Liver Transplant

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Line(s) of Business: HMO; PPO
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Section: Transplants
Place(s) of Service: Inpatient

Precertification is required for this service

I. Description

Liver transplantation is currently performed routinely as a treatment of last resort for patients with end-stage liver disease. Liver transplantation may be performed with liver donation after brain or cardiac death or with a liver segment donation from a living donor. Patients are prioritized for transplant by mortality risk and severity of illness criteria developed by the Organ Procurement and Transplantation Network (OPTN) and the United Network of Organ Sharing (UNOS). The severity of illness is determined by the model for end-stage liver disease (MELD) and pediatric end-stage liver disease (PELD) scores.

Liver transplant is an accepted treatment of end-stage liver disease that provides a survival benefit in appropriately selected patients and thus, may be considered medically necessary for the previously described indications which are also listed in the Policy Statement and in those otherwise meeting UNOS criteria. Liver transplantation is investigational in patients in whom the procedure is expected to be futile due to comorbid disease or in whom posttransplantation care is expected to significantly worsen comorbid conditions. Case series and case-control data indicate that HIV infection is not an absolute contraindication to liver transplant; for patients who meet selection criteria, these studies have demonstrated patient and graft survival rates are similar to those in the general population of kidney transplant recipients.

Recent literature continues to address expanded criteria for transplantation for HCC, predictors of recurrence, the role of neoadjuvant therapy in patients with hepatocellular carcinoma (HCC), expanded donor criteria, transplantation and retransplantation for hepatitis C, and living donor transplantation. Further study is needed before liver transplant selection criteria can be expanded for HCC. Additionally, further study is needed to address salvage liver transplantation for HCC recurrence after primary liver resection.
Liver transplantation for hilar cholangiocarcinoma is performed at some transplant centers, and long-term survival has been reported in select patients with unresectable disease. For metastatic neuroendocrine tumors (NETs), cure of disease is not achieved, and 5-year survival is generally not high. However, there have been reports of survival benefit in patients receiving liver transplantation for unresectable NET metastasis confined to the liver. Based on survival data and clinical vetting input, transplantation in patients with hilar cholangiocarcinoma who meet strict eligibility criteria may be considered medically necessary; transplantation for NET metastatic to the liver is considered investigational.

The literature on liver transplantation for pediatric hepatoblastoma is limited, but case series have demonstrated good outcomes and high rates of long-term survival. Additionally, nonmetastatic pediatric hepatoblastoma is included in UNOS criteria for patients eligible for liver transplantation. Therefore, liver transplantation for nonmetastatic pediatric hepatoblastoma may be considered medically necessary.

Case series have demonstrated favorable outcomes with liver retransplantation in certain populations, such as when criteria for an original liver transplantation are met for retransplantation. While some evidence suggests outcomes after retransplantation may be less favorable than for initial transplantation in some patients, long-term survival benefits have been demonstrated. There was support from clinical vetting for retransplantation following primary graft nonfunction, hepatic artery thrombosis, ischemic biliary injury after donation after cardiac death, chronic rejection or certain recurrent nonneoplastic diseases resulting in end-stage liver failure in a primary transplant. As a result, retransplantation after initial failed liver transplant may be considered medically necessary in these situations.

Background

**Recipients**

Liver transplantation is now routinely performed as a treatment of last resort for patients with end-stage liver disease. Liver transplantation may be performed with liver donation after brain or cardiac death or with a liver segment donation from a living donor. Patients are prioritized for transplant by mortality risk and severity of illness criteria developed by the Organ Procurement and Transplantation Network (OPTN) and the United Network of Organ Sharing (UNOS). The original liver allocation system was based on assignment to Status 1, 2A, 2B, or 3. Status 2A, 2B, and 3 were based on the Child-Turcotte-Pugh score, which included a subjective assessment of symptoms as part of the scoring system. In February 2002, Status 2A, 2B, and 3 were replaced with 2 disease severity scales: the model for end-stage liver disease (MELD) and pediatric end-stage liver disease (PELD) for patients younger than age 12 years scoring systems. In June 2013, OPTN/UNOS published its most recent allocation system, which previously expanded Status1 to Status 1A and 1B in September 2012. Status 1A patients have acute liver failure with a life expectancy of less than 7 days without a liver transplant. Status 1A patients also include primary graft nonfunction, hepatic artery thrombosis and acute Wilson’s disease. Status 1A patients must be recertified as Status 1A every 7 days. Status 1B patients are pediatric patients (age range, 0-17 years) with chronic liver disease listed as: fulminant liver failure, primary nonfunction, hepatic artery thrombosis, acute
decompensated Wilson’s disease, chronic liver disease; and nonmetastatic hepatoblastoma. Pediatric patients move to Status 1A upon age18 but still qualify for pediatric indications.

Following Status 1, donor livers will be prioritized to those with the highest scores on MELD or PELD. With this allocation system, the highest priority for liver transplantation is given to patients receiving the highest number of points. The scoring system for MELD and PELD is a continuous disease severity scale based entirely on objective laboratory values. These scales have been found to be highly predictive of the risk of dying from liver disease for patients waiting on the transplant list. The MELD score incorporates bilirubin, prothrombin time (ie, international normalized ratio [INR]), and creatinine into an equation, producing a number that ranges from 6 to 40. The PELD score incorporates albumin, bilirubin, INR growth failure, and age at listing. Waiting time will only be used to break ties among patients with the same MELD or PELD score and blood type compatibility. In the previous system, waiting time was often a key determinant of liver allocation, and yet, waiting time was found to be a poor predictor of the urgency of liver transplant because some patients were listed early in the course of their disease, while others were listed only when they became sicker. In the revised allocation systems, patients with a higher mortality risk and higher MELD/PELD scores will always be considered before those with lower scores, even if some patients with lower scores have waited longer. Status 7 describes patients who are temporarily inactive on the transplant waiting list due to being temporarily unsuitable for transplantation. Pediatric patients who turn 18 are status X.

**Donors**

Due to the scarcity of donor livers, a variety of strategies have been developed to expand the donor pool. For example, split graft refers to dividing a donor liver into 2 segments that can be used for 2 recipients. Living donor liver transplantation (LDLT) is now commonly performed for adults and children from a related or unrelated donor. Depending on the graft size needed for the recipient, either the right lobe, left lobe or the left lateral segment can be used for LDLT. In addition to addressing the problem of donor organ scarcity, LDLT allows the procedure to be scheduled electively before the recipient’s condition deteriorates or serious complications develop. LDLT also shortens the preservation time for the donor liver and decreases disease transmission from donor to recipient.

**II. Guidelines**

A. A liver transplant, using a cadaver or living donor, is covered (subject to Administrative Guidelines) for carefully selected patients with end-stage liver failure due to irreversibly damaged livers.

B. Etiologies of end-stage liver disease include, but are not limited to, the following:
   1. Hepatocellular diseases
      a. Alcoholic liver disease
      b. Viral hepatitis (either A, B, C, or non-A, non-B)
      c. Autoimmune hepatitis
      d. Alpha-1 antitrypsin deficiency
      e. Hemochromatosis
f. Non-alcoholic steatohepatitis  
g. Protoporphyria  
h. Wilson's disease  

2. Cholestatic liver diseases  
a. Primary biliary cirrhosis  
b. Primary sclerosing cholangitis with development of secondary biliary cirrhosis  
c. Biliary atresia  

3. Vascular disease  
a. Budd-Chiari syndrome  

4. Primary hepatocellular carcinoma  
5. Inborn errors of metabolism  
6. Trauma and toxic reactions  
7. Miscellaneous  
a. Familial amyloid polyneuropathy  

C. Liver transplantation is covered (subject to Administrative Guidelines) in patients with polycystic disease of the liver who have massive hepatomegaly causing obstruction or functional impairment.  

D. Liver transplantation is covered (subject to Administrative Guidelines) in patients with unresectable hilar cholangiocarcinoma.  

E. Liver transplantation is covered (subject to Administrative Guidelines) in pediatric patients with nonmetastatic hepatoblastoma.  

F. Liver retransplantation is covered (subject to Administrative Guidelines) in patients with:  
   1. primary graft nonfunction  
   2. hepatic artery thrombosis  
   3. chronic rejection  
   4. ischemic type biliary lesions after donation after cardiac death  
   5. recurrent non-neoplastic disease causing late graft failure  

III. Criteria  

General  
Potential contraindications subject to the judgment of the transplant center:  
   1. Known current malignancy, including metastatic cancer  
   2. Recent malignancy with high risk of recurrence  
   3. Untreated systemic infection making immunosuppression unsafe, including chronic infection  
   4. Other irreversible end-stage disease not attributed to liver disease  
   5. History of cancer with a moderate risk of recurrence  
   6. Systemic disease that could be exacerbated by immunosuppression  
   7. Psychosocial conditions or chemical dependency affecting ability to adhere to therapy
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Liver Specific Patient Selection Criteria
The MELD and PELD scores range from 6 (less ill) to 40 (gravely ill). The MELD and PELD scores will change during the course of a patient's tenure on the waiting list. Patients with liver disease related to alcohol or drug abuse must be actively involved in a substance abuse treatment program.

Patients with polycystic disease of the liver do not develop liver failure but may require transplantation due to the anatomic complications of a hugely enlarged liver. The MELD/PELD score may not apply to these cases. One of the following complications should be present:

1. Enlargement of liver impinging on respiratory function
2. Extremely painful enlargement of liver
3. Enlargement of liver significantly compressing and interfering with function of other abdominal organs

Patients with familial amyloid polyneuropathy do not experience liver disease, per se, but develop polyneuropathy and cardiac amyloidosis due to the production of a variant transthyretin molecule by the liver. MELD/PELD exception criteria and scores may apply to these cases. Candidacy for liver transplant is an individual consideration based on the morbidity of the polyneuropathy. Many patients may not be candidates for liver transplant alone due to coexisting cardiac disease.

Criteria used for patient selection of hepatocellular carcinoma patients eligible for liver transplant include the Milan criteria, which is considered the criterion standard, the University of California, San Francisco (UCSF) expanded criteria, and UNOS criteria.

**Milan Criteria**: a single tumor 5 cm or less in diameter or 2 to 3 tumors 3 cm or less

**UCSF expanded Criteria**: a single tumor 6.5 cm or less or up to 3 tumors 4.5 cm or less, and a total tumor size of 8 cm or less

**UNOS T2 Criteria**: a single tumor 1 cm or greater and up to 5 cm or less in diameter or 2 to 3 tumors 1 cm or greater and up to 3 cm or less and without extrahepatic spread or macrovascular invasion. UNOS criteria, which were updated in 2013, may prioritize T2 HCC that meet specified staging and imaging criteria by allocating additional points equivalent to a MELD score predicting a 15% probability of death within 3 months.

Patients with hepatocellular carcinoma are appropriate candidates for liver transplant only if the disease remains confined to the liver. Therefore, the patient should be periodically monitored while on the waiting list, and if metastatic disease develops, the patient should be removed from the transplant waiting list. In addition, at the time of transplant, a backup candidate should be scheduled. If locally extensive or metastatic cancer is discovered at the time of exploration prior to hepatectomy, the transplant should be aborted, and the backup candidate scheduled for transplant.

Note that liver transplantation for those with T3 HCC is not prohibited by UNOS guidelines, but these patients do not receive any priority on the waiting list. All patients with HCC awaiting
transplantation are reassessed at 3-month intervals. Those whose tumors have progressed and are no longer T2 tumors will lose the additional allocation points.

Additionally, nodules identified through imaging of cirrhotic livers are given a Class 5 designation. Class 5B and 5T nodules are eligible for automatic priority. Class 5B criteria consist of a single nodule 2 cm or larger and up to 5 cm (T2 stage) that meets specified imaging criteria. Class 5T nodules have undergone subsequent loco-regional treatment after being automatically approved on initial application or extension. A single Class 5A nodule (greater than 1 cm and less than 2 cm) corresponds to T1 HCC and does not qualify for automatic priority. However, combinations of Class 5A nodules are eligible for automatic priority if they meet stage T2 criteria. Class 5X lesions are outside of stage T2 and are not eligible for automatic exception points. Nodules less than 1 cm are considered indeterminate and are not considered for additional priority. Therefore, the UNOS allocation system provides strong incentives to use loco-regional therapies to downsize tumors to T2 status and to prevent progression while on the waiting list.

Cholangiocarcinoma
According to the OPTN policy on liver allocation, candidates with cholangiocarcinoma (CCA) meeting the following criteria will be eligible for a MELD/PELD exception with a 10% mortality equivalent increase every 3 months:

- Centers must submit a written protocol for patient care to the OPTN/UNOS Liver and Intestinal Organ Transplantation Committee before requesting a MELD score exception for a candidate with CCA. This protocol should include selection criteria, administration of neoadjuvant therapy before transplantation, and operative staging to exclude patients with regional hepatic lymph node metastases, intrahepatic metastases, and/or extrahepatic disease. The protocol should include data collection as deemed necessary by the OPTN/UNOS Liver and Intestinal Organ Transplantation Committee.
- Candidates must satisfy diagnostic criteria for hilar CCA: malignant-appearing stricture on cholangiography and one of the following: carbohydrate antigen 19-9 100 U/mL, or and biopsy or cytology results demonstrating malignancy, or aneuploidy. The tumor should be considered unresectable on the basis of technical considerations or underlying liver disease (eg, primary sclerosing cholangitis).
- If cross-sectional imaging studies (computed tomography [CT] scan, ultrasound, magnetic resonance imaging [MRI]) demonstrate a mass, the mass should be 3 cm or less.
- Intra- and extrahepatic metastases should be excluded by cross-sectional imaging studies of the chest and abdomen at the time of initial exception and every 3 months before score increases.
- Regional hepatic lymph node involvement and peritoneal metastases should be assessed by operative staging after completion of neoadjuvant therapy and before liver transplantation. Endoscopic ultrasound-guided aspiration of regional hepatic lymph nodes may be advisable to exclude patients with obvious metastases before neoadjuvant therapy is initiated.
- Transperitoneal aspiration or biopsy of the primary tumor (either by endoscopic ultrasound, operative, or percutaneous approaches) should be avoided because of the high risk of tumor seeding associated with these procedures.
Donor Criteria - Living-Related Adult-to-Adult Transplant

Donor morbidity and mortality are prime concerns in donors undergoing right lobe, left lobe, or left lateral segment donor partial hepatectomy as part of living-donor liver transplantation. Partial hepatectomy is a technically demanding surgery, the success of which may be related to the availability of an experienced surgical team. In 2000, the American Society of Transplant Surgeons proposed the following guidelines for living donors:

- Should be healthy individuals who are carefully evaluated and approved by a multidisciplinary team including hepatologists and surgeons to assure that they can tolerate the procedure
- Should undergo evaluation to assure that they fully understand the procedure and associated risks
- Should be of legal age and have sufficient intellectual ability to understand the procedures and give informed consent
- Should be emotionally related to the recipients
- Must be excluded if the donor is felt or known to be coerced
- Needs to have the ability and willingness to comply with long-term follow-up

IV. Limitations Exclusions

A. Liver transplantation is not covered in the following situations as it is not known to be effective in improving health outcomes:
   1. Patients with intrahepatic cholangiocarcinoma
   2. Patients with neuroendocrine tumors metastatic to the liver

B. Liver transplantation is not covered in the following patients as it is not known to be effective in improving health outcomes:
   1. Patients with hepatocellular carcinoma that has extended beyond the liver
   2. Patients with ongoing alcohol and/or drug abuse. (Evidence for abstinence may vary among liver transplant programs, but generally a minimum of 3 months is required.)

C. Liver transplantation is not covered in all other situations not described above.

V. Administrative Guidelines

Precertification is required for a transplant evaluation and for the transplant itself and should be submitted by the proposed treating facility. To precertify, please complete HMSA's Precertification Request and mail or fax the form, or use iExchange as indicated along with the required documentation.

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<th>CPT Codes</th>
<th>Description</th>
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<td>47133</td>
<td>Donor hepatectomy (including cold preservation); from cadaver donor</td>
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<td>47135</td>
<td>Liver allotransplantation; orthotopic; partial or whole, from cadaver or living donor, any age</td>
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<tr>
<td>47136</td>
<td>Liver allotransplantation; heterotopic, partial or whole, from cadaver or living donor, any age</td>
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<td>K75.81 Nonalcoholic steatohepatitis (NASH)</td>
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<tr>
<td>K77</td>
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K83.0-K83.9 Other diseases of biliary track; code range
Q44.6 Congenital Cystic disease of liver
S36.12xA-S36.13xS Injury of liver and gallbladder and bile duct; code range
T86.41 Liver transplant rejection
T86.42 Liver transplant failure
Z52.6 Liver donor

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<td>Surgical, transplantation, liver, open, code by qualifier (allogeneic or syngeneic)</td>
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VI. Scientific Background

This policy is regularly updated with searches of the MEDLINE database. The most recent literature search was performed for the period of December 18, 2013 through December 18, 2014. The following is a summary of the key findings to date.

Overview

Relevant outcomes for studies on liver transplantation include waiting time duration, dropout rates, survival time, and recurrence. As experience with liver transplant has matured, patient selection criteria have broadened to include a wide variety of etiologies. The most controversial etiologies include viral hepatitis and primary hepatocellular cancer. In particular, the presence of hepatitis B virus (HBV) and hepatitis C virus (HCV) have been controversial indications for liver transplantation because of the high potential for recurrence of the virus and subsequent recurrence of liver disease. However, registry data indicate a long-term survival rate (7 years) of 47% in HBV-positive transplant recipients, which is lower than that seen in other primary liver diseases such as primary biliary cirrhosis (71%) or alcoholic liver disease (57%).(6) Recurrence of HCV infection in transplant recipients has been nearly universal, and 10% to 20% of patients will develop cirrhosis within 5 years.(7) Although these statistics raise questions about the most appropriate use of a scarce resource (donor livers), the long-term survival rates are significant in a group of patients who have no other treatment options. Similarly, the long-term outcome in patients with primary hepatocellular malignancies was poor (19%) in the past compared to the overall survival of liver transplant recipients. However, recent use of standardized patient selection criteria, such as the Milan criteria (a solitary tumor with a maximum tumor diameter of 5 cm or less, or up to 3 tumors 3 cm or smaller and without extrahepatic spread or macrovascular invasion), has dramatically improved overall survival rates. In a systematic review of liver transplant for
hepatocellular carcinoma (HCC) in 2012, Maggs et al found 5-year overall survival rates ranged from 65% to 94.7% in reported studies. Nevertheless, transplant represents the only curative approach for many of these patients who present with unresectable organ-confined disease, and expansion of patient selection criteria, bridging to transplant or downstaging of disease to qualify for liver transplantation is frequently studied. Liver transplant cannot be considered curative in patients with locally extensive or metastatic liver cancer or in patients with isolated liver metastases with extrahepatic primaries or in cholangiocarcinoma.

Living Donor Liver Transplantation Donor Outcomes
Due to the scarcity of donor organs and the success of living donation, living donor liver transplantation has become accepted practice. The living donor undergoes hepatectomy of the right lobe, the left lobe, or the left lateral segment, which is then transplanted into the recipient. Since hepatectomy involves the resection of up to 70% of the total volume of the donor liver, the safety of the donor has been the major concern. For example, the surgical literature suggests that right hepatectomy of diseased or injured livers is associated with mortality rates of about 5%. However, initial reports suggest that right hepatectomy in healthy donors has a lower morbidity and mortality. The Medical College of Virginia reported the results of their first 40 adult-to-adult living donor liver transplantations, performed between June 1998 and October 1999. There were an equal number of related and unrelated donors. Minor complications occurred in 7 donors. The outcomes among recipients were similar to those associated with cadaveric donor livers performed during the same period of time. However, in the initial series of 20 patients, 4 of the 5 deaths occurred in recipients who were classified as 2A (see Description section). In the subsequent 20 patients, recipients classified as 2A were not considered candidates for living-donor transplant. Other case series have reported similar success rates. Reports of several donor deaths reemphasize the importance of careful patient selection based in part on a comprehensive consent process and an experienced surgical team. In December 2000, the National Institutes of Health (NIH) convened a workshop focusing on living-donor liver transplantation. A summary of this workshop was published in 2002. According to this document, the risk of mortality to the donor undergoing right hepatectomy was estimated to be approximately 0.2% to 0.5%. Based on survey results, the workshop reported that donor morbidity was common; 7% required reexploration, 10% had to be rehospitalized, and biliary tract complications occurred in 7%. The median complication rate reported by responding transplant centers was 21%.

Due to the potential morbidity and mortality experienced by the donor, the workshop also noted that donor consent for hepatectomy must be voluntary and free of coercion; therefore, it was preferable that the donor have a significant long-term and established relationship with the recipient. According to the workshop summary, “At the present time, nearly all centers strive to identify donors who are entirely healthy and at minimal risk during right hepatectomy. As a result, only approximately one third of persons originally interested in becoming a living liver donor complete the evaluation process and are accepted as candidates for this procedure.”

Criteria for a recipient of a living-related liver are also controversial, with some groups advocating that living-related donor livers be only used in those most critically ill; while others state that the risk to the donor is unacceptable in critically ill recipients due to the increased risk of postoperative
mortality of the recipient. According to this line of thought, living-related livers are best used in stable recipients who have a higher likelihood of achieving long-term survival.

In 2000, the American Society of Transplant Surgeons issued the following statement:

Living donor transplantation in children has proven to be safe and effective for both donors and recipients and has helped to make death on the waiting list a less common event. Since its introduction in 1990, many of the technical and ethical issues have been addressed and the procedure is generally applied.

The development of left or right hepatectomy for adult-to-adult living donor liver transplantation has been slower. Because of the ongoing shortage of cadaver livers suitable for transplantation, adult-to-adult living donor liver transplantation has been undertaken at a number of centers. While early results appear encouraging, sufficient data are not available to ascertain donor morbidity and mortality rates. There is general consensus that the health and safety of the donor is and must remain central to living organ donation.

Brown et al reported on the results of a survey focusing on adult living-related recipients in the United States. The following statistics were reported:

- The survey encompasses 449 adult-to-adult transplantations.
- Half of the responding programs already had performed at least 1 adult-to-adult living-donor liver transplantation, and 32 of the remaining 41 centers were planning to initiate such surgery.
- 14 centers had performed more than 10 such transplantations, and these centers accounted for 80% of these transplants.
- A total of 45% of those evaluated for living donation subsequently donated a liver lobe; 99% were genetically or emotionally related to the recipient.
- Complications in the donor were more frequent in the centers that performed the fewest living-related donor transplantations.
- There was 1 death among the donors, but complications were relatively common, ie, biliary complications in 6% and reoperation in 4.5%

In 2002, NIH sponsored a conference on living-donor liver transplantation.(10) This report offered the following observations:

- The incidence and type of complications encountered and mortality associated with living-donor liver transplant in both donors and recipients need to be determined and compared with those for patients undergoing cadaveric transplantation.
- The question of whether all U.S. transplant programs should perform this operation or this complex procedure should be limited to only a few select centers needs to be addressed.

**Living Donor versus Deceased Donor Liver Transplant Recipient Outcomes**

In 2013, Grant et al reported on a systematic review and meta-analysis of 16 studies to compare recipient outcomes between living donor liver transplants and deceased donor liver transplants for
HCC.(19) For disease-free survival after living donor liver transplantation, the combined hazard ratio (HR) was 1.59 (95% confidence interval [CI], 1.02 to 2.49) compared with deceased donor liver transplantation. For overall survival, the combined HR was 0.97 (95% CI, 0.73 to 1.27). The studies included in the review were mostly retrospective and considered to be of low quality. Further study is needed to determine any differences between living and deceased liver transplantation outcomes.

HIV-Positive Patients
This subgroup of recipients has long been controversial, due to the long-term prognosis for human immunodeficiency virus (HIV) positivity, the impact of immunosuppression on HIV disease, and the interactions of immunosuppressive therapy with antiretroviral therapy in the setting of a transplanted liver. For example, most antiretroviral agents are metabolized through the liver and can cause varying degrees of hepatotoxicity. HIV candidates for liver transplantation are frequently coinfected with hepatitis B or C, and viral coinfection can further exacerbate drug-related hepatotoxocities. Nevertheless, HIV positivity is not an absolute contraindication to liver transplant due to the advent of highly active antiretroviral therapy (HAART), which has markedly changed the natural history of the disease and the increasing experience with liver transplant in HIV-positive patients. Furthermore, the United Network of Organ Sharing (UNOS) states that asymptomatic HIV-positive patients should not necessarily be excluded for candidacy for organ transplantation, stating “A potential candidate for organ transplantation whose test for HIV is positive but who is in an asymptomatic state should not necessarily be excluded from candidacy for organ transplantation, but should be advised that he or she may be at increased risk of morbidity and mortality because of immunosuppressive therapy.” In 2001, the Clinical Practice Committee of the American Society of Transplantation proposed that the presence of AIDS [acquired immune deficiency syndrome] could be considered a contraindication to kidney transplant unless the following criteria were present. These criteria may be extrapolated to other organs:

- CD4 count greater than 200 cells/mm$^3$ for more than 6 months
- HIV-1 RNA undetectable
- On stable antiretroviral therapy more than 3 months
- No other complications from AIDS (eg, opportunistic infection, including aspergillus, tuberculosis, coccidioses mycosis, resistant fungal infections, Kaposi’s sarcoma, or other neoplasm).
- Meeting all other criteria for transplantation.

It is likely that each individual transplant center will have explicit patient selection criteria for HIV-positive patients.

In 2011, Cooper et al conducted a systematic review to evaluate liver transplantation in patients coinfected with HIV and hepatitis. The review included 15 cohort studies and 49 case series with individual patient data. The survival rate of patients was 84.4% (95% CI, 81.1% to 87.8%) at 12 months. Patients were 2.89 (95% CI, 1.41 to 5.91) times more likely to survive when HIV viral load at the time of transplantation was undetectable compared with those with detectable HIV viremia.
Terrault et al reported on a prospective, multicenter study to compare liver transplantation outcomes in 3 groups: patients with both HCV and HIV (n=89), patients with only HCV (n=235), and all transplant patients age 65 or older. Patient and graft survival reductions were significantly associated with only 1 factor: HIV infection. At 3 years, in the HCV only group, patient and graft survival rates were significantly better at 79% (95% CI, 72% to 84%) and 74% (95% CI, 66% to 79%), respectively, than the group with both HIV and HCV infection at 60% (95% CI, 47% to 71%) and 53% (95% CI, 40% to 64%). While HIV infection reduced 3-year survival rates after liver transplantation in patients also infected with HCV, there were still a majority of patients experiencing long-term survival.

**HCC Selection Criteria**

Patient selection criteria for liver transplantation for HCC have focused mainly on the number and size of tumors. In 1996 Mazzafaro et al identified patient criteria associated with improved outcomes after liver transplantation for HCC with cirrhosis. This patient selection criteria became known as the Milan criteria and specifies patients may have either a solitary tumor with a maximum tumor diameter of 5 cm or less, or up to 3 tumors 3 cm or less. An editorial by Llovet noted that the Milan criteria is considered the criterion standard for selecting transplant candidates. Patients with extrahepatic spread or macrovascular invasion have a poor prognosis. UNOS adopted the Milan criteria, combined with 1 additional criteria (no evidence of extrahepatic spread or macrovascular invasion), as its liver transplantation criteria. Interest in expanding liver transplant selection criteria for HCC and other indications is ongoing. A 2001 paper from the University of California, San Francisco (UCSF), proposed expanded criteria to include patients with a single tumor 6.5 cm or less in diameter, 3 or fewer tumors 4.5 cm or less, and a total tumor size of 8 cm or less. It should be noted that either set of criteria can be applied preoperatively (with imaging) or with pathology of the explanted liver at the time of intended transplant. Preoperative staging often underestimates what is seen on surgical pathology. To apply pathologic criteria, a backup candidate must be available in case preoperative staging is inaccurate. Given donor organ scarcity, any expansion of liver transplant selection criteria has the potential to prolong waiting times for all candidates. Important outcomes in assessing expanded criteria include waiting time duration, death, or deselection due to disease progression while waiting (dropout), survival time, and time to recurrence (or related outcomes such as disease-free survival). Survival time can be estimated beginning when the patient is placed on the waiting list, using the intention-to-treat principal, or at the time of transplantation. Llovet stated that 1-year dropout rates for patients meeting Milan criteria are 15% to 30%, and 5-year survival rates not reported by intention-to-treat should be adjusted down by 10% to 15%.

A limited body of evidence is available for outcomes among patients exceeding Milan criteria but meeting UCSF criteria (see Table 1). The largest series was conducted in 14 centers in France, including an intention-to-treat total of 44 patients based on preoperative imaging at the time of listing and a subset of 39 patients meeting pathologic UCSF criteria. The median waiting time was 4.5 months, shorter than the typical 6 to 12 months in North America. Dropouts comprised 11.4% of total. Posttransplant overall patient 5-year survival at 63.6%, was more favorable than the intention-to-treat probability (45.5%) but less favorable than among larger numbers of patients meeting Milan criteria. Similar findings were seen for disease-free survival and cumulative
incidence of recurrence. Three centers in Massachusetts included 10 patients beyond pathologic Milan criteria but within UCSF criteria. Two-year survival posttransplant was 77.1%, with 2 patients dying and 8 alive after a median of 32 months. A group of 74 patients meeting preoperative Milan criteria had a 2-year survival probability of about 73%, but it is inadvisable to compare different preoperative and pathologic staging criteria. From the series of patients who developed the expanded UCSF criteria, 14 satisfied those criteria on pathology but exceeded the Milan criteria. UCSF investigators did not provide survival duration data for this subgroup, but noted that 2 patients died. A center in Essen, Germany reported on 4 patients. Although the French series suggests that outcomes among patients exceeding Milan criteria and meeting UCSF criteria are worse than for patients meeting Milan criteria, it is unclear whether the latter group still achieves acceptable results. A benchmark of 50% 5-year survival has been established in the liver transplant community, and the French study meets this by posttransplant pathologic staging results (63.6%) and falls short by preoperative intention-to-treat results (45.5%).

In their 2008 review, Schwartz et al argue that selection based exclusively on the Milan criteria risks prognostic inaccuracy due to the diagnostic limitations of imaging procedures and the surrogate nature of size and number of tumors. They predict that evolution of allocation policy will involve the following: the development of a reliable prognostic staging system to help with allocation of therapeutic alternatives; new molecular markers that might improve prognostic accuracy; aggressive multimodality neoadjuvant therapy to downstage and limit tumor progression before transplant and possibly provide information about tumor biology based on response to therapy; and prioritization for transplantation should consider response to neoadjuvant therapy, time on waiting list, suitability of alternative donor sources. Two papers describe work on identifying predictors of survival and recurrence of disease. Ioannou et al analyzed UNOS data pre- and postadoption of the Model for End-stage Liver Disease (MELD) allocation system finding a 6-fold increase in recipients with HCC and that survival in the MELD era was similar to survival in patients without HCC. The subgroup of patients with larger (3-5 cm) tumors, serum alpha-fetoprotein level equal to or greater than 455 mg/mL, or a MELD score equal to or greater than 20, however, had poor transplantation survival. A predicting cancer recurrence scoring system was developed by Chan et al based on a retrospective review and analysis of liver transplants at 2 centers to determine factors associated with recurrence of HCC. Of 116 patients with findings of HCC in their explanted livers, 12 developed recurrent HCC. Four independent significant explant factors were identified by stepwise logistic regression: size of 1 tumor greater than 4.5 cm, macroinvasion, and bilobar tumor were positive predictors of recurrence, and the presence of only well-differentiated HCC was a negative predictor. Points were assigned to each factor in relation to its odds ratio (OR). The accuracy of the method was confirmed in 2 validation cohorts.

In 2010, Guiteau et al reported on 445 patients transplanted for HCC in a multicenter, prospective study in UNOS Region 4. On preoperative imaging, 363 patients met Milan criteria, and 82 patients were under expanded Milan criteria consisting of 1 lesion less than 6 cm, equal to or less than 3 lesions, none greater than 5 cm and total diameter less than 9 cm. Patient allograft and recurrence-free survival at 3 years did not differ significantly between patients meeting Milan criteria versus patients under the expanded criteria (72.9% and 77.1%, 71% and 70.2% and 90.5% and 86.9%, all respectively). While preliminary results showed similar outcomes when using expanded Milan
criteria, the authors noted their results were influenced by waiting times in Region 4 and that similar outcomes may be different in other regions with different waiting times. Additionally, the authors noted that a report from a 2010 national HCC consensus conference on liver allocation in HCC patients does not recommend expanding Milan criteria nationally and encourages regional agreement. The report addressed the need to better characterize the long-term outcomes of liver transplantation for patients with HCC and to assess whether it is justified to continue the policy of assigning increased priority for candidates with early-stage HCC on the transplant waiting list in the U.S. Overall, the evidence base is insufficient to permit conclusions about health outcomes after liver transplantation among patients exceeding Milan criteria and meeting expanded UCSF or other criteria.

Table 1. Outcomes Among Patients With Hepatocellular Carcinoma Exceeding Milan Selection Criteria and Meeting UCSF Criteria

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>Group</th>
<th>n</th>
<th>1 y Probability, %</th>
<th>2 y Probability, %</th>
<th>5 y Probability, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decaens et al (2006)(24)</td>
<td>Intention-to-treat, preoperative</td>
<td>Milan+</td>
<td>279</td>
<td>61.0</td>
<td>45.5</td>
<td>60.4</td>
</tr>
<tr>
<td></td>
<td>Overall patient survival</td>
<td>Milan-/UCSF</td>
<td></td>
<td></td>
<td></td>
<td>47.8</td>
</tr>
<tr>
<td></td>
<td>Cumulative incidence of recurrence</td>
<td>Milan+</td>
<td></td>
<td></td>
<td></td>
<td>70.4</td>
</tr>
<tr>
<td></td>
<td>Disease-free survival</td>
<td>Milan-/UCSF+</td>
<td></td>
<td></td>
<td></td>
<td>63.6</td>
</tr>
<tr>
<td></td>
<td>Posttransplant, pathologic (p)</td>
<td>pMilan+</td>
<td>184</td>
<td>77.1</td>
<td>50.9</td>
<td>47.8</td>
</tr>
<tr>
<td></td>
<td>Overall patient survival</td>
<td>pMilan-/pUCSF+</td>
<td></td>
<td></td>
<td></td>
<td>70.2</td>
</tr>
<tr>
<td></td>
<td>Cumulative incidence of recurrence</td>
<td>pMilan+</td>
<td></td>
<td></td>
<td></td>
<td>62.2</td>
</tr>
<tr>
<td></td>
<td>Disease-free survival</td>
<td>pMilan-/pUCSF+</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Milan-/UCSF+ median waiting time, 4.5 mo (0.1-20.4); 5/44 dropouts (11.4%)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>pMilan-/pUCSF+</td>
<td>10</td>
<td></td>
<td>77.1</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>2 patients died at 3 and 22 mo, 8 patients alive after median 32-mo follow-up (6.6-73.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yao et al (2002)(26) UCSF</td>
<td>Posttransplant overall patient survival</td>
<td>pMilan+</td>
<td>46</td>
<td>91</td>
<td>81</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>pMilan-/pUCSF+, n=14, 2 patients died, 8 alive but no information on survival duration, 1 patient retransplanted 5 mo after initial transplant</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sotiropoulos et al (2006)(32)</td>
<td>Milan-/UCSF+, n=4, 1 patient died at 20 mo, 3 patients alive at median follow-up 57 mo</td>
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</tbody>
</table>
Liver Transplantation Versus Liver Resection for HCC

Liver transplantation is the criterion standard treatment for HCC meeting Milan criteria in decompensated livers such as Child-Pugh class B or C (moderate to severe cirrhosis). Liver resection is generally used for early HCC in livers classified as Child-Pugh class A. Additionally, current UNOS criteria indicate a liver transplant candidate must not be eligible for resection. However, the best treatment approach for early HCC in well-compensated livers is controversial. In 2013, Zheng et al reported on a meta-analysis of 62 cohort studies (n=10,170 total patients) comparing liver transplantation to liver resection for HCC. Overall 1-year survival was similar between procedures (OR=1.08; 95% CI, 0.81 to 1.43; p=0.61). However, overall 3- and 5-year survival significantly favored liver transplantation over resection (OR=1.47; 95% CI, 1.18 to 1.84; p<0.001; OR=1.77; 95% CI, 1.45 to 2.16; p<0.001, respectively). Disease-free survival in liver transplant patients was 13%, 29%, and 39% higher than in liver resection patients at 1, 3, and 5 years, all respectively (p<0.001). Recurrence rates were also 30% lower in liver transplantation than resection (OR=0.20; 95% CI, 0.15 to 0.28; p<0.001). While liver transplantation outcomes appear favorable compared to liver resection, a shortage of donor organs may necessitate liver resection as an alternative to liver transplantation.

In patients who have a recurrence of HCC after primary liver resection, salvage liver transplantation has been considered a treatment alternative to repeat hepatic resection, chemotherapy, or other local therapies such as radiofrequency ablation, transarterial chemoembolization, percutaneous ethanol ablation, or cryoablation.

Several systematic reviews have evaluated the evidence on outcomes of salvage transplant compared with primary transplant. In a 2013 meta-analysis of 14 nonrandomized comparative studies by Zhu et al, (n=1272 for primary transplant and n=236 for salvage), overall survival at 1, 3, and 5 years and disease-free survival at 1 and 3 years was not significantly different between groups. Disease-free survival, however, was significantly lower at 5 years in salvage liver transplantation compared with primary transplantation (OR=0.62; 95% CI, 0.42 to 0.92; p=0.02). There was insufficient data to evaluate outcomes in patients exceeding Milan criteria, but in patients meeting Milan criteria, survival outcomes were not significantly different suggesting salvage liver transplantation may be a viable option in these patients.

In a 2012 meta-analysis, Li et al, compared primary liver transplantation to salvage liver transplantation (liver transplantation after liver resection) for HCC. Included in the meta-analysis were 11 case-controlled or cohort studies totaling 872 primary liver transplants and 141 salvage liver transplants.

Overall survival and disease-free survival rates between primary liver transplantation and salvage liver transplantation were not statistically significant at 1, 3, and 5 years (p>0.05). Survival rates of
patients who exceeded the Milan criteria at 1, 3, and 5 years were also not significantly different between the 2 groups (1-year OR=0.26; 95% CI, 0.01 to 4.94; p=0.37; 3-year OR=0.41; 95% CI, 0.01 to 24.54; p=0.67; 5-year OR=0.55; 95% CI, 0.07 to 4.48; p=0.57).

In 2013, Chan et al systematically reviewed 16 nonrandomized studies (n=319) on salvage liver transplantation after primary hepatic resection for HCC. The authors found that overall and disease-free survival outcomes with salvage liver transplantation were similar to reported primary liver transplantation outcomes. The median overall survival for salvage liver transplantation patients was 89%, 80% and 62% at 1, 3, and 5 years, respectively. Disease-free survival was 86%, 68% and 67% at 1, 3, and 5 years, respectively. Salvage liver transplantation studies had median overall survival rates of 62% (range, 41%-89%) compared with a range of 61% to 80% in the literature for primary liver transplantation. Median disease-free survival rates for salvage liver transplantation were 67% (range, 29%-100%) compared with a range of 58% to 89% for primary liver transplantation. Given a limited donor pool and increased surgical difficulty with salvage liver transplantation, further studies are needed. UNOS criteria indicate liver transplant candidates with HCC who subsequently undergo tumor resection must be prospectively reviewed by a regional review board for the extension application.

**Nonalcoholic Steatohepatitis**

Liver transplantation is a treatment option for patients with nonalcoholic steatohepatitis (NASH) who progress to liver cirrhosis and failure. In a 2013 systematic review and meta-analysis, Wang et al evaluated 9 studies comparing liver transplantation outcomes in patients with and without NASH. Patients with NASH had similar 1-, 3-, and 5-year survival outcomes after liver transplantation as patients without NASH. Patients with NASH also had lower graft failure risk than those without NASH (OR=0.21; 95% CI, 0.05 to 0.89; p=0.03). However, NASH liver transplant patients had a greater risk of death related to cardiovascular disease (OR=1.65; 95% CI, 1.01 to 2.70; p=0.05) and sepsis (OR=1.71; 95% CI, 1.17 to 2.50; p=0.006) than non-NASH liver transplant patients.

**Cholangiocarcinoma**

Reports on outcomes after liver transplantation for cholangiocarcinoma, or bile duct carcinoma generally distinguish between intrahepatic and extrahepatic tumors, the latter including hilar or perihilar tumors. Recent efforts have focused on pretransplant downstaging of disease with neoadjuvant radiochemotherapy.

In 2012, Gu et al reported on a systematic review and meta-analysis of 14 clinical trials on liver transplantation for cholangiocarcinoma. Overall 1-, 3-, and 5-year pooled survival rates from 605 study patients were 0.73 (95% CI, 0.65 to 0.80), 0.42 (95% CI, 0.33 to 0.51), and 0.39 (95% CI, 0.28 to 0.51), respectively. When patients received adjuvant therapies preoperatively, 1-, 3-, and 5-year pooled survival rates improved and were 0.83 (95% CI, 0.57 to 0.98), 0.57 (95% CI, 0.18 to 0.92), and 0.65 (95% CI, 0.40 to 0.87), respectively.

In 2012, Darwish Murad et al reported on 287 patients from 12 transplant centers treated with neoadjuvant therapy for perihilar cholangiocarcinoma followed by liver transplantation. Intent-to-
Liver Transplant

treat survival (after a loss of 71 patients before liver transplantation) was 68% at 2 years and 53% at 5 years, and recurrence-free survival rates posttransplant were 78% at 2 years and 65% at 5 years. Survival time was significantly shorter for patients who had a previous malignancy or did not meet UNOS criteria by having a tumor size greater than 3 cm, metastatic disease, or transperitoneal tumor biopsy (p<0.001).

The European Liver Transplant Registry was cited by a review article. Among 186 patients with intrahepatic cholangiocarcinoma, 1-year survival was 58%, and 5-year survival was 29%. In 169 patients with extrahepatic cholangiocarcinoma, the probabilities were 63% and 29%, respectively. The Cincinnati Transplant Registry reported on 207 patients with either intrahepatic or extrahepatic cholangiocarcinoma, finding a 1-year survival of 72% and a 5-year rate of 23%. The multicenter Spanish report included 36 patients with hilar tumors and 23 with peripheral intrahepatic disease. One-year survival was 82% and 77%, while 5-year survival was 30% and 23% in the 2 groups, respectively.

With Table 2 displaying all values discussed in this paragraph, among the individual centers, the Mayo Clinic in Minnesota has the most experience and most favorable results. Between 1993 and 2006, 65 patients underwent liver transplantation for unresectable perihilar cholangiocarcinoma or had perihilar tumor due to primary sclerosing cholangitis. Unresectable patients underwent neoadjuvant radiochemotherapy. One-year survival was 91% and 5-year survival was 76%. The University of California, Los Angeles (UCLA)/Cedars-Sinai, reported on 25 cases of both intrahepatic and extrahepatic cholangiocarcinoma. One-year survival was 71% and 3-year survival was 35%. The University of Pittsburgh found 1-year survival of 70% and 5-year survival of 18% among 20 patients with intrahepatic cholangiocarcinoma. A German study of 24 patients reported the poorest results. In 2011, Friman et al reported on 53 patients who received liver transplants for cholangiocarcinoma during the period of 1984-2005, in Norway, Sweden, and Finland. The 5-year survival rate was 25% overall, 36% in patients with TNM stage equal to or less than 2, and 10% in patients with TNM greater than 2. On further analysis using only data from those patients transplanted after 1995, the 5-year survival rate increased to 38% versus 0% for those transplanted before 1995. Additionally, the 5-year survival rate increased to 58% in those patients transplanted after 1995 with TNM stage equal to or less than 2 and a CA 19-9 equal to or less than 100. The authors suggest transplantation may have acceptable outcomes in select patients.

Table 2. Outcomes Among Patients With Cholangiocarcinoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>Group</th>
<th>n</th>
<th>1 y</th>
<th>2 y</th>
<th>3 y</th>
<th>5 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pascher et al (2003) review(41)</td>
<td>Overall patient survival</td>
<td>IH-CCA</td>
<td>186</td>
<td>58</td>
<td>38</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>European Liver Transplant Registry</td>
<td></td>
<td>EH-CCA</td>
<td>169</td>
<td>63</td>
<td>38</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Cincinnati Transplant Registrya</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple centers in Spain, 03/88-09/01b</td>
<td></td>
<td>Peripheral CCA</td>
<td>23</td>
<td>77</td>
<td>65</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>
### Overall Patient Survival

<table>
<thead>
<tr>
<th>Study</th>
<th>Institution/Location</th>
<th>Tumor-Free Survival</th>
<th>Disease-Free Survival</th>
<th>Crude Recurrence Rate</th>
<th>Median Onset of Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude recurrence rate</td>
<td>EH-CCA: 19/36 (53%); IH-CCA: 8/23 (35%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disease-free survival</td>
<td>IH-CCA</td>
<td>16/9</td>
<td>62/39</td>
<td>39/42</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EH-CCA</td>
<td>9/25</td>
<td>86/42</td>
<td>31/42</td>
</tr>
<tr>
<td></td>
<td>Tumor-free survival</td>
<td>All</td>
<td>20/67</td>
<td>31/31</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>TNM stage &gt;2</td>
<td>21/10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>TNM stage ≤2</td>
<td>32/36</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CCA: cholangiocarcinoma; EH: extrahepatic; IH: intrahepatic.

* Unresectable CCA, cholangiohepatoma; incidental median follow-up, 23 mo (<1-96).
* Hilar or peripheral CCA; unresectable, postoperative recurrent, or incidental.
* Aggressive neoadjuvant radiochemotherapy, unresectable perihilar CCA or perihilar CCA from primary sclerosing cholangitis; mean follow-up, 32 mo (2 d to 13 y).
* IH or EH CCA; median follow-up, 22.3 mo.
* Unresectable CCA.

Some articles have reported recurrence data using survival analysis techniques. In a series of 38 patients from the Mayo Clinic, cumulative recurrence was 0% at 1 year, 5% at 3 years, and 13% at 5 years. The series of 20 patients from the University of Pittsburgh experienced 67% 1-year tumor-free survival and a 31% 5-year rate. The multicenter Spanish series reported crude recurrence rates of 53% and 36% for extrahepatic and intrahepatic cholangiocarcinoma, respectively. The German center at Hannover found a crude recurrence rate of 63%.

Mayo Clinic has reported promising results after liver transplantation for cholangiocarcinoma. Five-year patient survival among 65 patients who received neoadjuvant radiochemotherapy was 76%. No other center or group of centers reported 5-year survival above 30%. The Mayo Clinic found a 5-year cumulative recurrence rate of 13% among 38 patients and additional recurrence data are quite limited. While a single center’s results are encouraging, it is important to see if other centers can produce similar findings before forming conclusions about outcomes after liver transplantation for cholangiocarcinoma.

In a 2008 review, Heimbach considers the published outcomes of the combined protocol in the context of data on outcomes for surgical resection and concludes that outcomes of neoadjuvant...
chemoradiotherapy with subsequent liver transplantation for patients with early-stage hilar cholangiocarcinoma, which is unresectable, or arising in the setting of primary sclerosing cholangitis are comparable to transplantation for patients with HCC and other chronic liver diseases and superior to resection. The author describes intraoperative challenges attributable to the neoadjuvant therapy including severe inflammatory changes and dense fibrosis and suggests that key principles to be considered by centers considering use of the combined protocol include a multidisciplinary approach, pretransplant staging, inclusion of only patients without lymph node metastasis, replacement of irradiated vessels (when possible), and monitoring for postoperative vascular complications. Wu et al describe an extensive surgical procedure combined with radiotherapy. They retrospectively review their experience with surveillance and early detection of cholangiocarcinoma and en bloc total hepatectomy-pancreaticoduodenectomy-orthotopic liver transplantation (OLT-Whipple) in a small series of patients with early-stage cholangiocarcinoma complicating primary sclerosing cholangitis. Surveillance involved endoscopic ultrasound and endoscopic retrograde cholangiopancreatography and cytological evaluation. Patients diagnosed with cholangiocarcinoma were treated with combined extra-beam radiotherapy, lesion-focused brachytherapy, and OLT-Whipple. Cholangiocarcinoma was detected in 8 of the 42 patients followed up according to the surveillance protocol between 1988 and 2001, and 6 patients underwent OLT-Whipple. One died at 55 months after transplant of an unrelated cause without tumor recurrence, and 5 are without recurrence at 5.7 to 10.1 years.

**Hepatitis C**

Mukherjee and Sorrell, reviewing controversies in liver transplantation for hepatitis C, indicate that the greatest opportunity for HCV eradication is pretransplant before hepatic decompensation. Challenges of treatment posttransplantation include immunosuppressive drugs and abnormal hematologic, infectious, and liver function parameters. The authors list the following factors associated with poor outcomes in liver transplantation for recurrent HCV: high HCV-RNA level pretransplant, non-Caucasian ethnicity, advanced donor age, T cell-depleting therapies, inappropriate treatment of Banff A1 acute cellular rejection (ACR) with steroid boluses, cytomegalovirus disease, and year of transplantation (worse with recent transplants). They cite the International Liver Transplantation Society Consensus on Retransplantation, which states that the following are associated with worse outcomes of retransplantation: total bilirubin level greater than 10mg/dL, creatinine level greater than 2 mg/dL, age greater than 55 years, development of cirrhosis in the first posttransplant year, and donor age greater than 40 years.

As noted above, Terrault et al reported on a prospective, multicenter study to compare liver transplantation outcomes in 3 groups: patients with both HIV and HCV infection (n=89), patients with only HCV (n=235), and all transplant patients age 65 and older. (23) HCV status was not significantly associated with reduced patient and graft survival. In the HCV-only group, patient and graft survival rates were significantly better at 79% (95% CI, 72% to 84%) and 74% (95% CI, 66% to 79%), respectively, than the group with HIV and HCV at 60% (95% CI, 47% to 71%) and 53% (95% CI, 40% to 64%). While HIV infection reduced 3-year survival rates after liver transplantation in patients also infected with HCV, there were still a majority of patients experiencing long-term survival.
**Metastatic Neuroendocrine Tumors**

Neuroendocrine tumors (NETs) are relatively rare neoplasms that are generally slow-growing but rarely cured when metastatic to the liver. Treatment options to control or downstage the disease include chemotherapy and debulking procedures, including hepatic resection. In select patients with nonresectable, hormonally active liver metastases refractory to medical therapy, liver transplantation has been considered as an option to extend survival and minimize endocrine symptoms.

In 2014, Fan et al reported on a systematic review of 46 studies on liver transplantation for NET liver metastases of any origin. A total of 706 patients were included in the studies reviewed. Reported overall 5-year survival rates ranged from 0 to 100%, while 5-year disease-free survival rates ranged from 0 to 80%. In studies with more than 100 patients, the 5-year overall survival rate and disease-free survival rate averaged about 50% and 30%, respectively. Frequent and early NET recurrences after liver transplantation were reported in most studies.

In 2011, Mathe et al conducted a systematic review of the literature to evaluate patient survival after liver transplantation for pancreatic NETs. Data from 89 transplanted patients from 20 clinical studies were included in the review. Sixty-nine patients had primary endocrine pancreatic tumors, 9 patients were carcinoids, and 11 patients were not further classified. Survival rates at 1, 3, and 5 years were 71%, 55%, and 44%, respectively. The mean calculated survival rate was 54.45 (6.31) months, and the median calculated survival rate was 41 months (95% CI, 22 to 76 months). While there may be centers that perform liver transplantation on select patients with NETs, further studies are needed to determine appropriate selection criteria. The quality of available studies is currently limited by their retrospective nature and heterogeneous populations.

**Pediatric Hepatoblastoma**

Hepatoblastoma is a rare malignant primary solid tumor of the liver that occurs in children. Treatment consists of chemotherapy and resection; however, often tumors are not discovered until they are unresectable. In cases of unresectable tumors, liver transplantation with pre- and/or postchemotherapy is a treatment option with reports of good outcomes and high rates of survival. UNOS guidelines list nonmetastatic hepatoblastoma as a condition eligible for pediatric liver transplantation. In 2011, Barrena et al reported on 15 children with hepatoblastoma requiring liver transplantation. Overall survival after liver transplant was 93.3% (6.4%) at 1, 5, and 10 years. In 2010, Malek et al reported on liver transplantation results for 27 patients with primary liver tumor identified from a retrospective review of patients treated between 1990 and 2007. Tumor recurrence occurred in 1 patient after liver transplantation, and overall survival was 93%. In 2008 Browne et al reported on 14 hepatoblastoma patients treated with liver transplantation. Mean follow-up was 46 months, with overall survival in 10 of 14 patients (71%). Tumor recurrence caused all 4 deaths. In the 10 patients receiving primary liver transplantation, 9 survived while only 1 of 4 patients transplanted after primary resection survived (90% vs 25%, p=0.02). While studies on liver transplantation for pediatric hepatoblastoma are limited, case series have demonstrated good outcomes and high rates of long-term survival. Additionally, nonmetastatic pediatric hepatoblastoma is included in UNOS criteria for patients eligible for liver transplantation.
Therefore, liver transplantation for nonmetastatic pediatric hepatoblastoma may be considered medically necessary.

**Retransplantation**
In 2012, Bellido et al reported on a retrospective cohort study of 68 consecutive adult liver retransplantations using registry data. Survival probability using Kaplan-Meier curves with log-rank tests to compare 21 urgent versus 47 elective retransplantations were calculated. Overall survival rates were significantly better in patients undergoing urgent procedures (87%), which were mostly due to vascular complications than elective procedures (76.5%), which were mostly related to chronic rejection.

In 2011, Remiszewski et al examined factors influencing survival outcomes in 43 liver retransplantation patients. When compared to primary liver transplantation patients, retransplantation patients had significantly lower 6-year survival rates (80% vs 58%, respectively; p<0.001). The authors also reported low negative correlations between survival time and time from original transplantation until retransplantation and between survival time and patient age. Survival time and cold ischemia time showed a low positive correlation.

Hong et al, in 2011, reported on a prospective study of 466 adults to identify risk factors for survival after liver retransplantation. Eight risk factors were identified as predictive of graft failure, including age of recipient, MELD score greater than 27, more than 1 prior liver transplant, need for mechanical ventilation, serum albumin of less than 2.5 g/dL, donor age older than 45 years, need for more than 30 units of packed red blood cells transfused intraoperatively, and time between prior transplantation and retransplantation between 15 and 180 days. The authors propose this risk-stratification model can be highly predictive of long-term outcomes after adult liver retransplantation and can be useful in patient selection.

**Ongoing and Unpublished Clinical Trials**
A search of online site ClinicalTrials.gov on November 19, 2014 identified many ongoing clinical trials on liver transplant. Study (NCT00074386 a multi-institutional prospective study of liver and kidney transplantation in HIV-positive recipients). The enrollment was 150 kidney transplant recipients and 125 liver transplant recipients.

Washington State University is conducting a prospective registry study of neoadjuvant chemoradiation in conjunction with liver transplantation for cholangiocarcinoma (NCT00301379). There is an estimated enrollment of 20 and an estimated completion date of November 2015.

A study on liver transplantation for hilar cholangiocarcinoma began in March 2012 in Italy (NCT01549795). This study will enroll 33 patients, is still recruiting and had a primary completion date of July 2013. Status of this study is unknown, last verified in July 2012.

Liver transplantation for metastatic NET is being evaluated in a German study (NCT 01201096). In this observational study, patients will receive neoadjuvant peptide receptor-mediated radiotherapy with 177 lutetium about 9 months prior to liver transplantation. This study is expected to enroll 50
patients and is scheduled for completion in September 2018. This study was last verified in September 2010.

A study on liver transplantation after downstaging HCC exceeding the Milan Criteria is ongoing in Italy (NCT01387503). This study is evaluating 260 patients and is expected to be completed in January 2014. The status of this study is unknown, last verified in June 2011.

**Clinical Input Received through Physician Specialty Societies and Academic Medical Centers**

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

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In response to requests, input was received from 3 physician specialty societies and 5 academic medical centers while this policy was under review. There was consensus of agreement by the reviewers that liver transplantation may be medically necessary for end-stage liver failure due to irreversibly damaged livers from various disease states such as those listed in the above policy statement. There was also consensus of agreement by the reviewers that liver retransplantation is appropriate in patients with acute or chronic liver failure such as primary graft nonfunction, ischemic type biliary injury after donation after cardiac death, hepatic artery thrombosis, chronic rejection or recurrent diseases such as primary sclerosing cholangitis (PSC), autoimmune hepatitis, and hepatitis C resulting in end-stage liver failure. There was general support for the use of liver transplantation for the treatment of cholangiocarcinoma for patients who meet strict eligibility criteria. In general, there was not support for the use of liver transplantation for NET metastatic to the liver.

**Summary of Evidence**

Liver transplant is an accepted treatment of end-stage liver disease that provides a survival benefit in appropriately selected patients and thus, may be considered medically necessary for the above indications listed in the Policy Statement and in those otherwise meeting United Network of Organ Sharing (UNOS) criteria. Liver transplantation is investigational in patients in whom the procedure is expected to be futile due to comorbid disease or in whom posttransplantation care is expected to significantly worsen comorbid conditions. Case series and case-control data indicate that human immunodeficiency virus (HIV)-infection is not an absolute contraindication to liver transplant; for patients who meet selection criteria, these studies have demonstrated patient and graft survival rates are similar to those in the general population of kidney transplant recipients.

Recent literature continues to address expanded criteria for transplantation for HCC, predictors of recurrence, the role of neoadjuvant therapy in patients with hepatocellular carcinoma (HCC), expanded donor criteria, transplantation and retransplantation for hepatitis C, and living donor transplantation. Further study is needed before liver transplant selection criteria can be expanded for HCC. Additionally, further study is needed to address salvage liver transplantation for HCC recurrence after primary liver resection.
Liver transplantation for hilar cholangiocarcinoma is performed at some transplant centers, and long-term survival has been reported in select patients with unresectable disease. For metastatic NET, cure of disease is not achieved, and 5-year survival is generally not high. However, there have been reports of survival benefit in patients receiving liver transplantation for unresectable neuroendocrine tumor metastasis confined to the liver. Based on survival data and clinical vetting input, transplantation in patients with hilar cholangiocarcinoma who meet strict eligibility criteria may be considered medically necessary; transplantation for NET metastatic to the liver is considered investigational.

The literature on liver transplantation for pediatric hepatoblastoma is limited, but case series have demonstrated good outcomes and high rates of long-term survival. Additionally, nonmetastatic pediatric hepatoblastoma is included in UNOS criteria for patients eligible for liver transplantation. Therefore, liver transplantation for nonmetastatic pediatric hepatoblastoma may be considered medically necessary.

Case series have demonstrated favorable outcomes with liver retransplantation in certain populations, such as when criteria for an original liver transplantation are met for retransplantation. While some evidence suggests outcomes after retransplantation may be less favorable than for initial transplantation in some patients, long-term survival benefits have been demonstrated. There was support from clinical vetting for retransplantation following primary graft nonfunction, hepatic artery thrombosis, ischemic biliary injury after donation after cardiac death, chronic rejection or certain recurrent nonneoplastic diseases resulting in end-stage liver failure in a primary transplant. As a result, retransplantation after initial failed liver transplant may be considered medically necessary in these situations.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements
In December 2010, 10 international liver diseases or transplantation societies held an international consensus conference on liver transplantation for HCC. Consensus criteria for selecting candidates for liver transplantation were developed at the conference. Milan criteria was recommended for use as the benchmark for patient selection, although it is noted the Milan criteria may be modestly expanded based on data from expansion studies that demonstrate outcomes that are comparable to outcomes from studies using the Milan criteria. Candidates for liver transplantation should also have a predicted survival of 5 years or more. The consensus criteria indicate alpha-fetoprotein concentrations may be used with imaging to assist in determining patient prognosis.

In regard to liver retransplantation, the consensus criteria issued a weak recommendation indicating retransplantation after graft failure of a living donor transplant for HCC is acceptable in patients meeting regional criteria for a deceased donor liver transplant. A strong recommendation was issued indicating liver retransplantation with a deceased donor for graft failure for patients exceeding regional criteria is not recommended. And the consensus criteria issued a strong recommendation that liver retransplantation for recurrent HCC is not appropriate. However, a de
novo HCC may be treated as a new tumor and retransplantation may be considered even though data to support this are limited.

In 2005, the American Association for the Study of Liver Diseases (AASLD) issued guidelines on evaluating patients for liver transplant. These guidelines state liver transplantation is indicated for acute or chronic liver failure from any cause after all effective medical treatments have been attempted. Furthermore, the AASLD guidelines indicate patients should be assessed by a transplantation center to determine whether liver transplantation is appropriate. While the AASLD guidelines indicate liver transplant may be appropriate in patients with cholangiocarcinoma and metastatic neuroendocrine tumors, these recommendations and many of the recommendations in the AASLD guidelines are based on opinion.

The European Neuroendocrine Society (ENETS) issued consensus guidelines in 2008 and updated in 2012 for the management of patients with liver metastases from neuroendocrine tumors. The ENETS guidelines indicate, in a “minimal consensus” statement, that liver transplantation may be considered for diffuse unresectable neuroendocrine tumor metastases or when hormonal disturbances that are refractory to medical therapy are life-threatening.

The National Comprehensive Cancer Network (NCCN) guidelines on hepatobiliary cancers V2.2014 recommends referral to a liver transplant center or bridge therapy for patients with HCC meeting UNOS criteria of a single tumor 5 cm or less, or 2 to 3 tumors 3 cm or less with no macrovascular involvement or extrahepatic disease. Patients should be referred to the transplant center before biopsy. In patients meeting UNOS criteria who are ineligible for transplant and in select patients with Child-Pugh Class A or B liver function with tumors that are resectable, NCCN indicates resection is the preferred treatment option or locoregional therapy may be considered. Patients with unresectable HCC should be evaluated for liver transplantation and if the patient is a transplant candidate, then referral to a transplant center should be given or bridge therapy should be considered. The NCCN guidelines on hepatobiliary cancers also indicate liver transplant is appropriate in select patients with extrahepatic cholangiocarcinoma, which is unresectable, but biliary and hepatic function is otherwise normal or when underlying chronic liver disease precludes surgery. These are level 2A recommendations based on lower-level evidence and uniform consensus.

The NCCN guidelines on neuroendocrine tumors V1.2015 indicate liver transplantation for neuroendocrine tumor liver metastases is considered investigational.

Liver transplantation guidelines for nonalcoholic steatohepatitis (NASH) were developed by the Council of the British Transplant Society and approved by the British Society of Gastroenterology, the British Association for the Study of Liver and NHS Blood and Transplant in 2012. These guidelines indicate liver transplantation may be considered for the treatment of NASH cirrhosis with end-stage liver disease or HCC. These guidelines are based primarily on consensus of expert opinion.
AASLD and the American Society of Transplantation issued a 2013 guideline for the long-term medical management of the pediatric patient after liver transplant. The guideline makes the following statement regarding liver transplant in children:

Pediatric liver transplant has dramatically changed the prognosis for many infants and children with liver failure and metabolic disease. As survival increases, long-term maintenance resources exceed perioperative care requirements. The most common indication for liver transplant in children is biliary atresia which accounts for 50% of all children requiring transplant in the U.S. and 74% in Europe.

**Medicare National Coverage**

Medicare covers adult liver transplantation for end-stage liver disease and HCC when performed in a facility which is approved by the Centers for Medicare and Medicaid Services (CMS) as meeting institutional coverage criteria for liver transplants. The following conditions must be met for coverage of HCC:

- The patient is not a candidate for subtotal liver resection;
- The patient's tumor(s) is less than or equal to 5 cm in diameter;
- There is no macrovascular involvement; and
- There is no identifiable extrahepatic spread of tumor to surrounding lymph nodes, lungs, abdominal organs or bone.

Beginning June 21, 2012, on review of this national coverage decision for new evidence, Medicare began offering coverage for adult liver transplantation, at Medicare administrative contractor discretion, for extrahepatic unresectable cholangiocarcinoma, liver metastases due to a neuroendocrine tumor and hemangioendothelioma. Adult liver transplantation is excluded for other malignancies.

Pediatric liver transplantation is covered for children (younger than age 18 years) when performed in a CMS-approved pediatric hospital for extrahepatic biliary atresia or any other form of end-stage liver disease, except that coverage is not provided for children with a malignancy extending beyond the margins of the liver or those with persistent viremia.

**VII. Important Reminder**

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.
This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VIII. References:


