# UPMC
# STARZL TRANSPLANTATION INSTITUTE
# LIVER TRANSPLANT POLICIES AND PROCEDURES

POLICY LT-HCC-0212
Hepatocellular Carcinoma and Liver Transplantation

## PURPOSE

To provide HCC screening parameters, selection criteria, and management guidelines for patients being evaluated for liver transplant and follow-up procedures for those having received a liver transplant for cirrhosis associated with HCC.

## DEFINITIONS

Milan Criteria : single tumor ≤5 cm, maximum of 3 total tumors with none >3 cm

UCSF Criteria: single tumor ≤6.5 cm, maximum of 3 total tumors with none >4.5 cm, and cumulative tumor size ≤8 cm

Downstaging: a treatment strategy to reduce HCC tumor burden to within Milan criteria in patients with HCC that is outside Milan criteria, but within UCSF criteria

American Liver Tumor Study Group Modified Tumor-Node-Metastasis (TNM) Staging Classification:

| Classification | Definition |
|---|---|
| **TX, NX,MX** | **Not assessed** |
| **TO, NO, MO** | **Not found** |
| **T1** | **1 nodule <=1.9 cm** |
| **T2** | **One nodule 2.0-5.0 cm; two or three nodules, all <3.0 cm** |
| **T3** | **One nodule >5.0 cm; two or three nodules, at least one >3.0 cm** |
| **T4a** | **Four or more nodules, any size** |
| **T4b** | **T2, T3, or T4a plus gross intrahepatic portal or hepatic vein involvement as indicated by CT, MRI, or US** |
| **N1** | **Regional (portal hepatis) nodes, involved** |
| **M1** | **Metastatic, including extrahepatic portal or hepatic vein involvement** |
| **Stage I** | **T1** |
| **Stage II** | **T2** |
| **Stage III** | **T3** |
| **Stage IVA1** | **T4a** |
| **Stage IVA2** | **T4b** |
| **Stage IVB** | **Any N1, any M1** |

## PERTINENT REGULATORY INFORMATION

UNOS Policy on HCC (as of 2/1/12)

**3.6.4.4 Liver Transplant Candidates with Hepatocellular Carcinoma (HCC).**
Candidates with stage T2 HCC that meet the staging and imaging criteria specified in sections A-E may receive extra priority on the Waiting List as specified below.

A. **Eligible Candidates**. A candidate with an HCC tumor that is stage T2 may be registered at a MELD/PELD score equivalent to a 15% probability of candidate death within 3 months if the criteria listed in sections B-D are also met. For the purposes of this policy, stage T2 lesions are defined as

--- 1 lesion >= 2 cm and <= 5cm; OR

--- 2 or 3 lesions, >= 1cm and <= 3cm in size.

The largest dimension of each tumor must be reported (i.e., 1.5cm x 2.5cm must be reported as 2.5cm). Nodules <1cm are indeterminate and cannot be considered for additional priority.

B. **Initial Assessment for Listing**. The candidate must have undergone a thorough assessment to evaluate the number and size of tumors and to rule out any extrahepatic spread (i.e. lymph node involvement) and/or macrovascular involvement (i.e., tumor thrombus in portal or hepatic vein)with dynamic contrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI). The assessment of the candidate prior to transplant listing must include a CT of the chest that rules out metastatic disease. The candidate must not be eligible for resection. The alpha-fetoprotein level is required for all HCC exception applications.

C. **Requirements for Imaging**. Any imaging examination performed for the purpose of obtaining or updating priority points on the transplant waitlist should meet minimum recommended technical and imaging protocol requirements for CT and MRI listed in Table 4 and Table 5. These must be interpreted by a radiologist at an OPTN approved transplant center. Technically inadequate or incomplete imaging examinations must be classified as OPTN Class 0 and must be repeated or completed in order to be considered for priority point allocation.

D. **Definitions of OPTN Class 5 Nodules.** Nodules found on imaging of cirrhotic livers must beclassified according to the OPTN classification shown in Table 6. OPTN class 5 nodules correspond toan imaging diagnosis of HCC and are as follows:

November 15, 2011**OPTN Class 5B** nodules: The combination of the following imaging findings constitutes an OPTN class 5B nodule and qualifies for automatic MELD priority score (all 3 criteria must be met):

1. Single nodule diameter greater than or equal to 2cm and less than or equal to 5cm. Maximum diameter of lesion(s) should be measured on late arterial or portal phase images.
2. Increased contrast enhancement on late hepatic arterial images (relative to hepatic parenchyma)
3. One of the following: • **Washout** on portal venous/delayed phase •**Late capsule or pseudocapsule enhancement** OR

• **Growth** (maximum diameter increase in the absence of ablative therapy) by 50% or more documented on serial MRI or CT obtained < 6 month apart. Serial imaging and measurements should be performed on corresponding contrast phases with the same modality preferred. ; OR

• **Biopsy**. Growth criteria do not apply to previously ablated lesions. A pre-listing biopsy is not mandatory.

**OPTN Class 5A** nodules are defined as follows:

1. Single nodule, maximum diameter of >1 cm and <2cm. Maximum diameter of lesion(s) should be

measured on late arterial or portal phase images.
2. Increased contrast enhancement on late arterial phase (relative to hepatic parenchyma)
3. Both of the following:
• **Washout** during the later contrast phases
**AND**
• **Peripheral rim enhancement** (capsule/pseudocapsule) on delayed phase;
**OR**
• Biopsy

**OPTN Class 5A-g** (growth) are defined as follows (all criteria must be met): • Single nodule, maximum diameter of >1 cm and <2cm. Maximum diameter of lesion(s) should be measured on late arterial or portal phase images.
• Increased contrast enhancement on late arterial phase (relative to hepatic parenchyma)
• Growth (maximum diameter increase) by 50% or more documented on serial MRI or CT obtained < 6 months apart. Growth criteria do not apply to ablated lesions.
(i.e. a 1.2 cm hyper-enhancing nodule documented on first CT scan is found to be 1.8 cm on scan obtained 3 months later would be classified as 5A-g. This individual lesion is not eligible for MELD priority score as the tumor is still at stage T1 but if found in conjunction with a second 5A or 5A-g lesion, the patient would be eligible for an automatic MELD priority score.)
**OPTN Class 5T** (Treated) nodules are defined as any OPTN Class 5 or biopsy-proven HCC lesion that was automatically approved upon initial application or extension and has subsequently undergone loco-regional treatment. OPTN Class 5T nodules qualify for continued priority points predicated on the pre-treatment classification of the nodule(s) and are defined as:
1. Past loco-regional treatment for HCC (OPTN class 5 lesion or biopsy proven prior to ablation).
2. Evidence of persistent/recurrent HCC such as nodular or crescentic extra-zonal or intra-zonal enhancing tissue on late arterial imaging (relative to hepatic parenchyma) may be present.
**OPTN Class 5X**: Lesions that meet radiologic criteria for HCC but are outside stage T2 as defined in section A will be considered Class 5X and are not eligible for automatic exception points. These cases may be considered by the Regional Review Board (RRB) as described in section G.
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**E. HCC Lesions Eligible for Automatic Upgrade.** Individual Class 5B and 5T are eligible for automatic priority. A single OPTN Class 5A nodule corresponds to T1 stage hepatocellular carcinoma and does not qualify for automatic priority MELD points but must be considered towards the overall staging of the patient according to criteria listed above. **Combinations of Class 5A nodules** that meet stage T2 criteria as described in section (A) are eligible for automatic priority.
**F. Extensions of HCC Exception Applications**. Candidates will receive additional MELD/PELD points equivalent to a 10 percentage point increase in candidate mortality to be assigned every 3 months until these candidates receive a transplant or are determined to be unsuitable for transplantation based on progression of their HCC. To receive the additional points at 3-month intervals, the transplant program must re- submit an HCC MELD/PELD score exception application with an updated narrative every three months. Continued documentation of the tumor via repeat CT or MRIis required every three months for the candidate to receive the additional 10 percentage point increase in mortality points while waiting. Invasive studies such as biopsies or ablative proceduresand repeated chest CTs are not required after the initial upgrade request is approved to maintainthe candidate's HCC priority scores.
If the number of tumors that can be documented at the time of extension is less than upon initial

application or prior extension, the type of ablative therapy must be specified on the extension application. Candidates whose tumors have been ablated after previously meeting the criteria for additional MELD/PELD points (OPTN Class 5T) will continue to receive additional MELD/PELD points (equivalent to a 10 percentage point increase in candidate mortality) every 3 months without RRB review, even if the estimated size of residual viable tumor falls below stage T2 criteria.

For candidates whose tumors have been resected since the initial HCC application or prior extension, the extension application must receive prospective review by the applicable RRB.

**G.Candidates Not Meeting Criteria (Class 5X)**. A candidate not meeting the above criteria may continue to be considered a liver transplant candidate in accordance with each center's own specific policy or philosophy, but the candidate must be listed at the calculated MELD/PELD score with no additional priority given because of the HCC diagnosis. All such candidates with HCC, including those with downsized tumors whose original/presenting tumor was greater than a stage T2, must be referred to the applicable RRB for prospective review in order to receive additional priority.

**H.Appeal Procedures for Candidates not Meeting Criteria**. If the initial request is denied by the RRB, the center may appeal via a

For example, a candidate would be eligible for additional priority with:

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Two 1.5 cm (5A) lesions; or One 1.5 cm lesion (5A) and one 2.5 cm lesion (5B); or One 3.5cm lesion (5B); or Two 2.1cm lesions (5B).

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conference call with the RRB but the candidate will not receive the additional MELD/PELD priority until the case is approved by the RRB. Cases where the appropriate RRB has found the listing center to be out of compliance with Policy 3.6.4.4 will be referred to the Liver and Intestinal Organ Transplantation Committee for review and possible action. Cases not resolved within 21 days will be referred to the Liver and Intestinal Organ Transplantation Committee for review; this review by the Liver and Intestinal Organ Transplantation Committee may result in further referral of the matter to the Membership and Professional Standards Committee for appropriate action in accordance with Appendix A of the Bylaws.

**I. Compliance Monitoring**. Documentation of the radiologic characteristics of each OPTN class 5 nodule (for an example, see Tables 7A–C) must be kept on file at the transplant center. If growth criteria are used to classify a nodule as HCC, prior and current dates of imaging, type of imaging and measurements of the nodule(s) must be documented in the radiology report.

For those candidates who receive a liver transplant while receiving additional priority under the HCC criteria, the recipient's explant pathology report must be sent to the OPTN contractor within 60 days of the transplant procedure. If the pathology report does not show evidence of HCC, the transplant center must also submit documentation and/or imaging studies confirming HCC at the time of listing. Additionally, if more than 10% of the HCC cases on an annual basis are not supported by pathologic confirmation or subsequent submission of clinical information, the center will be referred to the Liver and Intestinal Organ Transplantation Committee.

CMS Policy for Medicare Coverage:

"Effective September 1, 2001, Medicare covers adult liver transplantation for hepatocellular carcinoma when the following conditions are met:

1. The patient is not a candidate for subtotal liver resection;
2. The patient's tumor(s) is less than or equal to 5 cm in diameter;
3. There is no macrovascular involvement;
4. There is no identifiable extrahepatic spread of tumor to surrounding lymph nodes, lungs, abdominal organs or bone; and
5. The transplant is furnished in a facility which is approved by CMS as meeting institutional coverage criteria for liver transplants (See 65 FR 15006).

Coverage of adult liver transplantation is effective as of the date of the facility's approval, but for applications received before July 13, 1991, can be effective as early as March 8, 1990. (See ***Federal Register*** 56 FR 15006 dated April 12, 1991.)"

## SCREENING FOR HCC

Standard evaluation of all potential candidates will include:

1. Imaging—Abdominal CT with and without contrast, or MRI.
2. Tumor marker: AFP.
3. Bone scan will be performed for patients if tumor identified outside of Milan, but within UCSF criteria (ie, candidate for downstaging).
4. Biopsy of HCC lesions should be avoided if possible to avoid needle tract metastasis

## SELECTION CRITERIA FOR POTENTIAL LIVER CANDIDATES WITH HCC

Inclusion criteria:

1. Otherwise suitable candidates with HCC that is within Milan criteria
2. Otherwise suitable candidates with HCC within UCSF criteria and eligible for potential downstaging (will not receive MELD exception, so need plan for organ access such living donor or extended-criteria donor).

Downstaging:

Patients must not exceed UCSF criteria at any time. Downstaging must result in tumor coming within Milan criteria. IF AFP≥1000ng/ml, downstaging should decrease AFP to <500ng/ml (ref. 3). Neoadjuvant treatment of tumor may consist of TACE, DEB-TACE, or RFA at the discretion of the primary team. There should be a waiting period of3 months after treatment with re-evaluation by abdominal CT with and without contrast or MRI, along with CT chest, to ensure no evidence of extrahepatic disease and to judgethe nature of tumor aggressiveness.

*Note that MELD exception points are not given for downstaged results. Downstaged tumors must be reviewed by the RRB for extra MELD points. If turned down, an appeal can be made to the RRB by conference call. Medicare does not cover transplants for HCC past Milan, even if downstaged.

3. For candidates with HCC identified with measurements too small to meet Milan criteria, evaluation will proceed to determine overall suitability for transplant. Meanwhile, screening studies will be performed at 3-month intervals, including AFP and CT or MRI, until lesion is ≥2 cm, at which point patient will undergo bridge therapy (TACE or RFA)and receive MELD points for HCC. Unless initial tumor measurement is >1.9 cm, it is not necessary to rescan sooner than 3 months, as HCC average growth at early stage is generally <1.5 mm/month (reference attached).

Exclusion Criteria:

Any patient with tumor outside UCSF criteria.

**HCC cases where portal vein thrombus is identified will be reviewed to estimate the likelihood of vascular invasion as a contributor to the thrombosis. Therefore, segmental or subsegmental thrombus remote from an identified HCC will not be a direct contraindication to transplant. A patient with HCC and main portal vein thrombosis or thrombosis of a major branch, right or left, will be considered at high-risk for recurrence.

## WAITLIST MONITORING OF PATIENTS NOT KNOWN TO HAVE HCC

1. MRI or CT with contrast every 6 months while waiting. In cases of moderate renal insufficiency (CrCl between 30 and 60 ml/hr), MRI with half-strenth Multihance may be used. In patients with severe renal insufficiency but not on dialysis (CrCl < 30 ml/hr), Ultrasound may be used for screening (preferably at UPMC).

2. AFP should be ordered every 6 months.

## WAITLIST MONITORING OF HCC PATIENTS

1. Repeat metastatic evaluation every 3 months (unless otherwise specified)
   AFP
   Imaging----CT Scan of the abdomen with and without contrast, or MRI
   A CT scan without contrast of the chest

2. Bone scan, whole body (repeat at 6 months)

3. Repeat TACE or RFA if CT scan demonstrates a new lesion, if there is bilobar disease such that a repeat embolization or RFA is required for complete treatment, or if AFP is rising.

## DAY OF TRANSPLANT FOR HCC PATIENTS

1. No change from routine protocol
2. Tumor Marker: AFP on admission

## POST-LIVER TRANSPLANT FOLLOW-UP

1. AFP—measured at 1, 3, 6, 12, 18, and 24 months, then annually (if AFP elevated initially).

2. Imaging
    a. CT scan of the abdomen with and without contrast, or MRI, at 6 months, 12 months, 18 months, and 24 months post-transplant, then yearly until year 5.
    b. CT scan of the chest without contrast at 6 months and 12 months
    c. Bone scan at 6 months if HCC pathology on explant showed evidence of **high-risk for recurrence** (e.g., >3 lesions confirmed, any single lesion >5 cm in size, portal vein thrombosis, neurovascular invasion, nodal disease)

**Patients with HCC found incidentally on explant pathology will have follow-up according to the schedule above as these patients have not been found to have a survival advantage over those whose HCC was identified pre-transplant.

### HCC RECURRENCE POST-OLT

Patients with HCC recurrence identified in follow-up will have their case discussed by transplant surgery and hepatology to evaluate for potential treatment options, as well as be referred to oncology for potential adjuvant chemotherapy.