New OPTN/UNOS Policy for Liver Transplant Allocation: Standardization of Liver Imaging, Diagnosis, Classification, and Reporting of Hepatocellular Carcinoma

As background for this article, one must consider that, through 2011, 16,857 patients were awaiting liver transplantation (LT) (1), while 5618 adults actually received a liver (2). In light of this long-standing organ shortage, evaluating patients and determining those most in need of a liver transplant and allocation of resources are important issues that have changed over time. Patients with hepatocellular carcinoma (HCC) may receive priority on the transplant list if they meet certain criteria. The purpose of this editorial is to explain new policies on how imaging studies in these patients must be conducted and how findings must be reported.

HCC was not a widely accepted indication during the first 2 decades of routine LT surgery in the United States. However, this changed following publication of the landmark study by Mazzaferro and co-workers (3), reporting a high overall and recurrence-free survival rate 4 years after LT in patients who had met the restrictive Milan criteria, which defined early, limited stage disease as one HCC of 5 cm or smaller in diameter or up to three HCCs of 3 cm or smaller in diameter each. These criteria were widely validated and prompted the view that LT was recommended as an effective treatment for early-stage unresectable HCC (3). Access to transplantation in the United States for liver cancer patients remained a problem at that time, as the allocation system was based on medical status and waiting time. In 2002, the so-called waiting list dropout, the OPTN/UNOS policy increases


Carcinoma

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priority for candidates with HCC that are within the Milan criteria by assigning a MELD exception score, equating the risk of tumor progression beyond this limit with the risk of death in patients with chronic liver disease without HCC (8). Patients with HCC that are within the Milan criteria receive MELD scores that begin at a score of 22 and increase in a stepwise fashion (equivalent to additional 10% increase in candidate mortality) every 3 months after the results of repeat imaging with either computed tomography (CT) or magnetic resonance (MR) imaging have confirmed that criteria are still met. This procedure is repeated every 3 months until the candidate either undergoes transplantation or disease progresses beyond Milan criteria (4). In 2011, 1369 (24.3%) candidates underwent LT with MELD exception points. A biopsy was available in less than 5% of these patients. In the remainder, HCC diagnosis was based on imaging findings alone, underscoring the critical importance of optimal CT or MR imaging (A. Harper, UNOS, written communication, February 24, 2012).

The initial 2002 UNOS liver allocation policy included the following simplistic imaging-specific language: “the candidate must have... a vascular blush corresponding to the area of suspicion seen on... imaging studies [italics mine]” (4). Four years later, Freeman et al (9) undertook a retrospective analysis of UNOS data of patients with HCC who had undergone transplantation. Radiologic stage at listing was compared with pathologic stage in 789 LT patients with no ablative treatment. The authors found that radiologic stage equaled pathologic stage in only of 44.1% and concluded that prevailing liver allocation practice was unacceptable and future imaging-based liver allocation policy should require more accurate modalities and stricter diagnostic criteria for HCC diagnosis.

UNOS Consensus Conference: Process of Creation of a New UNOS Imaging Policy

A consensus conference was organized by the OPTN/UNOS Liver and Intestinal Committee in 2008 to better characterize the long-term outcome of LT for patients with HCC and to assess the practice of assigning increased priority for candidates with early-stage HCC. More than 180 world leaders in LT participated, and these world leaders included representatives from 50 of the most active U.S. LT programs and experts in pathology, radiology, and oncology. Objectives included development of more specific imaging criteria for HCC diagnosis and classification, as well as standardization of the report language required by UNOS to qualify LT candidates for automatic HCC MELD exception points. Participants agreed that any new allocation policy should attempt to create a level playing field for HCC and non-HCC patients with regard to risk of waiting list dropout, transplantation rates, and posttransplantation outcomes. Members of the imaging subgroup (Appendix E1 [online]) participated in an extensive premeeting effort to ascertain and consider prevailing clinical liver imaging practice. In conjunction with deliberations at the meeting, a policy revision for liver imaging was developed. Subsequently, input on this draft policy was solicited through an open national public online comment period, as well as directly from all UNOS regions and committees and the transplant societies. The OPTN/UNOS Board of Directors adopted the amended policy in November 2011. Implementation is pending finalization of the Web-based data entry system. Centers currently have a short remaining time window to incorporate the new policy into their clinical routine to ensure future compliance.

The New OPTN/UNOS Policy for LT in Patients with HCC

The new policy is designed to optimize and standardize the performance of high-quality imaging across a spectrum of diverse imaging facilities (4). Resulting images must be suitable to evaluate those qualitative and quantitative image findings relevant for the diagnosis of HCC. Five major issues are addressed: (a) recommended minimum technical specifications for hardware for CT scanners and MR imaging units, (b) recommended dynamic contrast material–enhanced liver imaging protocols, (c) mandatory diagnostic criteria for HCC on images, (d) reporting requirements (standardized language, specifically for HCC classification), and (e) requirement for interpretation of images at an OPTN-approved transplantation center.

The following comments are intended to provide background information. The explicit language of the policy is available online (4) and is summarized in Tables 1–3.

Recommended Minimum Technical Specifications for Dynamic Contrast-enhanced CT of the Liver

Table 1 details the specifications for dynamic contrast-enhanced CT of the liver. The imaging work group agreed that an eight–detector row multidetector CT scanner was the minimum acceptable machine type affording single-breath-hold acquisition of the entire liver during a particular contrast phase at an acceptable reconstructed image resolution. Nonenhanced imaging is considered optional. Emphasis is placed on adequate, weight-based dose of the contrast agent, sufficient flow rate of the contrast agent bolus, and meticulous timing of acquisition of the dynamic contrast-enhanced imaging series, specifically late arterial phase imaging. Qualitative hallmarks of correctly timed contrast-enhanced phases are provided in the policy. Bolus tracking is recommended to maximize HCC detection.

Recommended Minimum Technical Specifications for Dynamic Contrast-enhanced MR Imaging of the Liver

Table 2 delineates the specifications for dynamic contrast-enhanced MR imaging of the liver. High-field-strength magnets of 1.5 T or greater are required to obtain contemporary, high-quality liver imaging. The previously stated importance of properly timed imaging phases also apply to MR imaging. Because diagnostic criteria of the classification are based on the appearance of liver lesions in the dynamic phases of contrast-enhanced imaging, extracellular gadolinium-based contrast
Table 1

<table>
<thead>
<tr>
<th>Feature</th>
<th>Specification</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scanner type</td>
<td>Multi–detector row scanner</td>
<td></td>
</tr>
<tr>
<td>Detector type</td>
<td>Minimum of 8 detector rows</td>
<td>Need to be able to image entire liver during brief late arterial phase time window</td>
</tr>
<tr>
<td>Reconstructed section thickness</td>
<td>Minimum of 5-mm reconstructed section thickness</td>
<td>Thinner sections are preferable, especially if multiplanar reconstructions are obtained</td>
</tr>
<tr>
<td>Injector</td>
<td>Power injector, preferably dual-chamber injector with saline flush</td>
<td>Bolus tracking recommended</td>
</tr>
<tr>
<td>Contrast agent injection rate</td>
<td>Minimum, 3 mL/sec; better, 4–6 mL/sec with minimum of 300 mg iodine per milliliter or higher, for dose of 1.5 mL/kg of body weight</td>
<td></td>
</tr>
<tr>
<td>Mandatory dynamic phases during contrast-enhanced CT*</td>
<td>Late arterial phase, portal venous phase, and delayed phase</td>
<td>Artery fully enhanced, beginning contrast enhancement of portal vein; portal vein enhanced, peak liver parenchymal enhancement, beginning contrast enhancement of hepatic veins; variable appearance, &gt;120 sec after initial injection of contrast agent</td>
</tr>
<tr>
<td>Dynamic phases (timing)</td>
<td>Bolus tracking or timing bolus recommended for accurate timing</td>
<td></td>
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</tbody>
</table>

* Comments describe typical hallmark image features.

Table 2

<table>
<thead>
<tr>
<th>Feature</th>
<th>Specification</th>
<th>Comment</th>
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<tbody>
<tr>
<td>MR unit type</td>
<td>1.5-T or greater main magnetic field strength</td>
<td>Low-field-strength magnets not suitable</td>
</tr>
<tr>
<td>Coil type</td>
<td>Phased-array multichannel torso coil</td>
<td>Unless patient-related factors preclude use (eg, body habitus)</td>
</tr>
<tr>
<td>Minimum sequences</td>
<td>Nonenhanced and dynamic gadolinium–enhanced T1–weighted GRE sequence (3D preferable), T2–weighted (with and without fat saturation), T1–weighted in- and opposed-phase imaging</td>
<td></td>
</tr>
<tr>
<td>Injector</td>
<td>Dual-chamber power injector</td>
<td>Bolus tracking recommended</td>
</tr>
<tr>
<td>Contrast agent injection rate</td>
<td>For extracellular gadolinium chelate that does not have dominant biliary excretion, 2–3 mL/sec</td>
<td>Preferably resulting in vendor-recommended total dose</td>
</tr>
<tr>
<td>Mandatory dynamic phases at contrast-enhanced MR imaging*</td>
<td>Nonenhanced T1 weighted, late arterial phase, portal venous phase, delayed phase</td>
<td>For nonenhanced T1 weighted, do not change imaging parameters for contrast-enhanced imaging; for late arterial phase, artery fully enhanced, beginning contrast enhancement of portal vein; for portal venous phase, portal vein enhanced, peak liver parenchymal enhancement, beginning contrast enhancement of hepatic veins; for delayed phase, variable appearance, &gt;120 sec after initial injection of contrast agent</td>
</tr>
<tr>
<td>Dynamic phases, timing</td>
<td>Use of a bolus-tracking method for timing contrast agent arrival for late arterial phase imaging is preferable; portal venous phase (35–55 sec after initiation of late arterial phase imaging); delayed phase (120–180 sec after initial contrast agent injection)</td>
<td></td>
</tr>
<tr>
<td>Section thickness</td>
<td>For dynamic series, 5 mm or less; for other imaging, 8 mm or less</td>
<td></td>
</tr>
<tr>
<td>Breath holding</td>
<td>Maximum length of series requiring breath hold should be about 20 sec, with a minimum matrix of 128 × 256</td>
<td>Compliance with breath-hold instructions is very important; technologists need to understand the importance of patient instruction before and during imaging</td>
</tr>
</tbody>
</table>

Note.—GRE = gradient echo, 3D = three-dimensional.
* Comments describe typical hallmark image features.
agents without dominant biliary excretion were recommended (10–13). Centers may use other contrast agents, such as gadome- state disodium (Eovist; Bayer Healthcare Pharmaceuticals, Wayne, NJ), which ad-
ditionally allows hepatobiliary phase imaging (14). The hepatobiliary phase imaging
appearance of HCC was not included in the policy because the consensus meeting
took place shortly after Food and Drug Administration approval of the agent for
clinical use in the United States (July 9, 2008) and radiologists from the United
States had minimal or no experience with the agent at the time of the policy
generation. The capability of hepatobiliary phase imaging agents to aid accurate
diagnosis and staging of HCC (compared with expi anxiety pathologic analysis) currently
remains the subject of active scientific in-
vestigation and validation.

**Recommended Dynamic Contrast-
Enhanced Liver Imaging Protocols**

Protocol requirements are embed-
ded into the imaging unit specific tech-
nical recommendations of the policy (Tables 1, 2) and stress ade-
quate, weight-based dose of the con-
trast agent, sufficient flow rate of the
contrast agent bolus, and meticulous
timing of acquisition of the dynamic
contrast-enhanced image series.

**Mandatory Diagnostic Criteria for HCC
Classification in Patients with Chronic
Liver Disease**

Table 3 describes the mandatory diagnostic
criteria for HCC classification in patients with chronic liver disease. The classification criteria for HCC in the
UNOS/OPTN system were developed for the explicit purpose of driving
automatic MELD exception point allo-
cation in those patients with chronic liver disease in whom HCC can be unequivocally diagnosed by using imaging. The diagnostic criteria in the policy
were intentionally not optimized to achieve maximum sensitivity for HCC
detection but rather attempt to raise
the specificity of HCC diagnosis.

The diagnostic imaging criteria
driving HCC classification rely on the
characteristic appearance of HCC on
dynamic multiphasic contrast-enhanced
CT scans or MR images (15). The qual-
itive criteria take into consideration not only their common differential in-
creased arterialization but also the
relatively decreased presence of con-
trast agent in most HCC compared with
surrounding liver during portal
vein and/or equilibrium phase imaging
(16–20). A pseudocapsule (21–25),
often seen in well-differentiated HCC at
equilibrium phase imaging, is also con-
sidered in the diagnostic criteria, but
detection may not increase the di-
agnostic accuracy beyond the dynamic
criteria (24).

For the first time, rapidly growing
nodules are also included in the HCC
diagnosis if they exhibit at least some
qualitative features for HCC and have
a diameter of at least 10 mm at diagnos-
sis. For all nodules, the policy requires late arterial phase enhancement even
even hypointense in arterial phase
and later phase imaging (26,27). Em-
phasis on late arterial features of nodule
reflects concern about the acci-
dental misclassification of lesions such
as cholangiocarcinoma, a contraindi-
cation for LT. Perfusion abnormalities
and cholangiocarcinoma may grow and
and enhance arterially (28) and, thus,
the growth criteria should be invoked

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**Table 3**

<p>| OPTN Classification System for Nodules Seen on Images of Cirrhotic Livers |
|-----------------------------|-----------------------------------------------|</p>
<table>
<thead>
<tr>
<th><strong>Class and Description</strong></th>
<th><strong>Comment</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>OPTN class 0</td>
<td>Repeat study required for adequate assessment; automatic priority MELD points cannot be assigned on basis of an imaging study categorized as OPTN class 0</td>
</tr>
<tr>
<td>OPTN class 5</td>
<td>May qualify for automatic exception, depending on stage*</td>
</tr>
<tr>
<td>Class 5A: ≥1 cm and &lt;2 cm measured on late arterial or</td>
<td>Increased contrast enhancement in late hepatic arterial phase AND washout during later phases of contrast enhancement AND peripheral rim enhancement (capsule or pseudocapsule)</td>
</tr>
<tr>
<td>portal venous phase images</td>
<td>class 5A: same size as OPTN class 5A HCC</td>
</tr>
<tr>
<td>Class 5B: maximum diameter ≥2 cm and ≤5 cm</td>
<td>Increased contrast enhancement in late hepatic arterial phase AND either washout during later contrast phases OR peripheral rim enhancement (capsule or pseudocapsule) OR growth by 50% or more documented on serial CT or MR images obtained ≥6 months apart (OPTN class 5B-g)</td>
</tr>
<tr>
<td>Class 5T: prior regional treatment for HCC</td>
<td>Describes any residual lesion or perfusion defect at site of prior UNOS class 5 lesion</td>
</tr>
<tr>
<td>Class 5X: maximum diameter ≥5 cm</td>
<td>Increased contrast enhancement in late hepatic arterial phase AND either washout during later contrast phases OR peripheral rim enhancement (capsule or pseudocapsule)</td>
</tr>
</tbody>
</table>

* Note.—OPTN class number denotes whether an imaging examination is nondiagnostic (OPTN class 0) or the study includes an image that contains at least one treated or untreated HCC (OPTN class 5). OPTN class 5 is further subdivided by adding a capital letter to denote UNOS stage 1 disease (OPTN class 5A), UNOS stage 2 disease (OPTN class 5B), a treated HCC (OPTN class 5T), or HCC beyond acceptable size for transplantation (OPTN class 5X). The g in OPTN class 5A-g and OPTN class 5B-g is used to indicate that growth was used to arrive at the HCC diagnosis.

* See 3.6.4.4 section A in reference 4.
with great care in the absence of any other qualitative HCC criteria. In case of doubt, short-term follow-up imaging or biopsy can provide more certainty. The UNOS/OPTN system importantly standardizes the language that radiology reports must include to qualify for exception points. Hepatic nodules must be classified in accordance with the criteria listed in Table 3. All HCC are categorized as OPTN class 5 lesions. Nodules less than 1 cm are considered too small to be accurately characterized and are not considered for additional priority on the transplant waiting list. The new policy reserves OPTN class 0 for nondiagnostic studies (see below).

**Nondiagnostic Studies: OPTN Class 0**

Radiologists are instructed to categorize nondiagnostic studies as OPTN class 0 (nondiagnostic) if the images are not of sufficient quality to confidently apply the new criteria, signaling in the official report that results of a study are not fit to be used to either assign or deny automatic HCC exception MELD points. A repeat study with the same imaging modality or an alternative acceptable modality may subsequently be performed.

**HCC: OPTN Class 5**

**Early UNOS stage 1 HCC: class 5A and 5A-g.**—If a given nodule of 1 cm or larger and less than 2 cm meets all qualitative criteria for HCC, it should be categorized as an OPTN class 5A lesion, regardless of any growth. Alternatively, any arterially hyperenhancing nodule that demonstrates rapid growth of a 50% or larger in diameter increase on a CT scan or MR image obtained 6 months or less apart and that measures at least 10 mm at the time of diagnosis can be categorized as an OPTN class 5A-g lesion. The modifier g indicates that documented growth was used to invoke the cancer diagnosis. Care should be taken not to overcall non-masslike lesions such as perfusion abnormalities as small HCC. Under the current UNOS policy, HCC MELD exception points are not granted for a solitary OPTN class 5A lesion but the combination of two or three OPTN class 5A nodules cumulatively does constitute a disease stage in which a patient would be eligible for transplantation. Any doubt in regard to the diagnosis of HCC in a growing nodule should prompt other means of verification (eg, biopsy, follow-up).

**Intermediate UNOS stage 2 HCC: OPTN class 5B.**—Any nodule of 2 cm or larger and 5 cm or smaller that is arterially hyperenhancing and has at least one of two venous features of HCC, washout or pseudocapsule, is categorized as an OPTN class 5B HCC. Alternatively, any arterially hyperenhancing nodule of this size range that demonstrates rapid growth of a 50% or more diameter increase on a CT scan or an MR image obtained 6 months or less apart can be categorized as class 5B HCC.

Ancillary imaging features of HCC seen on MR images are used by some radiologists for the diagnosis of HCC in clinical practice (30,31). These features may include lipid content in a nodule and hyperintense signal on T2-weighted and diffusion-weighted images. Ancillary features should be used with caution to substantiate the diagnosis of HCC at the discretion of an experienced radiologist, as their added diagnostic value remains controversial (24). Automatic MELD exception points are not granted under the current policy for such cases where ancillary features drive the diagnosis for HCC but the strict UNOS/OPTN diagnostic criteria are not met. However, MELD exception points may still be requested in such individual cases, subject to review by the UNOS regional review board.

**Advanced stage HCC: OPTN class 5X.**—Any nodule larger than 5 cm that is arterially hyperenhancing and has at least one of two venous features of HCC, washout or pseudocapsule, is categorized as an OPTN class 5X HCC. This category indicates disease too advanced to qualify for LT, except for regions with exceptional downstaging arrangements.

**Treated HCC or liver nodules: OPTN class 5T.**—Any HCC diagnosed as OPTN class 5 or any biopsy-proved HCC that has subsequently undergone local-regional treatment is categorized as OPTN class 5T. Such HCC may qualify for continued MELD exception points predicated on their pretreatment classification and size rather than on their appearance after therapy. At this time, UNOS policy does not define any specific size or appearance criteria for treated HCC that would lead to inclusion or exclusion from LT. In many cases, the visible OPTN class 5T “lesion” on an image represents the treatment zone and residual tumor rather than just HCC. Therefore, none of the diameter or growth criteria listed under OPTN class 5A or 5B lesions apply to ablated HCC.

Identifying and quantifying recurrent tumor in association with a treatment zone remains a challenge in clinical practice. Concern for disease progression beyond limits for an LT candidate may need to be discussed with the interdisciplinary team at the respective center and/or the UNOS regional review board to determine continued eligibility.
Reporting Requirements

If there is at least one HCC, treated or untreated, present on an image and the report of the imaging study including that image is to be used for obtaining automatic exception MELD points, the clinician must use the OPTN classification terminology described above, spelling out the OPTN class for all treated and untreated lesions that meet the diagnostic criteria for HCC and labeling nondiagnostic studies as OPTN 0. A structured summary at the end of the clinician’s report is strongly encouraged that lists the total number, location (liver segment), size (largest diameter), and OPTN class of all treated or untreated HCC and that states whether the overall radiologic stage of a patient’s HCC meets the Milan criteria, taking into account all relevant current and prior imaging findings.

Interpretation at an OPTN/UNOS-approved Transplantation Center

No validated methods exist to ascertain radiologist competence in interpretation of liver imaging. It was decided to use active liver imaging practice at an accredited transplantation center as a proxy for competence. Radiologists at these centers are an integral part of ongoing interdisciplinary practice, subject to feedback from clinical colleagues and peer review. These radiologists are typically quite familiar with all diagnostic and minimally invasive image-guided intervention options for HCC patients, as well as surgical treatments including LT.

While images may be physically obtained at an imaging facility other than an accredited transplantation center, only reports furnished by a transplantation center are considered for automatic HCC exception point allocation.

Concordance of New Policy with Existing Practice Guidelines—Future Direction

The new OPTN/UNOS policy is substantially compatible with recently updated national and international practice guidelines germane to diagnosis and treatment of HCC (Appendix E2 [online]).

A prospective multicenter trial is currently under way in the United States, testing the performance of the new policy, and results are expected to inform future policy updates (Appendix E3 [online]).

Summary

A new liver allocation policy featuring improved imaging criteria for HCC exceptions has been developed and approved by OPTN/UNOS in late 2011. Included are minimum technical and protocol requirements for CT and MR imaging, diagnostic and classification criteria for HCC, and standardized reporting requirements. The intent is to improve the accuracy of radiologic diagnosis and staging of HCC, qualifying patients for automatic MELD exception points on the LT waiting list and in the absence of liver biopsy. Radiologists in accredited transplantation centers in the United States are now challenged to implement the policy.

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References


