OPTN | UNOS Briefing Paper

# Changes to HCC Criteria for Auto Approval

*OPTN/UNOS Liver and Intestinal Organ Transplantation Committee*

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# Changes to HCC Criteria for Auto Approval

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| *Public Comment Period:* | *August 15, 2016 – October 15, 2016* |

## Executive Summary

The current criteria for automatic approval of hepatocellular carcinoma (HCC) exceptions for liver candidates is problematic, in that they apply to patients that may do well without liver transplant, those that have a poor prognosis after transplant, and potentially exclude patients that may benefit from liver transplant. Additionally, it has been widely shown that successful downstaging of HCC in selected patients is associated with excellent post-transplantation outcome. However, language describing the eligibility criteria for candidates suitable for HCC downstaging through local-regional treatment is absent from current OPTN/UNOS policy, yet nearly all regional review boards currently approve patients who present outside of standard criteria and have undergone downstaging to be within standard policy criteria. This proposal seeks to make a more consistent national policy regarding HCC patients, increase equity in access to transplants and improve waitlisted patient and transplanted recipient outcomes through modifications to the current standardized HCC exception process.

# What problem will this proposal solve?

Implemented by the OPTN/UNOS in 2002, the model for end-stage liver disease (MELD) allocation policy provides "exception" scores for patients with hepatocellular carcinoma (HCC) that fall within T2 criteria.T2 is a definition of lesion size for automatic approval of exception requests.

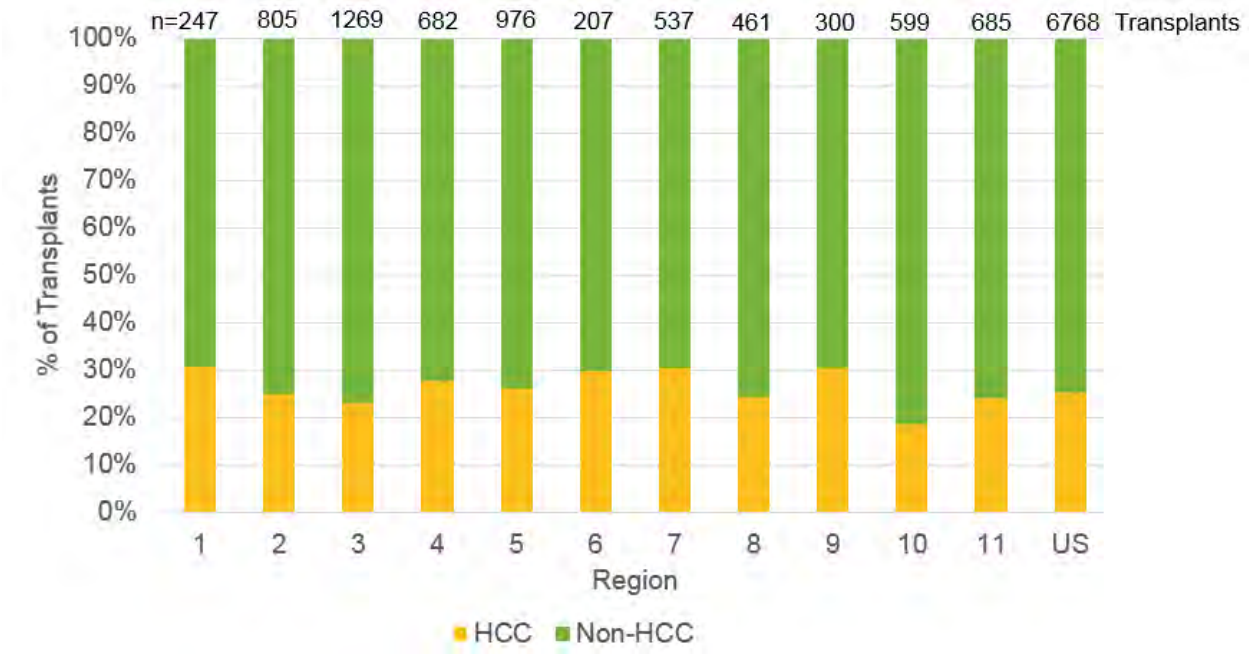
T2 criteria is described as:

- One lesion greater than or equal to 2 cm and less than or equal to 5 cm in size
- Two or three lesions each greater than or equal to 1 cm and less than or equal to 3 cm in size

The intention of the candidate's exception score is to demonstrate their expected risk of waitlist dropout caused by progression of the HCC lesion. The current allocation system for HCC candidates has been in place since 2006, though changes to HCC exception policies were implemented in 2015 (described below in "How was this proposal developed?").

In light of the critical shortage of available organs for transplant, it is imperative that policy is aligned with current medical evidence to increase appropriate utilization of organs. Candidates with a MELD score exception for HCC receive increased priority on the liver waiting list. Therefore, policy must appropriately balance prioritization between HCC candidates and non-HCC candidates, as well as prioritization among HCC candidates. Additionally, in nearly all regions, Regional Review Boards (RRB) grant MELD exceptions to patients with lesions beyond T2 though the criteria are not consistently applied across the regions.

**Figure 1. Deceased Donor Liver Transplants in 2015: Percentage with Approved HCC Exception at Transplant, by Region.**




*Candidates that do well without transplant*

Several studies have shown that a subset of HCC candidates that receive additional priority through the exception system have significantly lower dropout rates than non-HCC candidates[1]. These candidates

[1] Mehta, et al. "Identification of Liver Transplant Candidates with Hepatocellular Carcinoma and Very Low Dropout Risk: Implications for the Current Organ Allocation Policy" *Liver Transplantation* 2013: 12: 1343-1353

automatically receive exception points despite having a very low risk of disease progression or waiting list mortality. The Committee conjectures that within candidates that meet T2 criteria there is a subgroup of candidates with small, well-treated lesions that should not receive the same HCC exception points.

*Candidates with poor post-transplantation outcomes*
The current policy for HCC exceptions does not adequately filter candidates who demonstrate HCC characteristics indicative of poor post-transplantation outcomes. Current policy excludes candidates outside the T2 definition of lesions from automatic exception points; however, there is a subset of HCC candidates within T2 that exhibit characteristics suggesting a high probability of post-transplant recurrence and/or mortality, specifically those candidates with a high alpha-fetoprotein (AFP).[2] The OPTN is charged by the OPTN Final Rule with creating allocation policies that, among other goals, avoid futile transplants.[3]

*Candidates currently excluded that benefit from transplant*
The downstaging of HCC candidates with lesions outside T2 through local-regional treatment is widely accepted. The downstaging of HCC lesions involves decreasing the size of the lesion using local-regional treatment, specifically to reach the eligibility criteria for liver transplant. Data suggests that HCC candidates successfully downstaged to within T2 exhibit a low rate of HCC recurrence and excellent post-transplant survival, comparable to those meeting T2 without downstaging[4]. Current OPTN/UNOS policy does not describe eligibility criteria for candidates suitable for HCC downstaging through local-regional treatment. Candidates must initially present within T2 in order to receive automatic exception. However, nearly all regions currently approve patients who present outside of T2 criteria and have undergone downstaging to within T2.

# Why should you support this proposal?

The elements of this proposal address the current problems with the HCC exception system (described above). The Committee has combined current evidence in the literature with clinical consensus among committee members to propose the changes described in this proposal. The changes to the HCC exception system outlined in this proposal serve as a crucial piece of the larger effort to improve access to liver transplants. This proposal was available for public comment along with the adult MELD exception guidance and proposal, “Redesigning Liver Distribution.” Additionally, the Committee’s proposal to establish a National Liver Review Board (NLRB), along with guidance documents to aid the Review Boards’ award of MELD and PELD exceptions, will be available for a second round of public comment in January 2017. Improving the equity in access for HCC exceptions is an important piece in the overall effort to establish equity in organ distribution and access to liver transplants.

It is important to note that this proposal is not dependent on the future of Redistricting and/or the NLRB to be successful; the changes proposed to HCC exceptions can be implemented regardless of the trajectories of the other Committee projects.

**How is HCC related to the rest of the Committee work plan?**
In November 2012, the Board resolved that existing geographic disparity remains unacceptably high. It directed the organ-specific committees to investigate alternatives to the current OPTN/UNOS regions for distribution, considering optimization as a method. Since then, the Committee has been engaged in a transparent and consensus-driven process to develop the proposal “Redesigning Liver Distribution” (also referred to as “liver redistricting”) which was also released for public comment at the same time as this proposal. The development of that proposal included two public forums that influenced this proposal.

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[2] Hameed, et al. “Alpha-Fetoprotein Level > 1000 ng/mL as an Exclusion Criterion for Liver Transplantation in Patients With Hepatocellular Carcinoma Meeting the Milan Criteria” *Liver Transplantation* 2014: 20: 945-951
[3] 42 CFR §121.8, available at: Electronic Code of Federal Regulations
[4] Yao, et al. “Downstaging of Hepatocellular Cancer Before Liver Transplant: Long-Term Outcome Compared to Tumors Within Milan Criteria” *Hepatology* 2015: 6: 1968-1977

At the June 2015 public forum, the Committee received overwhelming feedback that geographic differences exist in the MELD and PELD exception submission, review, and award practices among the RRBs also contribute to geographic differences in access to liver transplant. Redistricting aims to give similar candidates equal access to transplant regardless of where they are registered. For redistricting, candidates are considered similar if they have equal MELD scores. This requires that MELD scores reflect a similar medical urgency regardless of where the candidate is registered. Current regional variation in review board practices creates variation in how these MELD exceptions are assigned. Therefore, the medical urgency of exception candidates cannot always be compared between regions based upon their MELD score.

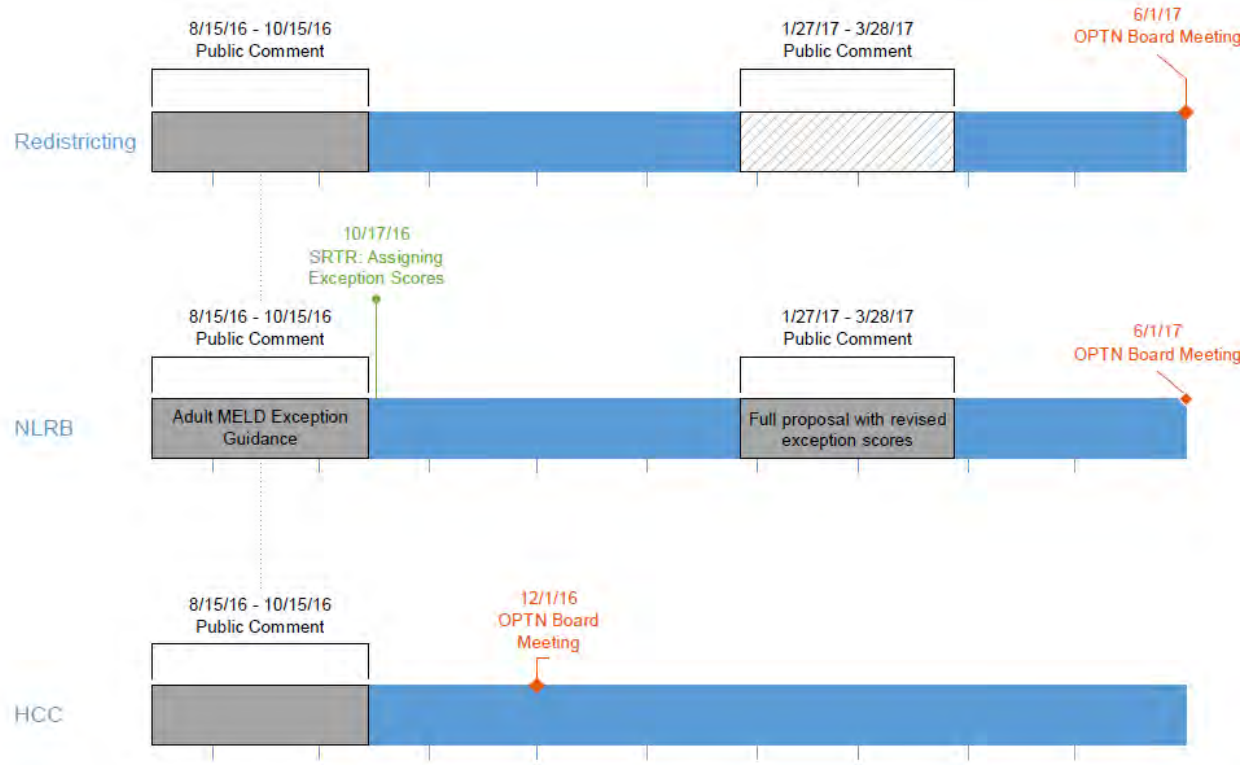
In response to community feedback, the Committee adopted a 2016-2017 work plan last January that is a series of interrelated projects that aim to improve equity in access to liver transplant (**Figure 2**). The Committee seeks to mitigate geographic differences in the exception system by replacing RRBs with a National Liver Review Board (NLRB). The proposed changes to HCC policy will replace regional agreements that have been developed for HCC and create a national standard for candidate eligibility for exception points.

As part of the NLRB project, the Committee is also considering revisions to the MELD scores assigned to candidates meeting exception criteria in policy as a means of curbing national inflation of the MELD score at transplant. It is likely that exception scores for HCC candidates still overestimate progression to a non-transplant state[5]. While this proposal establishes new eligibility criteria for HCC exception, it does maintain the requirement that adult candidates wait at their calculated MELD score for six months before receiving exception points or capping their exception score at MELD 34. As part of the NLRB project, the Committee is exploring the optimal method for assigning scores to exception candidates, including those with HCC. In January 2016, the Committee sought feedback from the community on the appropriate method and is currently gathering evidence to support the proposed change. The Committee anticipates submitting the full NLRB proposal, with the MELD/PELD exception score assignment, for public comment in January 2017.

With these revisions to the exception system, transplant professionals, patients, and the general public will be better able to trust that MELD and PELD exception scores accurately reflect the candidate's disease severity and are the same regardless of geography.

[5] Heimbach, et al. "Delayed Hepatocellular Carcinoma MELD Exception Score Improves Disparity in Access to Liver Transplant in the US" *Hepatology* 2015: 61 (5): 1643-1650

**Figure 2. OPTN/UNOS Liver and Intestinal Organ Transplantation Committee 2016-2017 Work Plan as of January 2016[6]**




# How was this proposal developed?

The long term-term outcomes of liver transplantation for patients with HCC, and the policy of assigning increased priority for HCC candidates has been discussed extensively, including a national consensus conference in 2008[7]. The Committee has previously addressed this topic with two separate proposals. In November 2014, the Board approved the proposal to cap HCC exceptions scores at 34, in effect giving candidates with calculated MELD/PELD scores of 35 or higher a better opportunity to receive offers under the new policy than those with HCC exceptions. The second proposal requires HCC candidates to be registered at their calculated MELD/PELD scores for the first three months (initial application) and for the first three-month extension, as long as the candidate continues to meet HCC policy criteria. With the implementation of both of these projects in the fall of 2015, the Committee's focus shifted towards the criteria required for automatic approval of HCC exceptions.

In December 2015, the MELD Exceptions and Enhancements Subcommittee ("the Subcommittee") was assigned the task of addressing a number of aspects in the current HCC policy, so that these efforts could align with the NLRB and Redistricting efforts due to the prevalence of HCC exceptions and their effect on the NLRB and Redistricting efforts. The Subcommittee is composed of physicians and surgeons from the Liver and Intestinal Organ Committee. The Subcommittee met frequently to identify specific areas of policy that need revising and develop recommendations for the full Committee to address the current problems (described above in "What problem will this proposal solve?").

[6] The timelines on the 2016-2017 were speculative and are subject to change in light of the feedback received in response to the Redistricting proposal. The HCC and NLRB policy proposals are still on track to achieve the timelines stated in this Work Plan.
[7] Pomfret, et al. "Report of a National Conference on Liver Allocation in Patients with Hepatocellular Carcinoma in the United States" *Liver Transplantation* 2010: 16: 262-278

The Committee agreed with the Subcommittee's proposed changes to current HCC policy, with small amendments to the recommended policy regarding exceptions for single, small HCC lesions. The specific changes are described below in "How well does this proposal address the problem statement?"

# How well does this proposal address the problem statement?

The proposed policy changes will modify the criteria for HCC exceptions so that these candidates' MELD score will more accurately reflect their disease severity. The proposal does this by focusing on three areas:

1) Single small lesion criteria
2) Downstaging
3) High alpha-fetoprotein threshold

**Single Small Lesion Criteria**

HCC candidates with single, well-treated small lesions have been shown to have a low-risk of waitlist dropout due to disease progression or waitlist mortality[8]. For the purposes of this proposal, the definition for a single, small lesion is described as 1 lesion between 2-3 cm, that has exhibited a complete response, defined as after receiving ablation, the tumor was less than 2 cm. Approximately 1,550 candidates were listed with an HCC exception that fit this criteria from 2011-2015. This is over 10% of the HCC candidates added to the waiting list during this time.

Current policy provides automatic priority for candidates that meet T2 criteria, described as:

- One lesion greater than or equal to 2 cm and less than or equal to 5 cm in size.
- Two or three lesions each greater than or equal to 1 cm and less than or equal to 3 cm in size.

The Subcommittee recommended that those HCC candidates with a single lesion, 2-3 cm in size, that have been completely ablated, do not receive automatic priority. These candidates would be required to undergo local-regional therapy prior to their exception request, and if the lesion exhibits a complete response, or is completely treated after one or more episodes of local-regional therapy, the candidate would not be eligible for automatic priority. To address small lesions with a higher risk of disease progression, the Subcommittee recommended that candidates would be eligible for automatic priority if the lesion persists after one or more episodes of local-regional therapy. The transplant programs can ask the review board to review cases in which they feel that local-regional therapy is contraindicated.

Proposed policy changes:

- Candidates who initially present with a single lesion between 2 and 3 cm must be treated with local-regional therapy in order to be eligible for automatic MELD exception.
- If the lesion is completely treated (Class 0) after 1 or more episodes of local-regional therapy, the candidate is not eligible for a standardized MELD exception until the lesion recurs or the candidate develops a new lesion.
- If the lesion persists or recurs (Class 5) after 1 or more episodes of local-regional therapy, the candidate is eligible for a standardized MELD exception.

The Committee estimates that about 300 candidates added to the waiting list each year would not be granted automatic priority under this proposed policy. The Committee proposes that these candidates with small, well-treated lesions likely do not require a liver transplant, and thus do not require HCC MELD exception points.

As described in the "Was this proposal changed in response to public comment?" section below, the Committee ultimately determined that the single small lesion criteria should be removed from the proposed policy.

[8] Mehta, et al. "Identification of Liver Transplant Candidates with Hepatocellular Carcinoma and Very Low Dropout Risk: Implications for the Current Organ Allocation Policy" *Liver Transplantation* 2013: 12: 1343-1353

**Downstaging**

The downstaging of HCC lesions involves decreasing the size of the lesion using local-regional treatment, specifically to reach the eligibility criteria for liver transplant. Successful downstaging of HCC to T2 criteria is associated with a low rate of HCC recurrence and excellent post-transplant survival, similar to those meeting T2 criteria without downstaging[9, 10]. The Subcommittee proposed expanding the criteria to allow more candidates to be eligible for automatic priority by defining a downstaging protocol in policy.

The proposed addition to current policy describes the eligibility criteria for inclusion in the downstaging protocol. Candidates meeting the criteria will be eligible for automatic priority following local-regional treatment, and their residual lesions fall within T2 criteria. After reaching T2 criteria, these candidates will have the same 6 month delay as candidates that initially present within T2.

Proposed policy changes:

- Candidates that meet one of the following criteria are eligible for inclusion in a downstaging protocol:
    - One lesion greater than 5 cm and less than or equal to 8 cm
    - Two or three lesions each less than 5 cm and total diameter of all lesions less than or equal to 8 cm
    - Four or five lesions each less than 3 cm and total diameter of all lesions less than or equal to 8 cm
- Candidates who are eligible and then complete local-regional therapy must be successfully downstaged into T2 criteria to receive a MELD exception.

**High Alpha-fetoprotein Threshold**

There is increasing evidence that clinical factors beyond lesion size and number are associated with a greater risk of HCC recurrence and poor post-transplant outcomes[11, 12]. The Subcommittee reviewed the use of alpha-fetoprotein (AFP) level as a criteria for eliminating the automatic priority for HCC candidates who demonstrate a high risk of poor outcomes after liver transplant. The AFP level is increasingly shown to predict poor outcomes, and recognized as a predictive marker for HCC recurrence. The Subcommittee discussed the evidence and their clinical experience to identify an AFP threshold for removing eligibility for an automatic approval of an HCC exception. UNOS staff performed a retrospective analysis using a Cox regression model of post-transplant mortality, adjusted for laboratory MELD at transplant.

[9] Yao, et al. “Downstaging of Hepatocellular Cancer Before Liver Transplant: Long-Term Outcome Compared to Tumors Within Milan Criteria” *Hepatology* 2015: 6: 1968-1977

[10] Ravaioli, et al. “Liver transplantation for hepatocellular carcinoma: results of downstaging in patients initially outside the Milan selection criteria” *Am J Transplant* 2008: 8(12): 2547-57

[11] Duvoux, et al. “Liver Transplantation for Hepatocellular Carcinoma: A Model Including Alpha-Fetoprotein Improves the Performance of Milan Criteria” *Gastroenterology* 2012: 143: 986-984

[12] Mehta, et al. “Moving Past “One Size (and Number) Fits All” in the Selection of Candidates With Hepatocellular Carcinoma for Liver Transplantation” *Liver Transplantation* 2013: 19: 1055-1058

**Figure 3. Distribution of AFP at Liver Transplant*, 2009-2014 (n=8232). *Primary, non-Status 1 deceased donor liver transplants for HCC.**

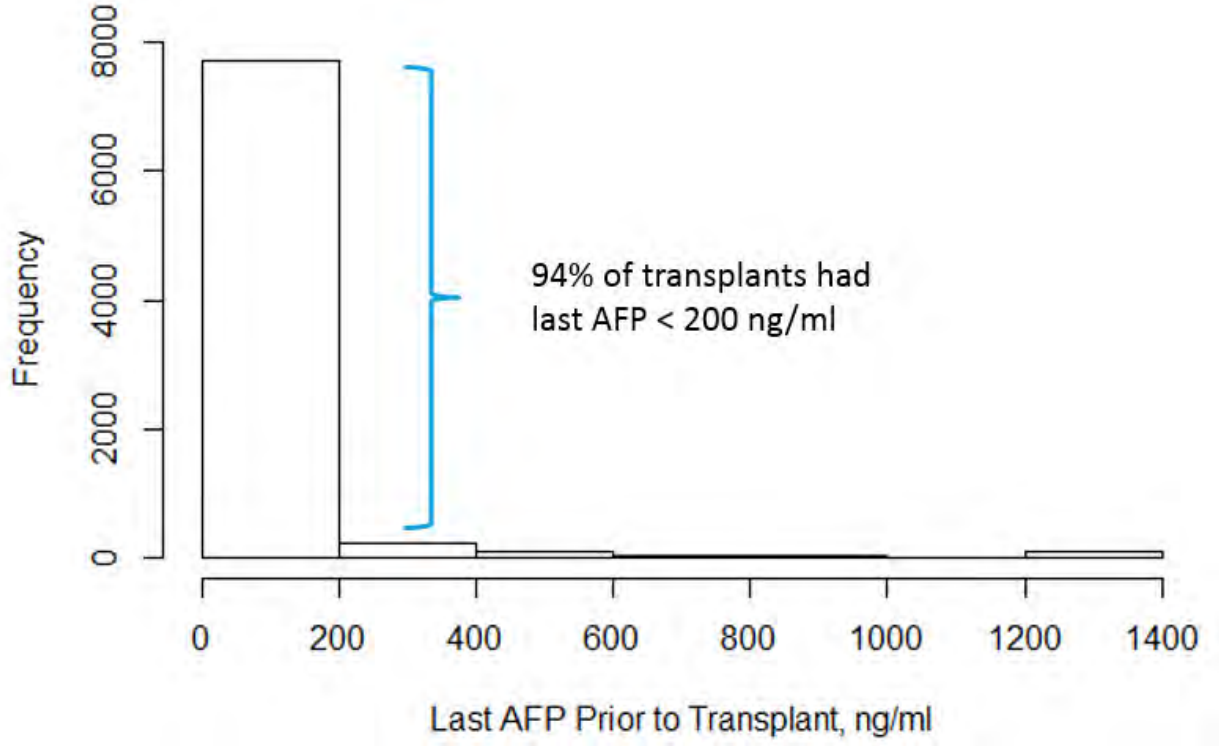
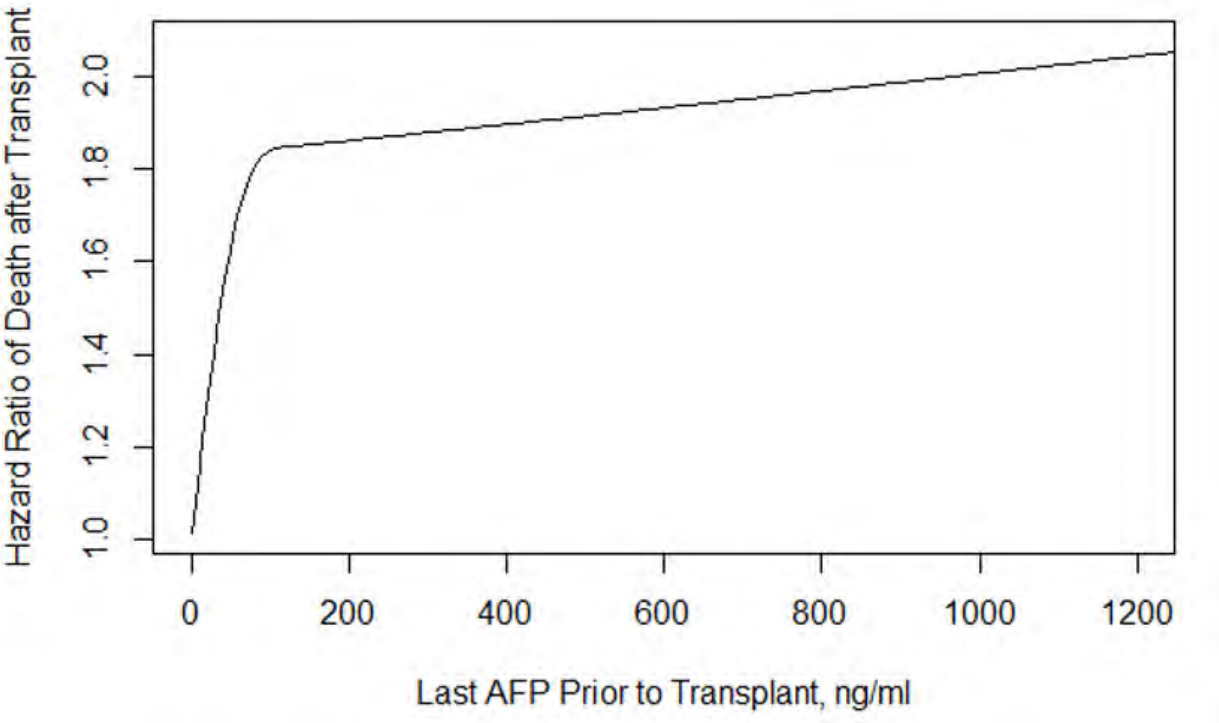



**Figure 4. Hazard Ratio of Mortality Following Liver Transplant* as a Function of AFP, 2009-2014 (n=8232). *Primary, non-status 1 deceased donor liver transplants for HCC adjusted for lab MELD at transplant.**



**Figures 3** and **4** show the distribution of AFP and its relationship with post-transplant mortality. The analysis shows that higher values of AFP are associated with an increased hazard ratio of mortality after transplant. Recipients whose final AFP value prior to transplant exceeded 1000 ng/ml had a hazard ratio of 2.45 [95% CI: 1.83, 3.27] compared to recipients whose AFP values never exceeded 1000 ng/ml.

An AFP greater than 1000 has been shown to be associated with poor post-transplant outcomes and a predictor of HCC recurrence[13]. The Subcommittee discussed the merits of several AFP thresholds, but ultimately decided that an AFP level greater than 1000 should remove eligibility for automatic priority. The Subcommittee further defined the eligibility for candidates whose AFP drops substantially following local-regional treatment.

Proposed policy changes:

- Candidates with lesions meeting T2 criteria but with an AFP greater than 1000 are not eligible for a standardized MELD exception.
    - If these lesions fall below 500 after local-regional therapy, the candidate is eligible for a standardized MELD exception
    - Candidates with an AFP level greater than or equal to 500 at any time point following local-regional therapy will be referred to the review board

**Extensions of HCC Exceptions**

Current policy does not require a candidate to meet criteria at the time of their extension. This creates a situation where a candidate would receive an extension of their MELD exception even if their lesion(s) no longer met T2 criteria. The Subcommittee ultimately decided that the transplant program must submit an updated exception request at the time of extension indicating that the candidate meets the initial eligibility criteria. This ensures that at the time of extension, candidates continue to meet the criteria that initially qualified them for MELD exception points.

**HCC Candidates under 18**

There are very few HCC candidates less than 18 years old. Due to the small population, the Subcommittee recommended that the new eligibility criteria described in this proposal for automatic priority do not apply to pediatric candidates.

If the program determines that the calculated MELD or PELD score does not reflect the candidate's medical urgency, candidates less than 18 years old upon submission of their initial exception request will be referred to the review board. Upon approval of the initial exception:

- Candidates 12 to 17 years old will be listed at a MELD score of 28.
- Candidates less than 12 years old will be listed at a PELD score of 41.

Pediatric candidates do not have to wait at their calculated MELD or PELD score for 6 months before receiving exception points. Their exception scores will also not be capped upon extension at MELD/PELD 34.

**Requirements for Dynamic Contrast-enhanced CT or MRI of the Liver**

Current policy provides recommendations on the imaging characteristics used for CT scans and MRIs performed for a HCC MELD or PELD score exception. The Subcommittee decided to remove the tables from policy that describe the recommended CT and MRI characteristics. These recommendations will be added to the forthcoming HCC guidance document, anticipated for public comment in January 2017. The proposed policy change to this section will reinforce the previous requirement that CT scans and MRIs performed for a HCC MELD or PELD score exception application request must be interpreted by a radiologist at a transplant hospital.

[13] Hameed, et al. "Alpha-Fetoprotein Level > 1000 ng/mL as an Exclusion Criterion for Liver Transplantation in Patients With Hepatocellular Carcinoma Meeting the Milan Criteria" *Liver Transplantation* 2014: 20: 945-951

# Was this proposal changed in response to public comment?

Yes, in response to public comment feedback, the Committee made one post-public comment change to the originally proposed policy changes, and voted (17-support, 0-oppose, 0-absentions) to send the modified proposal to the OPTN/UNOS Board of Directors for consideration during its December 2016 meeting.

**Post-public Comment Change**
The Committee voted (17-support, 0-oppose, 0-absentions) to remove the proposed single small lesion criteria from OPTN Policy 9.3.F *Candidates with Hepatocellular Carcinoma (HCC).* The Committee agreed to make this change to the proposal in response to public comment feedback that indicated strong opposition to the proposed single small lesion criteria. The Committee's intention with the proposed single small lesion criteria was to balance priority between HCC and non-HCC candidates by reducing priority for individuals with HCC that exhibit a low-risk of waitlist dropout due to disease progression or waitlist mortality. The proposed single small lesion criteria represented the majority of opposition during public comment, specifically at the regional meetings. The opposition in public comment focused on the difficulty of having a radiologist to confirm the proposed definitions of treated and new lesions and concern that the proposed policy could influence centers to intentionally under-treat single small lesions in order to meet criteria for automatic approval of an HCC exception.

The Committee discussed feedback regarding the logistics involved in confirming treatment of single small lesions. The Committee did not intend to add complexity to the process and discussed the reality that it is difficult to create a national definition of "completely treated" due to variation in radiology practice among centers. The Committee appreciates the public comment that expressed concern with the potential negative impact on treatment behavior due to the proposed policy. The Committee had not considered that centers might intentionally under-treat single small lesions in order to meet the T2 requirements and receive an automatic HCC exception. The Committee discussed this scenario at length and agreed that it is unlikely that the proposed policy would influence clinical treatment, however, the possibility is still an unintended effect of the proposed policy.

The Committee agreed that ideally the single small lesion criteria would reduce priority for HCC candidates that likely would not recur following treatment, however it may be "a little early" for such a change. As such, the Committee ultimately agreed to remove the proposed single small lesion criteria as a post-public comment modification.

**Response to Other Public Comment**
The proposal also received additional feedback regarding the proposed downstaging criteria and AFP criteria that did not prompt post-public comment modifications.

The Committee discussed the feedback on the proposed downstaging criteria. Seven of the regions supported the proposed downstaging criteria as written, with others expressing concern that the proposed criteria were too restrictive, and conversely, that the proposed criteria were too inclusive and the data for 4 or 5 lesions were inadequate. The Committee discussed both viewpoints and reiterated that the proposed policy only applies to automatic exceptions and candidates outside of the proposed criteria will still be able to seek exception points through the review board. Currently, there is not standardized downstaging criteria in policy although many regions approve exceptions for downstaged candidates. The Committee further discussed the need for mandatory reporting of post-transplant pathology forms to ensure accurate data related to HCC to judge the appropriateness of the proposed downstaging criteria. The Committee ultimately voted (17-support, 0-opposed, 0-abstentions) to send the downstaging criteria policy to the OPTN/UNOS Board of Directors as written with the provision that a future project by the Committee would address follow-up requirements and a definition of successful downstaging.

The Committee discussed the public comment on the proposed high AFP criteria. The majority of the regions (9) approved the proposed AFP criteria as written, with some expressing the need for the qualifying AFP score to be maintained for a period of time prior to granting the automatic exception. The

Committee stated that the previously approved cap and delay policy from 2015 addresses this concern by requiring candidates to be registered at their calculated MELD score for the first three months and for the first three-month extension, as long as the candidate continues to meet the policy criteria. The Committee voted (9-support, 6-opposed, 1-abstention) to send the AFP criteria policy as written to the OPTN/UNOS Board of Directors.

# Which populations are impacted by this proposal?

This proposal has the potential to effect all of the 14,629 candidates on the liver waiting list. The proposal will have the greatest impact on the 976 existing HCC candidates and potential candidates requesting an HCC exception. If approved, this proposal has the potential to decrease access to additional priority for candidates who do not meet the eligibility criteria described. However, this proposal would expand eligibility for priority to candidates who meet the downstaging protocol described.

# How does this proposal impact the OPTN Strategic Plan?

1. *Increase the number of transplants:* There is no impact on this goal.

2. *Improve equity in access to transplants:* The primary goal of this proposal is to modify the eligibility criteria for automatic priority for HCC exceptions, to increase equity in access to transplant between HCC candidates and non-HCC candidates, as well as equity among HCC candidates. This proposal establishes equitable and medically appropriate prioritization for those candidates with increased risk of waitlist mortality.

3. *Improve waitlisted patient, living donor, and transplant recipient outcomes:* The Committee expects that the new downstaging protocol criteria will improve waitlisted patient outcomes by providing priority to candidates who previously did not automatically qualify.

4. *Promote living donor and transplant recipient safety:* There is no impact on this goal.

5. *Promote the efficient management of the OPTN:* The Committee expects the improved criteria for automatic approval of HCC exceptions will remove some of the burden of the review boards. This is reinforced by the potential implementation of a National Liver Review Board (NLRB).

# How will the OPTN implement this proposal?

If this proposal is approved, the OPTN will take on a significant level of effort to implement the proposal. UNOS IT provides cost estimates for each public comment proposal that will require programming to implement. The estimates can be small (108-419 hrs.), medium (420-749 hrs.), large (750-1,649 hrs.), very large (1,650-3,999), or enterprise (4,000-8,000). The estimate for this proposal is Large. Due to the programming effort, the new policy would not become effective right away if approved. The implementation of this project is not dependent on the two other Committee projects (discussed in “Why should you support this proposal?”).

The Committee finalized the implementation plan for the proposal during its in-person meeting on October 24, 2016. Regarding the proposed policy changes, the options were that 1) at time of implementation all existing HCC candidates that do not meet the new criteria would lose their existing exception or 2) upon implementation candidates would need to meet the new criteria at their next exception extension. The Committee discussed the options and were decidedly in favor of the second option. The Committee voted that upon implementation, existing HCC candidates would maintain their exception until their next extension, at which time they would need to meet the new criteria.

Because of the significant impact of these policy changes, the OPTN will offer learning opportunities to specific audiences to impart knowledge, awareness, and compliance related to policy and system changes in advance of implementation. UNOS Communications and Instructional Innovations staff will work together to deliver communications to the membership when instructional offerings are available. Members should take advantage of relevant educational opportunities offered through UNOS.

# How will members implement this proposal?

## Transplant Hospitals

Liver programs will take on a significant level of effort to prepare for implementation of the new policy. Members will need to be aware of the new criteria for automatic approval of HCC exception requests. To be eligible for an exception for HCC, members will be required to document new information in their candidates' *MELD/PELD Exception Score Request Form* for the candidate's initial request. Members will also need to document new information in their candidates' *MELD/PELD Exception Score Request Form* to receive an extension on their HCC exception.

Resources should be allocated to ensure that the proposed criteria for automatic approval of HCC exception requests is understood by staff. This may involve training for staff and/or changes to current hospital processes regarding HCC Exception Requests. Transplants hospitals should specifically comment on the fiscal implications of the proposed policy changes.

# Will this proposal require members to submit additional data?

The proposed policy adds an additional requirement that transplant programs indicate whether the candidate has undergone local-regional treatment during the initial assessment of a candidate prior to requesting a standardized HCC exception. However, this is already a required field in the *MELD/PELD Exception Score Request Form*. Additionally, the proposed policy requires transplant centers to provide the candidate's alpha-fetoprotein (AFP) level in the *MELD/PELD Exception Score Request Form* at the time they request an extension of the exception score. However, this is already a required field in the *MELD/PELD Exception Score Request Form*.

# How will members be evaluated for compliance with this proposal?

The proposed language would not change the current routine monitoring of OPTN members. Any data entered in UNet℠ is still subject to OPTN review, and members are still required to provide documentation as requested.

# How will the sponsoring Committee evaluate whether this proposal was successful post implementation?

The OPTN will assess the impact of these policy changes using a pre vs. post analysis at 6-month intervals, up to 24 months after implementation. Analyses beyond 24 months will be performed at the request of the Committee. Several metrics will be monitored, including, but not limited to, the following:

Waiting List Metrics

- Number of approved exceptions for HCC
    - Meeting criteria
    - Outside of criteria

- Candidate characteristics
    - Demographics
    - Tumor characteristics
    - AFP value
    - Local-regional treatments
    - Other characteristics as possible

- Removal rates for death, too sick, and transplant for HCC compared to non-HCC candidates

Transplant Metrics

- Number of approved exceptions for HCC
    - Meeting criteria
    - Outside of criteria

- Recipient characteristics
    - Demographics
    - Tumor characteristics
    - AFP
    - Local-regional treatments
    - Other characteristics as possible

- Graft and patient survival
- HCC recurrence after transplant

Note that graft and patient survival rates and recurrence rates require sufficient follow-up data in order to report meaningful results. Such metrics are typically not provided prior to 1 year following implementation.

# Policy or Bylaws Language

Proposed new language is underlined (example) and language that is proposed for removal is struck through (~~example~~).

**RESOLVED, that changes to Policy *9.3.F (Candidates with Hepatocellular Carcinoma (HCC))*, as set forth below, are hereby approved, effective pending implementation and notice to OPTN members.**

## 9.3.F Candidates with Hepatocellular Carcinoma (HCC)

~~Upon submission of the required information to the OPTN Contractor, candidates with Hepatocellular Carcinoma (HCC) that have stage T2 lesions and meet the criteria according to *Policies 9.3.F.i* through *vi* below will be listed at their calculated MELD or PELD score.~~
Upon submission of the first exception request, a candidate that is:

- At least 18 years old with Hepatocellular Carcinoma (HCC) and meets the criteria according to Policies *9.3.F.i* through *vi* will receive a MELD score according to *Table 9-4*: *Exception Score Assignment for Candidates at least 18 Years Old upon Submission of Initial Exception Request*.
- Twelve to 17 years old, and the Regional Review Board (RRB) has determined that the candidate's calculated MELD score does not reflect the candidate's medical urgency, will be listed at a MELD score of 28.
- Less than 12 years old, and the RRB has determined that the candidate's calculated MELD score does not reflect the candidate's medical urgency, will be listed at a PELD score of 41.

### 9.3.F.ii ~~Initial Assessment for Registration~~ and Requirements for HCC Exception Requests

Prior to applying for a standardized MELD exception, the candidate must undergo a thorough assessment that includes *all* of the following:

1. An evaluation of the number and size of ~~tumors~~ lesions before local-regional therapy that meet Class 5 criteria using a dynamic contrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI)
2. ~~A CT or MRI to rule out any extrahepatic spread or macrovascular involvement~~ A CT of the chest to rule out metastatic disease
3. ~~A CT of the chest to rule out metastatic disease~~ A CT or MRI to rule out any other sites of extrahepatic spread or macrovascular involvement
4. An indication that the candidate is not eligible for resection
5. An indication whether the candidate has undergone local-regional therapy
~~5~~6. The candidate's alpha-fetoprotein (AFP) level

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.

For those candidates who receive a liver transplant while receiving additional priority under the HCC exception criteria, the transplant hospital must submit the *Post-Transplant Explant Pathology Form* to the OPTN Contractor within 60 days of transplant. If the pathology report does not show evidence of HCC, the transplant hospital must also submit documentation or imaging studies confirming HCC at the time of assignment. The Liver and Intestinal Organ Transplantation Committee will review a transplant hospital when more than 10 percent of the HCC cases in a one-

year period are not supported by the required pathologic confirmation or submission of clinical information.

### 9.3.F.ii Eligible Candidates Definition of T2 Lesions

~~Stage T2 lesions include *any* of the following:~~ Candidates who initially present with T2 HCC lesions are eligible for a standardized MELD exception if they have an alpha-fetoprotein (AFP) level less than 1000 ng/mL and *either* of the following:

- One lesion greater than or equal to 2 cm and less than or equal to 5 cm in size.
- Two or three lesions each greater than or equal to 1 cm and less than or equal to 3 cm in size.

### 9.3.F.iii Lesions Eligible for Downstaging Protocols

Candidates are eligible for inclusion in a downstaging protocol if they initially present with lesions that meet *one* of the following criteria:

- One lesion greater than 5 cm and less than or equal to 8 cm
- Two or three lesions each less than 5 cm and a total diameter of all lesions less than or equal to 8 cm
- Four or five lesions each less than 3 cm and a total diameter of all lesions less than or equal to 8 cm

For candidates who meet the downstaging criteria and then complete local-regional therapy, their residual lesions must subsequently meet the requirements for T2 lesions according to *Policy 9.3.F.ii: Eligible Candidates Definition of T2 Lesions* to be eligible for a standardized MELD exception. Downstaging to meet eligibility requirements for T2 lesions must be demonstrated by CT or MRI performed after local-regional treatment. Candidates with lesions that do not initially meet the downstaging protocol inclusion criteria who are later downstaged and then meet eligibility for T2 lesions are not automatically eligible for a standardized MELD exception and must be referred to the RRB for consideration of a MELD exception.

### 9.3.F.iv Candidates with Alpha-fetoprotein (AFP) Levels Greater than 1000

Candidates with lesions meeting T2 criteria according to *Policy 9.3.F.ii Eligible Candidates Definition of T2 Lesions* but with an alpha-fetoprotein (AFP) level greater than 1000 ng/mL may be treated with local-regional therapy. If the candidate's AFP level falls below 500 ng/mL after treatment, they are eligible for a standardized MELD exception. Candidates with an AFP level greater or equal to 500 ng/mL following local-regional therapy at any time must be referred to the RRB for consideration of a MELD exception.

### 9.3.F.~~iii~~iv Requirements~~commended Minimum Specifications~~ for Dynamic Contrast-enhanced CT or MRI of the Liver

CT scans and MRIs performed for a Hepatocellular Carcinoma (HCC) MELD or PELD score exception ~~application~~ request ~~should meet the criteria in Table 9-3 and Table 9-4 and~~ must be interpreted by a radiologist at a transplant hospital. If the scan is inadequate or incomplete then the lesion will be classified as OPTN Class 0 and imaging must be repeated or completed to receive an HCC MELD~~/~~ or PELD exception.

**Table 9-3: 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<br>2. Portal venous phase: portal vein enhanced, peak liver parenchymal enhancement, beginning contrast enhancement of hepatic veins<br>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 9-4: 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.<br>2. Late arterial phase: artery fully enhanced, beginning contrast enhancement of portal vein.<br>3. Portal venous phase: portal vein enhanced, peak liver parenchymal enhancement, beginning contrast enhancement of hepatic veins.<br>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. |

| ~~Feature~~ | ~~MRIs should meet the below specifications:~~ |
|---|---|
| ~~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 breathholding before and during scan.~~ |

## 9.3.F.~~iv~~vi Imaging Requirements for Class 5 Lesions

~~Nodules~~ Lesions found on images of cirrhotic livers are classified according to *Table 9-~~5~~3*. ~~Use the largest dimension of each tumor to report the size of Hepatocellular Carcinoma (HCC) lesions. Nodules less than 1 cm are indeterminate and are not eligible for additional priority.~~

**Table 9-~~5~~3: Classification System for ~~Nodules~~Lesions Seen on Imaging of Cirrhotic Livers**

| Class | Description |
|---|---|
| **0** | Incomplete or technically inadequate study |
| **5A** | Must meet *all* of the following:<br>1. ~~Single nodule~~ Maximum diameter of at least ≥1 cm and less than~~<~~ 2 cm~~. The maximum diameter of lesions should be~~, as measured on late arterial or portal phase images.<br>2. Increased contrast enhancement, relative to hepatic parenchyma, on late arterial phase ~~(relative to hepatic parenchyma)~~.<br>3. *Either* of the following:<br>• Washout during the later contrast phases and peripheral rim enhancement ~~(capsule/pseudocapsule)~~ on delayed phase ~~*or*~~<br>• ~~a b~~Biopsy ~~(A pre-listing biopsy is not mandatory.)~~ |
| **5A-g ~~(growth)~~** | Must meet *all* of the following:<br>1. ~~Single nodule~~ Maximum diameter of at least ≥1 cm and less than~~<~~ 2 cm~~. The maximum diameter of lesions should be~~, as measured on late arterial or portal phase images.<br>2. Increased contrast enhancement, relative to hepatic parenchyma, on late arterial phase ~~(relative to hepatic parenchyma)~~.<br>3. ~~Growth (m~~Maximum diameter increase~~) by~~ of at least 50%~~ or more~~ documented on serial MRI or CT obtained ≦ at least 6 months apart. ~~Growth criteria do not apply to ablated lesions.~~ |
| **5B** | Must meet *all* of the following:<br>1. ~~Single nodule~~ Maximum diameter of at least ≥ 2 cm and less than or equal to ≦ 5 cm~~. The maximum diameter of lesions should be~~, as measured on late arterial or portal phase images.<br>2. Increased contrast enhancement, relative to hepatic parenchyma, on late hepatic arterial images ~~(relative to hepatic parenchyma)~~.<br>3. *One* of the following:<br>a. Washout on portal venous/delayed phase.<br>b. ~~Late capsule or pseudocapsule~~ Peripheral rim enhancement.<br>c. ~~Growth (m~~Maximum diameter increase, in the absence of ~~ablative therapy)~~ ablation, by 50% or more and documented on serial MRI or CT obtained ≦ at least 6 months apart. Serial imaging and measurements must be performed on corresponding contrast phases ~~with the same modality preferred. Growth criteria do not apply to previously ablated lesions~~.<br>d. Biopsy. ~~A pre-listing biopsy is not mandatory.~~ |

| Class | Description |
|---|---|
| **5T ~~(Treated)~~** | Any ~~OPTN~~ Class ~~5~~ 5A, 5A-g, 5B ~~or biopsy-proven HCC~~ lesion that was automatically approved upon initial ~~application~~ request or extension and has subsequently ~~undergone loco-regional treatment~~been ablated. ~~OPTN Class 5T nodules qualify for continued priority points based on the pre-treatment classification of the nodules and are defined as:~~<br><br>~~Past loco-regional treatment for HCC (OPTN Class 5 lesion or biopsy proven prior to ablation).~~<br><br>~~Evidence of persistent/recurrent HCC such as, but not limited to, nodular or crescentic extra-zonal or intra-zonal enhancing tissue on late arterial imaging (relative to hepatic parenchyma) may be present.~~ |
| ~~**5X**~~ | ~~Lesions that meet radiologic criteria for HCC but are *Eligible Candidates Definition of T2 Lesions* outside stage T2 as defined above will be considered Class 5X and are not eligible for automatic exception points.~~ |

### ~~9.3.F.v HCC Lesions Eligible for Automatic Upgrade~~

~~Individual OPTN 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 OPTN Class 5A nodules that meet stage T2 criteria as described above are eligible for automatic priority.~~

### ~~9.3.F.vii Candidates Not Meeting Criteria (Class 5X)~~

~~A candidate not meeting any of the above criteria will not be given a standardized MELD/PELD exception and must be registered at the calculated MELD or PELD score with no additional priority given because of the HCC diagnosis. All such candidates with HCC, including those with downsized tumors whose original or presenting tumor was greater than a stage T2, must be referred to the applicable RRB for prospective review in order to receive additional priority.~~

### 9.3.F.vi~~i~~ Extensions of HCC Exceptions

In order for a candidate to maintain an ~~HCC~~ approved exception for HCC, the transplant program must submit an updated MELD/PELD Exception Score Request Form ~~MELD/PELD exception application~~ every three months. The candidate will receive the additional priority as long as they continue to meet initial eligibility criteria. ~~until transplanted or is found unsuitable for transplantation based on the HCC progression.~~

Exception scores for candidates that were at least 18 years old upon submission of their initial exception request are assigned according to *Table 9-4* below. The candidate's MELD exception score will be capped at 34.

~~Upon submission of the first extension, the candidate will be listed at the calculated MELD/PELD score. Upon submission of the second extension, the candidate will be assigned a MELD/PELD score equivalent to a 35 percent risk of 3-month mortality (MELD 28/PELD 41). For each subsequent extension, the candidate will receive~~

~~additional MELD or PELD points equivalent to a 10 percentage point increase in the candidate's mortality risk every three months.~~

~~The HCC exception score will be capped at 34. Upon implementation, candidates with HCC exception scores greater than 34 will receive a score of 34 for their remaining HCC exception extensions. Candidates with scores greater than 34 at the time of implementation may be referred to the RRB if they demonstrate the need for higher priority.~~

**Table 9-4: Exception Score Assignment for Candidates at least 18 Years Old upon Submission of Initial Exception Request**

| Exception Request | MELD Exception Score |
|---|---|
| **Initial** | Calculated MELD score |
| **1st extension** | Calculated MELD score |
| **2nd extension** | 28 |
| **3rd extension** | 30 |
| **4th extension** | 32 |
| **5th extension and all subsequent extensions** | 34 |

If a candidate was less than 18 years old upon submission of their initial exception request, the candidate will receive additional MELD or PELD points equivalent to a 10 percentage point increase in the candidate's mortality risk every three months according to *Table 9-5* below.

**Table 9-5: First Seven Exception Score Assignments for Candidates less than 18 Years Old upon Submission of Initial Exception Request**

| Exception Request | MELD or PELD Exception Score |
|---|---|
| **Initial** | MELD 28 or PELD 41 |
| **1st extension** | MELD 30 or PELD 44 |
| **2nd extension** | MELD 32 or PELD 47 |
| **3rd extension** | MELD 34 or PELD 50 |
| **4th extension** | MELD 36 or PELD 53 |
| **5th extension** | MELD 39 or PELD 56 |
| **6th extension** | MELD 40 or PELD 60 |

To receive the extension, the transplant program must submit an updated MELD/PELD Exception Score Request Form ~~MELD exception~~ that contains all of the following:

1. ~~Submit an Hepatocellular Carcinoma (HCC) MELD/PELD score exception application with a~~An updated narrative
2. Document the tumor using a CT or MRI
3. Specify the type of treatment if the number of tumors decreased since the last ~~application~~ request~~.~~
4. The candidate's alpha-fetoprotein (AFP) level

~~Invasive studies such as biopsies or ablative procedures and repeated chest CT scans are not required after the initial application is approved.~~ If a candidate's tumors have been resected since the previous ~~application~~ request, then the transplant

program must submit an updated MELD/PELD Exception Score Request Form ~~the extension application~~ to ~~its~~ the RRB for prospective review.

Candidates with Class 5T lesions will receive a MELD or PELD equivalent to a 10 percentage point increase in the candidate's mortality risk every three months, without RRB review, even if the estimated size of residual viable tumors falls below stage T2 criteria due to ablative therapy.

### 9.3.F.viii Appeal for Candidates not Meeting Criteria

If the RRB denies the initial HCC MELD/PELD Exception Score Request Form ~~exception application~~, the transplant program may appeal to the RRB, but the candidate will not receive the additional MELD or PELD priority until approved by the RRB. The RRB ~~will~~ may refer the matter to the Liver and Intestinal Organ Transplantation Committee for further review and possible action if the RRB finds the transplant program to be noncompliant with these Policies.

~~Applications~~ Requests and appeals not resolved by the RRB within 21 days will be referred to the Liver and Intestinal Organ Transplantation Committee for review. The Liver and Intestinal Organ Transplantation Committee may refer these matters to the MPSC for appropriate action according to *Appendix L* of the OPTN Bylaws.

### ~~9.3.F.ix Compliance Monitoring~~

~~The transplant hospital must maintain documentation of the radiologic characteristics of each OPTN Class 5 nodule. If growth criteria are used to classify a nodule as HCC, the radiology report must contain the prior and current dates of imaging, type of imaging and measurements of the nodule.~~

~~For those candidates who receive a liver transplant while receiving additional priority under the HCC exception criteria, the transplant hospital must submit the *Post-Transplant Explant Pathology Form* to the OPTN Contractor within 60 days of transplant. If the pathology report does not show evidence of HCC, the transplant hospital must also submit documentation or imaging studies confirming HCC at the time of assignment. The Liver and Intestinal Organ Transplantation Committee will review a transplant hospital when more than 10 percent of the HCC cases in a one-year period are not supported by the required pathologic confirmation or submission of clinical information.~~

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