




Response Assessment of Treated Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is a leading cause of morbidity and mortality worldwide, including in India. The incidence of HCC has been rising due to lifestyle diseases such as obesity, diabetes, non-alcoholic fatty liver disease (NAFLD), and alcoholic liver disease (ALD), as well as viral hepatitis infections. Various locoregional therapies (LRTs) are used to treat HCC, including thermal ablation, transarterial therapies, stereotactic body radiotherapy (SBRT), and transarterial radioembolization (TARE). Traditional response evaluation criteria like WHO and RECIST, which rely on size-based measurements, may not accurately assess treatment response to LRTs. To address this limitation, modified response evaluation criteria for solid tumors (mRECIST) and the LI-RADS treatment response algorithm (LR-TRA) have been developed. mRECIST assesses patient-level response, while LR-TRA provides lesion-level response assessment specifically for HCC treated with LRTs. This article discusses the imaging protocols for diagnosing HCC and the imaging appearances of treated lesions after different LRTs. It explains the criteria for categorizing treatment response, such as LR-TR viable, LR-TR non-viable, and LR-TR equivocal. It also highlights the challenges and future directions in response assessment, including the incorporation of ancillary findings, the assessment of patients receiving a combination of locoregional and systemic therapies, and the potential use of biomarkers like serum AFP, AFP-L3, and PIVKA-II. In conclusion, locoregional therapies have expanded the treatment options for HCC, and accurate response assessment is crucial for optimizing patient management. mRECIST and LR-TRA provide valuable tools for evaluating treatment response, and future updates are expected to address specific challenges and incorporate newer approaches like iRECIST and quantitative imaging assessment. Additionally, the use of biomarkers may complement imaging-based response assessment in the future.

Keywords

- ▶ HCC
- ▶ LR-TRA
- ▶ mRECIST
- ▶ response

Introduction

Hepatocellular carcinoma (HCC) is one of the leading causes of morbidity and mortality. The incidence of HCC has a rising trend globally as well as in India. This has been attributed to

rising lifestyle diseases like obesity, diabetes, nonalcoholic fatty liver disease (NAFLD), and alcoholic liver disease (ALD). Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections continue to be leading causes of HCC in India.¹ As per the National Comprehensive Cancer Network (NCCN) guidelines

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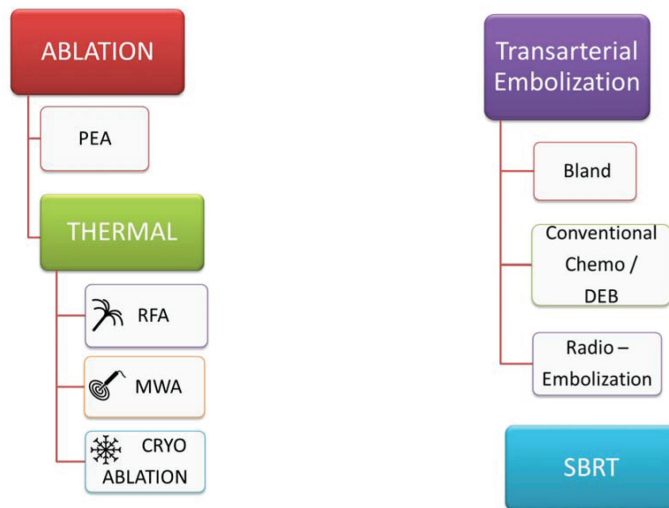


Fig. 1 Locoregional therapies.

for hepatobiliary cancers, version 2.2022, and Liver Imaging Reporting and Data System (LI-RADS),² features like arterial phase hyperenhancement (APHE), nonperipheral venous or delayed phase washout appearance, enhancement of capsule appearance, and threshold growth are considered characteristics of HCC in high-risk (cirrhosis, chronic hepatitis B, or current or prior HCC) patients with liver nodule(s), which are 10 mm or more in size.

Depending on the disease burden and patient's condition, the intent of therapy can be curative, bridge to transplant/downstaging for transplant eligibility, or palliation. Curative measure include surgery, locoregional therapies (LRTs), or liver transplant.³ LRTs (► **Fig. 1**) comprise thermal ablation methods (radiofrequency ablation [RFA], microwave ablation [MWA], and cryoablation), transarterial therapies (bland transarterial embolization [TAE], transarterial chemoembolization [TACE], drug-eluting bead transarterial chemoembolization [DEB-TACE], and transarterial radioembolization/selective internal radiation therapy [TARE/SIRT]), and stereotactic body radiotherapy (SBRT);).

The LRTs lead to alterations in tumor morphology, predominantly, secondary to ischemia and coagulation necrosis. In addition, TACE has local cytotoxic effect on the tumor. Traditional response evaluation criteria like WHO and response evaluation criteria for solid tumors (RECIST) define tumor response based on alterations in the size of the tumor, which do not provide optimal indication of response to LRTs, since LRTs can induce intratumoral necrosis without reduction in the tumor size. On the contrary, ablative therapies result in increase in the size of the ablation zone, since ablative therapies incorporate additional margin of at least 5 mm to address satellite micrometastasis and microvascular tumor extension, and reduce the likelihood of tumor recurrence.

To address the limitation of the traditional response evaluation criteria, modified RECIST (mRECIST) was developed, which assessed tumor response at patient level based on the residual viable enhancing portion of the treated tumor. The LI-RADS tumor response working group

(TRWG) created a lexicon for lesion level response assessment to LRTs, which targets specific lesions with single or multiple therapies over time or even different therapies to different lesions. The LI-RADS treatment response algorithm (LR-TRA) applies only to HCC treated with LRTs like ablation, TAE/TACE, and localized radiotherapy (SIRT/SBRT). The criteria are to be used with due precautions in patients receiving systemic therapy and/or concurrent/combined LRT.

Protocol and Imaging Strategy

As for diagnosis of HCC, imaging protocol should include triple-phase CT along with unenhanced acquisition, or dynamic contrast-enhanced magnetic resonance imaging (MRI) using extracellular or hepatobiliary contrast agents, with arterial, venous, and delayed phase acquisitions and subtraction imaging. With hepatobiliary contrast, additional hepatobiliary phase can be acquired at 20 minutes after injection of gadoxetate or 90 to 120 minutes after administration of gadobenate.

The American College of Radiology (ACR) LI-RADS recommends imaging at 1 month post-LRT and every 3 months thereafter, during the first year of the therapy, followed by longer scanning intervals (3–6 months) subsequently, in the event of involution of the treatment zone.⁴

Treatment Related Appearances

Thermal Ablation

Thermal ablative LRTs include RFA, MWA, and cryotherapy. To achieve adequate ablation and reduce likelihood of post-treatment recurrence, an ablation margin, 5- to 10-mm larger than the tumor, is ensured (► **Fig. 2**). This addresses adjoining satellite micrometastasis and microvascular invasion, reducing tumor recurrence likelihood. Usually, the larger the tumor, the larger the ablation margin. Hence, the ablation zone is always larger than the native tumor. It starts shrinking 6 months after ablation, until it stabilizes into a smaller ablation zone.⁵ On ultrasonography (USG), the

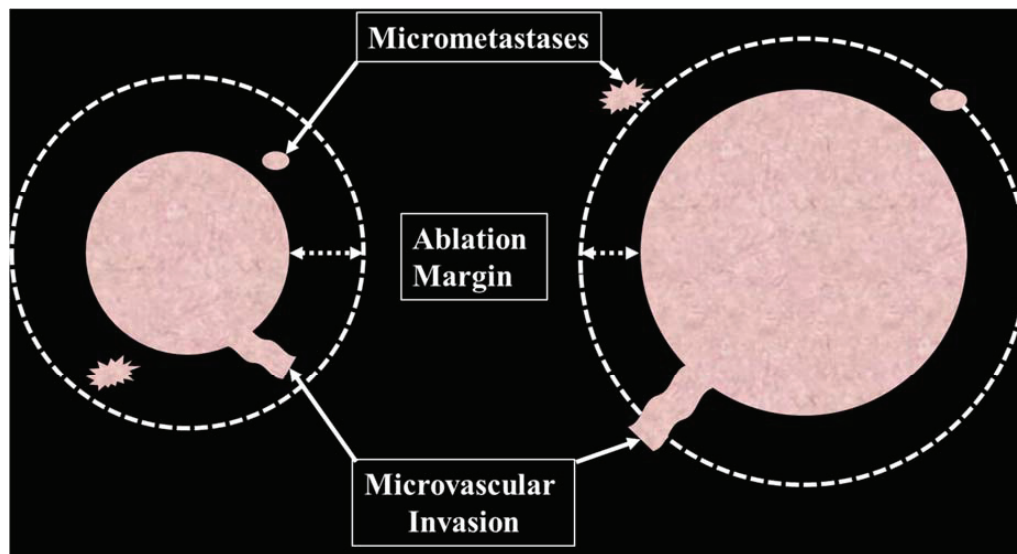


Fig. 2 Ablation margin.

HCC is usually hypoechoic on B mode and demonstrates increased echogenicity on the arterial phase followed by diminishing (washout) echogenicity on subsequent phases of contrast-enhanced ultrasound (CEUS). The posttreatment ablation zone is echogenic on B mode and is hypoechoic (lacks contrast uptake) on all phases of CEUS (→ **Fig. 3**).

The ablation zone initially has a core, which is hyperdense on computed tomography (CT) and hyperintense on T1-weighted MR image, owing to coagulation necrosis. Thermal ablation can also result in tissue vaporization and gas production. Most of the gas is usually absorbed in the blood stream. However, some gas can be entrapped in the ablation zone for several weeks in some cases, and should not be confused with infection at the initial (1-month) follow-up. Tumors undergoing cryoablation, however, demonstrate T1 hypointensity, after successful therapy.

Rim enhancement is an expected finding in the posttreatment setting. A peripheral, reactive arterial hyperenhancement may also be seen along the ablation zone. This transient hepatic attenuation defect/transient hepatic intensity defect (THAD/THID) is probably secondary to arterioportal fistula resulting from ablative procedure. It becomes isodense/isointense on the delayed images, does not washout, and resolves over time.

Transarterial Therapies

Transarterial LRTs involve bland embolization (TAE), conventional TACE, DEB-TACE, and TARE.

Nonradiation-based transarterial therapies involve administration of ethiodized oil (lipiodol) along with embolic and chemotherapeutic agents (single, double, or triple cocktail combination of 10 mg mitomycin C, 50 mg doxorubicin, and 100 mg cisplatin). Lipiodol is hyperdense on CT (unenhanced as well as postcontrast scan; → **Fig. 4**). Lipiodol is a good surrogate of tumor response that correlates well with histological evidence of tumor necrosis.^{6–8} However,

lipiodol, being hyperdense, can mask arterial phase enhancement of residual viable tumor. MRI signal is not affected by lipiodol and hence is favored for posttreatment assessment.⁹

Like ablative therapies, the posttreatment area can be larger due to the presence of necrosis and hemorrhage and shrink over time, in the absence of residual disease. Findings suggestive of tumor viability include irregular/nodular APHE, associated with washout, with or without pseudocapsule. Increase in the enhancing component is also an indicator of viability.

In the presence of posttreatment residual enhancing viable disease, it is apt to provide the largest dimension of the enhancing portion and its pretreatment measurement, to succinctly communicate the magnitude of treatment response, for example, LR-TR viable, largest enhancing dimension of 0.5 cm (pretreatment LR-5 HCC: 3 cm).¹⁰

Transarterial Radioembolization

TARE/SIRT includes administration of β -emitting radioisotope Yttrium-90, via superselective catheterization of the feeding arteries, in the tumor bed. Radiation leads to gradual cell death by apoptosis, over a long duration of time; hence, the arterial enhancement can persist for over 1 year. Posttreatment, CT/MRI may reveal necrosis or persistent arterial hyperenhancement involving the treated tumor bed. In some cases, the arterial enhancement can persist beyond 1 year post-TARE. Follow-up involves imaging every 3 months during the first year posttreatment. There tends to be gradual diminution of the arterial enhancement in the treated tumor bed, although it may remain stable as well.^{5,11–14}

Stereotactic Body Radiotherapy

SBRT is another form of locoregional radiation-based external radiotherapy. Imaging appearances are similar to SIRT, and identical response assessment criteria are applicable.

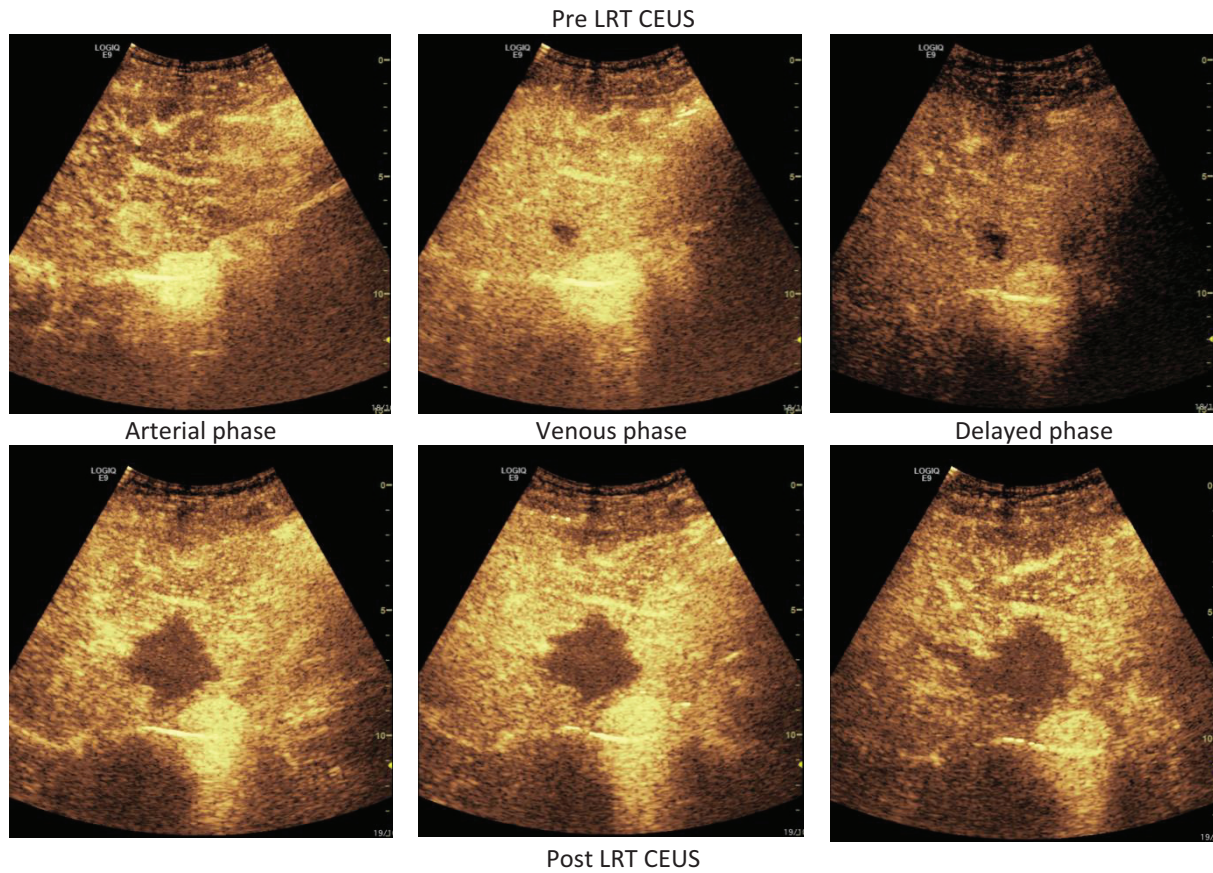


Fig. 3 Pre-LRT CEUS (top row) demonstrates arterial phase enhancement followed by washout in subsequent phases, consistent with LR5 observations. Post-LRT CEUS (bottom row) of same case, demonstrates complete absence of enhancement in the ablation zone, consistent with LR TR non-viable observation.

Response Assessment

The size-based bidimensional WHO and unidimensional RECIST criteria are not commonly used for posttreatment response assessment of HCC.

EASL and mRECIST

The European Association for the Study of the Liver (EASL) criteria was the first functional response evaluation approach for HCC treated with LRT.¹¹ EASL applied the WHO bidimensional measurement to residual arterially enhancing portion of treated HCC, with $\geq 50\%$ reduction in the sum of the product of enhancing diameters after 4 weeks of treatment representing partial response and $\geq 25\%$ increase as disease progression. Absence of arterial enhancement implies complete response. Any tumor not conforming to the above criteria would be categorized as a stable disease.

mRECIST incorporates both the EASL and the RECIST criteria, utilizing a single long-axis dimension of at least 1 cm of the residual arterially enhancing component of the treated HCC, for response assessment. A treated case would be considered as partial response, if the sum of long-axis dimensions of the residual arterial-phase enhancing components reduces by at least 30% and progressive disease if there is increase by at least 20%. Complete response represents

absence of any arterial enhancement. Any treated lesion not qualifying the above criteria would be considered a stable disease. mRECIST, like RECIST, limits response estimation to no more than two lesions per organ and no more than five in total.

The limitation of EASL and mRECIST criteria is that these criteria rely only on arterial phase enhancement, which may not be able to always correctly estimate the disease burden, for example, in cases of atypical HCC, which do not exhibit arterial enhancement.

An important concept to remember is that these criteria provide a systemic as well as patient level response assessment rather than lesion level estimation. For example, if a patient who has complete response to LRT develops a new lesion at a site remote from the treated lesion, he or she would be categorized progressive disease using these criteria. This should, however, not be considered as failure of locoregional treatment.

LI-RADS Treatment Response Assessment

The LR-TRA was first established in 2014 by the ACR (►Fig. 5; ►Table 1). LR-TRA applies to HCC treated with LRTs like ablation, TAE (bland as well as chemoembolization), TARE, or SBRT. LR-TRA cannot be applied to patients undergoing systemic therapy. ACR recommends caution while

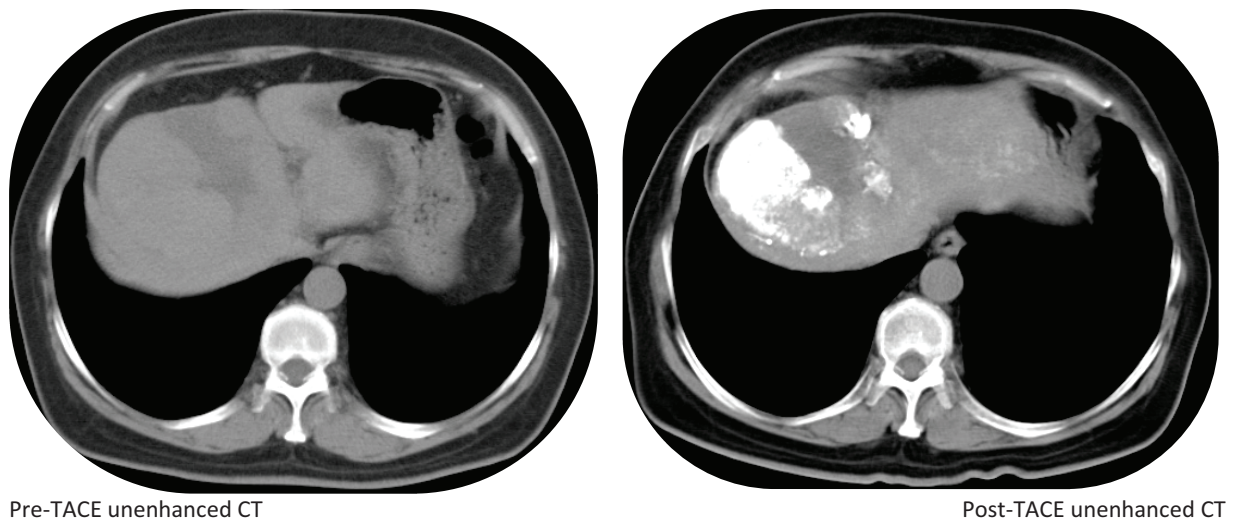


Fig. 4 (A) Pre-transarterial chemoembolization (pre-TACE) unenhanced computed tomography (CT). (B) Post-TACE unenhanced CT.

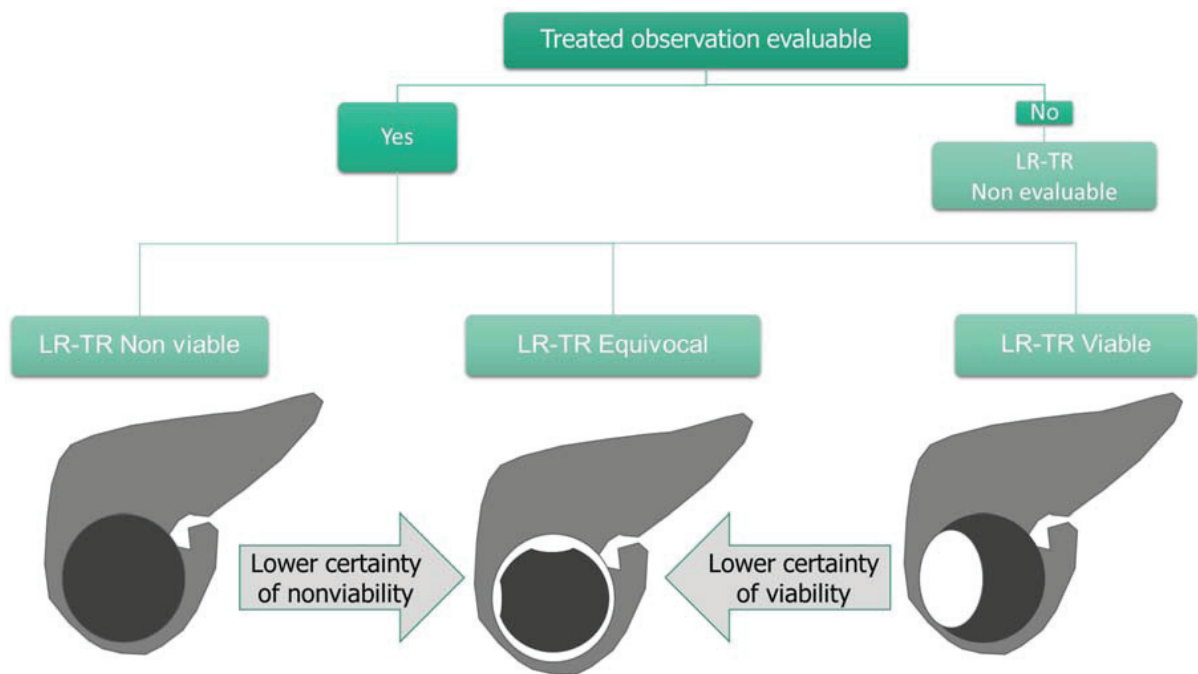


Fig. 5 Liver Imaging Reporting and Data System (LI-RADS) treatment response assessment. (Adapted from Kielar et al.¹⁰)

Table 1 Treatment response categories

| Treatment response categories | Criteria |
|--|--|
| LR-TR nonviable Treated, probably or definitely not viable | No lesional enhancement OR |
| | Treatment-specific expected enhancement pattern |
| | Equivocal findings: stable or reduced >1 y |
| LR-TR equivocal Treated, equivocally viable | Enhancement atypical for treatment-specific expected enhancement pattern and not meeting criteria for probably viable or definitely viable |
| LR-TR viable Treated, probably or definitely viable Nodular, masslike, or thick irregular tissue in or along the treated lesion with any of the following: | Arterial phase hyperenhancement OR |
| | Washout appearance OR |
| | Enhancement similar to pretreatment |

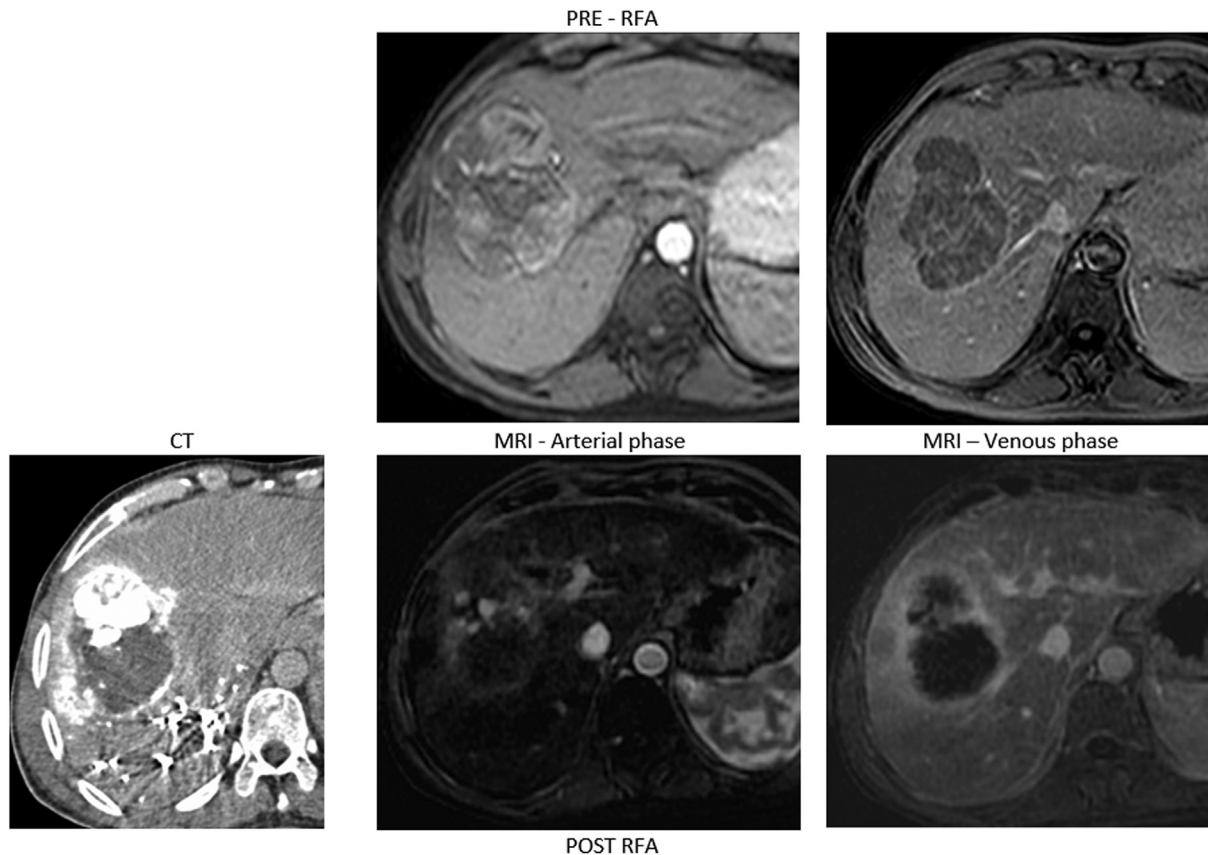


Fig. 6 Pre-radiofrequency ablation (RFA) magnetic resonance imaging (MRI; top row) demonstrated arterial phase hyperenhancement (APHE) and washout on the venous phase with a pseudocapsule, consistent with LR-5 observation. Post-transarterial chemoembolization (post-TACE) computed tomography (CT) and magnetic resonance imaging (MRI; bottom row) of the same patient showed lipiodol deposition in the arterially enhancing areas, which were masked by the high lipiodol density; however, dynamic contrast-enhanced MRI (DCE-MRI) revealed few nodules with APHE and washout on the venous phase, which represented LIRADS treatment response (LR-TR) viable observation.

applying LR-TRA in patients treated with a combination of systemic and LRT.⁴

The initial LR-TRA only categorized a lesion as either treated or untreated, without any reference to tumor viability in the treated lesion. The LR-TRA was revised in 2017 to indicate viability of an observation undergoing LRT.¹² The current v2018 LR-TR assessment categorizes the types of response as follows:

1. **LR-TR viable:** Viable lesion implies any posttreatment change with residual arterial phase enhancement or washout or enhancement pattern similar to the pretreatment pattern (►Fig. 6). For assessment of viable tumor, LR-TRA extends the mRECIST system of response assessment to lesions treated with LRT. In the presence of residual viable enhancement, single largest dimension of the viable enhancing portion should be stated. For measurement, it is recommended to avoid the intervening nonenhancing portion (►Fig. 7).
2. **LR-TR nonviable:** Complete absence of enhancement or expected perilesional enhancement qualifies as LR-TR nonviable (►Fig. 8). Expected perilesional enhancement can include rim enhancement and reactive geographic peripheral arterial phase enhancement without washout (►Fig. 9).

3. **LR-TR equivocal:** Any findings not meeting the above criteria are categorized LR-TR equivocal.

As discussed earlier, persistent arterial enhancement is now a known phenomenon in the post-TARE/SBRT setting. There is now growing consensus that this should be categorized as LR-TR equivocal (►Fig. 10) rather than viable tumor, unless there is increase in the size of the arterial enhancing component on follow-up. Lack of increase in the enhancing component on serial follow-up for a year can be considered as a surrogate of nonviability.^{12,13} Please note that this is not yet incorporated in the current v2018 LR-TRA criteria.

The above criteria can be applied if the treated observation is evaluable. The LR-TR nonevaluable criteria can be used when there is degradation of image or lack of multiphase study. Post-TACE observations on CT scan with hyperdense lipiodol deposition may be considered nonevaluable, as enhancement, used for response assessment, would be masked by the density of lipiodol.^{14,15}

LR-TRA, unlike the rest of the response evaluation criteria, allows for a lesion level rather than patient level assessment, by assigning an appropriate response category to individual lesions. For example, in a patient with complete response to RFA to one observation and partial response with residual enhancement post-TACE for another, the observations would

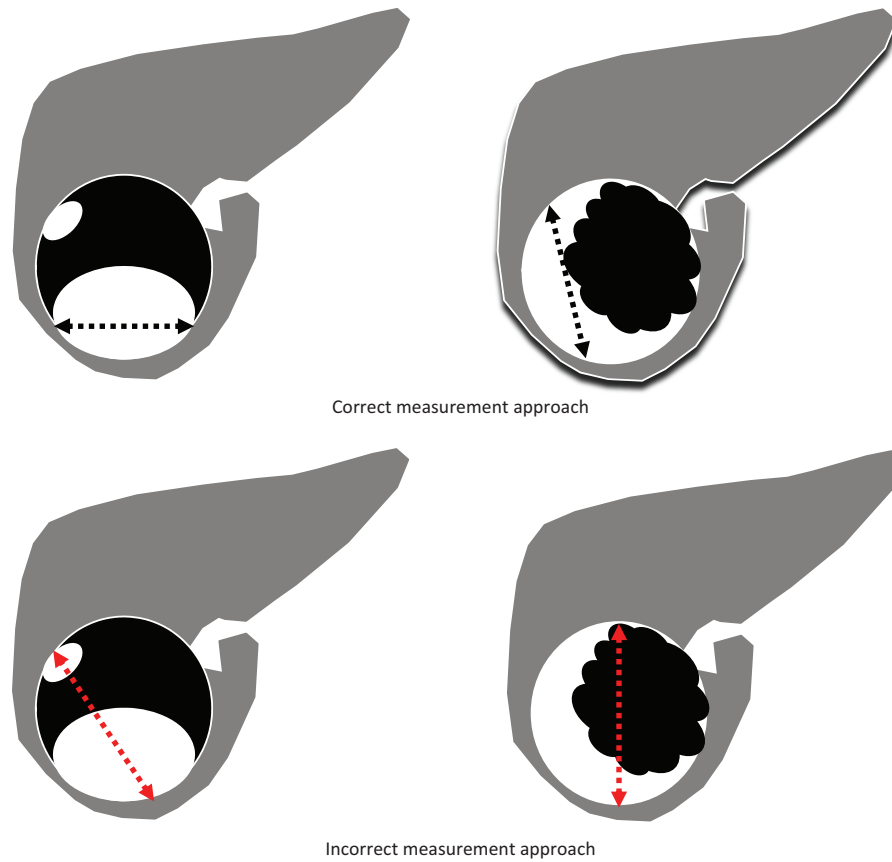


Fig. 7 Measurement approach.

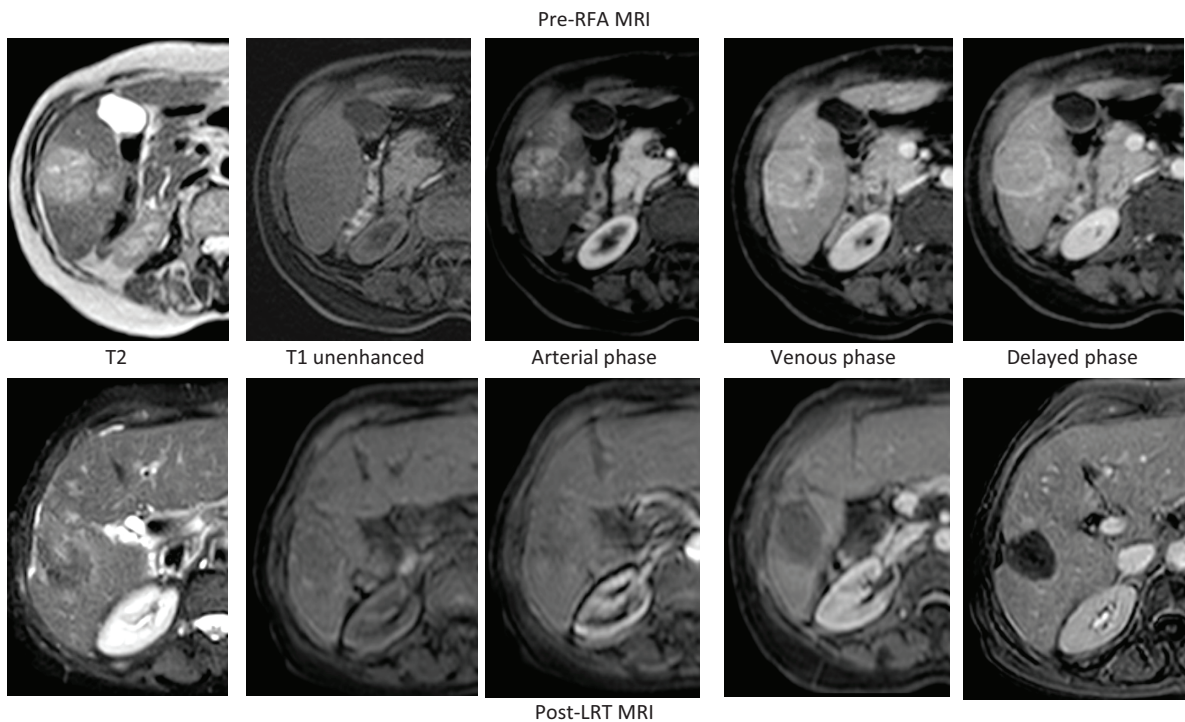


Fig. 8 Pre-locregional treatment (pre-LRT) magnetic resonance imaging (MRI; top row) showed a well-circumscribed T2 hyperintense observation in segment 6 of the liver. It was isointense on T1-weighted image and exhibited arterial phase hyperenhancement and capsule on delayed phase postcontrast T1-weighted fat-suppressed image, consistent with the LR-5 observation. Post-LRT MRI (bottom row) showed predominantly T2 hypointense ablation in segment 6, which was isointense on unenhanced T1-weighted image and did not enhance on dynamic contrast-enhanced MRI, consistent with LIRADS treatment response (LR-TR) nonviable observation.

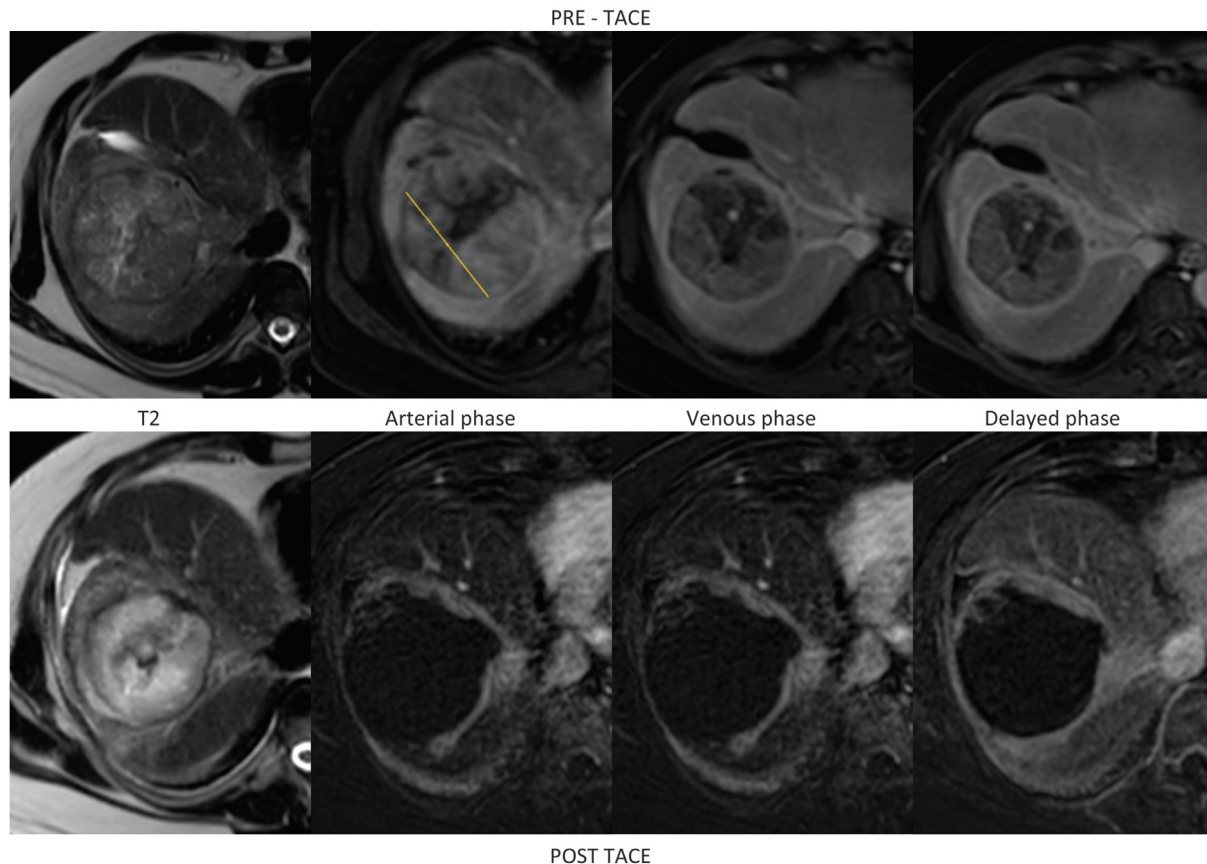


Fig. 9 Pre-transarterial chemoembolization (pre-TACE) magnetic resonance imaging (MRI; top row) demonstrated T2 heterogeneous observation, which had arterial phase hyperenhancement (APHE), washout, and pseudocapsule on delayed phase dynamic contrast-enhanced (DCE) MRI, consistent with LR5 observation. Post-TACE MRI (bottom row) showed predominantly T2 hyperintense treated observation with only a peripheral arterial enhancement without any washout, consistent with expected posttreatment observation—LRADS treatment response (LR-TR) nonviable.

be assigned LR-TR nonviable and LR-TR viable categories, respectively.

Current Challenges and Future of Response Assessment

The mRECIST and EASL criteria allow patient level response assessment, whereas LR-TRA is a lesion level response assessment system. Both have their own significance, as assessing treatment response on a lesion-by-lesion basis is important to understand the respective efficacy of various LRT modalities, while a holistic patient assessment would require an overall impression of the disease burden as well.

LR-TRA relies on the enhancement characteristics of the treated tumor for response assessment. Ancillary findings like T2 hyperintensity and diffusion restriction are not considered, given that associated coagulative necrosis and hemorrhage may cause pseudo-restriction and T2 hypointense signal. In practice, one can often observe soft-tissue enhancement in viable tumors without arterial hyperenhancement or washout. This can represent residual disease as well, especially when the treated observations did not exhibit characteristic APHE or washout, prior to therapy. It is important to note the type of LRT used, as radiation-related

treatment response may have a different appearance. The upcoming updated version of LR-TRA will address these issues and provide separate diagnostic algorithms for patients treated with thermal ablation or nonradiation intra-arterial embolic therapy and for those treated with radiation. Treated stable or regressing lesions postradiations could potentially be described as “evolving”¹² or “nonprogression.” Increasing the follow-up interval to more than 3 months between successive studies may be optimal for observations treated with radiation-based LRT.¹²

Clarity on assessing the treatment response in patients on a combination of locoregional and systemic therapy is also needed. In such situations, it is more important that the referring oncologist is clear on overall and lesion level picture, rather than just getting into the semantics of the response criteria to be used. Furthermore, immunotherapy is being increasingly offered for patients with HCC, and would warrant newer approaches like immunotherapy modified Response Evaluation Criteria in Solid Tumors (iRECIST). Quantitative imaging assessment like apparent diffusion coefficient (ADC) measurements or ADC threshold maps and volumetric assessment of treated observations can be of incremental value in addition to the current response assessment algorithm.

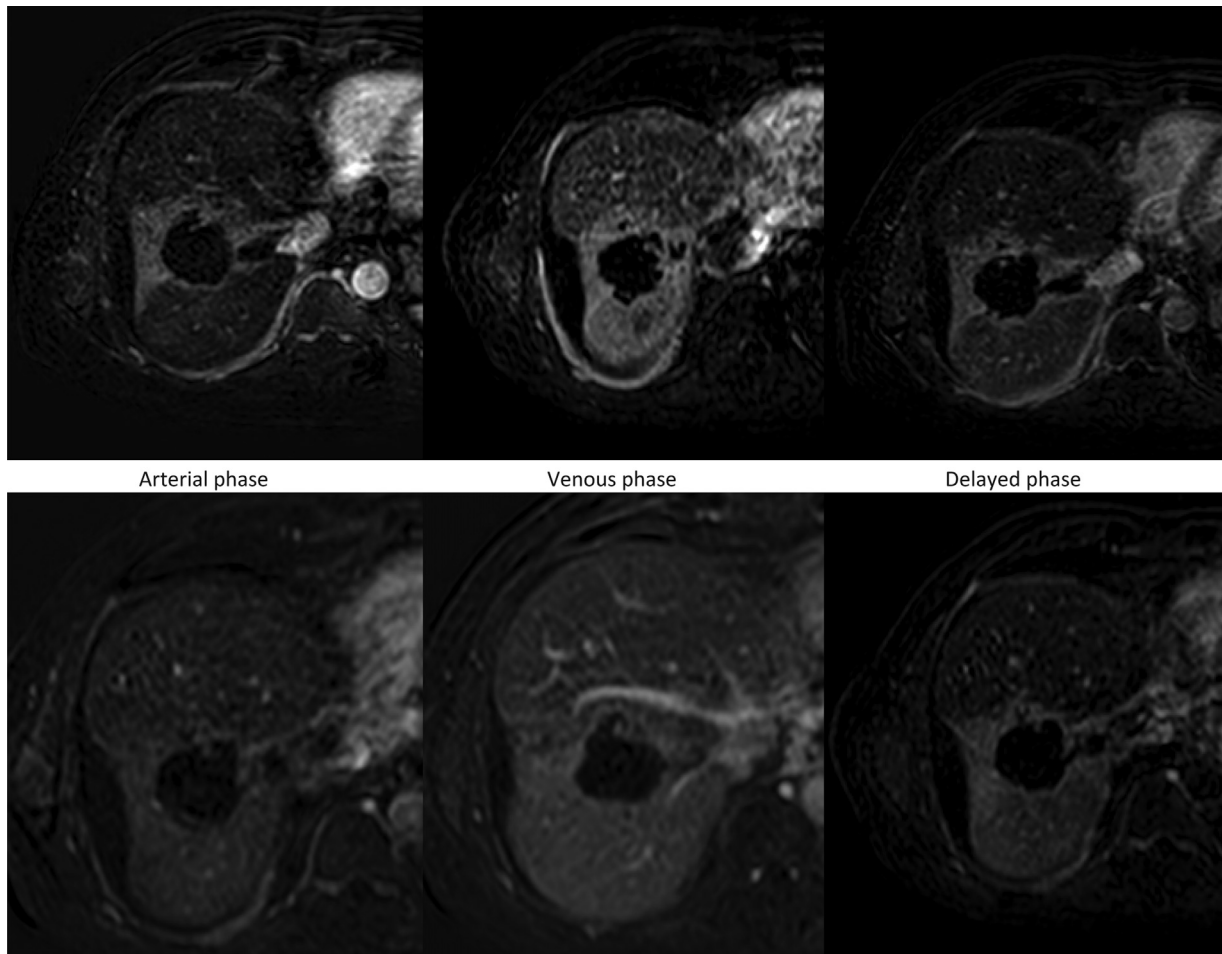


Fig. 10 Baseline magnetic resonance imaging (MRI; top row) 1 month after transarterial radioembolization (TARE) revealed peripheral arterial enhancement without washout or internal enhancement, consistent with Liver Imaging Reporting and Data System LIRADS treatment response (LR-TR) equivocal observation. Third month follow-up MRI (bottom row) showed resolution of peripheral arterial enhancement with faint delayed peripheral enhancement, consistent with LR-TR nonviable observation.

In addition to imaging-based response assessment, serum alpha-fetoprotein (AFP), AFP-L3 (lens culinaris agglutinin-reactive fraction of AFP), and prothrombin induced by vitamin K absence-II (PIVKA-II) also known as des-gamma-carboxyprothrombin (DCP) levels are potential complementary biomarkers for detection as well as response assessment of HCC. These biomarkers have recently been incorporated in the internationally validated GALAD (gender, age, AFP-L3, AFP, and DCP) model for diagnosis and prognosis of HCC.^{16–18}

Conclusion

LRTs have expanded the therapeutic options for patients with HCC, encompassing curative, palliative, and bridge therapies for transplant candidates. Each of the LRTs can have different posttreatment appearances. The mRECIST criteria assess the patient level response in patients undergoing liver-directed therapies or targeted systemic therapy. LR-TRA is used for lesion level response criteria, applicable to patients receiving LRT. Further revision of the LR-TRA criteria is likely, in the light of knowledge of radiation-based LRT appearances.

Conflict of Interest

None declared.

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