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

Summary and Goals

For many candidates 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 candidates 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 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)
- 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.

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[2] or, if less than 12 years old, a PELD[3] 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.[4] 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 centers should consult this resource when considering MELD exception requests for adult candidates with the following diagnoses.

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

The OPTN Liver and Intestinal Organ Transplantation Committee (hereafter, "the Committee") has developed guidance for adult MELD exceptions for Transplant Oncology. This guidance document is intended to provide recommendations for the review board considering hepatic neoplasm 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. 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 candidates 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.[5]

- Candidates beyond standard criteria who have continued progression while waiting despite locoregional are generally not acceptable candidates for HCC MELD exception.
- Candidates with AFP greater than 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 Adult Transplant Oncology Review Board to be considered. In general, these candidates are not suitable for HCC MELD exception but may be appropriate in some cases.
- Candidates 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 greater than 1,000. Imaging should be performed at least 4 weeks after last down-staging treatment. Candidates must still wait for 6 months from the time of the first request to be eligible for an HCC exception score.
- Candidates who presented with stage T2 HCC (LI-RADS 5 or biopsy proven; one lesion greater than 2 cm and less than 5 cm in size, two or three lesions greater than 1 cm and less than 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

[5] 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.

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.

Candidates with cirrhosis and HCC beyond T2 but within generally accepted criteria for down-staging (such as up to 5 lesions, total tumor volume less than 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 the larger tumor size, the 6 month delay is appropriate to ensure favorable tumor biology.

LI-RADS 5 requires the below criteria, which differ based on size and modality. Threshold growth is defined as greater than or equal to 50% increase in longest diameter in less than or equal to 6 months on CT/MRI.[6]

Table 1: LI-RADS 5 Criteria

Imaging Modality[7]	Observation size, mm	LR-5 criteria
CT/MRI	10-19mm	Nonrim arterial phase hyperenhancement (APHE) with at least one of the following: • Nonperipheral washout • Threshold growth
CT/MRI	Greater than or equal to 20 mm	Nonrim APHE with at least one of the following: • Nonperipheral washout • Threshold growth • Enhancing “capsule”
CEUS	Greater than or equal to 10 mm	Nonrim APHE with: • Late and mild washout

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

Table 2: Recommendations for Contrast-enhanced Multiphase 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

[6] American College of Radiology Committee on LI-RADS® (Liver) The LI-RADS v2018 Manual. Available at: https://www.acr.org//media/ACR/Files/Clinical-Resources/LIRADS/LI-RADS-2018-Manual-5Dec18.pdf. Accessed on November 6, 2024.

[7] OPTN Policy 9.5.I requires CT/MRI be Contrast-enhanced Multiphase.

Feature:	CT scans should meet the below specifications:
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 multiphase on contrast-enhanced MDCT	1. Late arterial phase: hepatic arterial branches are fully enhanced, the hepatic veins are not enhancing, and the portal vein is enhancing more than the liver 2. Portal venous phase: Acquired no more than 120 seconds after injection of a contrast agent when portal and hepatic veins are enhanced more than liver 3. Delayed phase: Acquired at least 120 seconds after injection of contrast when portal and hepatic veins are enhanced more than liver
Multiphase (Timing)	Use the bolus tracking or timing bolus

Table 3: Recommendations for Contrast-enhanced Multiphase 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 multiphase 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.

Feature	MRIs should meet the below specifications:
Mandatory multiphase on contrast-enhanced multiphase 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.
Multiphase (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 multiphase 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.

Table 4: Recommendations for Contrast-enhanced Ultrasound (CEUS) of the Liver

Feature	CEUS should meet the below specifications:
Scanner type	Ultrasound scanners equipped with appropriate software and hardware packages for contrast-enhanced imaging
Ultrasound transducer selection	CEUS imaging of the liver is typically performed with a curved array transducer, with higher frequency linear transducers reserved for small superficial liver lesions
Suggested imaging parameters	Dual screen imaging format showing a low mechanical index B-mode image alongside the contrast-only display. An acoustic window that allows the examined lesion to be scanned as close to the transducer as possible maintaining an approximately 2 cm distance from the transducer and allow for the target liver observation to be continuously visible during scanning.

Feature	CEUS should meet the below specifications:
Contrast dose	Contrast dose specified by the manufacturer should be used but the contrast dose may be modified in certain circumstances based on patient factors and sensitivity of the equipment used for CEUS examination
Contrast injection	Intravenous contrast bolus delivered over 2 – 3 seconds immediately followed by a 5-10 mL normal saline flush
Minimum required CEUS images	1. B-mode images of the examined observation 2. Continuous cine loop imaging from first bubble arrival through peak arterial phase enhancement. Optionally, the cine loop can be continued beyond the arterial phase enhancement peak until 60 seconds after injection. 3. Static image at 60 seconds and thereafter, imaging intermittently (every 30-60 seconds) saving static images or short cineloops to document and evaluate the presence, timing, and degree of washout.

To submit an HCC exception request, select *Hepatocellular carcinoma (HCC)* and fill out the associated form. If the candidates 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.[8, 9, 10, 11]

Based on current evidence-based medicine, transplant programs should provide the following elements when submitting an initial MELD exception for iCCA:

[8] 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.

[9] 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.

[10] 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.

[11] 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.

- Biopsy proven iCCA or mixed HCC-iCCA[12]
- 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)

Candidates with unresectable neuroendocrine liver metastasis limited to the liver, may benefit from liver transplantation. Tumors in the liver should have radiographic or histologic characteristics consistent with neuroendocrine liver metastasis.[13]

1. Only those with a NET of Gastro-entero-pancreatic (GEP) origin tumors 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.
2. Resection of primary malignancy and extra-hepatic disease without any evidence of recurrence at least six months prior to MELD exception request.
3. Lower - intermediate grade following the WHO classification, i.e. well differentiated (low grade, G1) and moderately differentiated (intermediate grade G2), based on primary lesion or the liver metastasis, with mitotic rate less than 20 per 10 HPF and index less than 20%.
4. No evidence for extra-hepatic tumor recurrence based on metastatic radiologic workup at least 3 months prior to initial or extension MELD exception request (submit date). Negative metastatic workup should include functional imaging, e.g. somatostatin receptor scintigraphy, gallium-68 somatostatin receptor imaging, and/or positron emission tomography (PET).

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

[13] Reference: Mazzaferro V, Pulvirenti A, Coppa J. Neuroendocrine tumors metastatic to the liver: how to select patients for liver transplantation? Journal of Hepatology, Oct 2007; 47(4): 460-6.

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

Occurrence of extra-hepatic progression – for instance lymph-nodal Ga68 positive locations – should indicate de-listing. Candidates may be re-considered for MELD exception if any extra-hepatic disease is zeroed and remained so for at least 6 months. Presence of extra-hepatic solid organ metastases (i.e. lungs, bones) should be a permanent exclusion.

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

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 candidates and has demonstrated a survival benefit in initial prospective clinical trials.[14, 15, 16, 17]

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[18]
- 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

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

[15] 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.

[16] 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.

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

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

- 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.[19]

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.[20]

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.[21]

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) greater than 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[22]
- No development of extrahepatic disease
- CEA less than 80 µg/L

[19] Pre transplant PET should be performed after a chemotherapy pause of at least 4 weeks.
[20] 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.
[21] 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
[22] Pre transplant PET should be performed after a chemotherapy pause of at least 4 weeks.

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. HEHE is a rare, low grade primary liver tumor of mesenchymal cell origin. [23, 24, 25] The presence of extrahepatic disease is not an absolute contraindication. Candidates who are being considered for MELD exception should meet the following criteria.

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

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

To submit an exception request for HEHE, select the *Hepatic Epithelioid Hemangioendothelioma* 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

Liver transplantation for hepatic adenomas (HA) remains a rare but viable treatment for select candidates. Candidates may qualify for an exception, if they meet *one* of the following criteria:

- 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 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)

[23] Lai Q, et al. HEHE and Adult Liver Transplantation: Proposal for a Prognostic Score Based on the Analysis of the ELTR-ELITA Registry. Transplantation. 2017;101(3):555-564.
[24] 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.
[25] 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.

The identification of these criteria is mandatory to aid in the decision-making process.[26,27,28,29]

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

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.

[26] 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.
[27] Chiche, L., A. David, R. Adam, et al. "Liver transplantation for adenomatosis: European experience." Liver Transplantation 22 (2016): 516-526.
[28] 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.
[29] 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.