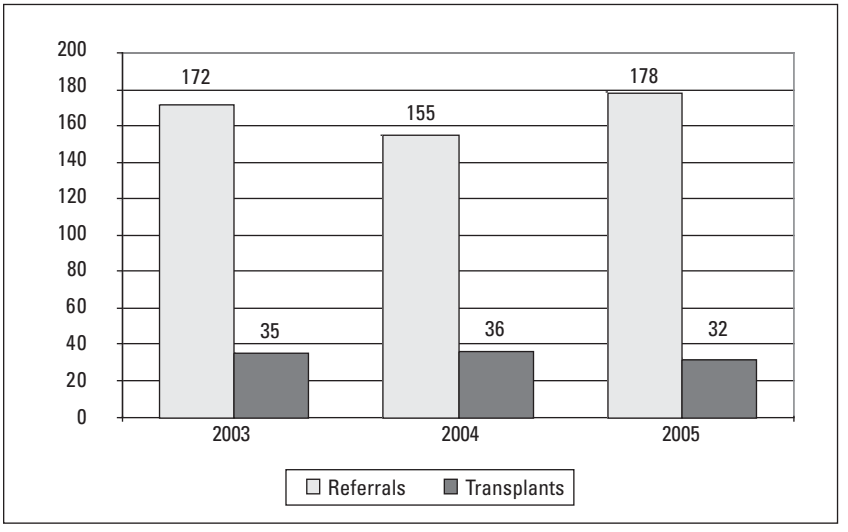

Figure 2. Number of referrals vs number of transplants in BC, 2003–2005.

Source: BC Transplant

Initial referrals for liver transplant assessment usually come from community specialists with expertise in the area who have decided that there are no options other than transplantation. While the number of liver transplants has increased across North America, there has been a greater increase in the number of patients who are on a liver transplant wait list. BC Transplant data for the number of referrals for transplantation and the number of transplants performed reflect the situation across North America, and mean longer waiting times for very ill patients (**Figure 2**). In recent years the rate of death on the wait list has been approximately 30%.

Patient selection

Careful patient selection and proper organ allocation are critical given the scarcity of this life-saving resource. The transplant team has an ethical obligation to act in the best interests of both the individual patient referred for assessment and the entire group of patients who are in need of transplantation.[6] A successful outcome depends on optimal patient selection and timing.

General considerations

A patient should be considered for liver transplantation if this option extends life expectancy and improves quality of life beyond the expectation of the natural history of the underlying liver disease. Current candidate selection in BC occurs in two stages. In the first stage, patients are assessed to see if they are suitable to be "activated" on the waiting list, and in the second stage a decision is made regarding which patient will receive a given donor organ.

During assessment, scoring systems are used to determine patient status and suitability. One of these systems is the model for end-stage liver disease (MELD), which was originally developed to estimate procedure-related mortality in patients undergoing transjugular intrahepatic portosystemic shunts.[7] Today MELD is the most commonly used prognostic model for estimating disease severity and survival in end-stage liver disease. It has been prospectively validated in several patient populations and is currently used by most transplant centres in the world. The MELD score is based on laboratory values for serum bilirubin, serum creatinine, and international normalized ratio (INR) in a log-transformed equation where Ln is the natural logarithm: (3.8[Ln serum bilirubin (mg/dL)] + 11.2[Ln INR] + 9.6[Ln serum creatinine (mg/dL)] + 6.4).

High MELD scores are associated with a poor short-term prognosis. (An online MELD calculator that accepts SI units is accessible at www.mdcalc.com/meld.) One of the requirements for listing in the United Network for Organ Sharing in the US is a MELD score of at least 14. With scores lower than 14, short-term prognosis without transplantation is predicted to be similar or better than that with transplantation. Conversely, 3-month survival drops to less than 20% in patients with a MELD score of 40. Some of these patients may be too sick for transplantation.

The Child-Turcotte-Pugh (CTP) is another scoring system for quantifying the severity of liver disease. It scores five variables: ascites, serum albumin, bilirubin, INR, and encephalopathy. CTP is less useful for assigning priority on a transplant wait list because two of the parameters (ascites and encephalopathy) are subjective. Furthermore, it has not been validated as a reliable indicator of short-term prognosis. For those reasons, MELD is now the only scoring system used in the United States for allocating organs from deceased liver donors. In BC we consider the global clinical assessment of the candidate as well as MELD and CTP scores when allocating a donor organ. Patients who receive organs in BC have usually been diagnosed with the conditions and diseases described below (**Figure 3**).

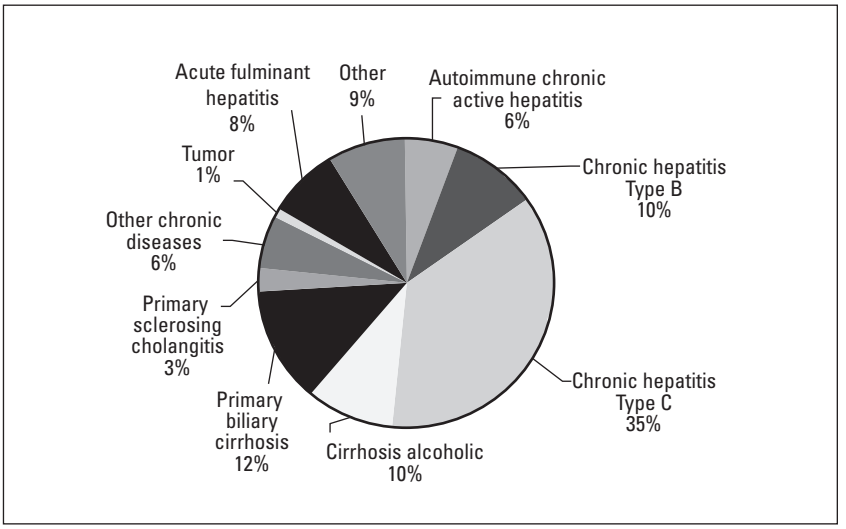

Figure 3. Liver transplants in BC by primary diagnosis, 2003–2005.

Source: BC Transplant

Fulminant hepatic failure

Fulminant hepatic failure (FHF) is the acute onset of liver failure with development of encephalopathy in a short period of time. Despite the differences in etiology, the progression of FHF is similar in all cases.[8] Without liver transplantation, patients with FHF will either have a complete recovery of liver function or will die. Early referral to a transplant centre gives patients the best chance for a favorable outcome.

Chronic hepatitis C

Up to 35% of all liver transplantations are done in patients with chronic hepatitis C–related liver disease. Recurrence of HCV infection in the transplanted organ is universal,[9,10] but the rate of progression is quite variable. About 20% of patients develop rapidly progressive fibrosis that may lead to graft failure within a few years of transplantation. However, most studies show 5-year survival rates in HCV-positive recipients to be similar to those in HCV-negative recipients. Some of these patients will have relatively quiescent disease for many years, but in general the rate of fibrosis progression is faster in the transplanted liver than in the native liver. Successful treatment of HCV before transplantation usually prevents postoperative recurrence but is often not feasible. Unfortunately, antiviral treatment after liver transplantation is often poorly tolerated.[11] The combination treatment of peginterferon and ribavirin is associated with sustained virological response of approximately 27% (23% to 31%).[12] Use of growth factors to support the hematological parameters may improve compliance and success of antiviral therapy after transplant.[9] Immunoglobulin therapy for HCV has been found to be ineffective.[13]

Chronic hepatitis B

Significant improvements have been made recently in the treatment of chronic hepatitis B infection; however, liver transplantation remains the only option for many patients with end-stage liver disease due to HBV.

After the incorporation of hepatitis B immunoglobulin (HBIG) along with combination antiviral therapy, the 1- and 5-year survival rates of patients transplanted for HBV equals that of non-HBV transplant patients.[14] Several reports show a combination of lamivudine and low-dose intramuscular HBIG are effective in preventing allograft reinfection by HBV at higher intravenous doses.[15] Studies have also suggested that the rate of

reinfection can be reduced further if the anti-HBs titers are kept consistently above 500 IU/L.[16] A recent study of intramuscular low-dose HBIG (400 to 800 IU daily for 1 week then monthly) plus lamivudine (100 mg daily) following liver transplantation showed patient survival was 92% at 1 year and 88% at 5 years. A higher HBV DNA titer at baseline was associated with an increased risk of recurrence. There is no consensus on the most appropriate initial antiviral therapy. A combination of lamivudine and adefovir/tenofovir, as well as entecavir, along with HBIG is currently used in our centre. Combination therapy allows more rapid viral suppression and minimizes the risk of drug resistance when compared with using each of these drugs alone. Active immunization using standard hepatitis B vaccines has been explored as an alternative to lifelong HBIG prophylaxis. Unfortunately, anti-HBs titers achieved in the responders were low despite the use of higher doses and multiple courses of vaccine.[17]

Alcoholic liver disease

Alcoholic liver disease (ALD) is the third most common indication for liver transplant in British Columbia and the second leading cause for transplant after viral hepatitis in many western countries, although the ALD group often has additional primary liver disease causes (e.g., hepatitis C). Due to the lack of consensus on a definition for "relapse," there is discrepancy among published reports of post-transplant alcoholism relapse rates, which range from less than 10% to 90%.[18]

Transplantation for alcoholic liver disease in an era of organ shortage and against a background of recidivism raises both ethical and clinical concerns. However, survival rates following liver transplant for both ALD and non-ALD are comparable.[18,19]

All Canadian transplant centres, as well as most American centres, require a documented 6-month minimum period of supervised abstinence in association with some form of alcohol rehabilitation before transplantation. Like BC, many centres expect patients to sign a contract to maintain abstinence. Six months of abstinence with a good social support system is associated with a favorable outcome.[20] A 6-month abstinence requirement also gives patients a chance to recover spontaneously from advanced liver disease and thereby avoid transplantation. When transplantation is necessary, abstinence also affects immediate postoperative outcome.

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide and is the most frequent primary malignancy of the liver. It ranks third among causes of cancer-related deaths. In the US, there has been a 70% increase in HCC over a 20-year period, which is likely due to the HCV epidemic,[21] and similar trends have been projected in a Canadian study.[22] It is not uncommon to find HCC in patients with viral hepatitis or alcoholic liver disease during pre-transplant assessment. Only selected patients with HCC who meet acceptable criteria (Milan criteria) are considered for transplant.

Vascular invasion is the most important prognostic factor for HCC and is present in up to 50% of tumors greater than 5 cm.[23] HCC is an aggressive tumor. The wait list dropout rate as a result of tumor progression beyond acceptable criteria is between 5% and 20%.[24] To overcome this problem, a MELD score of 22 is automatically assigned to high-risk HCC patients (solitary lesions 2 to 5 cm or up to three lesions of 3 cm) currently waiting for an organ. Bridging modalities such as transcatheter arterial chemoembolization, radiofrequency ablation, percutaneous ethanol injection, and surgical resection are also used in carefully selected patients.

Autoimmune hepatitis

Autoimmune hepatitis (AIH) is an excellent indication for liver transplantation. Five-year patient and graft survival after liver transplantation range from 83% to 92%.[25] There is a high prevalence of autoimmune liver disease, specifically AIH and primary biliary cirrhosis (PBC), among British Columbia's First Nations people.[26]

Patients with autoimmune liver disease may have fairly rapid clinical decompensation after a long period of disease stability. Such episodes may not be well tolerated and thus permit little time to undertake pre-transplant assessment. Liver transplantation is indicated for patients who are refractory to or intolerant of immunosuppressive therapy and develop end-stage liver disease. A subset of patients may present with fulminant hepatitis and liver failure. All patients with fulminant disease should be transferred to a liver transplant centre for monitoring and management. The rate of acute and chronic allograft rejection and steroid-resistant rejection is higher among AIH post-transplant patients. The recurrence rate of primary disease is also higher—at least 17%.[27]

Primary biliary cirrhosis

PBC is one of the most common indications for liver transplantation in British Columbia and the rest of the western world. The current 5-year survival rate for liver transplant because of PBC is 80% to 90%.[28] Management of progressive PBC requires predicting the prognosis and optimal time for transplantation. A model developed at the Mayo Clinic that does not require

liver biopsy has been used for prediction.[29] Prognosis is predicted from the patient's age, serum bilirubin, and albumin concentrations, the prothrombin time, and the presence of edema. Of these variables, serum bilirubin concentration is the most heavily weighted. Patients should be referred for transplant assessment when their serum bilirubin concentration approaches 100 µmol/L and before it reaches 150 µmol/L.[30]

Primary sclerosing cholangitis

Liver transplantation is the treatment of choice for patients with end-stage primary sclerosing cholangitis (PSC). Five-year survival after transplantation is as high as 85%.[31] As it has for PBC, the Mayo Clinic has devised a model for predicting lifespan in primary sclerosing cholangitis. It includes age, serum bilirubin, serum albumin, serum AST, and a history of variceal bleeding.[32] The model suggests that liver transplantation be undertaken when the estimated 6-month survival is less than 80%. A generally accepted list of indications in PSC also includes quality-of-life issues such as intractable itch or fatigue.

Recurrence of PSC following liver transplantation in up to 20% of patients has been reported in several studies.[33] The diagnosis of recurrence is based upon consistent findings on liver biopsy and cholangiography in the absence of other conditions that could lead to similar findings, such as hepatic artery thrombosis, dominant anastomotic stricture, or ABO blood group mismatched liver allograft.

The risk of cholangiocarcinoma is increased in PSC patients, with reported life-time prevalence rates varying from 5% to 20%.[34] Several reports have suggested that the incidence of colon cancer is increased in patients with ulcerative colitis and PSC who undergo liver transplantation.[35]

Metabolic diseases

Liver transplantation may play a vital role in the management of hemochromatosis, Wilson's disease (WD), and alpha-1 antitrypsin deficiency. Liver transplantation is the only effective option for those with WD who present with acute liver failure. It is also indicated for all patients with WD who have decompensated liver disease unresponsive to medical therapy. Liver transplantation corrects the hepatic metabolic defects of WD and may normalize extrahepatic copper metabolism.[36] One-year survival following liver transplantation ranges from 79% to 87%. Data collected between 1997 and 2006 from the United Network for Organ Sharing indicate that recipients with a diagnosis of hemochromatosis had 1-, 3-, and 5-year survival rates comparable to that of all other transplant recipients.[37] Transplantation may also cure the underlying metabolic disorder of alpha-1 antitrypsin deficiency since the metabolic defects reside within the liver.[38]

Contraindications and challenges

At present there are relatively few absolute contraindications to liver transplantation. Conditions that were considered as absolute contraindications in the recent past may no longer even qualify as relative contraindications. Current absolute contraindications include uncontrolled infection, extrahepatic malignancy, severe cardiopulmonary comorbidity, noncompliance, active substance abuse, advanced hepatoma, and cholangiocarcinoma. Relative contraindications include extreme age and difficult psychosocial factors.

At present there are relatively few absolute contraindications to liver transplantation. Conditions that were considered as absolute contraindications in the past may no longer even qualify as relative contraindications.

A retrospective study of BC Transplant data collected from 1997 to 2001 reveals that 150 of 737 patients referred for assessment were considered unsuitable. Of these, 74 patients (49%) were found unsuitable on medical grounds. The most common cause for medical unsuitability was no need for liver transplant—29 patients (39%). Other medical causes included hepatoma or extrahepatic malignancy—20 patients (27%)—and multisystem failure—12 patients (16%). Psychosocial contraindication accounted for 73 patients (49%). Within this group, failure to meet minimal alcohol abstinence criteria excluded the largest number of patients (39, 53.4%) followed by unsatisfactory social support (12, 16.4%), medical noncompliance (10, 13.7%), and active substance abuse (6, 8.2%).[39]

HIV

Prior to the introduction of highly active antiretroviral therapy (HAART), the transplantation outcomes for patients with human immunodeficiency virus infection were unfavorable.[40] Because HIV and HCV have similar transmission routes, 16% to 29% of HIV-infected patients have coinfection with hepatitis C.[41] While survival of HIV infection is improving on HAART, hepatitis-related end-stage liver disease has become a major cause of morbidity and mortality in this group. Patients with HIV and HCV coinfection progress faster to cirrhosis than patients with HCV alone; the morbidity and mortality risk of end-stage liver disease and hepatocellular carcinoma is also increased.

Patients can be considered for transplantation with a current CD4 count of more than 200 per mL, low HIV viral load, and limited opportunistic complications with standard listing criteria. The cumulative survival in a study among HIV patients was similar to that among age and race comparable patients without HIV.[42] British Columbia is one of the few centres in Canada that have been routinely assessing HIV patients with end-stage liver diseases for transplantation. Complex drug interactions, immunosuppressive dosing, and the possibility of HCV recurrence are the main issues that require the special consideration of an experienced multidisciplinary team.

Patients progressing beyond their 1-year post-transplant anniversary will mostly be stable and will need their primary care providers to actively participate in surveillance and treatment of their global health needs.

Age

Transplantation in extreme-age patients, either very young or old, is difficult. However, the age boundary is ever-changing. It has been reported that there are no differences in post-transplant outcomes in older versus younger patients in several centres. Transplant can be successfully performed in patients as old as 70. In BC the general philosophy is to consider the "biological age" rather than the "chronological age."

Comorbidities

It is part of the assessment process to evaluate any existing comorbidity and decide whether it increases surgical and anesthetic risk. Cardiovascular and pulmonary morbidity, including coronary artery disease, need careful consideration. Potential surgical problems such as portal vein thrombosis and other anatomical difficulties resulting from previous abdominal surgeries and trauma are also carefully explored.

Living donor liver transplantation

In response to the growing shortage of organs from deceased donors, adult living donor liver transplantation (LDLT) was introduced in 1998.[43] This is a technically demanding procedure and carries higher risks of postoperative complications than a deceased donor transplant. There are also significant risks to the donor that must be addressed when considering risks and benefits of LDLT versus deceased donor liver transplantation.

Retransplantation

Currently, retransplantation accounts for almost 10% of all liver transplants. Retransplantation is effective in the setting of primary nonfunction. Survival after retransplantation for late-onset graft failure is less than after initial transplantation.[44] The outcome of retransplantation for recurrent HCV is poor and this remains a controversial subject.

Role of the primary care physician

Primary care physicians play a very important role in liver transplantation. All physicians in BC need to understand that the role of BC Transplant is limited to assessment and investigation for transplant suitability and feasibility in the pre-transplant period. As pre-transplant referrals arise from all regions of BC and the Yukon, it is not possible for the Liver Transplant Program to assume primary and secondary care of these patients, so the community primary care physicians and specialists still need to follow these patients. Post-transplant, the Liver Transplant Program follows all patients carefully and manages all post-transplant complications. However, patients progressing beyond their 1-year post-transplant anniversary will mostly be stable and will need their primary care providers to actively participate in surveillance and treatment of their global health needs.

Conclusions

Over the past 20 years liver transplantation has evolved in BC from a pro-

cedure considered experimental to standard therapy for patients with end-stage liver disease. Today the main limitation is the tragic disparity between organ availability and organ need. Given the scarcity of available donor organs and the physiologically demanding nature of every liver transplant operation, candidates need to be evaluated carefully for medical and psychological comorbidities to improve the post-transplant outcome. Although not all patients referred for liver transplantation can undergo liver transplantation, the Liver Transplant Program ensures that all are treated fairly.

Acknowledgments

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Competing interests

Dr Steinbrecher served on an Astellas Pharma advisory board for clinical trials in 2009 and received a liver transplant fellow stipend from 2004 to 2009. Dr Yoshida has received honoraria and unrestricted research grants from a range of pharmaceutical companies, including Roche, Schering-Plough, Gilead, and Novartis.

Given the scarcity of available donor organs and the physiologically demanding nature of every liver transplant operation, candidates need to be evaluated carefully to improve the post-transplant outcome.

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