
Medical Policy



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***Current Policy Effective Date: 11/1/26**
(See policy history boxes for previous effective dates)

Title: Transplant-Liver

Description

Liver transplantation is currently the treatment of last resort for individuals with end-stage liver disease. Liver transplantation may be performed with a liver donation after a brain or cardiac death or with a liver segment donation from a living donor. Individuals are prioritized for transplant by mortality risk and severity of illness criteria developed by the Organ Procurement and Transplantation Network and the United Network of Organ Sharing. The severity of illness is determined by the Model for End-stage Liver Disease and Pediatric End-stage Liver Disease scores.

Medical Policy Statement

Liver transplantation and retransplantation are established 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 requested transplanting center's selection criteria.

Inclusions for liver transplant:

- I. Individuals 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
- Metabolic dysfunction-associated steatohepatitis (MASH)
- Protoporphyrria
- 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. Individuals with polycystic disease of the liver who have massive hepatomegaly causing obstruction or functional impairment.

III. Pediatric individuals with nonmetastatic hepatoblastoma

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

V. Individuals with nonresectable colorectal cancer liver-only metastases (CRCLM) (see below)^a

VI. Cholangiocarcinoma

VII. Unresectable solitary intrahepatic cholangiocarcinoma (iCCA) or mixed hepatocellular carcinoma/intrahepatic cholangiocarcinoma (mixed HCC-iCCA) when **ALL** of the following criteria are met:

- Less than or equal to 3cm
- 6 months of tumor stability after last therapy
- No extrahepatic disease

VIII. Hepatocellular Adenomas when **one** of the following criteria is met:

- Unresectable adenoma
- Unresponsive to non-operative medical management
- Progressive adenoma with complications such as hemorrhage, rupture or malignant transformation

IX. Hepatic Epithelioid Hemangioendothelioma (HEHE)

- Biopsy proven diagnosis of HEHE and exclude hemangiosarcoma
- Absence of macrovascular invasion on biopsy or imaging
- Lesions are unresectable

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:

- Individuals 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

Individuals 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 18 years 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 declined 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 individuals must meet BOTH institution's protocol requirements and policy criteria.

Exclusions for Individuals 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.

Inclusions for Liver Retransplant:

Liver retransplant is established for individuals 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 Retransplant:

Individuals not meeting the above inclusionary criteria for retransplant.

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 diseases are not attributed to liver disease.
- Systemic diseases that could be exacerbated by immunosuppression.
- Psychosocial conditions or chemical dependency affecting ability to adhere to therapy.

Conditions that Require MELD Exception Applications

MELD exception points are additional priority points awarded to liver transplant candidates whose laboratory results do not accurately reflect the actual severity, urgency, or mortality risk of their underlying liver disease. While the standard Model for End-Stage Liver Disease (MELD) score relies strictly on objective blood tests (bilirubin, international normalized ratio (INR), creatinine, and sodium), certain complications can be life-threatening without significantly altering these specific lab values. Exception points artificially raise a patient's listed MELD score, allowing them to move higher up the organ waitlist and receive a transplant sooner. The MMat is the midpoint of MELD scores of all liver transplant recipients at hospitals within a 250-nautical-mile radius of the donor hospital over the previous 365 days.

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 metastases 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-tetraazacyclododecane-N, N', N'', N'''-tetraacetic acid (DOTA)-D-Phe1-Tyr3-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. Individuals may come back to the list if any extra-hepatic disease is zeroed and remained so for at least 6 months.
- 10) The presence of extra-hepatic solid organ metastases (i.e., lungs, bones) should be a permanent exclusion criterion.

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

individuals 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 level of 100 U/mL or higher, **or**
 - 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 individuals 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 is 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.

D. Hepatocellular Adenomas

1) Candidates may qualify for an exception if they meet one of the following criteria:

- a. Adenoma in the presence of glycogen storage disease or Abernethy malformation.
- b. Unresectable adenoma with β -catenin mutation.
- c. Unresectable adenoma in a candidate with liver adenomatosis (greater than 10 HA).
- d. Adenoma(s) with all three of the following criteria:
 - Unresectable
 - Unresponsive to non-operative management (e.g., observation after withholding estrogen-containing medications, observation after efforts to maintain an ideal body weight, transarterial embolization, or radiofrequency ablation)
 - Progressive or with complication such as hemorrhage, rupture, or malignant transformation (please provide supportive details including size)

2) Candidates meeting the criteria described above should be considered for a MELD exception score equal to MMat-3.

E. Hepatic Epithelioid Hemangioendothelioma (HEHE)

Candidates with hepatic epithelioid hemangioendothelioma should be considered for a MELD exception extension if they continue to meet all of the following criteria:

- a. Biopsy proven diagnosis of HEHE and exclude hemangiosarcoma
- b. Absence of macrovascular invasion on biopsy or imaging
- c. Lesions are unresectable

F. Intrahepatic cholangiocarcinoma (iCCA) or mixed hepatocellular carcinoma/intrahepatic cholangiocarcinoma (mixed HCC-iCCA)

- 1) Candidates with less than or equal to 3 cm with 6 months of tumor stability after locoregional or systemic therapy should be considered for MELD exception points if they meet the following criteria:
 - a. Biopsy proven iCCA or mixed HCC-iCCA
 - b. Presence of cirrhosis
 - c. Unresectable
 - d. Locoregional or systemic therapy for iCCA
 - e. 6 months from time of diagnosis or last treatment of tumor stability meaning less than or equal to 3 cm, no new lesions, or extrahepatic disease
- 2) Candidates meeting the criteria described above should be considered for a MELD exception score equal to MMat-3

G. Colorectal Cancer Liver Metastasis (CRLM)

Candidates with CRLM should be considered for a MELD exception extension if they continue to meet all of the following criteria:

- a. Every 3 months from initial MELD exception:
 - Perform CT or MRI (chest, abdomen and pelvis)
 - Perform CEA testing
- b. No progression of hepatic disease
- c. No development of extrahepatic disease
- d. CEA < 80 µg/L

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

..... Liver Specific Guidelines/Background Information

Individuals 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).

Individuals 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

Individuals 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 transplantation is an individual consideration based on the morbidity of polyneuropathy. Many individuals may not be candidates for liver transplant alone due to coexisting cardiac disease.

Criteria used for patient selection of hepatocellular carcinoma individuals 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.

Individuals 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 individuals do not receive any priority on the waiting list. All individuals 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 as 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 individuals 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

Background

Solid organ transplantation offers a treatment option for individuals 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. Individuals 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 individuals 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 individuals 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 individuals with nonresectable colorectal liver metastasis (CRLM). In general, the premise of liver transplantation in CRLM relies on the ability to select individuals 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 individuals with a predictive 5-year survival probability above 60–70% to justify transplantation and avoid the futile use of liver grafts.

For many individuals with chronic liver disease, the risk of death without access to liver transplantation can be accurately estimated using the MELD score, which is used to prioritize candidates on the transplant waiting list. However, for some candidates, the need for liver transplantation is driven not by the severity of liver dysfunction itself, but by complications associated with the underlying liver disease. These complications may increase the risk of mortality or waitlist dropout if timely transplantation is not available, yet they are not reflected in the calculated MELD score.

The Adult MELD Exceptions for Transplant Oncology summarizes the available evidence to support clinical reviewers in evaluating requests for MELD exception approval in the setting of hepatic neoplasms. It provides guidance for specific clinical scenarios to assist the review board in assessing common exception requests for adult candidates with the following diagnoses:

- Hepatocellular carcinoma (HCC)
- Intrahepatic cholangiocarcinoma (iCCA)
- Neuroendocrine tumors (NET)
- Colorectal liver metastases (CRLM)
- Hepatic epithelioid hemangioendothelioma (HEHE)
- Hepatic adenomas

These guidelines are intended to promote consistent review of these diagnoses and summarize the Committee's recommendations to the OPTN Board of Directors.

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 individuals who have no other treatment options. In addition, survival can be improved by eradication of hepatitis virus

before transplantation. For individuals with metabolic dysfunction associated steatohepatitis, OS rates have been shown to be similar to other indications for liver transplantation. There is sufficient evidence to determine that the technology results in an improvement in net health outcomes.

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 individuals with primary hepatocellular malignancies was poor (19%) 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 individuals, liver transplants have been shown to result in higher survival rates than resection. In individuals 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. There is sufficient evidence to determine that the technology results in an improvement in net health outcomes.

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 individuals 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 individuals with extrahepatic cholangiocarcinoma that is unresectable. There is sufficient evidence to determine that the technology results in an improvement in net health outcomes.

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 individuals 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 individuals with intrahepatic cholangiocarcinoma or in mixed populations of individuals with extrahepatic and intrahepatic cholangiocarcinoma have reported 5-year survival rates of less than 30%. In a study, researchers found that individuals with intrahepatic CCA who underwent liver transplantation had an improved prognosis compared to those who underwent resection in unmatched (HR, 0.65; $P = .002$) and matched (HR, 0.62; $P = .002$) cohorts.⁷⁵ In a prospective case-series, out of 6 individuals who underwent transplantation for intrahepatic CCA, 50% had RFS at 5 years. OS was 83.3% at 5 years.⁷⁶ Evaluation for liver transplantation should also be considered as individuals who meet the criteria will be eligible for transplant exception points. There is sufficient evidence to determine that the technology results in an improvement in net 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 individuals 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 individuals with NETs, the available studies are limited by their heterogeneous

populations. There is sufficient evidence to determine that the technology results in an improvement in net 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. There is sufficient evidence to determine that the technology results in an improvement in net health outcomes.

For individuals who have unresectable hepatic epithelioid hemangioendothelioma (HEHE) who receive a liver transplant, the evidence includes nonrandomized, observational studies. Relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. Post transplant survival among patients with HEHE was similar to those undergoing liver transplant for other indications. Results from large case series and database studies from Europe and North America confirm the value of LT in the treatment of this rare disorder and have demonstrated 5-year overall survival rates ranging between 55% and 83% even in the presence of lymph node or vascular involvement or extrahepatic disease. The 2024 American College of Gastroenterology (ACG) Clinical Guideline on Focal Liver Lesions states that surgical resection is the preferred treatment when feasible, but when resection is not possible, liver transplantation offers the best survival, with 5-year overall survival (OS) of about 77%. The 2025 American Association for the Study of Liver Diseases (AASLD) and American Society of Transplantation (AST) Practice Guidelines on Adult Liver Transplantation states that liver transplant should be considered in individuals with biopsy-confirmed HEHE (strong recommendation), and identifies liver transplantation as the most effective treatment, with survival rates up to 90-100% in 1 year and about 70% in 5 years. There is sufficient evidence to determine that the technology results in an improvement in net health outcomes.

For individuals who have hepatic adenomas who receive a liver transplant, the evidence includes nonrandomized observational studies and a systematic review of these studies. Relevant outcomes include OS, morbid events, and treatment-related morbidity and mortality. Treatment options range from regular follow-up accompanied by imaging and withdrawal of hormone-containing pills to liver resection or liver transplantation (LT). The current United Network for Organ Sharing (UNOS) guidance for granting exception points for HA includes having HA with risk of malignant transformation, not amenable to resection, and either or both (1) biopsy-proven malignancy or (2) presence of glycogen storage disease (GSD). The most common reasons for LT appear to be the inability to surgically resect the hepatic adenoma, suspicion for malignancy, increase in size and risk of rupture, underlying liver disease, or recurrence after liver resection. Liver adenomatosis is a rare indication for liver transplantation, with acceptable post-transplant outcomes. Unresectable adenomas with high-risk or confirmed malignant transformation are the main indications for transplant. The largest US dataset comes from a UNOS registry analysis (1988-2013) published in JAMA surgery, which identified 62 liver transplants for hepatic adenomas. Survival rates were favorable with 1-year survival of 98.4% and 5-year survival of 91.6%. Strict selection criteria are essential for overall favorable outcome. There is sufficient evidence to determine that the technology results in an improvement in net health outcomes.

For individuals who have pediatric hepatoblastoma who receive liver transplant, the evidence includes a 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 individuals eligible for liver transplantation. There is sufficient evidence to determine that the technology results in an improvement in net health outcomes.

For individuals who have a failed liver transplant and 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 individuals, long-term survival benefits have been demonstrated. There is sufficient evidence to determine that the technology results in an improvement in net health outcomes.

Liver transplant is an accepted treatment of end-stage liver disease that provides a survival benefit in appropriately selected individuals 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 individuals 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 individuals 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. There is sufficient evidence to determine that the technology results in an improvement in net health outcomes.

Rationale

Evidence reviews assess 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 individuals 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. The following is a summary of the key literature to date.

LIVER TRANSPLANT FOR HEPATOCELLULAR DISEASE

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 individuals 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.

Metabolic Dysfunction-Associated Steatohepatitis

Systematic Reviews

Liver transplantation is a treatment option for individuals with nonalcoholic steatohepatitis (MASH) who progress to liver cirrhosis and failure. In a 2013 systematic review and meta-analysis, Wang et al evaluated 9 studies of 717 individuals with MASH and 3520 without MASH comparing liver transplantation outcomes.⁵ Individuals with MASH had similar 1-, 3-, and 5-year survival outcomes after liver transplantation as individuals without MASH. Individuals with MASH also had lower graft failure risk than those without MASH (OR=0.21; 95% CI, 0.05 to 0.89; p=0.03). However, MASH liver transplant individuals 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-MASH liver transplant individuals.

Yong et al (2021) presented an updated meta-analysis and systematic review analyzing 15 studies of 119,327 individuals who received liver transplants.⁶ The pooled prevalence of MASH across studies was 20.2%. The pooled 1-, 5-, and 10-year all-cause mortality in MASH individuals after liver transplant were 12.5%, 24.4%, and 37.9%, respectively. Overall survival was comparable between liver transplant recipients with MASH versus non-MASH (hazard ratio [HR], 0.91; 95% CI, 0.76 to 1.10; p=.34). There was no significant difference between individuals with MASH or without MASH 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 individuals who underwent liver transplantation for MASH versus non-MASH (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 individuals with MASH compared to individuals without MASH 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 MASH individuals 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 MASH-related liver transplantation.⁷ In all, 63,061 individuals underwent liver transplant from 2003 to 2014. MASH accounted for 17.38% of liver transplants in 2014. During the observation period, liver transplants secondary to MASH 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 individuals who had MASH (77.81%; 95% confidence interval [CI], 76.37% to 79.25%) was higher than individuals who had hepatitis C (72.15%; 95% CI, 71.37 to 72.93; $p<0.001$). Individuals with MASH also demonstrated significantly higher post-transplant survival than individuals with hepatitis C (hazard ratio [HR], 0.75; 95% CI, 0.71 to 0.79; $p<0.001$).

LIVER TRANSPLANT FOR PRIMARY HEPATOCELLULAR CARCINOMA

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 individuals 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 individuals with early HCC (8 studies) was analyzed, 1-year follow-up showed comparable survival rates between surgically treated individuals (92.14%), and transplanted individuals (90.38%) (OR=0.97; 95% CI, 0.63 to 1.50; $p=0.89$). At 5 years, transplanted individuals had a significantly higher survival rate (66.67%) than surgically treated individuals (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 individuals was 13%, 29%, and 39% higher than in liver resection individuals 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 individuals who received transplants for HCC in a multicenter, prospective study in UNOS Region 4.¹⁰ On preoperative imaging, 363 individuals met Milan criteria, and 82 individuals 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 individuals meeting Milan criteria and individuals 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 individuals 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 individuals without HCC.¹² The subgroup of individuals 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 individuals with HCC in their explanted livers, 12 developed recurrent HCC. Four significant independent 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 individuals may have either a solitary tumor with a maximum diameter of 5 cm or less, or up to 3 tumors 3 cm or less. Individuals with extrahepatic spread or macrovascular invasion have poor prognosis. The United Network of Organ Sharing (UNOS) adopted the Milan criteria, combined with an additional criterion (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 individuals 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 individuals 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 individuals 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 individuals 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 difference 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 individuals with HCC after CLRT 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 individuals 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 individuals exceeding Milan criteria, but in individuals meeting Milan criteria, survival outcomes were not significantly different suggesting salvage liver transplantation may be a viable option in these individuals.

Liver Transplant for Extrahepatic Cholangiocarcinoma (Hilar or Perihilar)

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 individuals 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 individuals 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 individuals 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 individuals with HCC and other chronic liver diseases and neoadjuvant chemoradiotherapy with subsequent liver transplantation for individuals with early-stage hilar cholangiocarcinoma, which is unresectable, or arose in the setting of primary sclerosing cholangitis. The reviewer concluded that both methods were superior to resection.

Observational Studies

In 2012, Darwish Murad et al. reported on 287 individuals 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 individuals 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 individuals 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 individuals 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 individuals 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

Data from the European Liver Transplant Registry was assessed in a review article by Pascher et al (2003).²⁸ In 169 patients with extrahepatic cholangiocarcinoma, the probabilities for 1-

and 5-year survival 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

Friman et al (2011) reported on 53 patients who received liver transplants for cholangiocarcinoma from 1984 to 2005, in Norway, Sweden, and Finland.²⁹ The 5-year survival rate was 25% overall, 36% in patients with TNM stage 2 or less, and 10% in patients with TNM greater than stage 2. On further analysis using only data from those patients transplanted after 1995, the 5-year survival rate increased to 38% versus 0% for those transplanted before 1995 (see Table 2). Additionally, the 5-year survival rate increased to 58% in those patients transplanted after 1995 with TNM stage 2 or less and a CA 19-9 level of 100 or less.

Meyers et al (2000) reported on data from 207 patients with intrahepatic or extrahepatic cholangiocarcinoma from the Cincinnati Transplant Registry, finding a 1-year survival of 72% and a 5-year rate of 23%.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

Liver Transplant for Intrahepatic Cholangiocarcinoma

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 individuals, including Casavilla et al (1997) and Friman et al (2011), noted below, and a registry study of 385 individuals. 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. Individuals 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 individuals 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 individuals 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 individuals in each group).

One additional observational study reported on survival rates for 54 individuals 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 individuals 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 individuals with intrahepatic cholangiocarcinoma includes registry studies. In a registry study comparing outcomes in individuals 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. However, in another study, researchers found that patients with intrahepatic CCA who underwent liver transplantation had an improved prognosis compared to those who underwent resection in unmatched and matched cohorts.⁷⁵ In a prospective case-series, out of 6 patients who underwent transplantation for intrahepatic CCA, 50% had RFS at 5 years. OS was 83.3% at 5 years.⁷⁶ Evaluation for liver transplantation

should also be considered as patients who meet the criteria will be eligible for transplant exception points.

LIVER TRANSPLANT FOR INDIVIDUALS WITH METASTATIC NEUROENDOCRINE TUMORS

Systematic Reviews

Three 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.

Palaniappan et al (2023) conducted a systematic review of 15 studies (N=755 individuals) focusing on long-term outcomes of liver transplantation for the management of neuroendocrine neoplasms.³⁵ Across studies, the median overall survival was 87% at 1 year (range 73% to 100%; 11 studies), 65% at 5 years (range 36% to 97.2%, 11 studies), and 50% at 10 years (range 46.1% to 88.8%; 3 studies). Reported disease-free/recurrence-free survival at 1 year was 70% (range 56% to 80%; 7 studies) and 36.5% at 5 years (range 11% to 86.9%; 8 studies).

Fan et al (2015) reported on a systematic review of 46 studies (total N=706 individuals) on liver transplantation for NET liver metastases of any origin.³⁶ 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 individuals, 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.³⁷ Data from 89 transplanted individuals treated at 20 clinical studies were reviewed. Sixty-nine individuals had primary endocrine pancreatic tumors, 9 individuals were carcinoids, and 11 individuals 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 selecting individuals 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 transplants.³⁸ He initially proposed selection criteria for individuals 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 individuals, the group from Milan recommended patient selection criteria for liver transplants for individuals 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 the limited number of individuals. 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 individuals undergoing conservative management. They also observed that liver transplantation was associated with a recurrence free survival of about 80% over 5 years, which is significantly higher compared to less than 50% associated with 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.³⁹ From 1989 to 2005, 85 individuals 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 $\geq 120\%$ of estimated standard liver volume) was observed in 53 individuals (62%). Extrahepatic resection was performed concomitantly with LTx in 34 individuals (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. The five-year survival rate was 12% for the 23 individuals presenting both unfavorable prognostic factors versus 68% for the individuals presenting one or neither factor ($p < 10^{-7}$).

In 2014, Fan et al reported on a systematic review of 46 studies on liver transplantation for NET liver metastases of any origin.³⁶ A total of 706 individuals 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 individuals, 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.³⁷ Data from 89 transplanted individuals from 20 clinical studies were included in the review. Sixty-nine individuals had primary endocrine pancreatic tumors, 9 individuals were carcinoids, and 11 individuals 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).

Liver Transplant for Nonresectable Colorectal Cancer Liver-Only Metastases

Review of Evidence

Randomized Controlled Trials

Adam et al (2024) published the first RCT (TransMet) comparing chemotherapy alone to chemotherapy plus liver transplant in patients with unresectable colorectal liver metastases.³⁸ A total of 94 patients were enrolled and followed up at a median of 59.3 months. Five-year OS was significantly improved with transplant. In selected patients with permanently unresectable colorectal liver metastases, liver transplantation plus chemotherapy with organ allocation priority significantly improved survival versus chemotherapy alone. These results

support the validation of liver transplantation as a new standard option for patients with permanently unresectable liver-only metastases.

Table 3. Summary of Key RCT

Characteristics Study; Trial	Countries	Sites	Dates	Participants	Interventions	
Adam et al (2024); TransMet	EU	20	2016-2021	Adults with unresectable CRLM (n=94) responsive to systemic chemotherapy and no extrahepatic disease	Active: Liver transplant + chemotherapy (n=47)	Comparator: Chemotherapy alone (n=47)

CRLM: colorectal liver metastases; RCT: randomized controlled trial.

Table 4. Summary of Key RCT Results

Study	5-year OS ^a	Median survival	5-year PFS ^b	Serious AEs	Any toxicity ≥3
Adam et al (2024); TransMet ³⁸ ,	n=94	n=94	n=72	NR	n=62
Transplant + chemotherapy	56.6% (95% CI, 43.2-74.1)	Not reached	19.9% (95% CI, 9.0-44.1)	110 events in 32 patients	36%
Chemotherapy alone	12.6% (95% CI, 5.2 to 30.1)	26.6 months (95% CI, 16.5-35.7)	0%	69 events in 45 patients	47%
HR (95% CI); p	0.37 (0.21-0.65); p=.0003	0.16 (0.07-0.33); p<.0001	0.34 (0.20-0.57); p<.0001	NR	NR

AE: adverse event; CI: confidence interval; HR: hazard ratio; NR, not reported; OS: overall survival; RCT: randomized controlled trial.

^a Intention to treat analysis.

^b Per protocol analysis.

Nonrandomized Studies

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).³⁹ 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 the reported outcome for chemotherapy. Hagness et al (2014) reported on patterns of recurrences after liver transplantation (LT) for CLM and the effect on survival. 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 slowly growing, and several were accessible to surgical treatment. When chest computed tomographic scans were re-examined, seven individuals 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 individuals who developed metastases to the transplanted liver died from metastatic disease.

In a prospective (SECA-I) study, Dueland et al (2020), included colorectal cancer individuals with nonresectable liver-only metastases determined by computed tomography (CT)/magnetic resonance imaging/positron emission tomography scans and at least 10% response to chemotherapy.⁴⁰ 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 the 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 ($P = 0.044$). Individuals included in the present study had significantly better prognostic factors than the previous SECA-I study.

Dueland et al (2021) reported a comparative effectiveness study which compared patients with colorectal liver metastases who were enrolled in the above summarized liver transplant studies (SECA-I and SECA-II; $n=50$) with database information from 53 patients who had received portal vein embolization and liver resection.⁴¹ The 5-year OS rate for patients with high tumor load was 33.4% for those who underwent liver transplant and 6.7% for those who underwent pulmonary vein embolization. Among patients with high tumor load and left-sided primary tumors, the 5-year OS rate was 45.3% for transplant patients and 12.5% for those treated with embolization and resection. The authors concluded that individuals with nonresectable disease, an extensive liver tumor load, and left-sided primary tumors had long OS after liver transplant, exceeding the survival outcome for those patients treated with PVE and liver resection.

Table 5. Summary of Key Nonrandomized Trials

Study	Study Type	Country	Dates	Participants	Treatment	Treatment	Follow-Up
Hagness et al (2013); SECA-I	Prospective cohort	Norway	2006-2011	Patients with unresectable colorectal liver-only metastases ($N=21$)	Liver transplant	N/A	NR
Dueland et al (2020); SECA-II	Prospective cohort	Norway	2012-2016	Patients with unresectable colorectal liver-only metastases ($N=15$)	Liver transplant	N/A	Up to 10 years
Dueland et al (2021)	Comparative effectiveness	Norway	2006-2019	Patients with CRLM ($n= 50$ enrolled in liver transplant studies and $n=53$ who had received Portal vein embolization and resection)	Liver transplant	Portal vein embolization and resection	NR

CRLM: colorectal liver metastases; N/A: not applicable; NR, not reported.

Line et al (2020) summarized recent developments within the field of LT for CRLMs. The author's findings included that more stringent selection criteria can yield 5-year survival rates that are similar to conventional indications for liver transplantation.⁸⁵ 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 seems far smaller. Recent studies put into question whether technical nonresectability *per se* is a valid inclusion criterion for liver transplantation. In individuals 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 individuals with CRLM after LT using extended criteria for both individuals and donors.⁸⁶ Individuals 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. Individuals who had resectable pulmonary metastases were eligible for inclusion. The main exclusion criteria were BMI above 30 kg/m² and liver metastases larger than 10 cm. Survival was estimated using Kaplan-Meier analysis and liver metastases larger than 10 cm. Ten individuals (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 individuals had (y)pN2 disease, six had poorly differentiated or signet ring cell-differentiated primary tumors, 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 post-transplant outcomes for the indication of CRLM.⁸⁷ Adult, primary LT individuals 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 individuals were listed, and 46 received LT for CRLM in 15 centers. Of 46 individuals who underwent LT for CRLM, 26 individuals (56.5%) received LTs using living donor LT(LDLT), and 20 individuals 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 individuals included in a phase III trial on triplet chemotherapy + antiEGFR.⁸⁸ The COLT trial is an investigator-driven, multicenter, non-randomized, open-label, controlled, prospective, parallel trial. Hyperselected individuals 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 to 1:5 with those obtained in a matched cohort from the TRIPLETE trial. The primary endpoint is to compare the 3 and 5-years OS of individuals enrolled in the COLT trial with COLT-eligible population enrolled in the TRIPLETE trial. An expected gain in OS of 40% at 5-years is 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 individuals with CLM. Improving the selection strategies can give individuals a 5-year OS similar to other indications for LT and a better outcome than those undergoing chemotherapy alone.

Liver Transplant for Individuals with Nonresectable Hepatic Epithelioid Hemangioendothelioma

Review of Evidence

Nonrandomized Studies

Several studies have evaluated liver transplant for HEHE utilizing data from healthcare registries. Larson et al (2025) published the largest and most recent study using the UNOS/OPTN database.⁴² The authors compared post-transplant outcomes of 121 patients undergoing liver transplant for HEHE to those undergoing transplant for other diagnoses. Individuals undergoing transplant for HEHE were younger, more likely to be female, and had lower body mass indices than other transplant recipients. Similar post-transplant survival was observed for recipients with HEHE (16.6 years) compared with other diagnoses (13.8 years; log-rank p=.28), even after adjusting for baseline donor and recipient characteristics (adjusted HR 1.28; 95% CI, 0.94 to 1.74; p=.12). An earlier analysis of the UNOS/OPTN database by Rodriguez et al (2008) included HEHE patients transplanted from 1987 to 2005.⁴³ At a median follow-up duration of 24 months (range, 0 to 181 months), the 1-year, 3-year, and 5-year OS rates were 80%, 68%, and 64%, respectively. Lerut et al (2007) reported the outcomes of 59 patients with HEHE from the European Liver Transplant Registry.⁴⁴ Overall survival rates at 1, 5, and 10 years (as calculated from time of transplant) were 93%, 83%, and 72%. A total of 14 (23.7%) patients had recurrent disease after a median of 49 months. Disease-free survival rates at 1, 5, and 10 years were 90%, 82%, and 64%.

Table 8. Summary of Key Nonrandomized Trials

Study	Study Type	Country	Dates	Participants	Treatment	Follow-Up
Larson et al (2025)	Retrospective cohort	US	2002-2021	Adults with first liver transplant (N=111,558)	Liver transplant	Through 2023
Rodriguez et al (2008)	Retrospective cohort	US	1987-2005	Patients with HEHE who received liver transplant (N=110)	Liver transplant	NR
Lerut et al (2007)	Retrospective cohort	EU	1989-2004	Patients with HEHE who received liver transplant (N=59)	Liver transplant	NR

HEHE: hepatic hemangioendothelioma; NR: not reported.

Liver Transplant for Individuals with Hepatic Adenoma

Review of Evidence

Ziogas et al (2022) reviewed all patients listed or transplanted for hepatic adenoma from 1987 to 2020 (N=199) in the US and performed a systematic review of published literature.⁴⁵ From 199 patients listed, 142 underwent liver transplant. Most patients did not convert to hepatocellular carcinoma (89.4%), and at a median follow-up of 62.9 months, 18.3% of

patients died. Overall survival rates at 1, 3, and 5 years were 94.2%, 89.7%, and 86.3%, respectively. A total of 61 articles describing 99 patients who underwent liver transplant for hepatic adenoma were identified in the systematic review. Over a median follow-up of 36.5 months, 6% of patients died. Overall survival rates at 1, 3, and 5 years were all 95%. Post-transplant complications were reported in 25% of patients including acute rejection in 13.1%; retransplantation was required in 2.3%. The authors noted a need for optimal selection criteria to further improve outcomes.

Liver transplantation (LT) has been reported as a treatment option for hepatic adenomas; however, standardized criteria for patient selection have not been well established. As reported by Desari et al (2025), to address this gap, a Fixed Term Working Group (FTWG), convened by the National Health Service (NHS) Blood and Transplant (NHSBT) Liver Advisory Group (LAG), recommended a systematic evaluation process and the use of strict national selection criteria.⁸⁹ Input was obtained from patient representatives and multidisciplinary experts, including hepatologists, histopathologists, liver transplant and hepatobiliary surgeons, and radiologists with experience in hepatic adenoma management and familiarity with United Kingdom (UK) transplant pathways. The group reviewed the broad spectrum of radiologic, histologic, and clinical features of hepatic adenomas and developed key clinical questions to guide consideration of LT. These discussions informed proposed patient selection criteria, referral processes, and transplant listing pathways. The paper summarizes proposed UK selection criteria for LT in individuals with hepatic adenomas and outlines the recommended investigation framework, pre-transplant assessment, and referral pathway. This manuscript presents a standardized protocol for the work-up, referral, and selection of patients with hepatic adenomas being considered for LT, representing an important advancement in the management of this patient population.

LIVER TRANSPLANT FOR PEDIATRIC HEPATOBLASTOMA

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.⁴⁶ 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.⁴⁷ 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 individuals with primary liver tumor identified from a retrospective review of individuals treated between 1990 and 2007.⁴⁸ Tumor recurrence occurred in one patient after liver transplantation, and overall survival was 93%. In 2008 Browne et al reported on 14 hepatoblastoma individuals treated with liver transplantation. Mean follow-up was 46 months, with overall survival in 10 of 14 individuals (71%).⁴⁹ Tumor recurrence caused all 4 deaths. In the 10 individuals receiving primary liver transplantation, 9 survived while only 1 of 4 individuals transplanted after primary resection survived (90% vs. 25%, $p=0.02$).

LIVER RETRANSPLANT FOR A FAILED LIVER TRANSPLANT

Review of Evidence

Cohort Studies

Salimi et al (2021) reported on a retrospective cohort using records from 1030 individuals 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.⁵² The mortality rate was significantly higher among individuals who underwent retransplantation (54.68%) compared to individuals 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 individuals undergoing initial transplant and 59%, 43%, and 32%, respectively, for individuals undergoing retransplant. Individuals who underwent retransplantation also had significantly higher MELD scores (10.73 ± 25.89) compared to individuals 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.⁵³ 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 individuals undergoing urgent procedures (87%), which were mostly due to vascular complications than elective procedures (76.5%), which were mostly related to chronic rejection. Remiszewski et al (2011) examined factors influencing survival outcomes in 43 liver retransplantation patients.⁵⁴ When compared with primary liver transplantation patients, retransplantation patients had significantly lower 6-year survival rates (80% vs 58%, respectively; $p < .001$). The authors also reported low negative correlations between survival time and time from original transplantation until retransplantation and between survival time and patient age. Survival time and cold ischemia time showed a low positive correlation.

Hong et al, in 2011, reported on a prospective study of 466 adults to identify risk factors for survival after liver retransplantation.⁵⁵ 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.

POTENTIAL CONTRAINDICATIONS (APPLIES TO ALL PREVIOUS 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 the right hepatectomy of diseased or injured livers is associated with mortality rates of about 5%. However, initial reports suggest that the right hepatectomy in healthy donors has a lower morbidity and mortality. Reports of several donor deaths have been reported.⁶²⁻⁶⁵

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.⁶⁶ According to this document, the risk of mortality to the donor undergoing the right hepatectomy was estimated to be approximately 0.2% to 0.5%. The median complication rate reported by responding to 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.⁶⁶

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.⁶⁷ 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 individuals with end-stage liver disease.⁶⁸ 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 Individuals

Solid-organ transplant for individuals 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 coinfecting 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 individuals co-infected with HIV and hepatitis.⁶⁹ The review included 15 cohort studies and 49 case series with individual patient data. The survival rate of individuals was 84.4% (95% confidence interval [CI]: 81.1-87.8%) at 12 months. Individuals 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: individuals with both HCV and HIV (n=89), individuals

with only HCV (n=235), and all transplant individuals age 65 or older.⁷⁰ 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 individuals also infected with HCV, there were still a majority of individuals experiencing long-term survival.

The current OPTN policy permits HIV-positive transplant candidates.⁷¹

The American Society of Transplantation (2019) published a guideline on solid organ transplantation in HIV-infected individuals.⁷² 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 individuals 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 individuals 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 individuals. Individuals with HIV and concomitant controlled hepatitis B infection may be considered for transplant. Caution is recommended in hepatitis C coinfecting individuals who have not been initiated on direct acting antiviral therapy.

A recent observational, noninferiority study published by Durand et al (2024) compared transplantation of kidneys from deceased donors with HIV and donors without HIV to recipients with HIV.⁷³ The primary outcome was a safety event (a composite of death from any cause, graft loss, serious adverse events, HIV breakthrough infection, persistent failure of HIV treatment, or opportunistic infection), assessed for noninferiority. One hundred ninety-eight enrolled candidates received a kidney from a deceased donor; 99 received a kidney from a donor with HIV and 99 from a donor without HIV. The adjusted HR for the composite primary outcome was 1.00 (95% CI, 0.73 to 1.38) which demonstrated noninferiority. Based on results, in individuals with HIV, transplantation from donors with HIV appeared to be noninferior to that of donors without HIV. While this study used kidney transplantation, results could impact all solid organ transplantations, including liver.

Hepatitis Infection

Terrault et al (2012) reported on a prospective, multicenter study to compare liver transplantation outcomes in 3 groups: individuals with both HIV and HCV infection (n=89), individuals with only HCV (n=235), and all transplant individuals age 65 and older.⁷⁰ 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%).

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 individuals 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 individuals who meet strict eligibility criteria. In general, there was no support for the use of liver transplantation for NET metastatic to the liver.

PRACTICE GUIDELINES AND POSITION STATEMENTS

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they are issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Association for the Study of Liver Diseases and American Society of Transplantation

In 2013, the American Association for the Study of Liver Diseases (AASLD) and the American Society of Transplantation (AST) issued guidelines on evaluating individuals for liver transplant.⁷⁴ 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
 - α 1-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.”
- “Individuals 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 individuals for liver transplant.⁷⁵ 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 individuals, 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.⁷⁶ 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 individuals into higher- or lesser-risk strata for relapse.

In 2023, the AASLD released a practice guideline on the management of hepatocellular carcinoma.⁷⁷ 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 individuals with early-stage HCC occurring in the 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 individuals 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 individuals 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)
- Individuals 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)"

In July 2025, AASLD published a critical update to the guidance based on newly published data.⁷⁸ However, the update was related to immunotherapy in the adjuvant setting and did not change any previous recommendations related to transplantation.

International Consensus Conference

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 HCC.⁷⁹ 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.

The Milan criteria were recommended for use as the benchmark for patient selection, although it was suggested that the Milan criteria might be modestly expanded based on data from expansion studies that demonstrated outcomes are comparable with 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.

Regarding liver retransplantation, the consensus criteria issued a weak recommendation for retransplantation after graft failure of a living donor transplant for HCC in patients meeting regional criteria for a deceased donor liver transplant. A strong recommendation was issued against liver retransplantation with a deceased donor for graft failure for patients exceeding

regional criteria. Also, the consensus criteria issued a strong recommendation that liver retransplantation for recurrent HCC would not be appropriate. However, a de novo case of HCC may be treated as a new tumor, and retransplantation may be considered even though data to support this is limited.

In 2024, another international joint conference was held convening the International Liver Transplantation Society (ILTS) and International Liver Cancer Association (ILCA) to update its consensus on liver transplantation for HCC and intrahepatic cholangiocarcinoma.⁸⁰ Similarly to 2010, the Conference came up with recommendations beginning from the assessment of candidates with HCC or intrahepatic cholangiocarcinoma and managing patients on waitlists, to the role of liver transplantation and post-transplantation management. Some notable recommendations are summarized in Table 9, below.

Table 9. Notable Recommendations From 2024 ILTS and ILCA Conference on Liver Transplantation in HCC and iCCA

Recommendation	Level of evidence	Strength of recommendation
HCC		
Liver transplantation should not be restricted to HCC patients who have a predicted 5-year survival rate comparable to non-HCC patients. However, organ availability in different regions should be considered in allocation policies to avoid disadvantaging non-HCC patients.	Moderate	Moderate
Criteria for listing patients with HCC for liver transplantation must not rely solely on tumor size and number and should consider biomarkers (mainly AFP) and their dynamics on the waitlist. Emerging data suggest the use of AFP-L3, DCP, and PET-CT can add prognostic value.	Moderate	Strong
Salvage liver transplantation in patients with HCC recurrence or liver insufficiency can be as safe and effective as primary transplantation for HCC in patients that meet transplantation criteria.	Weak	Moderate
Given that the outcomes with regards to overall and disease-free survival are on-par and, in certain cases, better than DDLT, LDLT should be considered as an oncologically durable and safe alternative to DDLT. In regions where the waiting time (>3 mo) or where LDLT is the predominant type of LT, LDLT may be a preferred option for HCC within and beyond standard criteria.	Moderate	Moderate
iCCA		
In cirrhotic patients with iCCA, liver transplantation may be considered as a potential therapeutic option in tumors ≤3 cm in diameter after a period of observation with stability and without extrahepatic metastasis, as it offers a chance of curative treatment and improved survival.	Moderate	Moderate
In non-cirrhotic patients with intrahepatic cholangiocarcinoma, liver transplantation is not routinely recommended but may be considered as part of investigational protocols for patients with unresectable, liver-confined disease after at least 6 mo of stability after systemic therapy. Limitations on tumor size and number should be explored in prospective clinical trials.	Moderate	Weak

AFP: alpha-fetoprotein; DCP: des-gamma-carboxy prothrombin; DDLT: deceased donor liver transplantation; HCC: hepatocellular carcinoma; iCCA: intrahepatic cholangiocarcinoma; ILCA: International Liver Cancer Association; ILTS: International Liver Transplantation Society; LDLT: living donor liver transplantation; LT: liver transplantation; PET-CT: positron emission tomography-computed tomography

Many recommendations deferred to local or regional protocols, but there seemed to be interest in expansion of liver transplantation protocols from the 2010 consensus.

National Comprehensive Cancer Network^{16,81}

The National Comprehensive Cancer Network (NCCN) guidelines on hepatocellular carcinoma (v.1.2026) recommend a referral to a liver transplant center or bridge therapy for individuals with HCC meeting UNOS criteria. NCCN guidelines for biliary tract cancers (v. 1.2026) states before biopsy, evaluate if a patient is a resection or transplant candidate. If a patient is a potential transplant candidate, consider referral to the 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.1.2026) indicate liver transplantation for NET liver metastases is considered investigational despite “encouraging” 5-year survival rates.

The NCCN guidelines on intrahepatic cholangiocarcinoma (v. 1.2026) recommend evaluation for liver transplantation in patients who meet the following eligibility criteria for transplant exception points: biopsy-proven intrahepatic CCA or mixed HCC-intrahepatic CCA, presence of cirrhosis, unresectable, received locoregional or systemic therapy, and 6 months from time of diagnosis or last treatment with no new lesions or extrahepatic disease.

National Liver Review Board

In July 2025 the board revised guidance for specific clinical situations to evaluate common exception case requests for adult liver transplant candidates.⁸² This resource is not OPTN Policy, so it does not carry the monitoring or enforcement implications of policy. It is not an official guideline for clinical practice, nor is it intended to be clinically prescriptive or to define a standard of care. This resource is intended to provide guidance to transplant programs and the review board. This guidance replaces any independent criteria that OPTN regions used to request and approve exceptions, commonly referred to as “regional agreements.” This guidance document is intended to provide recommendations for the review board considering hepatic neoplasm cases which are outside standard policy.

They should use this resource when considering MELD exception case requests for adult candidates with the following diagnoses:

- Hepatocellular Carcinoma (HCC)
- Intrahepatic Cholangiocarcinoma (iCCA)
- Neuroendocrine Tumors (NET)
- Colorectal Liver Metastases (CRLM)
- Hepatic Epithelioid Hemangioendothelioma (HEHE)
- Hepatic Adenomas

Hepatocellular Carcinoma

Patients with the following are contraindications for HCC exception score:

- Macro-vascular invasion of main portal vein or hepatic vein
- Extra-hepatic metastatic disease
- Ruptured HCC
- T1 stage HCC

Intrahepatic Cholangiocarcinoma

According to the OPTN policy on liver allocation, candidates with unresectable intrahepatic cholangiocarcinoma can be considered if all of the following criteria are met:

- Biopsy proven, unresectable, solitary intrahepatic cholangiocarcinoma or mixed hepatocellular carcinoma/intrahepatic cholangiocarcinoma;
- History of locoregional or systemic therapy;
- ≤ 3 cm tumor with stable disease for 6 months (no new lesions or extrahepatic disease) and imaging every 3 months to ensure tumor is ≤ 3 cm.

Neuroendocrine Tumors

According to the OPTN policy on liver allocation, candidates with unresectable neuroendocrine liver metastasis can be considered if all of the following criteria are met:

- Tumor must be of gastro-entero-pancreatic (GEP) origin with portal system drainage (neuroendocrine tumors with the primary located in the lower rectum, esophagus, lung, adrenal gland, and thyroid are not candidates for MELD exception);
- Resection of primary malignancy and extrahepatic disease without any evidence of recurrence for ≥ 6 months;
- Lower-intermediate grade following the WHO classification;
- No evidence for extrahepatic tumor recurrence based on metastatic radiologic workup ≥ 3 months prior to initial or extension MELD exception request (negative metastatic workup should include functional imaging).

Colorectal Liver Metastases

According to the OPTN policy on liver allocation, candidates with unresectable colorectal liver metastases can be considered if all of the following criteria are met:

- Primary diagnosis of colon/rectal adenocarcinoma that is BRAF wild type and microsatellite stable of at least 12 months duration;
- Standard resection of the primary tumor with negative resection margins and no evidence of local recurrence by colonoscopy within 12 months prior to request;
- No signs of extrahepatic disease or local recurrence;
- Received or receiving first-line chemo- or immunotherapy with stability or disease regression with systemic and/or locoregional therapy for at least 6 months;
- Individuals with synchronous colon lesions must also have resection of the primary tumor more than 6 months after initial diagnosis and a minimum of 6 months of chemotherapy after primary tumor resection with disease stability of at least 12 months after diagnosis.

Hepatic Epithelioid Hemangioendothelioma

According to the OPTN policy on liver allocation, candidates with unresectable hepatic epithelioid hemangioendothelioma (HEHE) can be considered if all of the following criteria are met:

- Biopsy proven diagnosis of HEHE and exclude hemangiosarcoma;
- Absence of macrovascular invasion on biopsy or imaging;
- Lesions are unresectable.

Hepatic Adenoma

According to the OPTN policy on liver allocation, candidates with unresectable hepatic adenoma can be considered if one of the following criteria are met:

- Adenoma in the presence of glycogen storage disease or Abernethy malformation;

- Unresectable adenoma with β -catenin mutation;
- Unresectable adenoma in a candidate with liver adenomatosis (greater than 10 HA);
- Adenoma(s) with all 3 of the following criteria:
 - Unresectable;
 - Unresponsive to non-operative management (e.g., observation after withholding estrogen-containing medications, observation after efforts to maintain an ideal body weight, transarterial embolization, or radiofrequency ablation);
 - Progressive or with complication such as hemorrhage, rupture, or malignant transformation.

U.S. Preventive Services Task Force Recommendations

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

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 10.

Table 10. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
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
NCT06140134	Liver Transplantation in Intrahepatic Cholangiocarcinoma	30	Nov 2029
NCT06910722	Liver Transplantation for Locally Advanced Intrahepatic Cholangiocarcinoma After SIRT and Chemotherapy (RIS-TH)	36	Oct 2034
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			
NCT05944042	Hepatic Transplantation Registry	300	Feb 2025 (unknown status)

NCT: national clinical trial.

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.

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 & Medicaid 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)

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through July 2026, the date the research was completed.

DALLAS Consensus Statement on Liver Transplantation for Alcohol Related Hepatitis⁶³

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 the use of less stigmatizing terminology.
2. Individuals with severe AH may be assessed for corticosteroid therapy.
3. Select individuals 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 individuals 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 comprehensive psychosocial evaluation.

Recommendations for LT for alcohol related hepatitis

- A. The goals of LT for AH include:
 1. Avoiding LT in individuals 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 an 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 patients 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 relapses 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 are 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 Score⁶⁴

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 individuals 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 retransplantation 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 individuals.
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 ○ Changed meld score to <10 ○ 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)
11/1/25	8/19/25		• Updated policy to remove intrahepatic CCA from the list of exclusions. • Updated policy to add intrahepatic cholangiocarcinoma (iCCA) to list of inclusions. • Added UNOS MELD exception point criteria for iCCA. Mixed HCC-iCCA, and CRLM. • Added coverage for hepatocellular Adenomas. • Policy formatting changes made. Routine policy maintenance. Vendor managed: N/A (ds)
11/1/26	8/18/26		Rationale updated, references added. Added coverage for hepatic epithelioid hemangioendothelioma with coverage criteria from UNOS MELD exception. Vendor managed: N/A (ds, no)

Next Review Date:

3rd Qtr. 2027

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.