Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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(See policy history boxes for previous effective dates)

Title: Transplant-Liver

Description/Background

Solid organ transplantation offers a treatment option for patients with different types of end stage organ failure that can be lifesaving or provide significant improvements to a patient's quality of life.[1] Many advances have been made in the last several decades to reduce perioperative complications. Available data supports improvement in long-term survival as well as improved quality of life particularly for liver, kidney, pancreas, heart, and lung transplants. Allograft rejection remains a key early and late complication risk for any organ transplantation. Transplant recipients require life-long immunosuppression to prevent rejection. Patients are prioritized for transplant by mortality risk and severity of illness criteria developed by Organ Procurement and Transplantation Network and United Network of Organ Sharing.

Liver transplantation
Liver transplantation is routinely performed as a treatment of last resort for patients with end-stage liver disease. Liver transplantation may be performed with liver donation after a brain or cardiac death or with a liver segment donation from a living donor. Certain populations are prioritized as Status 1A (e.g., acute liver failure with a life expectancy of fewer than seven days without a liver transplant) or Status 1B (pediatric patients with chronic liver disease). Following Status 1, donor livers are prioritized to those with the highest scores on the Model for End-stage Liver Disease (MELD) and Pediatric End-stage Liver Disease (PELD) scales. Due to the scarcity of donor livers, a variety of strategies have been developed to expand the donor pool. For example, a split graft refers to dividing a donor liver into two segments that can be used for two 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.

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.

Liver transplantation (LT) for colorectal cancer with liver metastases only has emerged as a treatment option for highly selected patients with nonresectable colorectal liver metastasis (CRLM). In general, the premise of liver transplantation in CRLM relies on the ability to select patients where the liver is the sole metastatic location, and that the disease displays a favorable 'tumor biological phenotype. The goal of the selection process is to try to identify patients with a predictive 5-year survival probability above 60–70% to justify transplantation and avoid the futile use of liver grafts.

Regulatory Status

Solid organ transplants are a surgical procedure and, as such, are not subject to regulation by the U.S. Food and Drug Administration (FDA).

The FDA regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation Title 21, parts 1270 and 1271. Solid organs used for transplantation are subject to these regulations.

Medical Policy Statement

The safety and effectiveness of liver transplantation and retransplantation have been established. It may be considered a useful therapeutic procedure in carefully selected patients when criteria are met.

Inclusionary and Exclusionary Guidelines

Note: *Liver Transplants (cadaver or living-donor) are covered for the indications listed below when adolescents or adults have met the requesting transplanting center's selection criteria and one of the following.*

1. *Model of End-stage Liver Disease (MELD) score greater than 10 (≤10 score may be considered when appropriate) or*
2. *Approval for transplant received from the United Network for Organ Sharing (UNOS) Regional Review Board.*

Inclusions for liver transplant:

I. Patients with end-stage liver disease. Etiologies of end-stage liver disease include, but are not limited to, the following:

A. Hepatocellular diseases

- Alcoholic liver disease
- Viral hepatitis (either A, B, C, or non-A, non-B)
- Autoimmune hepatitis
- Alpha-1 antitrypsin deficiency

- Hemochromatosis
- Non-alcoholic steatohepatitis
- Protoporphyria
- Wilson's disease

B. Cholestatic liver diseases

- Primary biliary cirrhosis
- Primary sclerosing cholangitis with development of secondary biliary cirrhosis
- Biliary atresia

C. Vascular disease

- Budd-Chiari syndrome

*D. Neuroendocrine tumors metastatic to the liver***(see NET criteria below)*

E. Primary hepatocellular carcinoma

F. Inborn errors of metabolism

G. Trauma and toxic reactions

H. Miscellaneous indications

- Familial amyloid polyneuropathy

II. Patients with polycystic disease of the liver who have massive hepatomegaly causing obstruction or functional impairment.

III. Pediatric patients with nonmetastatic hepatoblastoma

IV. Patients with unresectable hilar cholangiocarcinoma if additional inclusionary criteria are met (see below)**.

V. Patients with nonresectable colorectal cancer liver-only metastases (CRCLM) (see below)[a]

VI. Cholangiocarcinoma

Note: The consideration for a risk-reducing procedure (e.g., CABG) performed at the same time as the organ transplant is a consideration based on the medical consultation review.

Exclusions for Liver Transplant:

- Patients with intrahepatic cholangiocarcinoma
    a. Patients with hepatocellular carcinoma that has extended beyond the liver
- 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 or enrollment in a sanctioned program which may accompany shorter periods of abstinence)
- Severe cardiac or pulmonary disease
- AIDS
- Uncontrolled sepsis
- Anatomic abnormality that precludes liver transplantation
- Hemangiosarcoma
- Persistent noncompliance

Patients with conditions not included in the inclusions section.

Inclusions for Liver Transplant for Nonresectable Colorectal Cancer Liver-Only Metastases[a]

1) To Be Considered for a Liver Transplant Evaluation:

a. Histologically confirmed adenocarcinoma of the colon or the upper rectum, pT 3, pN0 or pN1, resection with adequate tumor free margin;

b. At least twelve months from resection of the primary colorectal cancer (CRC) to evaluation of LT. A minimal observation period from the time of diagnosis to transplant listing of at least 12 months is recommended to ensure disease stability;

c. At least six months of chemotherapy before LT evaluation demonstrating tumor response or stable disease;

2) If a candidate for Liver Transplant After Above Evaluation Results (**must meet ALL**):

a. Age greater than or equal to 18years of age;
b. Absence of extra-hepatic metastatic disease or local recurrence using imaging as determined by the treating institution which includes CT scan with contrast, MRI, whole body PET/CT scans within three months of transplant evaluation;
c. performance status of 0-1 using Eastern Cooperative Oncology Group (ECOG) status of 0-1 criteria;
d. Oslo* score of 0-2;
e. CEA level < 80 at the time of diagnosis and declining at the time of evaluation;
f. Liver metastases not eligible for curative liver resection;
f. The institutional protocol for liver transplantation for colorectal cancer with liver metastases only (CRCLM) must be available for review, and individual must meet BOTH institution's protocol requirements and policy criteria;

Exclusions for Patients with CRCLM:

a. The tumor must not be undifferentiated primary or have signet ring histology;
b. Molecular genetic testing of B-Raf proto-oncogene, serine/threonine kinase (BRAF) mutation and Microsatellite Stability (MSS)-High, MMR deficient DNA mismatch repair;
c. Diagnosis of a previous malignancy within the prior 5 years (unless cleared by the oncologist that the recurrence risk is low);
d. See additional exclusions as outlined above for liver transplant.

*Oslo score is based on four parameters. For each criterion met by the patient pretransplant, 1 point is assigned. Scores range from 0 to 4 points.
Largest hepatic tumor > 5.5 cm in diameter.
CEA level >80 µg/L.
Time from resection of primary tumor to LT >2 years.
Disease progression on chemotherapy.

Conditions that require MELD Exception Applications

A. Neuroendocrine Tumors (NET) Metastatic to the Liver

Inclusions:

1) Recipient age <60 years
2) Resection of primary malignancy and extra-hepatic disease without any evidence of recurrence at least six months prior to MELD exception request.
3) Liver-limited Neuroendocrine Liver Metastasis (NLM), Bi-lobar, not amenable to resection. Tumors in the liver should meet the following radiographic characteristics:
    a. **CT Scan**: Triple phase contrast
        i. Lesions may be seen on only one of the three phases
        ii. Arterial phase: may demonstrate a strong enhancement
        iii. Large lesions can become necrotic/calcified
    b. **MRI Appearance**:
        i. Liver metastasis are hypodense on T1 and hypervascular in T2 wave images
        ii. Diffusion restriction

iii. Majority of lesions are hypervascular on arterial phase with wash –out during portal venous phase IV. Hepatobiliary phase post Gadoxetate Disodium (Eovist): Hypointense lesions are characteristics of NET

4) Consider for exception only those with a NET of Gastro-entero-pancreatic (GEP) origin tumors with portal system drainage. Note: Neuroendocrine tumors whose primary is located in the lower rectum, esophagus, lung, adrenal gland and thyroid are not candidates for automatic MELD exception.
5) Lower — intermediate grade following the WHO classification. Only well differentiated (Low grade, G1) and moderately differentiated (intermediate grade G2). Mitotic rate <20 per 10 HPF with less than 20% ki-67 positive markers.
6) Tumor metastatic replacement should not exceed 50% of the total liver volume
7) Negative metastatic workup should include one of the following:
    a. Positron emission tomography (PET scan
    b. Somatostatin receptor scintigraphy
    c. Gallium-68 (68Ga) labeled somatostatin analogue 1,4,7,10-tetraazacyclododedcane-N, N′, N″,N‴-tetraacetic acid (DOTA)-D-Phe1-Try3–octreotide (DOTATOC), or other scintigraphy to rule out extra-hepatic disease, especially bone metastasis.

Note: Exploratory laparotomy and or laparoscopy is not required prior to MELD exception request.

8) No evidence for extra-hepatic tumor recurrence based on metastatic radiologic workup at least 3 months prior to MELD exception request (submit date).
9) Recheck metastatic workup every 3 months for MELD exception increase consideration by the Regional Review Board. Occurrence of extra-hepatic progression – for instance lymph-nodal Ga68 positive locations – should indicate de-listing. Patients may come back to the list if any extra-hepatic disease is zeroed and remained so for at least 6 months.
10) Presence of extra-hepatic solid organ metastases (i.e., lungs, bones) should be a permanent exclusion criteria.

B. **Cholangiocarcinoma Hilar-Extrahepatic** (Available online at: https://optn.transplant.hrsa.gov/.

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:

1) 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.
2) ***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 (e.g., primary sclerosing cholangitis).

3) If cross-sectional imaging studies (computed tomography scan, ultrasound, magnetic resonance imaging) demonstrate a mass, the mass should be less than 3 cm .
4) 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.
5) 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.
6) 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.

C. Hepatocellular Carcinoma-Initial Assessment and Requirements for Exception Score Requests:

1) Prior to applying for a standardized MELD or PELD exception, the candidate must undergo a thorough assessment that includes all of the following:
   a. An evaluation of the number and size of lesions before locoregional therapy that meet Class 5 criteria using a dynamic contrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI)
   b. A CT of the chest to rule out metastatic disease. This is only required prior to applying for an initial exception. A CT of the chest is not required for exception extensions.
   c. A CT or MRI to rule out any other sites of extrahepatic spread or macrovascular involvement
   d. An indication that the candidate is not eligible for resection
   e. An indication whether the candidate has undergone locoregional therapy
   f. The candidate's alpha-fetoprotein (AFP) level
   g. Candidates with hepatic lesions that meet T2 stage are eligible for a standardized MELD or PELD exception if they have an alpha-fetoprotein (AFP) level less than or equal to 1000 ng/mL. T2 stage is defined as candidates with either of the following:
      • One Class 5 lesion greater than or equal to 2 cm and less than or equal to 5 cm in size.
      • Two or three Class 5 lesions each greater than or equal to 1 cm and less than or equal to 3 cm in size.
   h. The transplant hospital must maintain documentation of the radiologic images and assessments of all OPTN Class 5 lesions in the candidate's medical record. If growth criteria are used to classify a lesion as HCC, the radiology report must contain the prior and current dates of imaging, type of imaging, and measurements of the lesion.
2) Candidates with Alpha-fetoprotein (AFP) Levels Greater than 1000:
   a. Eligible Candidates with lesions meeting T2 Stage but with an alpha-fetoprotein (AFP) level greater than 1000 ng/mL may be treated with locoregional therapy.
   b. If the candidate's AFP level falls below 500 ng/mL after treatment, the candidate is eligible for a standardized MELD or PELD exception as long as the candidate's AFP level remains below 500 ng/mL.

c. Candidates with an AFP level greater than or equal to 500 ng/mL following locoregional therapy at any time must be referred to the NLRB for consideration of a MELD or PELD exception.

All transplants must be prior authorized through the Human Organ Transplant Program.

Inclusions for Liver *Re*transplant:

Liver *re*transplant is established for patients with:

- Primary graft non-function
- Hepatic artery thrombosis
- Chronic rejection
- Ischemic type biliary lesions after donation after cardiac death
- Recurrent non-neoplastic disease causing late graft failure

Exclusions for Liver *Re*transplant:

Patients not meeting above inclusionary criteria for *re*transplant.

Potential Contraindications for Transplant/Retransplant:

Note: Final patient eligibility for transplant is subject to the judgment and discretion of the requesting transplant center.

Potential contraindications represent situations where proceeding with transplant is not advisable in the context of limited organ availability. Contraindications may evolve over time as transplant experience grows in the medical community. Clinical documentation supplied to the health plan should demonstrate that attending staff at the transplant center have considered *all* contraindications as part of their overall evaluation of potential organ transplant recipients and have decided to proceed.

- Known current malignancy, including metastatic cancer;
- Recent malignancy with high or moderate risk of recurrence;
- Untreated systemic infection making immunosuppression unsafe, including chronic infection;
- Other irreversible end-stage disease not attributed to liver disease;
- Systemic disease that could be exacerbated by immunosuppression;
- Psychosocial conditions or chemical dependency affecting ability to adhere to therapy.

Liver Specific Guidelines/Background Information

Patients with liver disease related to alcohol or drug abuse must be actively involved in a substance abuse treatment program consistent with DALLAS consensus criteria or the Sustained Alcohol Use Post-Liver Transplant (SALT) criteria/score (see appendix for additional information).

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:

- Enlargement of liver impinging on respiratory function
- Extremely painful enlargement of liver
- 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. The 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,[1] which is considered the criterion standard,[2] the University of California, San Francisco (UCSF) expanded criteria,[3] and UNOS criteria.[4]

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 (HCC) 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 locoregional treatment after

being automatically approved on initial application or extension. A single class 5A nodule (>1 cm and <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 locoregional therapies to downsize tumors to T2 status and to prevent progression while on the waiting list.

HIV-positive patients who meet the following criteria, as stated in the 2001 guidelines of the American Society of Transplantation, could be considered candidates for liver transplantation:

- CD4 count >200 cells per cubic millimeter for >6 months
- Undetectable HIV-1 RNA
- On stable antiretroviral therapy >3 months
- No other complications from AIDS (e.g., opportunistic infection, including aspergillus, tuberculosis, coccidioidomycosis, resistant fungal infections, Kaposi sarcoma, other neoplasm), and
- Meeting all other criteria for transplantation

Donor Criteria: Living Donor Liver 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:

1) 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
2) Should undergo evaluation to assure that they fully understand the procedure and associated risks
3) Should be of legal age and have sufficient intellectual ability to understand the procedures and give informed consent
4) Should be emotionally related to the recipients
5) Must be excluded if the donor is felt or known to be coerced
6) Needs to have the ability and willingness to comply with long-term follow-up

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

47133	47135	47140	47141	47142	47143
47144	47145	47146	47147	47399	

Other codes (investigational, not medically necessary, etc.):

N/A

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

LIVER TRANSPLANT FOR HEPATOCELLULAR DISEASE

Clinical Context and Test Purpose

The purpose of a liver transplant for individuals who have severe hepatocellular disease (i.e., viral hepatitis or nonalcoholic steatohepatitis) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following **PICOs** were used to select literature to inform this review.

Populations

The relevant population of interest is individuals with hepatocellular disease, such as viral hepatitis or nonalcoholic steatohepatitis.

Viral hepatitis is an infection that causes liver inflammation and damage. Hepatitis B, C, and D viruses can cause acute, chronic infections and lead to cirrhosis, liver failure, and liver cancer.

Nonalcoholic steatohepatitis is caused by a buildup of fat in the liver which leads to inflammation and damage. While many patients have no symptoms or problems, in some cases, the condition can worsen to cause liver scarring and cirrhosis. As noted by the name of the condition, patients with nonalcoholic steatohepatitis do not abuse alcohol.

Interventions

The therapy being considered is liver transplant, which is provided in a hospital setting with specialized staff who are equipped to perform the surgical procedure and manage postsurgical intensive care..

Comparators
The following practice is currently being used to make decisions about end-stage hepatocellular disease: medical management.

Outcomes
The general outcomes of interest are overall survival (OS) and treatment-related adverse events (e.g., immunosuppression, graft failure, surgical complications, infections). See the Potential Contraindications section for a detailed discussion.

Review of Evidence

Viral Hepatitis
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 have indicated 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%).[2] Recurrence of HCV infection in transplant recipients has been nearly universal, and 10% to 20% of patients will develop cirrhosis within 5 years.[3]

Historical data demonstrating inferior survival in transplant recipients with HCV is not applicable to the current treatment landscape with the availability of direct acting antiviral agents, which are associated with sustained virological response rates over 95%.[4] Timing the receipt of direct acting antiviral agents either before or after transplantation is still controversial and the decision should be individualized based the presence of compensated/decompensated disease, Model for End-Stage Liver Disease (MELD) score, current quality of life, and the proportion of HCV-positive donors in the local and regional areas.

Nonalcoholic Steatohepatitis

Systematic Reviews
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 of 717 patients with NASH and 3520 without NASH comparing liver transplantation outcomes.[5] 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.

Yong et al (2021) presented an updated meta-analysis and systematic review analyzing 15 studies of 119,327 patients who received liver transplants.[6.] The pooled prevalence of NASH across studies was 20.2%. The pooled 1-, 5-, and 10-year all-cause mortality in NASH patients after liver transplant were 12.5%, 24.4%, and 37.9%, respectively. Overall survival was comparable between liver transplant recipients with NASH versus non-NASH (hazard ratio [HR], 0.91; 95% CI, 0.76 to 1.10; p=.34). There was no significant difference between patients

with NASH or without NASH for all secondary outcomes, including infection rates, biliary complications, cardiovascular disease events, cardiac failure, cerebrovascular accident, and length of stay. Additionally, there were no significant differences in graft survival between patients who underwent liver transplantation for NASH versus non-NASH (n=6 studies; HR, 0.95; 95% CI, 0.88 to 1.03; p=.20). Meta-regression demonstrated that a higher MELD score was associated with significantly worse overall survival in patients with NASH compared to patients without NASH after liver transplantation (95% CI, -0.0856 to -0.0181; p=.0026). There was no evidence of publication bias from the funnel plot conducted. This analysis is limited by large heterogeneity between studies, and a lack of information on donor quality to fully explore the association between higher MELD scores and early versus late mortality for NASH patients with liver transplantation.

Registry Studies

Cholakeril et al (2017) published a retrospective cohort analysis of records from 2003 to 2014 in the United Network Organ Sharing and Organ Procurement and Transplantation Network database to evaluate the frequency of NASH-related liver transplantation.[7] In all, 63,061 patients underwent liver transplant from 2003 to 2014. NASH accounted for 17.38% of liver transplants in 2014. During the observation period, liver transplants secondary to NASH increased by 162.0%, a greater increase than either hepatitis C (33.0% increase) and alcoholic liver disease (55.0% increase). Five-year survival post-transplant in patients who had NASH (77.81%; 95% confidence interval [CI], 76.37% to 79.25%) was higher than patients who had hepatitis C (72.15%; 95% CI, 71.37 to 72.93; p<0.001). Patients with NASH also demonstrated significantly higher post-transplant survival than patients with hepatitis C (hazard ratio [HR], 0.75; 95% CI, 0.71 to 0.79; p<0.001).

Section Summary: Hepatocellular Disease

The evidence on liver transplantation for hepatocellular disease includes case series, registry studies, and systematic reviews. Long-term survival rates in patients with viral hepatitis are significant in a group of patients who have no other treatment options. In addition, survival can be improved by eradication of hepatitis virus before transplantation. For patients with NASH, a 2013 systematic review has indicated that overall survival rates are similar to other indications for liver transplantation.

LIVER TRANSPLANT FOR HEPATOCELLULAR CARCINOMA

Clinical Context and Therapy Purpose

The purpose of a liver transplant for individuals who have hepatocellular carcinoma (HCC) is to provide a treatment option that is an alternative to or an improvement on existing therapies. The criteria used to select HCC patients eligible for liver transplant include the Milan criteria, the University of California, San Francisco expanded criteria, and United Network of Organ Sharing criteria.

The following **PICOs** were used to select literature to inform this review.

Populations

The relevant population of interest is individuals with HCC. See the detailed discussion in the Recipient Selection Criteria section below.

Interventions
The therapy being considered is liver transplant.

Comparators
The following practices are currently being used to make decisions about managing HCC: medical management, including chemotherapy, and medical procedures, including surgery.

Outcomes
The general outcomes of interest are OS and treatment-related adverse events (e.g., immunosuppression, graft failure, surgical complications, infections). See the Potential Contraindications section for a detailed discussion.

Review of Evidence

Liver Transplantation vs. Liver Resection for Hepatocellular Carcinoma
Schoenberg et al (2017) published a systematic review and meta-analysis of 54 retrospective studies (N=13,794) comparing liver resection (n=7990) with transplantation (n=5804) in patients with HCC.[8] At 1-year follow-up, survival rates were higher in those receiving resection (86.17%) than in those receiving liver transplant (80.58%) (OR=1.19; 95% CI, 0.99 to 1.43; p=0.07). At 5-year follow-up, survival rates were better for those who received transplantation (61.26%) than for those receiving surgery (51.9%; OR=0.62; 95% CI, 0.50 to 0.76; p<0.001). When a subgroup of patients with early HCC (8 studies) was analyzed, 1-year follow-up showed comparable survival rates between surgically-treated patients (92.14%), and transplanted patients (90.38%) (OR=0.97; 95% CI, 0.63 to 1.50; p=0.89). At 5 years, transplanted patients had a significantly higher survival rate (66.67%) than surgically treated patients (60.35%; OR=0.60; 95% CI, 0.45 to 0.78; p<0.001). Review limitations included a high level of heterogeneity between studies analyzed.

In 2014, Zheng et al reported on a meta-analysis of 62 cohort studies (n=10,170) comparing liver transplantation to liver resection for HCC.[9] 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).

Recipient Selection Criteria
Recipient selection criteria for liver transplantation for HCC have focused mainly on the number and size of tumors. Guiteau et al (2010) reported on 445 patients who received transplants for HCC in a multicenter, prospective study in UNOS Region 4.[10] On preoperative imaging, 363 patients met Milan criteria, and 82 patients were under expanded Milan criteria; these expanded criteria consisted of 1 lesion less than 6 cm, 3 or fewer lesions, none greater than 5 cm and a total diameter less than 9 cm. Patient allograft survival and recurrence-free survival at 3 years did not differ significantly between patients meeting Milan criteria and patients not meeting the expanded criteria (71% vs. 70.2% and 90.5% vs. 86.9%, 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 outcomes might differ in other regions with different waiting times. Additionally, the authors

noted that a report from a 2010 national consensus conference on liver allocation for patients with HCC did not recommend expanding Milan criteria nationally and encouraged regional agreement.[11]

Ioannou et al (2008) analyzed UNOS data pre- and post-adoption 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.[12] The subgroup of patients with larger (3-5 cm) tumors, serum alpha-fetoprotein level 455 mg/mL or greater, or a MELD score 20 or greater, 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.[13] 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, illumination, 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.

Mazzafaro et al (1996) identified patient criteria associated with improved outcomes after liver transplantation for HCC with cirrhosis.[14] These selection criteria became known as the Milan criteria and specify patients may have either a solitary tumor with a maximum diameter of 5 cm or less, or up to 3 tumors 3 cm or less. Patients with extrahepatic spread or macrovascular invasion have a poor prognosis. The United Network of Organ Sharing (UNOS) adopted the Milan criteria, combined with an 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. 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 principle, or at the time of transplantation.

Newer algorithms for selecting transplant recipients, which review more than the number and size of tumors, have been proposed as alternatives to Milan criteria.[15] However, these criteria are preliminary and need prospective evaluation.

Salvage Liver Transplantation

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.[16] 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.

Yadav et al (2018) published a systematic review and meta-analysis comparing salvage liver transplant (SLT) and primary liver transplant (PLT) for individuals with HCC.[17] Twenty

retrospective studies (10 of which were also included in Murali et al [2017]) with a total of 9879 patients were included in the analysis. One-year OS was better for SLT (74.30%) than PLT (77.01%, OR 0.86, 95% CI 0.75–0.98, p=0.03). SLT also had higher 3-year (55.69% and 59.07%, respectively; OR 0.85, 95% CI 0.76–0.96, p=0.01) and 5-year (48.67% and 52.32%, respectively; OR 0.85, 95% CI 0.76–0.96, p=0.009) OS than PLT. One-year (OR 0.86, 95% CI 0.75–0.99, p=0.03), 3-year (OR 0.56, 95% CI 0.39–0.81, p=0.002), and 5-year DFS (OR 0.75, 95% CI 0.66–0.86, p<0.001) were worse for PLT (70.03%, 74.08%, and 47.09%, respectively) than for SLT (67.69%, 57.02%, and 41.27%, respectively). There was no significant difference between the 2 groups for postoperative biliary complications (p=0.19) or sepsis (p=0.68). No limitations to the analysis were reported.

Murali et al (2017) conducted a systematic review and meta-analysis of studies comparing survival of patients treated who received locoregional therapy with curative intent (CLRT) with those who received liver transplant, stratified by liver disease stage, extent of cancer, and whether salvage liver transplant was offered.[18] Among the 48 studies selected, 9835 patients were analyzed. For all categories of CLRT combined, 5-year OS and disease-free survival were worse than for primary liver transplant (OR for OS= 0.59; 95% CI, 0.48 to 0.71; p<0.01). Intention-to-treat analysis showed no significant different in 5-year OS (OR=1.0; 95% CI, 0.6 to 1.7) between CLRT followed by salvage liver transplant when salvage liver transplant was offered after CLRT, though noninferiority could not be shown. Only 32.5% of patients with HCC after CRLT received salvage liver transplant, because the rest were medically ineligible. Disease-free survival was worse with CLRT and salvage liver transplant than with liver transplant (OR=0.31; 95% CI, 0.2 to 0.6).

In a systematic review of liver transplantation for HCC, Maggs et al (2012) found 5-year OS rates ranged from 65% to 94.7% in reported studies.[19]

In 2014, Chan et al systematically reviewed 16 nonrandomized studies (n=319) on salvage liver transplantation after primary hepatic resection for HCC.[20] 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.

In a 2013 meta-analysis of 14 nonrandomized comparative studies by Zhu et al, (n=1272 for primary transplant, n=236 for salvage).[21] 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.

Section Summary: Hepatocellular Carcinoma
Use of standardized patient selection criteria, such as the Milan criteria (a solitary tumor with a maximum tumor diameter of ≤5 cm, or up to 3 tumors ≤3 cm and without extrahepatic spread or macrovascular invasion), has led to improved overall survival rates. A 2012 systematic review reported 5-year OS rates ranged from 65% to 94.7%. Liver transplant was also been shown in a 2013 meta-analysis to result in higher survival rates than resection. Similar outcomes were identified in a 2017 meta-analysis, in which transplantation showed significantly improved survival benefit, especially for patients with early HCC. In patients who present with unresectable organ-confined disease, transplant represents the only curative approach.

Expansion of patient selection criteria, bridging to transplant or down-staging of disease to qualify for liver transplantation is frequently studied. 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.

Liver Transplant for Extrahepatic Cholangiocarcinoma (Hilar or Perihilar)

Clinical Context and Test Purpose
The purpose of a liver transplant for individuals who have cholangiocarcinoma is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following **PICOs** were used to select literature to inform this review.

Populations
The relevant population of interest is individuals with extra- or intrahepatic cholangiocarcinoma.

Interventions
The therapy being considered is liver transplant.

Comparators
The following practice is currently being used to make decisions about managing cholangiocarcinoma: medical management.

Outcomes
The general outcomes of interest are OS and treatment-related adverse events (e.g., immunosuppression, graft failure, surgical complications, infections). See the Potential Contraindications section for a detailed discussion.

Review of Evidence

Systematic Reviews
Cambridge et al (2021) reported on a systematic review and meta-analysis/meta-regression of 20 observational studies (N=428) on orthotopic liver transplantation for unresectable perihilar cholangiocarcinoma.[22,] Pooled 1- (n=265), 3- (n=240), and 5-year (n=309) survival rates were 76.9% (95% CI, 69.5% to 83.5%), 55.3% (95% CI, 43.7% to 66.5%), and 44.9% (95% CI, 31.4% to 58.8%), respectively. In patients who received neoadjuvant chemoradiation, 1- (n=109), 3- (n=89), and 5-year (n=210) pooled survival rates improved to 82.8% (95% CI, 73%

to 90.8%), 65.5% (95% CI, 48.7% to 80.5%), and 65.1% (95% CI, 55.1% to 74.5%), respectively.

In 2012, Gu and colleagues reported on a systematic review and meta-analysis of 14 clinical trials on liver transplantation for cholangiocarcinoma.[23] Overall 1-, 3-, and 5-year pooled survival rates from 605 study patients were 0.73 (95% CI: 0.65-0.80), 0.42 (95% CI: 0.33-0.51), and 0.39 (95% CI: 0.28-0.51), respectively. When patients received adjuvant therapies preoperatively, 1-, 3-, and 5-year pooled survival rates improved and were 0.83 (95% CI: 0.57-0.98), 0.57 (95% CI: 0.18-0.92), and 0.65 (95% CI: 0.40-0.87), respectively.

In a review, Heimbach (2008) considered the published outcomes of the combined protocol in the context of data on outcomes for surgical resection.[24] Heimbach concluded that outcomes were comparable between transplantation for patients with HCC and other chronic liver diseases and neoadjuvant chemoradiotherapy with subsequent liver transplantation for patients with early-stage hilar cholangiocarcinoma, which is unresectable, or arose in the setting of primary sclerosing cholangitis. The reviewer further concluded that both methods were superior to resection.

Observational Studies

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.[25] Intent-to-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 post-transplant 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 ($p<0.001$).

Heimbach et al (2006) reported on 65 patients who underwent liver transplantation for unresectable perihilar cholangiocarcinoma or for perihilar tumor due to primary sclerosing cholangitis between 1993 and 2006 (see Table 1).[26,27] Unresectable patients underwent neoadjuvant radiochemotherapy. The 1-year survival rate was 91%, and the 5-year survival rate was 76% (see Table 2).

Populations With Intrahepatic or Mixed Cholangiocarcinoma

Systematic Reviews

The European Liver Transplant Registry was cited by a review article.[28] 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. Among 186 patients with intrahepatic cholangiocarcinoma, the 1-year survival rate was 58%, and the 5-year survival rate was 29%.

Observational Studies

In 2011, Friman and colleagues reported on 53 patients who received liver transplants for cholangiocarcinoma during the period of 1984-2005, in Norway, Sweden, and Finland.[30] In a multicenter study, Robles et al (2004) reported on 36 patients with hilar tumors and 23 with peripheral intrahepatic disease.[31,] One-year survival was 82% and 77%, while 5-year survival was 30% and 23% for those with hilar tumors compared with peripheral intrahepatic disease, respectively.

Table 1. Summary of Key Case Series Characteristics for Extrahepatic or Intrahepatic Cholangiocarcinoma

Study	Country	Participants	Treatment	Follow-up, y
Darwish Murad et al (2012)	U.S.	287	Liver transplant	5
Friman et al (2011)	Norway, Sweden, Finland	53	Liver transplant	5
Heimbach et al (2006), Rea et al (2005)	U.S.	65	Liver transplant	5
Robles et al (2004)	Spain	59	Liver transplant	5
Meyer et al (2000)	U.S.	207	Liver transplant	5
Casavilla et al (1997)	U.S.	54	Liver transplant	6.8

Table 2. Summary of Key Case Series Results for Extrahepatic or Intrahepatic Cholangiocarcinoma

Study	Treatment	Group	Overall Survival, %		
			Years		
			1	3	5
Darwish Murad et al (2012)	Liver transplant	EH perihilar			53
Heimbach et al (2006), Rea et al (2005)	Liver transplant	EH perihilar	91		76
Meyer et al (2000)	Liver transplant	IH/EH	72		23
Robles et al (2004)	Liver transplant	EH hilar	82	53	30
		IH	77	65	23
Casavilla et al (1997)	Liver transplant	IH	70	29	18
Friman et al (2011)	Liver transplant	IH/EH			25

EH: extrahepatic; IH: intrahepatic
[a] Unresectable cholangiohepatoma
[b] Hilar or peripheral cholangiohepatoma; unresectable, post-operative recurrent, or incidental
[c] Aggressive neoadjuvant radiochemotherapy
[d] Unresectable cholangiohepatoma

Section Summary: Liver Transplant for Extrahepatic Cholangiocarcinoma

The evidence on liver transplant in patients with cholangiocarcinoma includes registry studies and a systematic review and meta-analysis of observational studies.

For patients with extrahepatic (hilar or perihilar) cholangiocarcinoma treated with liver transplant and adjuvant chemotherapy, survival rates have been reported to be as high as 76%. As a result UNOS does identify this condition as an option to extend survival with a liver transplant and MELD exception points are considered when criteria are met.

Liver Transplant for Intrahepatic Cholangiocarcinoma

Clinical Context and Therapy Purpose

The purpose of a liver transplant for individuals who have intrahepatic cholangiocarcinoma is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following **PICO** was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with intrahepatic cholangiocarcinoma.

Interventions
The therapy being considered is a liver transplant.

Comparators
The following practice is currently being used to make decisions about managing intrahepatic cholangiocarcinoma: medical management.

Outcomes
The general outcomes of interest are OS and treatment-related adverse events (e.g., immunosuppression, graft failure, surgical complications, infections).Short-term follow-up ranges from immediate post-surgery to 30 days post transplantation; lifelong follow-up (out to 10 years or more given current survival data) is necessary due to ongoing immunosuppression and risk of graft failure. See the Potential Contraindications section for a detailed discussion.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews
A systematic review and meta-analysis conducted by Ziogas et al (2021) pooled available data to assess liver transplantation for intrahepatic cholangiocarcinoma.[33] They included 18 studies with 355 patients, including Casavilla et al (1997) and Friman et al (2011), noted below, and a registry study of 385 patients. The pooled 1-, 3-, and 5-year OS rates were 75% (95% CI, 64 to 84), 56% (95% CI, 46 to 67), and 42% (95% CI, 29 to 55), respectively. The pooled 1-, 3-, and 5-year recurrence-free survival rates were 70% (95% CI, 63 to 75), 49% (95% CI, 41 to 57), and 38% (95% CI, 27 to 50), respectively. Cirrhosis was positively associated with recurrence-free survival but incidental diagnosis was not. The pooled overall recurrence rate was 42% (95% CI, 33 to 53) over a mean follow-up of 40.6+37.7 months. Patients with very early (single <2 cm) intrahepatic cholangiocarcinoma exhibited superior pooled 5-year recurrence-free survival (67%; 95% CI, 47 to 86) versus advanced intrahepatic cholangiocarcinoma (34%; 95% CI, 23 to 46). This study is limited by the retrospective nature of the articles included and the potential presence of publication bias regarding the pooled OS data.

Observational Studies

Hue et al (2020) used registry data from the National Cancer Database to compare outcomes among patients with intrahepatic cholangiocarcinoma who received liver transplantation (n=74) to those who received surgical resection of the liver (n=1879).[34] Median OS was not significantly different when comparing patients who received liver resection versus those who received a liver transplant, respectively, at 1- (82.6% vs 89.4%), 3- (50.2% vs 53%), or 5-years (33% vs 40.8%) posttransplant; the overall median survival was 36.1 months in both groups (p=.34). Length of stay and unplanned 30-day readmission rates were also similar between groups (p=.11 and.18, respectively). These differences all remained nonsignificant in a propensity score matched analysis (n=57 patients in each group).

One additional observational study reported on survival rates for 54 patients with intrahepatic cholangiocarcinoma.[32,] Survival rates at 1-, 3-, and 5-years posttransplant were reported to be 70%, 29%, and 18%, respectively. In studies of mixed populations of patients with extrahepatic or intrahepatic cholangiocarcinoma (see Tables 1 and 2 above), a single study reported a 1-year survival rate of 72%.[30,] Five-year survival rates ranged between 23% and 25% in 2 studies.[30,29]

Section Summary: Liver Transplant for Intrahepatic Cholangiocarcinoma

The evidence on liver transplantation in patients with intrahepatic cholangiocarcinoma includes registry studies. In a registry study comparing outcomes in patients with intrahepatic cholangiocarcinoma who received liver transplantation to those who received surgical resection of the liver, no differences were found in OS, length of stay, or unplanned 30-day readmission rates between groups. Additional studies reporting survival rates in patients with intrahepatic cholangiocarcinoma or in mixed populations of patients with extrahepatic and intrahepatic cholangiocarcinoma have reported 5-year survival rates of less than 30%.

LIVER TRANSPLANT FOR INDIVIDUALS WITH METASTATIC NEUROENDOCRINE TUMORS

Clinical Context and Therapy Purpose

The purpose of a liver transplant for individuals who have metastatic neuroendocrine tumors (NETs) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following **PICOs** were used to select literature to inform this review.

Populations

The relevant population of interest is individuals with metastatic NETs.

Interventions

The therapy being considered is liver transplant.

Comparators

The following practice is currently being used to make decisions about managing metastatic NETs: medical management. Treatment options to control or downstage the disease include chemotherapy and debulking procedures, including hepatic resection.

Outcomes
The general outcomes of interest are OS and treatment-related adverse events (e.g., immunosuppression, graft failure, surgical complications, infections). Short-term follow-up ranges from immediate post-surgery to 30 days post-transplantation; lifelong follow-up (out to at 10 years or more given current survival data) is necessary due to ongoing immunosuppression and risk of graft failure. See the Potential Contraindications section for a detailed discussion.

Systematic Reviews
Two systematic reviews of case series have assessed metastatic NETs. NETs are relatively rare neoplasms that are slow-growing but rarely cured when metastatic to the liver.

Fan et al (2015) reported on a systematic review of 46 studies (total N=706 patients) on liver transplantation for NET liver metastases of any origin.[35] 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.

Mathe et al (2011) conducted a systematic review of the literature on patient survival after liver transplant for pancreatic NETs.[36] Data from 89 transplanted patients treated at 20 clinical studies were reviewed. 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 was 54.45 months, and the median calculated survival was 41 months (95% CI, 22 to 76 months).

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 non-resectable, hormonally active liver metastases refractory to medical therapy, liver transplantation has been considered as an option to extend survival and minimize endocrine symptoms.

In 2007, Mazzaferro et al emphasized the importance of patient selection when considering a patient with unresectable liver metastases from NET for liver transplant.[37] He initially proposed selection criteria for patients undergoing transplantation for HCC, which has been used now for several years in transplant centers around the world. More recently, and based on his previous results with HCC patients, the group from Milan recommended patient selection criteria for liver transplant for patients with a diagnosis of liver metastases from NET. They proposed that age less than 55, Ki-67 proliferation index of less than 10%, primary that is limited to tumors with portal venous drainage, no other spread to a secondary organ other than the liver, and metastatic disease involving no more than 50% of the hepatic volume. The criteria were based on limited number of patients. However, using this approach, they reported excellent results with a 5-year survival rate close to 90%. These results were significantly better than those obtained in similar patients undergoing conservative management. They also observed that liver transplantation was associated with a recurrence free survival of about 80% at 5 years, which is significantly higher compared to less than 50% associated with the non-transplant management.

In 2008, Le Treut et al reported on the predictors of long-term survival after liver transplantation for metastatic neuroendocrine tumors in an 85 case French multicentric report.[38] From 1989 to 2005, 85 patients underwent LTx for MET. The primary tumor was located in the pancreas or duodenum in 40 cases, digestive tract in 26 and bronchial tree in five. In the remaining 14 cases, primary location was undetermined at the time of liver transplant. Hepatomegaly (explanted liver ≥120% of estimated standard liver volume) was observed in 53 patients (62%). Extrahepatic resection was performed concomitantly with LTx in 34 patients (40%), including upper abdominal exenteration (UAE) in seven. Postoperative in-hospital mortality was 14%. Overall 5-year survival was 47%. Independent factors of poor prognosis according to multivariate analysis included UAE (relative risk [RR]: 3.72), primary tumor in duodenum or pancreas (RR: 2.94) and hepatomegaly (RR: 2.63). After exclusion of cases involving concomitant UAE, the other two factors were combined into a risk model. Five-year survival rate was 12% for the 23 patients presenting both unfavorable prognostic factors versus 68% for the patients presenting one or neither factor ($p < 10^{-7}$).

In a 2014 article, Alagusundaramoorthy et al stated, "(Liver) transplantation should be considered in selected patients with abdominal portal vein drained NET in which primary lesion has been resected, less than 50% of liver involvement, no extrahepatic disease and in those with disease stability for a period of time prior to surgery."[39]

In 2014, Fan et al reported on a systematic review of 46 studies on liver transplantation for NET liver metastases of any origin.[40] 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 and colleagues conducted a systematic review of the literature to evaluate patient survival after liver transplant for pancreatic NETs.[41] 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: 22–76 months).

Section Summary: Metastatic Neuroendocrine Tumors
The evidence on liver transplant for NETs includes systematic reviews of NETs for metastases of any origin. 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. While there may be centers that perform liver transplantation on select patients with NETs, the available studies are limited by their heterogeneous populations.

Liver Transplant for Nonresectable Colorectal Cancer Liver-Only Metastases

Clinical Context and Therapy Purpose
The purpose of a liver transplant for individuals with nonresectable colorectal cancer liver-only metastases is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following **PICOs** were used to select literature to inform this review.

Populations
The relevant population of interest is individuals with nonresectable colorectal cancer liver-only metastases.

Interventions
The therapy being considered is liver transplant.

Comparators
The following practice is currently being used to make decisions about managing individuals with colorectal cancer with metastases to the liver only: medical management (Chemotherapy regimens).

Outcomes
The general outcomes of interest are OS and treatment-related adverse events (e.g., immunosuppression, graft failure, surgical complications, infections).

Review of Evidence
In 2013, Hagness et al reported on a prospective pilot study investigating the potential for long-term overall survival (OS) after liver transplantation for colorectal liver metastases (CLMs).[42] In this pilot study, liver transplantation for nonresectable CLMs was performed (n= 21). Main inclusion criteria were liver-only CLMs, excised primary tumors, and at least 6 weeks of chemotherapy. Kaplan-Meier estimates of the OS rate at 1, 3, and 5 years were 95%, 68%, and 60%,respectively. Metastatic recurrence of disease was common (mainly pulmonary). However, a significant proportion of the recurrences were accessible for surgery, and at follow-up (after median of 27months; range, 8-60), 33% had no evidence of disease. Hepatic tumor load before liver transplantation, time from primary surgery to liver transplantation, and progressive disease on chemotherapy were identified as significant prognostic factors. The authors concluded that OS exceeds by far reported outcome for chemotherapy.
Hagness et al (2014) reported on patterns of recurrences after liver transplantation (LT) for CLM and the effect on survival.[43] Characterization of metastatic lesions in a prospective study for LT for nonresectable CLM was performed (n = 21). The study included reexamination of chest computed tomographic scans taken before LT. At the time of first recurrence, 16 were a single site, and three were multiple sites. Thirteen of the single sites were pulmonary recurrences. The pulmonary recurrences appeared early and were slow growing, and several were accessible to surgical treatment. When chest computed tomographic scans were reexamined, seven patients had pulmonary nodules at the time of LT without an effect on survival. There was no first single-site hepatic recurrence. Six of the seven patients who developed metastases to the transplanted liver died from metastatic disease.

In a prospective (SECA-I) study, Dueland et al (2020), included colorectal cancer patients with nonresectable liver-only metastases determined by computed tomography (CT)/magnetic resonance imaging/positron emission tomography scans and at least 10% response to

chemotherapy.[44] Time from diagnosis to liver transplant was required to be more than 1 year. At a median follow-up of 36 months, Kaplan-Meier overall survival at 1, 3, and 5 years were 100%, 83%, and 83%, respectively. Disease-free survival at 1, 2, and 3 years were 53%, 44%, and 35%, respectively. Overall survival from time of relapse at 1, 2, and 4 years were 100%, 73%, and 73%,respectively. Recurrence was mainly slow growing pulmonary metastases amenable to curative resection. Fong Clinical Risk Score of 1 to 2 at the time of diagnosis resulted in longer disease-free survival than score 3 to 4 (P = 0.044). Patients included in the present study had significantly better prognostic factors than the previous SECA-I study.

Line et al (2020) summarized recent developments within the field of LT for CRLMs. The authors findings included that more stringent selection criteria can yield 5-year survival rates that are similar to conventional indications for liver transplantation.[45] Response to chemotherapy, low carcinoembryonic antigen levels, limited tumor volume and stable disease with observation time exceeding 12 months are fundamental requirements in this context. Radiomic analysis of pre transplant PET/computed tomography scans to determine metabolic tumor volume (MTV) in the liver seems particularly promising with regards to prediction of a favorable tumor biology. MTV values below 70 cm3 are associated with excellent long-term survival after transplantation, whereas the MTV threshold for liver resection seem far smaller. Recent studies put into question whether technical nonresectability per seis a valid inclusion criterion for liver transplantation. In patients with high hepatic tumor burden, but otherwise favorable prognostic features as assessed by the Oslo score, liver transplantation could possibly give a clinically relevant survival benefit compared with liver resection.

Smedman et al (2020) evaluated the survival of patients with CRLM after LT using extended criteria for both patients and donors.[46] Patients with synchronous unresectable CRLM who were not suitable for arms A, B or C of the SEcondary CAncer (SECA) II study who had undergone radical resection of the primary tumour and received chemotherapy were included; they underwent liver transplantation with extended criteria donor grafts. Patients who had resectable pulmonary metastases were eligible for inclusion. The main exclusion criteria were BMI above 30 kg/m^2 and liver metastases larger than 10 cm. Survival was estimated using Kaplan-Meier analysis and liver metastases larger than 10 cm. Ten patients (median age 54 years; 3 women) were included. They had an extensive liver tumour load with a median of 20 (range 1-45) lesions; the median size of the largest lesion was 59(range 15-94) mm. Eight patients had (y)pN2 disease, six had poorly differentiated or signet ring cell-differentiated primary tumours, and five had primary tumour in the ascending colon. The median Fong clinical risk score was 3 (range 2-5) and the median Oslo score was 1 (range 1-4). The median plasma carcinoembryonic antigen level was 4·3 (range 2-4346) μg/l. Median disease-free and overall survival was 4 and 18 months, respectively.

Sasaki et al (2023) summarized donor, recipient, and transplant center characteristics and posttransplant outcomes for the indication of CRLM.[47] Adult, primary LT patients listed between December 2017 and March 2022 were identified by using United Network Organ Sharing database. LT for CRLM was identified from variables: "DIAG_OSTXT"; "DGN_OSTXT_TCR"; "DGN2_OSTXT_TCR"; and "MALIG_TY_OSTXT." During this study period, 64 patients were listed, and 46 received LT for CRLM in 15 centers. Of 46 patients who underwent LT for CRLM, 26 patients (56.5%) received LTs using living donor LT(LDLT), and 20 patients received LT using deceased donor (DDLT) (43.5%). The median laboratory MELD-Na score at the time of listing was statistically similar between the LDLT and DDLT groups (8 vs.9, P = 0.14). This persisted at the time of LT (8 vs. 12, P = 0.06). The 1-, 2-, and 3-year,

disease-free, survival rates were 75.1, 53.7, and 53.7%. Overall survival rates were 89.0, 60.4, and 60.4%, respectively.

In 2023, Sposito et al reported on a study that assesses the efficacy of LT in liver-only metastatic CRC compared with a matched cohort of patients included in a phase III trial on triplet chemotherapy + antiEGFR.[48] The COLT trial is an investigator-driven, multicenter, non-randomized, open-label, controlled, prospective, parallel trial. Hyperselected patients with liver-limited unresectable CLM, RAS and BRAF wild-type and curatively removed primary colon cancer are included. The observed post-transplant outcomes are prospectively compared 1:5 with those obtained in a matched cohort from the TRIPLETE trial. Primary endpoint is to compare the 3 and 5-years OS of patients enrolled in the COLT trial with COLT-eligible population enrolled in the TRIPLETE trial. An expected gain in OS of 40% at 5-yearsis predicted for the COLT population (the expected OS at 5-years in COLT vs. TRIPLETE is 70% vs. 30%).Secondary endpoints are to compare the 5-years disease-free survival and to assess the safety of LT(Dindo-Clavien Classification and the Comprehensive Complication Index). The authors conclude that LT offers the longest OS reported in selected patients with CLM. Improving the selection strategies can give patients a 5-year OS similar to other indications for LT and a better outcome than those undergoing chemotherapy alone.

Section Summary: Liver Transplant for Nonresectable Colorectal Cancer Liver-Only Metastases.
The evidence on liver transplant for nonresectable CLM includes pilot studies, prospective studies and reviews. LT for selected individuals can increase overall survival rates compared to chemotherapy and had overall favorable prognosis.

LIVER TRANSPLANT FOR PEDIATRIC HEPATOBLASTOMA

Clinical Context and Therapy Purpose
The purpose of a liver transplant for children who have pediatric hepatoblastoma is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following **PICOs** were used to select literature to inform this review.

Populations
The relevant population of interest is children with pediatric hepatoblastoma.

Interventions
The therapy being considered is liver transplant.

Comparators
The following practice is currently being used to make decisions about managing pediatric hepatoblastoma: medical management.

Outcomes
The general outcomes of interest are OS and treatment-related adverse events (e.g., immunosuppression, graft failure, surgical complications, infections). Short-term follow-up ranges from immediate post-surgery to 30 days post-transplantation; lifelong follow-up (out to at 10 years or more given current survival data) is necessary due to ongoing

immunosuppression and risk of graft failure. See the Potential Contraindications section for a detailed discussion.

Review of Evidence

Case Series

Pediatric hepatoblastoma is a rare condition, and the available evidence consists of small case series. Most recently, Hamilton et al (2017) reported on 376 children with hepatoblastoma requiring liver transplantation; this was part of a larger cohort of 544 children receiving a liver transplant from 1987 to 2012, as recorded in the United Network for Organ Sharing database.[49] The 5-year patient survival rate after liver transplant for hepatoblastoma was 73%, with 5-year graft survival rate of 74%. Recurrent or metastatic disease was the most common (57%) cause of death for this population. In 2011 Barrena et al reported on 15 children with hepatoblastoma requiring liver transplantation.[50] 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.[51] Tumor recurrence occurred in one 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%).[52] 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).

Section Summary: Liver Transplant for 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 post chemotherapy is a treatment option with reports of good outcomes and high rates of survival.[53] UNOS guidelines list nonmetastatic hepatoblastoma as a condition eligible for pediatric liver transplantation.[47]

LIVER RETRANSPLANT FOR A FAILED LIVER TRANSPLANT

Clinical Context and Therapy Purpose

The purpose of a liver transplant for individuals who have a failed liver transplant is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following **PICOs** were used to select literature to inform this review.

Populations

The relevant population of interest is individuals with a failed liver transplant.

Interventions

The therapy being considered is liver retransplant.

Comparators

The following practice is currently being used to make decisions about failed liver transplant: medical management.

Outcomes
The general outcomes of interest are OS and treatment-related adverse events (e.g., immunosuppression, graft failure, surgical complications, infections). See the Potential Contraindications section for a detailed discussion.

Review of Evidence

Cohort Studies
Salimi et al (2021) reported on a retrospective cohort using records from 1030 patients who underwent liver transplantation at a liver transplantation center in Iran between the years 2000 and 2016; of these, 966 were initial transplants and 64 were retransplants.[54] The mortality rate was significantly higher among patients who underwent retransplantation (54.68%) compared to patients who underwent primary liver transplantation (21.32%; p<.001). Overall survival at 1-, 3-, and 5-years posttransplant was 82%, 80%, and 70%, respectively, for patients undergoing initial transplant and 59%, 43%, and 32%, respectively, for patients undergoing retransplant. Patients who underwent retransplantation also had significantly higher MELD scores (10.73 ± 25.89) compared to patients who underwent primary liver transplantation (5.65 ± 20.51; p=.004).

In 2012, Bellido et al reported on a retrospective cohort study of 68 consecutive adult liver retransplantations using registry data.[55] 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.

Hong et al, in 2011, reported on a prospective study of 466 adults to identify risk factors for survival after liver retransplantation.[56] 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.

Section Summary: Liver Retransplant for Failed Liver Transplant
Observational studies have evaluated the risk factors with a failed liver transplant for survival after liver retransplantation. Reported OS rates are lower after retransplantation than after initial liver transplantation, but survival rates are acceptable in appropriately selected patients given the lack of treatment-related options.

POTENTIAL CONTRAINDICATIONS (APPLIES TO ALL PREVOUS INDICATIONS)

Living Donor vs. Deceased Donor Liver Transplant Recipient 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. Because hepatectomy involves 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. Reports of several donor deaths have been reported.[56-59]

In December 2000, the National Institutes of Health (NIH) convened a workshop focusing on living-donor liver transplantation. Shiffman et al (2002) summarized this workshop.[60] According to this document, the risk of mortality to the donor undergoing right hepatectomy was estimated to be approximately 0.2% to 0.5%. 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.

Criteria for a recipient of a living-related liver were 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.[56]

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.[61] 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. Another systematic review and meta-analysis by Tang et al (2020) compared outcomes between LDLT and deceased donor liver transplants from 39 studies (N=38563; mainly retrospective in nature) of patients with end-stage liver disease.[62] Perioperative mortality, hospital length of stay, retransplantation rates, and recurrence rates for HCV and HCC were similar between groups. Living donor LT were associated with significant improvements in 1- (OR, 1.32; 95% CI, 1.01 to 1.72; p=.04), 3- (OR, 1.39; 95% CI, 1.14 to 1.69; p=.0010), and 5-year (OR, 1.33; 95% CI, 1.04 to 1.70; p=.02) OS and vascular (OR, 2.00; 95% CI, 1.31 to 3.07; p=.001) and biliary (OR, 2.23; 95% CI, 1.59 to 3.13; p<.00001) complication rates compared to deceased donor liver transplants.

HIV-Positive Patients

Solid-organ transplant for patients who are HIV-positive was historically controversial, due to the long-term prognosis for HIV positivity and the impact of immunosuppression on HIV disease. HIV candidates for liver transplantation are frequently coinfected with hepatitis B or C, and viral coinfection can further exacerbate drug-related hepatotoxicities. Hepatitis is discussed below.

In 2011, Cooper and colleagues conducted a systematic review to evaluate liver transplantation in patients co-infected with HIV and hepatitis.[63] The review included 15 cohort studies and 49 case series with individual patient data. The survival rate of patients was 84.4% (95% confidence interval [CI]: 81.1-87.8%) at 12 months. Patients were 2.89 (95% CI: 1.41-5.91) times more likely to survive when HIV viral load at the time of transplantation was undetectable compared to those with detectable HIV viremia.

Terrault et al (2012) 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.[64] Patient and graft survival reductions were significantly associated with only one factor: HIV infection. At 3 years, in the HCV only group, patient and graft survival rates were significantly better at 79% (95% CI:72-84%) and 74% (95% CI: 66-79%), respectively, than the group with both HIV and HCV infection at 60% (95% CI: 47-71%) and 53% (95% CI: 40-64%). 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.

Current OPTN policy permits HIV-positive transplant candidates.[65]
The American Society of Transplantation (2019) published a guideline on solid organ transplantation in HIV-infected patients.[66] For liver transplants, the following criteria for transplantation are suggested:

- Cluster of differentiation 4 (CD4) count >100 cells/mL with no history of AIDS-defining illnesses such as opportunistic infection or malignancy or CD4 count >200 cells/mL for at least 3 months
- Undetectable HIV viral load while receiving antiretroviral therapy or a detectable HIV viral load in patients with intolerance to antiretroviral therapy that can be suppressed posttransplant
- Documented compliance with a stable antiretroviral therapy regimen
- Absence of active opportunistic infection and malignancy
- Absence of chronic wasting or severe malnutrition
- Appropriate follow-up with providers experienced in HIV management and ready access to immunosuppressive medication therapeutic drug monitoring

The guideline authors note that patients with a previous history of progressive multifocal leukoencephalopathy, chronic interstitial cryptosporidiosis, primary central nervous system lymphoma, or visceral Kaposi's sarcoma were excluded from studies of solid organ transplantation in HIV-infected patients. Patients with HIV and concomitant controlled hepatitis B infection may be considered for transplant. Caution is recommended in hepatitis C coinfected patients who have not been initiated on direct acting antiviral therapy.

Hepatitis Infection
Terrault et al (2012) 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.[67] 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: 72-84%) and 74% (95% CI: 66-79%), respectively, than the group with HIV and HCV at 60% (95% CI: 47-71%) and 53% (95% CI: 40-64%).

Section Summary: Potential Contraindications
Living donor liver transplantation has become accepted practice with careful screening of donors. 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 liver transplant recipients. HCV status is not significantly associated with reduced patient survival. Although 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.

SUMMARY OF EVIDENCE

For individuals who have hepatocellular disease who receive liver transplant, the evidence includes case series, registry studies, and systematic reviews. Relevant outcomes include overall survival (OS), morbid events, and treatment-related morbidity and mortality. Studies on liver transplantation for viral hepatitis find that survival is lower than for other liver diseases. 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. In addition, survival can be improved by eradication of hepatitis virus before transplantation. For patients with nonalcoholic steatohepatitis, OS rates have been shown to be similar to other indications for liver transplantation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have hepatocellular carcinoma who receive liver transplant, the evidence includes systematic reviews of observational studies. Relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. The long-term outcome in patients with primary hepatocellular malignancies was poor (19%) in the past compared with the OS of liver transplant recipients. However, recent use of standardized patient selection criteria, such as the Milan criteria diameter, has dramatically improved OS rates. In appropriately selected patients, liver transplant has been shown to result in higher survival rates than resection. In patients who present with unresectable organ-confined disease, transplant represents the only curative approach. Overall, the evidence base is insufficient to permit conclusions about health outcomes after liver. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have extrahepatic cholangiocarcinoma who receive liver transplant, the evidence includes a systematic review and meta-analysis of observational studies Relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. For patients with extrahepatic (hilar or perihilar) cholangiocarcinoma who are treated with adjuvant chemotherapy, 5-year survival rates have been reported as high as 76%. Society guidelines also support liver transplant in select patients with extrahepatic cholangiocarcinoma that is unresectable. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have intrahepatic cholangiocarcinoma who receive liver transplant, the evidence includes registry studies. Relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. In a registry study comparing outcomes in patients with intrahepatic cholangiocarcinoma who received liver transplantation to those who received surgical resection of the liver, no differences were found in OS, length of stay, or unplanned 30-day readmission rates between groups. Additional studies reporting survival rates in patients with intrahepatic cholangiocarcinoma or in mixed populations of patients with extrahepatic and intrahepatic cholangiocarcinoma have reported 5-year survival rates of less than 30%. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have metastatic neuroendocrine tumors who receive liver transplant, the evidence includes systematic reviews of NETs for metastases of any origin. 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. While there may be centers that perform liver transplantation on select patients with NETs, the available studies are limited by their heterogeneous populations. The evidence is sufficient to determine the effects of the technology on health outcomes.

For individuals who have colorectal cancer with liver-only metastases the evidence includes pilot studies, prospective studies and reviews. Although the literature on LT for CRLM is limited, it shows an increased overall survival rate exceeding the overall survival rate of chemotherapy alone. The evidence is sufficient to determine the effects of the technology on health outcomes.

For individuals who have pediatric hepatoblastoma who receive liver transplant, the evidence includes case series. Relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. 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 United Network for Organ Sharing criteria for patients eligible for liver transplantation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have a failed liver transplant who receive liver retransplant, the evidence includes observational studies. Relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. 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. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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 indications listed in the Policy Statement and in those otherwise meeting United Network of Organ Sharing criteria. Liver transplantation is investigational in patients in whom the procedure is expected to be futile due to comorbid disease or in whom post transplantation care is expected to significantly worsen comorbid conditions. 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 neuroendocrine tumors metastatic to the liver is considered investigational. 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.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02878473	Liver transplantation for the treatment of early stages of intrahepatic cholangiocarcinoma in cirrhotics	30	Jan 2029
NCT05944042	Hepatic Transplantation Registry	300	Feb 2025
NCT04742621	Liver Transplantation for Unresectable Liver Limited Colorectal Metastases	20	Jul 2035
NCT04993131	Liver Transplantation for Non-resectable Perihilar Cholangiocarcinoma (TESLA II)	15	May 2045
Unpublished			
NCT03500315	HOPE in action prospective multicenter, clinical trial of deceased HIVD+ kidney transplants for HIV+ recipients	160	Dec 2022

NCT: national clinical trial.

SUPPLEMENTAL INFORMATION

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.

2012 Input

In response to requests, BCBSA received input 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 non-function, 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.

PRACTICE GUIDELINES AND POSITION STATEMENTS

International Consensus Conference[68]

In 2010, an International Consensus Conference, including representation from the U.S., convened with the goal of reviewing current practice regarding liver transplantation in patients with hepatocellular carcinoma (HCC). The Conference ultimately came up with recommendations beginning from the assessment of candidates with HCC for liver transplantation and managing patients on waitlists, to the role of liver transplantation and post-transplant management. Some notable recommendations are described.

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 regards 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. In addition, 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.

American Association for the Study of Liver Diseases and American Society of Transplantation[69]

In 2013, the American Association for the Study of Liver Diseases (AASLD) and the American Society of Transplantation (AST) issued guidelines on evaluating patients for liver transplant.[56] These guidelines state liver transplantation for severe acute or advanced chronic liver disease is indicated after all effective medical treatments have been attempted. The formal evaluation should confirm the irreversible nature of the liver disease and lack of effective medical therapy.

The AASLD and AST guidelines stated that liver transplant is indicated for:

- Acute liver failure from complications of cirrhosis
- Liver-based metabolic condition with systemic manifestations
    - α1-antitrypsin deficiency
    - Familial amyloidosis
    - Glycogen storage disease
    - Hemochromatosis
    - Primary oxaluria
    - Wilson disease
- Systemic complications of chronic liver disease

In addition, the guidelines included 1-A (strong recommendation with a high quality of evidence) recommendations for liver transplant that:

- “Tobacco consumption should be prohibited in LT (liver transplant) candidates.”
- “Patients with HIV infection are candidates for LT if immune function is adequate and the virus is expected to be undetectable by the time of LT.”
- “LT candidates with HCV have the same indications for LT as for other etiologies of cirrhosis.”

Contraindications to liver transplant are:

- “MELD score <15
- Severe cardiac or pulmonary disease
- AIDS
- Ongoing alcohol or illicit substance abuse
- Hepatocellular carcinoma with metastatic spread
- Uncontrolled sepsis

- Anatomic abnormality that precludes liver transplantation Intrahepatic cholangiocarcinoma
- Extrahepatic malignancy
- Fulminant hepatic failure
- Hemangiosarcoma
- Persistent noncompliance
- Lack of adequate social support system”

In 2014, the AASLD, AST, and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition issued joint guidelines on the evaluation of the pediatric patients for liver transplant.[70] The guidelines stated that "disease categories suitable for referral to a pediatric LT program are similar to adults: acute liver failure, autoimmune, cholestasis, metabolic or genetic, oncologic, vascular, and infectious. However, specific etiologies and outcomes differ widely from adult patients, justifying independent pediatric guidelines." The indications listed for liver transplantation included biliary atresia, Alagille syndrome, pediatric acute liver failure, hepatic tumors, HCC, hemangioendothelioma, cystic fibrosis-associated liver disease, urea cycle disorders, immune-mediated liver disease, along with other metabolic or genetic disorders.

In 2019, the AASLD guideline on alcohol-associated liver disease provided recommendations on the timing of referral and selection of candidates for liver transplant.[71] The guidance notes that the patient's history of addiction to alcohol is a primary driver in selecting appropriate candidates for liver transplantation. Clinical characteristics that should trigger an evaluation and consideration for liver transplant include decompensated alcohol-associated cirrhosis, Child-Pugh-Turcotte class C cirrhosis, or a MELD-Na score ≥21. Additionally, the guideline notes that candidate selection "should not be based solely on a fixed interval of abstinence" and instead a formal psychological evaluation can help stratify patients into higher- or lesser-risk strata for relapse.

In 2023, the AASLD released a practice guideline on the management of hepatocellular carcinoma.[72] Evidence recommendations by the expert panel are rated based on the Oxford Center for Evidence-Based Medicine and the strength of recommendations are Categorized based on the level of evidence, risk–benefit ratio, and patient preferences. Recommendations regarding liver transplantation are listed below.

- "Liver transplantation should be the treatment of choice for transplant-eligible patients with early-stage HCC occurring inthe setting of clinically significant portal hypertension and/or decompensated cirrhosis (Level 2, Strong Recommendation)
- AASLD advises the use of pre-transplant locoregional bridging therapy for patients being evaluated or listed for liver transplantation, if they have adequate hepatic reserve, to reduce the risk of waitlist dropout in the context of anticipated prolonged wait times for transplant (Level 3, Strong Recommendation)
- AASLD advises patients with decompensated cirrhosis who develop T1 HCC and are eligible for LT be monitored with cross-sectional imaging at least every 3 months until criteria are met for MELD exception before pursuing LRT [locoregional therapy] (Level 3, Weak Recommendation)
- Patients who are otherwise transplant-eligible except with initial tumor burden exceeding the Milan criteria, especially those meeting United Network of Organ Sharing (UNOS) downstaging criteria, should be considered for LT following successful

downstaging to within Milan criteria after a 3-to-6-month period of observation (Level 2, Strong Recommendation)
- AASLD advises surveillance for detection of post-transplant HCC recurrence using multiphasic contrast-enhanced abdominal CT [computed tomography] or MRI [magnetic resonance imaging] and chest CT scan (Level 2, Strong Recommendation)"

National Comprehensive Cancer Network[73,74]
The National Comprehensive Cancer Network (NCCN) guidelines on hepatocellular carcinoma (v.1.2024 recommends referral to a liver transplant center or bridge therapy for patients with HCC meeting UNOS criteria. NCCN guidelines for biliary tract cancers (v. 2.2024) states before biopsy, evaluate if patient is a resection or transplant candidate. If patient is a potential transplant candidate, consider referral to transplant center before biopsy. Unresectable perihilar or hilar CCAs that measure ≤3 cm in radial diameter, with the absence of intrahepatic or extrahepatic metastases and without nodal disease, as well as those with primary sclerosing cholangitis, may be considered for liver transplantation at a transplant center that has an UNOS approved protocol for transplantation of CCA.

The NCCN guidelines on NETs (v.1.2024) indicate liver transplantation for NET liver metastases is considered investigational despite “encouraging” 5-year survival rates.

U.S. Preventive Services Task Force Recommendations
The U.S. Preventive Services Task Force has not addressed liver transplant.

Government Regulations
National:

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.[69,70] 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, upon 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 (<18 years of age) 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.

Local:
There is no separate WPS local coverage determination on this topic.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Transplant-Heart
- Transplant Heart-Lung (Combined)
- Transplant Liver-Kidney (Combined)
- Transplant Lung and Lobar Lung
- Transplant Pancreas
- Transplant Small Bowel and Liver or Multivisceral
- Transplant Small Bowel Transplant (Isolated)

References

1. Black CK, Termanini KM, Aguirre O, et al. Solid organ transplantation in the 21 st century. Ann Transl Med. Oct 2018; 6(20): 409. PMID 30498736
2. Belle SH, Beringer KC, Detre KM. An update on liver transplantation in the United States: recipient characteristics and outcome. Clin Transpl. 1995: 19-33. PMID 8794252
3. Sheiner P, Rochon C. Recurrent hepatitis C after liver transplantation. Mt Sinai J Med. Mar-Apr 2012; 79(2): 190-8. PMID 22499490
4. Gadiparthi C, Cholankeril G, Perumpail BJ, et al. Use of direct-acting antiviral agents in hepatitis C virus-infected liver transplant candidates. World J Gastroenterol. Jan 21 2018; 24(3): 315-322. PMID 29391754
5. Wang X, Li J, Riaz DR, et al. Outcomes of liver transplantation for nonalcoholic steatohepatitis: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. Mar 2014; 12(3): 394-402.e1. PMID 24076414
6. Cholankeril G, Wong RJ, Hu M, et al. Liver Transplantation for Nonalcoholic Steatohepatitis in the US: Temporal Trends and Outcomes. Dig Dis Sci. Oct 2017; 62(10): 2915-2922. PMID 28744836
7. Schoenberg MB, Bucher JN, Vater A, et al. Resection or Transplant in Early Hepatocellular Carcinoma. Dtsch Arztebl Int. Aug 07 2017; 114(31-32): 519-526. PMID 28835324
8. Zheng Z, Liang W, Milgrom DP, et al. Liver transplantation versus liver resection in the treatment of hepatocellular carcinoma: a meta-analysis of observational studies. Transplantation. Jan 27 2014; 97(2): 227-34. PMID 24142034
9. Guiteau JJ, Cotton RT, Washburn WK, et al. An early regional experience with expansion of Milan Criteria for liver transplant recipients. Am J Transplant. Sep 2010; 10(9): 2092-8. PMID 20883543
10. Pomfret EA, Washburn K, Wald C, et al. Report of a national conference on liver allocation in patients with hepatocellular carcinoma in the United States. Liver Transpl. Mar 2010; 16(3): 262-78. PMID 20209641
11. Ioannou GN, Perkins JD, Carithers RL. Liver transplantation for hepatocellular carcinoma: impact of the MELD allocation system and predictors of survival. Gastroenterology. May 2008; 134(5): 1342-51. PMID 18471511

12. Chan EY, Larson AM, Fix OK, et al. Identifying risk for recurrent hepatocellular carcinoma after liver transplantation: implications for surveillance studies and new adjuvant therapies. Liver Transpl. Jul 2008; 14(7): 956-65. PMID 18581511
13. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. Mar 14 1996; 334(11): 693-9. PMID 8594428
14. Firl DJ, Kimura S, McVey J, et al. Reframing the approach to patients with hepatocellular carcinoma: Longitudinal assessment with hazard associated with liver transplantation for HCC (HALTHCC) improves ablate and wait strategy. Hepatology. Oct 2018; 68(4): 1448-1458. PMID 29604231
15. National Comprehensive Cancer Network. Hepatobiliary Cancers. Version 3.2021. https://www.nccn.org/professionals/physician_gls/PDF/hepatobiliary.pdf. Accessed July 8, 2021.
16. Yadav DK, Chen W, Bai X, et al. Salvage Liver Transplant versus Primary Liver Transplant for Patients with Hepatocellular Carcinoma. Ann Transplant. Aug 03 2018; 23: 524-545. PMID 30072683
17. Murali AR, Patil S, Phillips KT, et al. Locoregional Therapy With Curative Intent Versus Primary Liver Transplant for Hepatocellular Carcinoma: Systematic Review and Meta-Analysis. Transplantation. Aug 2017; 101(8): e249-e257. PMID 28282359
18. Maggs JR, Suddle AR, Aluvihare V, et al. Systematic review: the role of liver transplantation in the management of hepatocellular carcinoma. Aliment Pharmacol Ther. May 2012; 35(10): 1113-34. PMID 22432733
19. Chan DL, Alzahrani NA, Morris DL, et al. Systematic review of efficacy and outcomes of salvage liver transplantation after primary hepatic resection for hepatocellular carcinoma. J Gastroenterol Hepatol. Jan 2014; 29(1): 31-41. PMID 24117517
20. Zhu Y, Dong J, Wang WL, et al. Short- and long-term outcomes after salvage liver transplantation versus primary liver transplantation for hepatocellular carcinoma: a meta-analysis. Transplant Proc. Nov 2013; 45(9): 3329-42. PMID 24182812
21. Cambridge WA, Fairfield C, Powell JJ, et al. Meta-analysis and Meta-regression of Survival After Liver Transplantation for Unresectable Perihilar Cholangiocarcinoma. Ann Surg. Feb 01 2021; 273(2): 240-250. PMID 32097164
22. Gu J, Bai J, Shi X, et al. Efficacy and safety of liver transplantation in patients with cholangiocarcinoma: a systematic review and meta-analysis. Int J Cancer. May 01 2012; 130(9): 2155-63. PMID 21387295
23. Heimbach JK. Successful liver transplantation for hilar cholangiocarcinoma. Curr Opin Gastroenterol. May 2008; 24(3): 384-8. PMID 18408469
24. Darwish Murad S, Kim WR, Harnois DM, et al. Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. Gastroenterology. Jul 2012; 143(1): 88-98.e3; quiz e14. PMID 22504095
25. Heimbach JK, Gores GJ, Haddock MG, et al. Predictors of disease recurrence following neoadjuvant chemoradiotherapy and liver transplantation for unresectable perihilar cholangiocarcinoma. Transplantation. Dec 27 2006; 82(12): 1703-7. PMID 17198263
26. Rea DJ, Heimbach JK, Rosen CB, et al. Liver transplantation with neoadjuvant chemoradiation is more effective than resection for hilar cholangiocarcinoma. Ann Surg. Sep 2005; 242(3): 451-8; discussion 458-61. PMID 16135931
27. Pascher A, Jonas S, Neuhaus P. Intrahepatic cholangiocarcinoma: indication for transplantation. J Hepatobiliary Pancreat Surg. 2003; 10(4): 282-7. PMID 14598146

28. Friman S, Foss A, Isoniemi H, et al. Liver transplantation for cholangiocarcinoma: selection is essential for acceptable results. Scand J Gastroenterol. Mar 2011; 46(3): 370-5. PMID 21073376
29. Meyer CG, Penn I, James L. Liver transplantation for cholangiocarcinoma: results in 207 patients. Transplantation. Apr 27 2000; 69(8): 1633-7. PMID 10836374
30. Robles R, Figueras J, Turrion VS, et al. Spanish experience in liver transplantation for hilar and peripheral cholangiocarcinoma. Ann Surg. Feb 2004; 239(2): 265-71. PMID 14745336
31. Casavilla FA, Marsh JW, Iwatsuki S, et al. Hepatic resection and transplantation for peripheral cholangiocarcinoma. J Am Coll Surg. Nov 1997; 185(5): 429-36. PMID 9358085
32. Hue JJ, Rocha FG, Ammori JB, et al. A comparison of surgical resection and liver transplantation in the treatment of intrahepatic cholangiocarcinoma in the era of modern chemotherapy: An analysis of the National Cancer Database. J Surg Oncol. Mar 2021; 123(4): 949-956. PMID 33400841
33. Fan ST, Le Treut YP, Mazzaferro V, et al. Liver transplantation for neuroendocrine tumour liver metastases. HPB (Oxford). Jan 2015; 17(1): 23-8. PMID 24992381
34. Mathe Z, Tagkalos E, Paul A, et al. Liver transplantation for hepatic metastases of neuroendocrine pancreatic tumors: a survival-based analysis. Transplantation. Mar 15 2011; 91(5): 575-82. PMID 21200365
35. Hamilton EC, Balogh J, Nguyen DT, et al. Liver transplantation for primary hepatic malignancies of childhood: The UNOS experience. J Pediatr Surg. Oct 12 2017. PMID 29108844
36. Barrena S, Hernandez F, Miguel M, et al. High-risk hepatoblastoma: results in a pediatric liver transplantation center. Eur J Pediatr Surg. Jan 2011; 21(1): 18-20. PMID 20938901
37. Malek MM, Shah SR, Atri P, et al. Review of outcomes of primary liver cancers in children: our institutional experience with resection and transplantation. Surgery. Oct 2010; 148(4): 778-82; discussion 782-4. PMID 20728194
38. Browne M, Sher D, Grant D, et al. Survival after liver transplantation for hepatoblastoma: a 2-center experience. J Pediatr Surg. Nov 2008; 43(11): 1973-81. PMID 18970927
39. Czauderna P, Otte JB, Aronson DC, et al. Guidelines for surgical treatment of hepatoblastoma in the modern era—recommendations from the Childhood Liver Tumour Strategy Group of the International Society of Paediatric Oncology (SIOPEL). Eur J Cancer. May 2005; 41(7): 1031-6. PMID 15862752
40. Organ Procurement and Transplantation Network (OPTN). Policy 9: Allocation of Livers and Liver-Intestines. 2021; https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf#nameddest=Policy_01. Accessed July 7, 2021.
41. Salimi J, Jafarian A, Fakhar N, et al. Study of re-transplantation and prognosis in liver transplant center in Iran. Gastroenterol Hepatol Bed Bench. 2021; 14(3): 237-242. PMID 34221263
42. Hagness M, Foss A, Line PD, et al. Liver transplantation for nonresectable liver metastases from colorectal cancer. Ann Surg. May 2013; 257(5): 800-806. PMID: 23360920
43. Hagness M, Foss, A, Egge TS, Dueland S. Patterns of recurrence after liver transplantation for nonresectable liver metastases from colorectal cancer. Ann Surg Oncol. April 2014; 21(4): 1323-1329. PMID: 24370906
44. Dueland S, Syversveen T, Solheim JM, et al. Survival following liver transplantation for patients with nonresectable liver-only colorectal metastases. Ann Surg. Feb 2020; 271(2): 212-218. PMID: 31188200
45. Line PD. Liver transplantation for colorectal liver metastases: what do we need to know? International J Surgery. 2020; 82: 87-92.

46. Smedman TM, Line PD, Hagness M, et al. Liver transplantation for unresectable colorectal liver metastases in patients and donors with extended criteria (SECA-II arm D study). BJS Open. June 2020; 4(3): 467-477. PMID: 32333527
47. Sasaki K, Ruffolo L, Kim MH, et al. The current state of liver transplantation for colorectal liver metastases in the United States: a call for standardized reporting. Ann Surg Oncol. May 2023; 30(5): 2769-2777. PMID: 36719568
48. Sposito C, Pietrantonio F, Maspero M, et al. Improving outcome of selected patients with nonresectable hepatic metastases from colorectal cancer with liver transplantation: a prospective parallel trial (COLT trial). Clin Colorectal Cancer. June 2023; 22(2): 250-255. PMID: 36822922
49. Bellido CB, Martinez JM, Artacho GS, et al. Have we changed the liver retransplantation survival?. Transplant Proc. Jul-Aug 2012; 44(6): 1526-9. PMID 22841203
50. Hong JC, Kaldas FM, Kositamongkol P, et al. Predictive index for long-term survival after retransplantation of the liver in adult recipients: analysis of a 26-year experience in a single center. Ann Surg. Sep 2011; 254(3): 444-8; discussion 448-9. PMID 21817890
51. Marcos A, Ham JM, Fisher RA, et al. Single-center analysis of the first 40 adult-to-adult living donor liver transplants using the right lobe. Liver Transpl. May 2000; 6(3): 296-301. PMID 10827229
52. Malago M, Testa G, Marcos A, et al. Ethical considerations and rationale of adult-to-adult living donor liver transplantation. Liver Transpl. Oct 2001; 7(10): 921-7. PMID 11679994
53. Renz JF, Busuttil RW. Adult-to-adult living-donor liver transplantation: a critical analysis. Semin Liver Dis. 2000; 20(4): 411-24. PMID 11200412
54. Bak T, Wachs M, Trotter J, et al. Adult-to-adult living donor liver transplantation using right-lobe grafts: results and lessons learned from a single-center experience. Liver Transpl. Aug 2001; 7(8): 680-6. PMID 11510011
55. Shiffman ML, Brown RS, Olthoff KM, et al. Living donor liver transplantation: summary of a conference at The National Institutes of Health. Liver Transpl. Feb 2002; 8(2): 174-88. PMID 11862598
56. Grant RC, Sandhu L, Dixon PR, et al. Living vs. deceased donor liver transplantation for hepatocellular carcinoma: a systematic review and meta-analysis. Clin Transplant. Jan-Feb 2013; 27(1): 140-7. PMID 23157398
57. Tang W, Qiu JG, Cai Y, et al. Increased Surgical Complications but Improved Overall Survival with Adult Living Donor Compared to Deceased Donor Liver Transplantation: A Systematic Review and Meta-Analysis. Biomed Res Int. 2020; 2020: 1320830. PMID 32908865
58. Cooper C, Kanters S, Klein M, et al. Liver transplant outcomes in HIV-infected patients: a systematic review and meta-analysis with synthetic cohort. AIDS. Mar 27 2011; 25(6): 777-86. PMID 21412058
59. Terrault NA, Roland ME, Schiano T, et al. Outcomes of liver transplant recipients with hepatitis C and human immunodeficiency virus coinfection. Liver Transpl. Jun 2012; 18(6): 716-26. PMID 22328294
60. Organ Procurement and Transplantation Network (OPTN). Organ Procurement and Transplantation Network Policies. 2021; https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf. Accessed July 2024.
61. Blumberg EA, Rogers CC. Solid organ transplantation in the HIV-infected patient: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. Sep 2019; 33(9): e13499. PMID 30773688

62. American Association for the Study of Liver Diseases, American Society of Transplantation. Liver transplantation, evaluation of the adult patient. 2013; https://www.aasld.org/publications/practice-guidelines-0. Accessed July 2024.
63. Squires RH, Ng V, Romero R, et al. Evaluation of the pediatric patient for liver transplantation: 2014 practice guideline by the American Association for the Study of Liver Diseases, American Society of Transplantation and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Hepatology. Jul 2014; 60(1): 362-98. PMID 24782219
64. American Association for the Study of Liver Diseases. Diagnosis and Treatment of Alcohol Associated Liver Diseases: 2019 Practice Guidance From the American Association for the Study of Liver Diseases. https://aasldpubs.onlinelibrary.wiley.com/doi/full/10.1002/hep.30866. Accessed July 2024.
65. Squires RH, Ng V, Romero R, et al. Evaluation of the pediatric patient for liver transplantation: 2014 practice guideline bythe American Association for the Study of Liver Diseases, American Society of Transplantation and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Hepatology. Jul 2014; 60(1): 362-98. PMID 24782219
66. American Association for the Study of Liver Diseases. Diagnosis and Treatment of Alcohol Associated Liver Diseases:2019 Practice Guidance From the American Association for the Study of Liver Diseases. https://www.aasld.org/practice-guidelines/alcohol-associated-liver-disease. Accessed July 2024.
67. Singal AG, Llovet JM, Yarchoan M, et al. AASLD practice guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. Hepatology. May 22 2023. PMID 37199193
59. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Hepatocarcinoma. Version 1.2024. https://www.nccn.org/professionals/physician_gls/pdf. Accessed July 2024.
60. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine and Adrenal Tumors. Version 1.2024. https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf. Accessed July 2024.
61. Centers for Medicare & Medicaid Services. National Coverage Determination (NCD) for Adult Liver Transplantation (260.1). 2012; https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCAId=259&NcaName=Liver+Transplantation+for+Malignancies&ExpandComments=n&Comment Period=0&NCDId=70&ncdver=3&id=186&bc=gABAAAAAEEAAAA%3D%3D&. Accessed July 2024.
62. Centers for Medicare & Medicaid Services. National Coverage Determination (NCD) for Pediatric Liver Transplantation (260.2). 1991; https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?MCDId=17&ExpandComments=n&McdName=Clinical+Pharmacology+Compendium+Revision+Re quest+-+CAG-00392&mcdtypename=Compendia&MCDIndexType=6&NCDId=71&ncdver=1&bc=AgAEAAAAAgAA&. Accessed July 2024.
63. Asrani SK, Trotter J, Lake J, et al. Meeting report: the DALLAS consensus conference on liver transplantation for alcohol related hepatitis. Liver Transpl. Jan 2020; 26(1):127-140

64. Lee BP, Vittinghoff E, Hsu C, et al. Predicting low-risk for sustained alcohol use after early liver transplant for acute alcoholic hepatitis: the SALT score. Hepatology. Apr 2019; 69(4):1477-1487
65. Blue Cross Blue Shield Association. Liver Transplant. Medical Policy Reference Manual. Policy #7.03.06, Issue 9:2017, original policy date 12/1/95, last review date September 2023.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through July 2024, the date the research was completed.

Appendix:

DALLAS Consensus Statement on Liver Transplantation for Alcohol Related Hepatitis[63]

SUMMARY OF RECOMMENDATIONS
General recommendations: Alcohol related hepatitis

1. There should be efforts to standardize nomenclature and definition of alcohol related hepatitis (AH) with an emphasis on use of less stigmatizing terminology.
2. Patients with severe AH may be assessed for corticosteroid therapy.
3. Select patients with severe AH that are unresponsive or ineligible for medical management may be considered for liver transplantation.
4. Predicting response to therapy or pre-LT mortality is best achieved by assessing response over time (change in Model for end stage liver disease (MELD) score, Lille score or a combination of MELD score plus Lille). Mortality is lower for those that have a Lille score <0.45, respond to therapy, have a declining bilirubin, or are abstinent and these patients may not require LT.
5. An inflexible period of abstinence prior to transplantation is not desirable. Acceptance for LT listing should be based upon the severity of liver dysfunction and a comprehensive psychosocial evaluation.

Recommendations for LT for alcohol related hepatitis

A. The goals of LT for AH include:
- **1.** Avoiding LT in patients who will recover without it
- **2.** Avoiding futility and achieving short- and long-term survival comparable to other indications for LT
- **3.** Avoiding creation of further disparity in LT either by indication (versus other indications), geography, sex, race, insurance status or other sociodemographic factors.
- **4.** Identification of LT candidates likely to have long-term abstinence
- **5.** Incorporation treatment of alcohol use disorder (AUD) into pre and post-LT care
- **6.** Consensus of paramedical and medical staff

B. Criteria related to AH
- **1.** First presentation with decompensated alcohol-related liver disease
- **2.** Absence of severe uncontrolled medical or psychiatric comorbidities.
- **3.** Non-response to or ineligible for medical therapy.

C. Criteria related to AUD
- **1.** Establish acceptable risk of relapse by assessment with a multidisciplinary psychosocial team including a social worker and an addiction medicine specialist/mental health professional with addiction and transplantation expertise.
- **2.** Assessment of coherent patient by addiction specialist (i.e., not intubated or floridly encephalopathic).

3. Lack of repeated unsuccessful attempts at addiction rehabilitation.
4. Lack of current other substance use/dependency.
5. Acceptance of ALD diagnosis with insight.
6. Commitment of patient to lifelong sobriety and support of sober caregivers to assist patient with abstinence goals.
7. Presence of close, supportive family members or caregivers

D. Post LT requirements
1. Pre-LT confirmation of plan for AUD treatment after LT
2. Robust post-transplant monitoring for alcohol slips or relapse during post-LT clinic appointments to include direct interviewing of patient and caregivers about alcohol use.
3. Routine monitoring of alcohol use (e.g., with Phosphatidylethanol (PEth), Urinary ethyl glucuronide) for at least 2 years, with frequency and duration individualized beyond this time period.

E. Center requirements
1. Transparency in the candidate selection process and structured collection of objective data to assess outcomes
2. Ongoing support of abstinence that is integrated into post LT care such as concurrent follow-up by addiction specialist/mental health professional with addiction and transplantation expertise.
3. Oversight of program adherence to harmonize listing practices and outcomes.

LT: liver transplant; AH: alcohol related hepatitis; AUD: alcohol use disorder; Peth: phosphatidylethanol; ETG: urinary ethyl glucuronide

The SALT Score[64]

SALT Score to Predict Sustained Alcohol Use Post-LT

Variable	Points
>10 Drinks/day at Presentation	+4
≥2 Prior Failed Rehabilitation Attempts	+4
Any History of Prior Alcohol-Related Legal Issues	+2
History of Non-THC Illicit Substance abuse	+1

The SALT Score was generated from a full LASSO logistic point-score model to predict sustained alcohol use post-LT. The score assigns points to variables which were associated with sustained alcohol use post-LT, and ranges 0–11. Using a cutoff of 5, the SALT score had a c-statistic estimate of 0.76 to predict sustained alcohol use post-LT.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
2/17/03	2/17/03	2/17/03	Joint policy established
1/21/04	1/21/04	3/12/04	Routine maintenance
1/14/05	1/14/05	2/01/05	Routine maintenance
9/1/06	7/10/06	7/6/06	Routine maintenance
9/1/07	7/3/07	7/22/07	Routine maintenance
9/1/08	7/3/08	7/3/08	Routine maintenance
9/1/09	6/16/09	6/16/09	Routine maintenance
12/1/12	9/27/12	9/27/12	Routine maintenance. Policy reformatted to match BCBSA policy. Added absolute and relative contraindications to liver transplant to this policy. Added general statement to contraindications to indicate that the transplant facility has the final approval for patients as transplant candidates. Updated Medicare approved diagnoses and matched the BCBSM/BCN diagnoses to match Medicare.
3/1/14	12/10/13	1/6/14	Additional covered indications for liver transplant added to policy, including non-alcoholic steatohepatitis cirrhosis, hilar cholangiocarcinoma and intrahepatic cholangiocarcinoma. A statement added that *re*transplantation may be considered medically necessary in specified instances.
7/1/15	4/21/15	5/8/15	Additional information added to policy regarding topics, including liver transplantation versus liver resection for HCC, nonalcoholic steatohepatitis and pediatric hepatoblastoma. Moved condition of “neuroendocrine tumors (NET) metastatic to the liver” to the Inclusions section (formerly was an exclusion). Added specific criteria and rationale for patient selection for NET patients.
7/1/16	4/19/16	4/19/16	Routine maintenance
3/1/17	12/13/16	12/13/16	Deleted code 47136, added code 47399. Deleted reference to Blue Cross Complete.
3/1/18	12/12/17	12/12/17	Rationale section reformatted and references 43 and 47 were added. No changes in policy status.
3/1/19	12/11/18		Rationale section reformatted and references 5, 7, 14, 16, 32 and 55-56 were added. No changes in policy status.

3/1/20	12/17/19		Routine policy maintenance. No change in policy status.
11/1/20	8/18/20		Changes made to exclusions for liver transplant section o Changed meld score to <10 o Removed “fulminant hepatic failure” No change in policy status.
11/1/21	8/17/21		Removed MELD score from inclusion / exclusion section. No change in policy status.
11/1/22	8/16/22		Rationale updated, reference 21 and 41 added. No change in policy status.
1/1/23	10/18/22		Added “(<10 score may be considered when appropriate)” to inclusion section. No change in policy status.
11/1/23	8/15/23		Updated rationale, added 4 references. Updated inclusion section with DALLAS and SALT score language. Discussed liver transplant due to colorectal metastases. Vendor managed: N/A. (ds)
11/1/24	8/23/24		Added coverage for colorectal cancer liver only metastases. Updated rationale added references 42-48 and 65-67. Title change to Transplant-Liver. Vendor managed: N/A (ds)

Next Review Date: 3rd Qtr. 2025

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN: 6/1/99	Revised: 10/25/00, 4/16/02 (Transplants-Solid Organ)
BCBSM: N/A	Revised: N/A

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: TRANSPLANT-LIVER

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered, policy guidelines apply Transportation, meals and lodging expenses related to the transplant are not covered unless specifically noted in the member's certificate/rider
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service. Transportation, meals and lodging expenses related to the transplant are not covered

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.