OPTN

Notice of OPTN Policy and Guidance Changes

National Liver Review Board (NLRB) Updates Related to Transplant Oncology

Sponsoring Committee:	**Liver & Intestinal Organ Transplantation**
Policy Affected:	***9.5.A: Requirements for Cholangiocarcinoma (CCA) MELD or PELD Score Exceptions***
Guidance Affected:	***Guidance to Liver Transplant Programs and the National Liver Review Board for Adult MELD Exceptions for Hepatocellular Carcinoma; Guidance to Liver Transplant Programs and the National Liver Review Board for Adult MELD Exception Review; National Liver Review Board Operational Guidelines***
Public Comment:	**January 23, 2024 – March 19, 2024**
Board Approved:	**June 17-18, 2024**
Effective Date:	**Pending implementation and notice to OPTN members**

Purpose of Policy and Guidance Changes

The National Liver Review Board (NLRB) was implemented on May 14, 2019.[1] The purpose of the National Liver Review Board (NLRB) is to provide equitable access to transplant for liver transplant candidates whose calculated model for end-stage liver disease (MELD) score or pediatric end-stage liver disease (PELD) score does not accurately reflect the candidate's medical urgency for transplant. Since implementation, the OPTN Liver and Intestinal Organ Transplantation Committee (the Committee) has regularly evaluated the NLRB to identify opportunities for improvement.

This proposal has several changes related to liver oncology as an indication for liver transplant. The first of these changes is the creation of new guidance that seeks to increase access to transplant for candidates with colorectal liver metastases or intrahepatic cholangiocarcinoma through non-standard exceptions. Additionally, the Committee is proposing for the Adult Hepatocellular Carcinoma (HCC) Review Board to become an Adult Transplant Oncology Review Board to ensure that non-standard exception cases specific to liver cancers and tumors are reviewed by specialists in the field. Lastly, a policy clarification is included in this proposal to ensure the current practice for reviewing and approving hilar cholangiocarcinoma (CCA) protocols aligns with language in Policy *9.5.A: Requirements for CCA MELD or PELD Score Exceptions*.

[1] Proposal to Establish a National Liver Review Board, OPTN Liver and Intestinal Organ Transplantation Committee, June 2017, Available at https://optn.transplant.hrsa.gov/.

Proposal History

Prior to the implementation of the NLRB, MELD, and PELD exception requests were reviewed by regional review boards (RRBs). The implementation of the NLRB was a significant change in the process for reviewing MELD or PELD exception requests and because of the significance and complexity of the change, the Committee has continued to receive feedback on areas for improvement to the NLRB guidance and policy. This project is the latest in a series of improvements to the NLRB since it was implemented.

Summary of Changes

- The addition of OPTN guidance specific to colorectal liver metastases and intrahepatic cholangiocarcinoma (iCCA) for the NLRB.
- Expanding the purview of the Adult HCC Review Board to review non-standard exception cases related to liver cancers and tumors. The Adult HCC Review Board will now be broadened and renamed the Adult Transplant Oncology Review Board.
- The proposed Adult Transplant Oncology guidance document includes guidance for HCC, iCCA, neuroendocrine tumors, colorectal liver metastases, hepatic epithelioid hemangioendothelioma, and hepatic adenomas. The Adult Transplant Oncology Review Board will review non-standard exception cases for these diagnoses as well as any non-standard exception requests for CCA, and any other liver cancer or tumor-related request.
- Two clarifications to *Policy 9.5.A: Requirements for CCA MELD or PELD Score Exceptions* to ensure consistency and accuracy of the policy.
- The Committee made minor clarifications post-public comment to the NLRB guidance document to further define timeframe and tumor stability related to iCCA. These post-public comment changes did not alter the substance or intent of the original proposal.

Implementation

Transplant programs will need to be familiar with the proposed changes to NLRB guidance documents when submitting exception requests for liver candidates. Transplant programs will also need to be aware of updated diagnoses to ensure accurate data entry when submitting exception requests for liver candidates. Representatives of the Adult Transplant Oncology Review Board may have additional cases to review during their term.

Any case that is up for extension or is currently in the appeal process that was based upon a decision from the Adult Other Diagnosis Review Board will continue to be reviewed by the Adult Other Diagnosis Review Board. This will ensure consistency in decision-making. Transplant programs can re-submit an initial exception should they wish for the Adult Transplant Oncology specialty board to review their case.

Relevant guidance documents will be updated. The OPTN computer system will need to be updated to reflect changes to the Adult Transplant Oncology Review Board and route liver cancer and tumor cases accordingly. There are no modifications to the structure of the review board, the review process, or the appeal process. The OPTN will communicate any changes prior to implementation and will provide educational resources as appropriate.

Affected Policy Language

New language is underlined (example) and language that is deleted is struck through (~~example~~).

9.5 Specific Standardized MELD or PELD Score Exceptions

Candidates are eligible for MELD or PELD score exceptions or extensions that do not require evaluation by the NLRB if they meet *any* of the following requirements for a specific diagnosis of *any* of the following:

- Hilar Cholangiocarcinoma (CCA), according to *Policy 9.5.A: Requirements for Hilar Cholangiocarcinoma MELD or PELD Score Exceptions*
- Cystic fibrosis, according to *Policy 9.5.B: Requirements for Cystic Fibrosis MELD or PELD Score Exceptions*
- Familial amyloid polyneuropathy, according to *Policy 9.5.C: Requirements for Familial Amyloid Polyneuropathy (FAP) MELD or PELD Score Exceptions*
- Hepatic artery thrombosis, according to *Policy 9.5.D: Requirements for Hepatic Artery Thrombosis (HAT) MELD Score Exceptions*
- Hepatopulmonary syndrome, according to *Policy 9.5.E: Requirements for Hepatopulmonary Syndrome (HPS) MELD or PELD Score Exceptions*
- Metabolic disease, according to *Policy 9.5.F: Requirements for Metabolic Disease MELD or PELD Score Exceptions*
- Portopulmonary hypertension, according to *Policy 9.5.G: Requirements for Portopulmonary Hypertension MELD or PELD Score Exceptions*
- Primary hyperoxaluria, according to *Policy 9.5.H: Requirements for Primary Hyperoxaluria MELD or PELD Score Exceptions*
- Hepatocellular carcinoma, according to *Policy 9.5.I: Requirements for Hepatocellular Carcinoma (HCC) MELD or PELD Score Exception*

9.5.A Requirements for Hilar Cholangiocarcinoma (CCA) MELD or PELD Score Exceptions

A candidate will receive a MELD or PELD score exception for hilar CCA, if the candidate's transplant program meets *all* the following qualifications:

1. Submits a written protocol for patient care to the Liver and Intestinal Organ Transplantation Committee for review and approval. The written protocol ~~that~~ must include *all* of the following:
   i. Candidate selection criteria
   ii. Administration of neoadjuvant therapy before transplantation
   iii. Operative staging to exclude any patient with regional hepatic lymph node metastases, intrahepatic metastases, or extrahepatic disease
   iv. Any data requested by the Liver and Intestinal Organ Transplantation Committee

2. Documents that the candidate meets the diagnostic criteria for hilar CCA with a malignant appearing stricture on cholangiography and at least *one* of the following:
   - Biopsy or cytology results demonstrating malignancy
   - Carbohydrate antigen 19-9 greater than 100 U/mL in absence of cholangitis
   - Aneuploidy
   - Hilar mass, which is less than 3 cm in radial diameter.

The tumor must be considered un-resectable because of technical considerations or underlying liver disease.

3. Submits cross-sectional imaging studies. If cross-sectional imaging studies demonstrate a mass, the mass must be single and less than three cm in radial (perpendicular to the duct) diameter. The longitudinal extension of the stricture along the bile duct is not considered in the measurement of a mass.

4. Documents the exclusion of intrahepatic and extrahepatic metastases by cross-sectional imaging studies of the chest and abdomen within 90 days prior to submission of the initial exception request.

5. Assesses regional hepatic lymph node involvement and peritoneal metastases by operative staging after completion of neoadjuvant therapy and before liver transplantation. Endoscopic ultrasound-guided aspiration of regional hepatic lymph nodes may be advisable to exclude patients with obvious metastases before neo-adjuvant therapy is initiated.

6. Transperitoneal aspiration or biopsy of the primary tumor (either by endoscopic ultrasound, operative or percutaneous approaches) must be avoided because of the high risk of tumor seeding associated with these procedures.

A candidate who meets the requirements for a standardized MELD or PELD score exception will receive a score according to *Table 9-2*.

Table 9-2: Hilar CCA Exception Scores

Age	Age at registration	Score
At least 18 years old	At least 18 years old	3 points below MMaT
At least 12 years old	Less than 18 years old	Equal to MMaT
Less than 12 years old	Less than 12 years old	Equal to MPaT

In order to be approved for an extension of this MELD or PELD score exception, transplant programs must submit an exception extension request according to *Policy 9.4.C: MELD or PELD Exception Extensions,* and provide cross-sectional imaging studies of the chest and abdomen that exclude intrahepatic and extrahepatic metastases. These required imaging studies must have been completed within 30 days prior to the submission of the extension request.

Guidance to Liver Transplant Programs and the National Liver Review Board for:
Adult MELD Exceptions for
~~Hepatocellular Carcinoma (HCC)~~ Transplant Oncology

Summary and Goals

For many patients with chronic liver disease the risk of death without access to liver transplant can be accurately predicted by the MELD score, which is used to prioritize candidates on the waiting list. However, for some patients the need for liver transplant is not based on the degree of liver dysfunction due to the underlying liver disease but rather a complication of the liver disease. These complications have an increased risk of mortality or waitlist dropout without access to timely transplant and are not reflected in the calculated MELD score.[2] This document summarizes available evidence to assist clinical reviewers in approving candidates for MELD exceptions in the specific setting of hepatic neoplasms. It contains guidance for specific clinical situations for use by the review board to evaluate common exception case requests for adult candidates with the following diagnoses:

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

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

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.

Background

A liver candidate receives a MELD[3] or, if less than 12 years old, a PELD[4] score that is used for liver allocation. The score is intended to reflect the candidate's disease severity, or the risk of 3-month mortality without access to liver transplant. When the calculated score does not reflect the candidate's medical urgency, a liver transplant program may request an exception score. A candidate that meets the criteria for one of nine diagnoses in policy is approved for a standardized MELD exception.[5] If the candidate does not meet criteria for standardized exception, the request is considered by the review board.

This guidance replaces any independent criteria that OPTN regions used to request and approve exceptions, commonly referred to as "regional agreements." Review board members and transplant

[2] Waitlist dropout is removal from the waiting list due to the candidate being too sick to transplant.
[3] Model for End-Stage Liver Disease.
[4] Pediatric End-Stage Liver Disease.
[5] See OPTN *Policy 9.5: Specific Standardized MELD or PELD Exceptions*, Available at https://optn.transplant.hrsa.gov/.

centers should consult this resource when considering MELD exception requests for adult candidates with the following diagnoses.

The OPTN Liver and Intestinal Organ Transplantation Committee (hereafter, "the Committee") has developed guidance for adult MELD exceptions for Transplant Oncology ~~Hepatocellular Carcinoma (HCC)~~. This guidance document is intended to provide recommendations for the review board considering hepatic neoplasm ~~HCC~~ cases which are outside standard policy.

Instructions for Submitting a Non-Standard Exception Request

Instructions for how to submit a non-standard exception request can be found in each relevant diagnosis section. For any other diagnosis that should be reviewed by the Adult Transplant Oncology review board, select "other liver cancer or tumor specify", indicate the diagnosis, and submit a written justification narrative.

Recommendations

Hepatocellular Carcinoma (HCC)

1. 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

While in most cases, ruptured HCC and primary portal vein branch invasion of HCC would be contraindications, some patients who remain stable for a prolonged (minimum of 12 months) interval after treatment for primary portal vein branch invasion or after ruptured HCC may be suitable for consideration.

Evidence for the use of immunotherapy as a downstaging or bridging therapy is preliminary. However, based on the published data in transplant and non-transplant setting, the use of immunotherapy does not preclude consideration for an HCC exception.[6]

- Patients beyond standard criteria who have continued progression while waiting despite locoregional are generally not acceptable candidates for HCC MELD exception.
- Patients with AFP>1000 who do not respond to treatment to achieve an AFP below 500 are not eligible for standard MELD exception, and must be reviewed by the ~~HCC~~ Adult Transplant Oncology Review Board to be considered. In general, these patients are not suitable for HCC MELD exception but may be appropriate in some cases.
- Patients with HCC beyond standard down-staging criteria who are able to be successfully downstaged to T2 may be appropriate for MELD exception, as long as there is no evidence of metastasis outside the liver, or macrovascular invasion, or AFP >1,000. Imaging should be performed at least 4 weeks after last down-staging treatment. Patients must still wait for 6 months from the time of the first request to be eligible for an HCC exception score.

[6] Parissa Tabrizian, Sander S. Florman, and Myron E. Schwartz, "PD-1 Inhibitor as Bridge Therapy to Liver Transplantation?," *American Journal of Transplantation* 21, no. 5 (February 2021): pp. 1979-1980, https://doi.org/10.1111/ajt.16448.

- Patients who presented with stage T2 HCC (LI-RADS 5 or biopsy proven; one lesion >2 cm and <5 cm in size, two or three lesions >1 cm and <3 cm in size) which was treated by locoregional therapy or resected but developed T1 or T2 HCC (LI-RADS 5 or biopsy proven) recurrence and the transplant program is requesting an initial HCC exception more than 6 months but less than 60 months following initial treatment or resection are eligible for a MELD score exception without a six month delay period.

Patients with cirrhosis and HCC beyond T2 but within generally accepted criteria for down-staging (such as up to 5 lesions, total tumor volume <8 cm based on resection pathology) who underwent complete resection with negative margins and developed T1 or T2 HCC (LI-RADS 5 or biopsy proven) recurrence may also be considered for MELD score exception for HCC. Because of the larger tumor size, the 6-month delay is appropriate to ensure favorable tumor biology.

Recommendations for Dynamic Contrast-enhanced CT or MRI of the Liver

Table 1: Recommendations for Dynamic Contrast-enhanced CT of the Liver

Feature:	CT scans should meet the below specifications:
Scanner type	Multidetector row scanner
Detector type	Minimum of 8 detector rows and must be able to image the entire liver during brief late arterial phase time window
Slice thickness	Minimum of 5 mm reconstructed slice thickness; thinner slices are preferable especially if multiplanar reconstructions are performed
Injector	Power injector, preferably dual chamber injector with saline flush and bolus tracking recommended
Contrast injection rate	3 mL/sec minimum, better 4-6 mL/sec with minimum of 300 mg I/mL or higher, for dose of 1.5 mL/kg body weight
Mandatory dynamic phases on contrast-enhanced MDCT	1. Late arterial phase: artery fully enhanced, beginning contrast enhancement of portal vein 2. Portal venous phase: portal vein enhanced, peak liver parenchymal enhancement, beginning contrast enhancement of hepatic veins 3. Delayed phase: variable appearance, greater than 120 seconds after initial injection of contrast
Dynamic phases (Timing)	Use the bolus tracking or timing bolus

Table 2: Recommendations for Dynamic Contrast-enhanced MRI of the Liver

Feature	MRIs should meet the below specifications:
Scanner type	1.5T Tesla or greater main magnetic field strength. Low field magnets are not suitable.
Coil type	Phased array multichannel torso coil, unless patient-related factors precludes its use.
Minimum sequences	Pre-contrast and dynamic post gadolinium T1-weighted gradient echo sequence (3D preferable), T2 (with and without fat saturation), T1-weighted in and out of phase imaging.
Injector	Dual chamber power injector with bolus tracking recommended.
Contrast injection rate	2-3 mL/sec of extracellular gadolinium chelate that does not have dominant biliary excretion, preferably resulting in vendor-recommended total dose.
Mandatory dynamic phases on contrast-enhanced MRI	1. Pre-contrast T1W: do not change scan parameters for post contrast imaging. 2. Late arterial phase: artery fully enhanced, beginning contrast enhancement of portal vein. 3. Portal venous phase: portal vein enhanced, peak liver parenchymal enhancement, beginning contrast enhancement of hepatic veins. 4. Delayed phase: variable appearance, greater than 120 seconds after initial injection of contrast.
Dynamic phases (Timing)	The use of the bolus tracking method for timing contrast arrival for late arterial phase imaging is preferable. Portal vein phase images should be acquired 35 to 55 seconds after initiation of late arterial phase. Delayed phase images should be acquired 120 to 180 seconds after the initial contrast injection.
Slice thickness	5 mm or less for dynamic series, 8 mm or less for other imaging.
Breath-holding	Maximum length of series requiring breath-holding should be about 20-seconds with a minimum matrix of 128 x 256. Technologists must understand the importance of patient instruction about breath-holding before and during scan.

To submit an HCC exception request, select *Hepatocellular carcinoma (HCC)* and fill out the associated form. If the candidate does not meet the standardized criteria per Policy 9.5. I or seeks a different exception score, the system will direct the transplant program to write and submit a justification narrative that will be reviewed by the Adult Transplant Oncology Review Board.

Intrahepatic Cholangiocarcinoma

Candidates with biopsy proven unresectable solitary intrahepatic cholangiocarcinoma (iCCA) or mixed hepatocellular carcinoma/intrahepatic cholangiocarcinoma (mixed HCC-iCCA) 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 based on existing data supporting the role of liver transplantation in this setting.[7, 8, 9, 10] Based on current evidence-based medicine, transplant programs should provide the following elements when submitting an initial MELD exception for iCCA:

- Biopsy proven iCCA or mixed HCC-iCCA[11]
- Presence of cirrhosis
- Unresectable
- Locoregional or systemic therapy for iCCA
- 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 before applying for exception

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

- Imaging every 3 months to ensure tumor less than or equal to 3 cm
- No extrahepatic disease prior to extending the MELD exception

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

To submit an iCCA exception request, select *Cholangiocarcinoma (CCA)* and fill out the associated form. The transplant program will then be directed to submit a justification narrative that will be reviewed by the Adult Transplant Oncology Review Board. Utilize this same process if submitting an exception request for mixed HCC-iCCA.

Neuroendocrine Tumors (NET)

A review of the literature supports that candidates with NET are expected to have a low risk of waiting list drop-out.

[7] Sapisochin G, de Lope CR, Gastaca M, de Urbina JO, Lopez-Andujar R, Palacios F, et al. Intrahepatic cholangiocarcinoma or mixed hepatocellular-cholangiocarcinoma in patients undergoing liver transplantation: a Spanish matched cohort multicenter study. Ann Surg; 2014. p. 944-52.

[8] Fu BS, Zhang T, Li H, Yi SH, Wang GS, Xu C. The role of liver transplantation for intrahepatic cholangiocarcinoma: a single-center experience. European Surgical; 2011.

[9] Hayashi A, Misumi K, Shibahara J, Arita J, Sakamoto Y, Hasegawa K, et al. Distinct Clinicopathologic and Genetic Features of 2 Histologic Subtypes of Intrahepatic Cholangiocarcinoma. The American Journal of Surgical Pathology. 2016;40(8):1021-30.

[10] Sapisochin G, Facciuto M, Rubbia-Brandt L, Marti J, Mehta N, Yao FY, et al. Liver transplantation for "very early" intrahepatic cholangiocarcinoma: International retrospective study supporting a prospective assessment. Hepatology. 2016;64(4):1178-88.

[11] There may be worse survival outcomes with poor differentiation of tumor on biopsy.

Transplant programs should be aware of the following criteria when submitting exceptions for NET. The review board should consider the following criteria when reviewing exception applications for candidates with NET.

- Resection of primary malignancy and extra-hepatic disease without any evidence of recurrence for at least six months prior to MELD exception request.
- Neuroendocrine Liver Metastasis (NLM) limited to the liver, Bi-lobar, not amenable to resection.

  Tumors in the liver should meet the following radiographic characteristics on *either* CT or MRI:

  1. If CT Scan:
     a. Triple phase contrast Lesions may be seen on only one of the three phases
     b. Arterial phase: may demonstrate a strong enhancement
     c. Large lesions can become necrotic/calcified
  2. If MRI Appearance:
     a. Liver metastasis are hypodense on T1 and hypervascular in T2 wave images
     b. Diffusion restriction
     c. Majority of lesions are hypervascular on arterial phase with wash –out during portal venous phase
     d. Hepatobiliary phase post Gadoxetate Disodium (Eovist): Hypointense lesions are characteristics of NET

1. Consider for exception only those with a NET of Gastro-entero-pancreatic (GEP) origin tumors with portal system drainage. Note: Neuroendocrine tumors with the primary located in the lower rectum, esophagus, lung, adrenal gland and thyroid are not candidates for automatic MELD exception.
2. 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.
3. Tumor metastatic replacement should not exceed 50% of the total liver volume.
4. Negative metastatic workup should include one of the following:
   a. Positron emission tomography (PET scan)
   b. Somatostatin receptor scintigraphy
   c. Gallium-68 (68Ga) labeled somatostatin analogue 1,4,7,10-tetraazacyclododedcane-N, N', N",N'"-tetraacetic acid (DOTA)-D-Phe1-Try3–octreotide (DOTATOC), or other scintigraphy to rule out extra-hepatic disease, especially bone metastasis.

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

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

To submit an exception request for NET, select the *Neuroendocrine Tumor (NET)* option. Transplant programs will be directed to write and submit a justification narrative that will be reviewed by the Adult Transplant Oncology Review Board.

Colorectal Liver Metastases

The diagnosis of unresectable colorectal liver metastases (CRLM) has a poor prognosis despite improved local and systemic treatments. Published studies support liver transplantation in highly selected patients and has demonstrated a survival benefit in initial prospective clinical trials.[12, 13, 14, 15]

Based on currently available published studies, transplant programs should provide the following elements when submitting an initial MELD exception for CRLM:

Initial MELD Exception Criteria

Candidates can be considered for MELD exception points for CRLM if all of the following criteria are met:

Primary diagnosis:

- Histological diagnosis of colon/rectal adenocarcinoma
- BRAF wild type, microsatellite stable[16]
- At least 12 months from time of CRLM diagnosis to time of initial exception request

Treatment of primary colorectal cancer

- Standard resection of the primary tumor with negative resection margins
- No evidence of local recurrence by colonoscopy within 12 months prior to time of initial exception request

Evaluation of extrahepatic disease

- No signs of extrahepatic disease or local recurrence, based on CT/MRI (chest, abdomen and pelvis) and PET scan within one month of initial exception request.[17]

Evaluation of hepatic disease and prior systemic/liver directed treatment

- Received or receiving first-line chemotherapy/immunotherapy
- Relapse of liver metastases after liver resection or liver metastases not eligible for curative resection
- No hepatic lesion should be greater than 10 cm before start of treatment
- Must have stability or regression of disease with systemic and/or locoregional therapy for at least 6 months.[18]

[12] Hagness, M., et al., *Liver transplantation for nonresectable liver metastases from colorectal cancer.* Ann Surg, 2013. 257(5): p. 800-6.

[13] Dueland, S., et al., *Survival Outcomes After Portal Vein Embolization and Liver Resection Compared With Liver Transplant for Patients With Extensive Colorectal Cancer Liver Metastases.* JAMA Surgery, 2021. 156(6): p. 550-557.

[14] Line, P.-D. and S. Dueland, *Liver transplantation for secondary liver tumours: The difficult balance between survival and recurrence.* Journal of Hepatology, 2020. 73(6): p. 1557-1562.

[15] Dueland, S., et al., *Survival Following Liver Transplantation for Patients With Nonresectable Liver-only Colorectal Metastases.* Annals of Surgery, 2020. 271(2).

[16] Insufficient data to include KRAS as exclusionary factor but should be considered as a negative prognostic factor.

[17] Pre transplant PET should be performed after a chemotherapy pause of at least 4 weeks.

[18] Progression is defined as more than 10% increase in diameter of existing lesions (according to RECIST 1.1) OR any new lesions detected on imaging.

In cases of synchronous colon lesions, in addition to above criteria, all of the following are required:

- Resection of the primary tumor is performed more than 6 months after initial diagnosis
- Minimum of 6 months of chemotherapy after primary tumor resection before exception request with stability of disease for a total of at least 12 months after initial diagnosis.[19]

Candidates meeting the criteria described should be considered for a MELD exception score equal to MMaT-20. If MMaT-20 results in an exception score below 15, the candidate's exception score **will automatically be set to a MELD score of 15** per OPTN Policy 9.4.E: *MELD or PELD Exception Scores Relative to Median MELD or PELD at Transplant*.

Exclusion Criteria

Candidates should not be considered for an initial MELD exception for CRLM if any of the following criteria are met:

- Extra-hepatic disease after primary tumor resection (including lymphadenopathy outside of the primary lymph node resection)
- Local relapse of primary disease
- Carcinoembryonic antigen (CEA) >80 µg/L with or without radiographic evidence of disease progression or new lesion.

MELD Exception Extension Criteria

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

- Every 3 months from initial MELD exception:
  - Perform CT or MRI (chest, abdomen and pelvis)
  - Perform CEA testing
- No progression of hepatic disease[20]
- No development of extrahepatic disease
- CEA < 80 µg/L

To submit an exception request for CRLM, select the *Colorectal liver metastases* option. Transplant programs will be directed to write and submit a justification narrative that will be reviewed by the Adult Transplant Oncology Review Board.

Hepatic Epithelioid Hemangioendothelioma

Approval of MELD exception points for adult candidates with unresectable Hepatic Epithelioid Hemangioendothelioma (HEHE) may be appropriate in some instances.

Biopsy must be performed to establish the diagnosis of HEHE, and exclude hemangiosarcoma. HEHE is a rare, low grade primary liver tumor of mesenchymal cell origin. Because of the rarity of the diagnosis, as well as the variability in presentation, the optimal treatment strategies are not fully established. However, for lesions which cannot be resected, liver transplant is associated with 1, 5, and 10-year patient survival rates of 97%, 83%, and 74%; with more favorable results occurring in patients without microvascular invasion. The presence of extra-hepatic disease has not been associated with decreased survival post liver transplant and therefore should not be an absolute contraindication. Controversy

[19] Progression is defined as more than 10% increase in diameter of existing lesions (according to RECIST 1.1) OR any new lesions detected on imaging.

[20] Pre transplant PET should be performed after a chemotherapy pause of at least 4 weeks.

regarding the role of liver transplant in treating HEHE relates to the variable course of disease in the absence of liver transplant, with some patients demonstrating regression or stabilization of disease and prolonged survival.[21,22]

To submit an exception request for HEHE, select the *Hepatic Epithelioid Hemangioendothelioma (HEHE)* option. Transplant programs will be directed to write and submit a justification narrative that will be reviewed by the Adult Transplant Oncology Review Board.

Hepatic Adenomas

Orthotopic liver transplantation for hepatic adenomas (HA) remains an extremely rare indication; however, it is a valid therapeutic option in select patients with adenoma meeting one of the following categories:

- Adenoma in the presence of Glycogen Storage Disease
- Unresectable β Catenin (+) Adenoma
- Adenoma(s) with all three below:
    - Unresponsive to medical management
    - Unresectable
    - Progressive or with complication such as hemorrhage or malignant transformation (must specify)

The identification of these criteria is mandatory to aid in the decision-making process.[23,24,25,26]

To submit an exception request for HA, select the *Hepatic Adenomas* option. Transplant programs will be directed to write and submit a justification narrative that will be reviewed by the Adult Transplant Oncology Review Board.

[21]Lerut, J.P., G. Orlando, R. Adam, et al. "The place of liver transplantation in the treatment of hepatic epitheloid hemangioendothelioma: report of the European liver transplant registry." Ann Surg 246 (2007): 949-57.
[22]Nudo, C.G., E.M. Yoshida, V.G. Bain, et al. "Liver transplantation for hepatic epithelioid hemangioendothelioma: the Canadian multicentre experience." Can J Gastroenterol 22 (2008):821-4.
[23]Blanc, J.F., N. Frulio, L. Chiche, et al. "Hepatocellular adenoma management: call for shared guidelines and multidisciplinary approach." Clinics and research in hepatology and gastroenterology 39 (2015): 180-187.
[24]Chiche, L., A. David, R. Adam, et al. "Liver transplantation for adenomatosis: European experience." Liver Transplantation 22 (2016): 516-526.
[25]Alagusundaramoorthy, S. S., V. Vilchez, A. Zanni, et al. "Role of transplantation in the treatment of benign solid tumors of the liver: a review of the United Network of Organ Sharing data set." JAMA Surgery 150 (2015): 337-342.
[26]Dokmak, S., V. Paradis, V. Vilgrain, et al. "A single-center surgical experience of 122 patients with single and multiple hepatocellular adenomas." Gastroenterology 137 (2009): 1698-1705.

Guidance to Liver Transplant Programs and the National Liver Review Board for: Adult MELD Exception Review

Summary and Goals

For many patients with chronic liver disease the risk of death without access to liver transplant can be accurately predicted by the MELD score, which is used to prioritize candidates on the waiting list. However, for some patients the need for liver transplant is not based on the degree of liver dysfunction due to the underlying liver disease but rather a complication of the liver disease. These complications have an increased risk of mortality or waitlist dropout without access to timely transplant and are not reflected in the calculated MELD score.[1] This document summarizes available evidence to assist clinical reviewers in approving candidates for MELD exceptions. It contains guidance for specific clinical situations for use by the review board to evaluate common exceptional case requests for adult candidates with the following diagnoses, not all of which are appropriate for MELD exception:

- Ascites
- Budd Chiari
- GI Bleeding
- Hepatic Encephalopathy
- ~~Hepatic Epithelioid Hemangioendothelioma~~
- Hepatic Hydrothorax
- Hereditary Hemorrhagic Telangiectasia
- ~~Hepatic Adenomas~~
- ~~Neuroendocrine Tumors (NET)~~
- Polycystic Liver Disease (PLD)
- Portopulmonary Hypertension
- Primary Sclerosing Cholangitis (PSC) or Secondary Sclerosing Cholangitis (SSC)
- Metabolic Disease
- Multivisceral Transplant Candidates
- Post-Transplant Complications, including Small for Size Syndrome, Chronic Rejection, Diffuse Ischemic Cholangiopathy, and Late Vascular Complications
- Pruritus

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

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.

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~~Hepatic Epithelioid Hemangioendothelioma~~

~~**Approval of MELD exception points for adult candidates with unresectable Hepatic Epithelioid Hemangioendothelioma (HEHE) may be appropriate in some instances.**~~

~~Biopsy must be performed to establish the diagnosis of HEHE, and exclude hemangiosarcoma. HEHE is a~~

[1] Waitlist dropout is removal from the waiting list due to the candidate being too sick to transplant.

rare, low grade primary liver tumor of mesenchymal cell origin. Because of the rarity of the diagnosis, as well as the variability in presentation, the optimal treatment strategies are not fully established. However, for lesions which cannot be resected, liver transplant is associated with 1, 5, and 10-year patient survival rates of 97%, 83%, and 74%; with more favorable results occurring in patients without microvascular invasion. The presence of extra-hepatic disease has not been associated with decreased survival post liver transplant and therefore should not be an absolute contraindication. Controversy regarding the role of liver transplant in treating HEHE relates to the variable course of disease in the absence of liver transplant, with some patients demonstrating regression or stabilization of disease and prolonged survival.[2,3]

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Hepatic Adenomas

Orthotopic liver transplantation for hepatic adenomas (HA) remains an extremely rare indication; however, it is a valid therapeutic option in select patients with adenoma meeting one of the following categories:

- Adenoma in the presence of Glycogen Storage Disease
- Unresectable β Catenin (+) Adenoma
- Adenoma(s) with all three below:
    - Unresponsive to medical management
    - Unresectable
    - Progressive or with complication such as hemorrhage or malignant transformation (must specify)

The identification of these criteria is mandatory to aid in the decision-making process.[4,5,6,7]

Neuroendocrine Tumors (NET)

A review of the literature supports that candidates with NET are expected to have a low risk of waiting list drop-out.

Transplant programs should be aware of the following criteria when submitting exceptions for NET. The review board should consider the following criteria when reviewing exception applications for candidates with NET.

- Resection of primary malignancy and extra-hepatic disease without any evidence of recurrence at least six months prior to MELD exception request.
- Neuroendocrine Liver Metastasis (NLM) limited to the liver, Bi-lobar, not amenable to resection.

[2]Lerut, J.P., G. Orlando, R. Adam, et al. "The place of liver transplantation in the treatment of hepatic epitheloid hemangioendothelioma: report of the European liver transplant registry." Ann Surg 246 (2007): 949-57.

[3]Nudo, C.G., E.M. Yoshida, V.G. Bain, et al. "Liver transplantation for hepatic epithelioid hemangioendothelioma: the Canadian multicentre experience." Can J Gastroenterol 22 (2008):821-4.

[4]Blanc, J.F., N. Frulio, L. Chiche, et al. "Hepatocellular adenoma management: call for shared guidelines and multidisciplinary approach." Clinics and research in hepatology and gastroenterology 39 (2015): 180-187.

[5]Chiche, L., A. David, R. Adam, et al. "Liver transplantation for adenomatosis: European experience." Liver Transplantation 22 (2016): 516-526.

[6]Alagusundaramoorthy, S. S., V. Vilchez, A. Zanni, et al. "Role of transplantation in the treatment of benign solid tumors of the liver: a review of the United Network of Organ Sharing data set." JAMA Surgery 150 (2015): 337-342.

[7]Dokmak, S., V. Paradis, V. Vilgrain, et al. "A single-center surgical experience of 122 patients with single and multiple hepatocellular adenomas." Gastroenterology 137 (2009): 1698-1705.

Tumors in the liver should meet the following radiographic characteristics on *either* CT or MRI:

1. If CT Scan:
    a. Triple phase contrast Lesions may be seen on only one of the three phases
    b. Arterial phase: may demonstrate a strong enhancement
    c. Large lesions can become necrotic/calcified
2. If MRI Appearance:
    a. Liver metastasis are hypodense on T1 and hypervascular in T2 wave images
    b. Diffusion restriction
    c. Majority of lesions are hypervascular on arterial phase with wash –out during portal venous phase
    d. Hepatobiliary phase post Gadoxetate Disodium (Eovist): Hypointense lesions are characteristics of NET

1. Consider for exception only those with a NET of Gastro-entero-pancreatic (GEP) origin tumors with portal system drainage. Note: Neuroendocrine tumors with the primary located in the lower rectum, esophagus, lung, adrenal gland and thyroid are not candidates for automatic MELD exception.
2. 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.
3. Tumor metastatic replacement should not exceed 50% of the total liver volume.
4. 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-Try3–octreotide (DOTATOC), or other scintigraphy to rule out extra-hepatic disease, especially bone metastasis.

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

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

National Liver Review Board Operational Guidelines

1. Overview

The purpose of the National Liver Review Board (NLRB) is to provide fair, equitable, and prompt peer review of exceptional candidates whose medical urgency is not accurately reflected by the calculated MELD/PELD score. The NLRB will base decisions on policy, the guidance documents, and in cases which lack specific guidance, the medical urgency of the candidate as compared to other candidates with the same MELD or PELD score adjustment or specific MELD or PELD score.

The NLRB is comprised of specialty boards, including:

- Adult ~~Hepatocellular Carcinoma (HCC)~~ Transplant Oncology
- Adult Other Diagnosis
- Pediatrics, which reviews requests made on behalf of any candidate registered prior to turning 18 years old and adults with certain pediatric diagnoses

The immediate past-Chair of the Liver and Intestinal Organ Transplantation Committee serves as the Chair of the NLRB for a two year term.

2. Representation

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6. Appeals Review Team (ART)

At the beginning of each new service term, nine NLRB members from the Adult Other Diagnosis and Adult ~~HCC~~ Transplant Oncology specialty boards are assigned to serve each month of the year on the Adult ART and nine NLRB members from the Pediatric specialty board are assigned to serve each month of the year on the Pediatric ART. There may be multiple ARTs, depending on the volume of cases. Each ART will be scheduled to meet via conference call according to a predetermined schedule.

ART appeals from the Adult Other Diagnosis and Adult ~~HCC~~ Transplant Oncology specialty boards will be reviewed by the Adult ART. ART appeals from the Pediatric specialty board will be reviewed by the Pediatric ART.

In the event of a planned absence, the ART member may designate their alternate to serve. The representative must notify the OPTN of this in the OPTN Computer System.

Five members of the ART must participate in the call. If at least five members do not attend the call, the appeal will be rescheduled for the following regularly scheduled conference call. If at least five members do not attend the second attempt to review the appeal, the candidate's exception request is automatically approved.

The appeal must achieve a majority plus one affirmative votes in order to be approved.

A representative at the petitioning program may serve as the candidate's advocate. If a representative is unable to attend the conference call, the program may ask for the appeal to be scheduled for the

following regularly scheduled conference call. If after two attempts a representative is unable to attend the call, the ART will review the appeal without the program's participation. In the absence of a representative on the conference call, the program may submit written information for the ART's consideration.

A current member of the Liver Committee serving on either the Adult Other Diagnosis specialty board or Adult ~~HCC~~ Transplant Oncology specialty board will be appointed to serve as the ART leader for the Adult ART prior to each service term. A current member of the Liver Committee or current member of the OPTN Pediatric Transplantation Committee (Pediatric Committee) serving on the Pediatric specialty board will be appointed to serve as the ART leader for the Pediatric ART prior to each service term. If no current member of either the Liver Committee or the Pediatric Committee is available to serve as the ART leader, prior members of each Committee or other members of the NLRB may be appointed to serve as ART leader. The ART leader will be prepared to lead ART discussion and provide feedback to the Liver Committee.

The ART will work with the OPTN to document the content of the discussion and final decision in the OPTN Computer System.

7. Liver Committee Review

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