Hepatocellular carcinoma (HCC) or hepatoma is the most common primary malignancy of the liver. It ranks as the fifth most common tumor in the world and the third most common cause of cancer-related death. The incidence rates of HCC in the United States have historically been lower than in many countries. However, in recent decades, HCC age-adjusted incidence rates have doubled. This is largely due to an increasing prevalence of ailments that predispose to hepatic cirrhosis, such as chronic viral hepatitis, obesity and alcohol abuse.

At present, curative treatment options for HCC include liver transplantation, partial hepatic resection and, in some reported instances, percutaneous or surgical ablation. In 1996, Dr. Vincenzo Mazzaferro and colleagues defined the subset of patients with unresectable HCC for whom liver transplantation was the optimal treatment. Termed the “Milan criteria,” patients with a single HCC tumor < 5 cm in diameter or 2-3 tumors all < 3 cm in diameter, demonstrated overall and recurrence-free survival rates of 75% and 83%, respectively, at 4 years. Unfortunately, wait time for liver transplantation in patients with HCC has risen, increasing waitlist dropout rates and associated mortality.

Dropout rates after 1 year of waiting for a liver transplant have been reported at 20% to 60%. Thus, to control tumor burden of those meeting Milan criteria, reduce the waitlist dropout for patients awaiting orthotopic liver transplantation (OLT), and provide downstaging of disease for those exceeding criteria, many centers have relied on pretransplant transarterial locoregional therapy (LRT).

The increased use of LRT emphasizes the diagnostic radiologist’s need to be familiar with common therapies for treating and managing HCC. The radiologic hallmark of HCC, contrast uptake in the arterial phase and washout in the venous/late phase (Figure 1), remains fundamental to the diagnosis and post-treatment evaluation of lesions. This focused review will introduce the basic principles and forms of transarterial LRTs, briefly discuss the role of LRT in the management of HCC, examine assessment of imaging response to LRT procedures, and attempt to illuminate the nuances of interpreting post-treatment imaging.

**Principles of Transarterial Locoregional Therapy**

The normal liver receives a dual blood supply from the hepatic artery (25%) and the portal vein (75%). As the hypervascular HCC tumor grows, it increasingly depends on the hepatic artery for blood supply. Once an HCC tumor nodule reaches a diameter of ≥ 2 cm, most of the blood supply derives from the hepatic artery (Figure 2). This unique dual blood supply property of the liver provides the rationale for exploitation via transarterial embolization, or purposeful blocking of the hepatic tumoral arterial supply, as the nutrient portal venous flow to the liver remains intact.

Transarterial LRTs play an important role in the management of HCC. The varying types of LRTs exert their effect by delivering ischemic, chemical or radioactive doses to targeted liver lesions. These common therapies have been shown to achieve reproducible downstaging for patients outside of Milan criteria attempting to be listed for transplantation (Figure 3), and extend bridging of patients already listed and awaiting liver transplantation. Some authors have also shown increased survival for transarterial chemoembolization (TACE) in 2 randomized controlled studies. Similarly, longer time to progression has been suggested with transarterial radioembolization (TARE) compared to TACE. The practice of treating HCC patients with transarterial
LRT is common in transplant centers for the purpose of downstaging or bridging to transplantation, and palliation in those with preserved liver function and adequate performance status. The form of transarterial LRT utilized derives from a comprehensive understanding of the patient’s performance status, oncologic tumor stage, and laboratory results, and is usually discussed at a multidisciplinary conference involving hepatologists, radiologists, and transplant surgeons.

Transarterial embolization (TAE), also known as bland embolization, and TACE consist of the selective angiographic occlusion of the arterial blood supply to a targeted lesion with a variety of embolic agents, with or without use of a chemotherapeutic agent. The bland occlusion by embolic particles only, as seen in TAE, results in tumor hypoxia and necrosis. In theory, the addition of chemotherapy produces an additive cytotoxic anti-tumor effect, as seen in TACE. However, controversy exists regarding the efficacy of TACE over TAE and a recent meta-analysis suggests that TAE is as equally effective as TACE at a lower cost point and with potentially fewer side effects. For both TAE and TACE, portal venous thrombosis is a relative contraindication.

Multiple forms of TACE are used in clinical practice. Conventional TACE...
Imaging of Hepatocellular Carcinoma, Montgomery

(cTACE) is a single agent or cocktail of chemotherapeutic agents coupled with either gelfoam or iodinated poppy seed oil as the embolic agent. The presence of iodinated oil mandates 4-phase imaging, and inclusion of a noncontrast sequence, when evaluating with computed tomography (CT) post treatment (Figure 4). There is significant heterogeneity to the cocktail regimen and embolic material utilized for cTACE in clinical practice, making it difficult to study. Similarly, drug-eluting bead TACE (DEB-TACE) is a common form of LRT used at many centers. DEB-TACE is typically a single drug, most commonly doxorubicin, loaded on polyvinyl alcohol or acrylic polymeric beads (Figure 5). The potential benefit of DEB-TACE is delivery of a local, controlled, sustained dose of chemotherapeutic agent to the tumor with the potential for less systemic toxicity and post embolization syndrome (PES). A summary of PES is seen in Table 1. A randomized controlled trial of 212 patients with HCC showed greater complete response, objective response, and disease control at 6 months with DEB-TACE vs. cTACE with a suggestion of improved tolerability, reduced liver toxicity and doxorubicin-related side effects. Given its microembolic effect, Y90 can be used in patients with compromised portal venous flow (ie, bland thrombus, tumor thrombus, or hepatofugal flow), a clear practical advantage when compared to TAE or TACE. Following radioembolization, arterial embolization is much less extensive compared to TAE or TACE. The goal of TARE is not to produce an extensive embolization, but rather to administer the highest radiation dose possible to the tumor. This concept spares the nontumorous liver from radiation-induced liver damage and maintains the patency of the artery for future transarterial treatments. TARE has the unique benefit of inducing hypertrophy of the future liver remnant (Figure 6), augmenting surgical resection.

Radiologic Assessment of HCC Tumor Response

**Tumor Morphology Assessments**

The formal assessment of HCC response to LRT has experienced a natural progression and evolution as our...
knowledge and understanding of both HCC and LRT has grown. The World Health Organization (WHO) criteria\textsuperscript{13} followed by the Response Criteria in Solid Tumors (RECIST) guidelines, were early standardized approaches to report degrees of tumor response, recurrence and disease-free interval. WHO and RECIST provide guidelines in which radiologic observations can be quantified for the measurement of tumor response to therapy and have provided the basis of response assessment in clinical trials.\textsuperscript{14,15}

Both techniques rely on lesion size as the indicator of response, summarized in Tables 2 and 3. Hallmark to WHO is the bilinear product approach, which is calculated by multiplying the maximal diameter of a lesion by its longest perpendicular diameter, while the RECIST group proposed a model of single linear summation for target lesions (Figure 7).

The limitations of WHO and RECIST guidelines are due to their reliance upon changes in tumor dimension as the measure of radiologic response, ie, tumor shrinkage. The WHO criteria and RECIST do not take into account tumor necrosis that occurs without a reduction in overall tumor size. Furthermore, neither criteria mandate arterial phase imaging to demonstrate the radiologic hallmark finding of HCC. Recent literature has

\begin{table}[h]
\centering
\caption{Summary of Post Embolization Syndrome (PES)}
\begin{tabular}{|l|}
\hline
• Majority of patients (40\% to 86\%) \\
• NOT a complication but an expected outcome of transarterial locoregional therapy  \\
  - Fever (74\%) \\
  - Abdominal pain (45\%) \\
  - Nausea/emesis (59\%) \\
  - Transaminitis (54\%) \\
  - Leukocytosis without bandemia \\
• Self-limited requiring supportive therapy  \\
• Defervesce and LFTs normalize in ~3 days \\
• Neither the presence or severity of PES correlates to patient outcomes \\
\hline
\end{tabular}
\end{table}

FIGURE 5. Treatment with drug-eluting bead transarterial chemoembolization (DEB-TACE). Axial contrast-enhanced (computed tomography) CT image (A) shows a < 3 cm hepatoma in left lobe of liver. The patient underwent segmental DEB-TACE using 1 vial of 70-150 µm beads loaded with 75 mg of doxorubicin. Axial contrast-enhanced CT image 6 weeks after treatment shows no residual enhancement. The patient was successfully bridged to transplantation. Note that this response would be stable disease by the World Health Organization (WHO) and Response Criteria in Solid Tumors (RECIST), but a complete response by modified RECIST (mRECIST).

FIGURE 6. Partial hepatic hypertrophy following transarterial radioembolization (TARE) in a 71-year-old man with nonalcoholic steatohepatitis and a single 3-cm right hepatoma (not shown). Axial T1 late arterial phase MR sequence of the liver with fat-suppression prior to right lobar Y90 (A) shows a relatively small left hepatic lobe. Late arterial phase CT image of liver performed 21 months after Y90 TARE (B) shows moderate hypertrophy of the future liver remnant. Patient went on to partial right hepatectomy.
shown that assessments of radiologic response based only on size criteria do not correlate well with clinical benefit from LRT.\textsuperscript{15,16}

**Tumor Viability Assessments**

In 2000, the European Association for the Study of Liver Disease (EASL) panel of experts put forth a new model for evaluating response in solid tumors. The EASL guidelines take into account tumor necrosis induced by treatments\textsuperscript{17} as shown in Figure 8. The EASL panel mandated evaluation with contrast-enhanced radiologic imaging for assessing treatment response. Viable tumor was defined as enhancement in the arterial phase on dynamic CT or MRI. This concept was further supported in 2005 by the American Association for the Study of Liver Disease.\textsuperscript{18}

Given the complexities and unique properties of HCC, a more practical model for tumor assessment was required to augment trial design and facilitate clinical management. As a result, the modified RECIST (mRECIST) criteria were proposed and are based on measurements of tumor viability as indicated by arterial phase enhancement\textsuperscript{19,20} as depicted in Figure 8. mRECIST also include guidelines for assessing pleural effusions and ascites, porta hepatis lymph nodes, portal vein thrombosis, and the development of new lesions. The mRECIST is now the most widely used criteria for assessing tumor response to LRTs.

### Table 2. World Health Organization (WHO) Criteria

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>No lesions detected for at least 4 weeks</td>
</tr>
<tr>
<td>Partial response</td>
<td>≥ 50% decrease in the SPD diameters from baseline confirmed at 4 weeks</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>≥ 25% increase in SPD in one or more lesions or new lesions</td>
</tr>
<tr>
<td>Stable disease</td>
<td>None of the above</td>
</tr>
</tbody>
</table>

Sum of the product diameters (SPD) is longest overall tumor diameter and longest diameter perpendicular to the longest overall diameter.

### Table 3. Response Evaluation Criteria in Solid Tumors

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>Disappearance of all target lesions</td>
</tr>
<tr>
<td>Partial response</td>
<td>≥ 30% decrease in sum of longest diameter (SLD) of target lesions</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>≥ 20% increase in SLD of target lesions or new lesions</td>
</tr>
<tr>
<td>Stable disease</td>
<td>None of the above</td>
</tr>
</tbody>
</table>

**FIGURE 7.** Comparison between World Health Organization (WHO) (A) and Response Criteria in Solid Tumors (RECIST) guidelines (B). Lesion size, not arterial phase enhancement, is the hallmark of WHO and RECIST. WHO utilizes a bilinear product approach (product of A x B), while RECIST utilizes a single linear summation of RECIST (dimension of line A).

**FIGURE 8.** Tumor viability assessment with the European Association for the Study of Liver Disease EASL (A) and modified Response Criteria in Solid Tumors mRECIST (B) models. The white oval represents enhancing tumor in the arterial phase. The black portion represents nonviable necrosis in a treated hepatoma. Note that only the enhancing portion is measured in greatest dimension; the necrotic nonviable tissue of the target lesion is excluded from measurement.
Imaging of Hepatocellular Carcinoma, Montgomery

Table 4. Modified Response Evaluation Criteria in Solid Tumors (mRECIST)

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>Disappearance of arterial phase enhancement in all target lesions</td>
</tr>
<tr>
<td>Partial response</td>
<td>≥30% decrease in SLD of <em>viable</em> target lesion (arterial phase enhancement)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>≥20% increase in SLD of <em>viable</em> target lesion (arterial phase enhancement)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>None of the above</td>
</tr>
</tbody>
</table>

Perilesional arterial and portovenous phase enhancement is a common benign finding that results from arterioporal shunting after LRT (Figure 9).

For an HCC target lesion to be assessed by mRECIST, the following must exist: > 1 cm per RECIST, suitability for repeat measurement, and classic intratumoral arterial enhancement on CT or MRI. Therefore, infiltrative forms of HCC should be excluded from mRE-

Figure 9. Benign perilesional enhancement from arterioporal shunting after locoregional therapy (LRT). Axial T1 contrast-enhanced pre-treatment arterial phase MR image with fat-suppression (A) demonstrates a right hepatic hepatoma measuring 4.1 cm. Axial T1 contrast-enhanced arterial phase MR image with fat-suppression 12 months after Y90 radioembolization (B) reveals no residual enhancement of lesion. This patient was successfully bridged to transplantation. Images (B) and post-treatment axial T1 contrast-enhanced MR image with fat-suppression in the portovenous phase (C) show perilesional arterial (B) and portovenous (C) phase enhancement, consistent with benign arterioporal shunting, a common post-treatment finding.

Table 5. LI-RADS Lexicon Reporting Categories and Definitions

<table>
<thead>
<tr>
<th>LI-RADS Code</th>
<th>Category</th>
<th>Concept</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR-1</td>
<td>Definitely Benign</td>
<td>100% certainty observation is benign.</td>
<td>Observation with imaging features diagnostic of a benign entity, or definite disappearance at follow up in absence of treatment.</td>
</tr>
<tr>
<td>LR-2</td>
<td>Probably Benign</td>
<td>High probability observation is benign.</td>
<td>Observation with imaging features suggestive but not diagnostic of a benign entity.</td>
</tr>
<tr>
<td>LR-3</td>
<td>Intermediate probability for HCC</td>
<td>Both HCC and benign entity have moderate probability.</td>
<td>Observation that does not meet criteria for other LI-RADS categories.</td>
</tr>
<tr>
<td>LR-4</td>
<td>Probably HCC</td>
<td>High probability observation is HCC but there is not 100% certainty.</td>
<td>Observation with imaging features suggestive but not diagnostic of HCC.</td>
</tr>
<tr>
<td>LR-5</td>
<td>Definitely HCC</td>
<td>100% certainty observation is HCC.</td>
<td>Observation with imaging features diagnostic of HCC or proven to be HCC at histology.</td>
</tr>
<tr>
<td>LR-5V</td>
<td>Definitely HCC with tumor in vein</td>
<td>100% certainty that observation is HCC invading vein.</td>
<td>Observation with imaging features diagnostic of HCC invading vein.</td>
</tr>
<tr>
<td>LR-M</td>
<td>Probable malignancy, not specific for HCC</td>
<td>High probability that observation is a malignancy, but imaging features are not specific for HCC.</td>
<td>Observation with one or more imaging features that favor non-HCC malignancy.</td>
</tr>
<tr>
<td>LR-Treated</td>
<td>Treated Observation</td>
<td>Loco-regionally treated observation.</td>
<td>Observation that has undergone loco-regional treatment.</td>
</tr>
</tbody>
</table>
CIST evaluation. Even with these limitations, the mRECIST criteria allows for reproducible, objective, quantitative measures needed to define a common language between radiologists and clinicians facilitating informed treatment decisions.

Functional MRI techniques, such as diffusion-weighted imaging (DWI) have been recently investigated, aiding specificity to locoregional therapy response assessment and outcome prediction. Additionally, the degree of fluorodeoxyglucose (FDG) uptake on positron emission tomography (PET)/CT has since been updated and evolved into a widely accepted standardization of the performance, interpretation, and reporting of lesions on CT or MR in those at high risk for HCC. LI-RADS is a structured diagnostic algorithmic system that categorizes lesions from LR-1 (definitely benign) to LR-5 (definitely HCC) (Table 5). LI-RADS clearly mandates imaging technique performance standards as seen in Figure 10, and includes protocols for MRI hepatobiliary imaging agents not mandated by the United Network for Organ Sharing and Organ Procurement and Transplantation Network (UNOS-OPTN). LI-RADS LR-5 lesions, those which demonstrate the radiologic hallmark of HCC, do not require biopsy for diagnosis. LR-5 lesions are essentially equivalent to UNOS-OPTN Class 5 lesions, are diagnostic of HCC, and are a classification upon which transplant candidacy is determined. The use of LI-RADS after LRT is really quite simple. A lesion after locoregional therapy is simply categorized as LR-Treated (LR-T) as shown in Figure 11, and either has residual/recurrent disease (Figure 12) or is without residual/recurrent disease. A more comprehensive algorithmic approach to deal with the variable appearances and complexities of the LR-T category is expected from the ACR, to be termed ACR TR-LIRADS. For a more comprehensive review of LI-RADS visit http://www.acr.org/quality-safety/resources/LIRADS.

Liver Imaging Reporting and Data System (LI-RADS)

In 2011, the American College of Radiology (ACR) developed LI-RADS to address inconsistencies in imaging technique and reporting standards. It
Conclusion
Radiologic assessment of HCC after LRT has substantially improved over time and has become increasingly important to clinicians for patient management. With continually evolving assessment criteria, it is critical that diagnostic radiologists remain abreast of new guidelines and familiarize themselves with the bevy of HCC treatment regimens. At present TAE, TACE and TARE have become cornerstone therapies for bridging to transplant, downstaging to transplant, and palliation of HCC. mRECIST has emerged as the standard image-driven means of assessing response to LRTs, serves as the basis for response in clinical trials, and demonstrates significant improvement over prior guidelines. LI-RADS is a structured algorithmic system that standardizes the performance, interpretation, and reporting of lesions on CT or MR in those at high risk for HCC. LI-RADS LR-T lesions can be difficult to evaluate in the presence of benign post-procedural changes and in tumors presenting with a heterogeneous pattern of enhancement. ACR TR-LIRADS guidelines are expected and will likely elucidate the many challenges of interpretation and standardize the evaluation of hepatoma after LRT.

REFERENCES