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Assessment of Hepatocellular Carcinoma Response to Locoregional Therapy: Imaging Criteria, Algorithms, and Emerging Radiologic Tools

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is the most prevalent primary liver malignancy and a leading cause of cancer-related mortality globally. Locoregional therapies (LRTs) such as radiofrequency ablation (RFA), microwave ablation (MWA), and transarterial chemoembolization (TACE) are frequently utilized for curative or palliative purposes in patients with unresectable HCC. Accurate post-treatment response assessment is essential for guiding further management, determining prognosis, and evaluating treatment efficacy. Conventional size-based criteria, like RECIST 1.1, have shown limitations due to their inability to capture the complex pathophysiology of tumor necrosis and vascularity changes post-LRT. This review aims to provide a comprehensive overview of current radiologic approaches to assessing HCC response following locoregional therapy, focusing on structured algorithms such as modified RECIST (mRECIST) and Liver Imaging Reporting and Data System (LI-RADS) Treatment Response (LR-TR). It also highlights novel imaging biomarkers and advanced MRI techniques, including diffusion-weighted imaging (DWI), arterial subtraction, hepatobiliary phase imaging, and perfusion MRI, that have emerged as promising adjuncts in response evaluation.

Conclusion: Structured imaging criteria such as mRECIST and LI-RADS TR algorithms have significantly enhanced consistency in evaluating HCC treatment response, particularly in identifying viable tumor components based on enhancement patterns rather than size alone. However, challenges remain, including inter-reader variability and limitations in assessing atypical enhancement patterns. Advances in MRI techniques and the integration of quantitative biomarkers like ADC values and perfusion parameters may further improve diagnostic accuracy.

Keywords: *Hepatocellular Carcinoma, Locoregional Therapy, Imaging Criteria*

Introduction

Hepatocellular carcinoma (HCC) represents the most prevalent primary liver malignancy, accounting for over 90% of primary hepatic cancers worldwide. It is the third leading cause of cancer-related deaths globally, with increasing incidence driven by chronic viral hepatitis, alcohol-related liver

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disease, and the growing burden of nonalcoholic fatty liver disease [1]. Given its often late-stage presentation, many patients are ineligible for curative options such as resection or transplantation at the time of diagnosis.

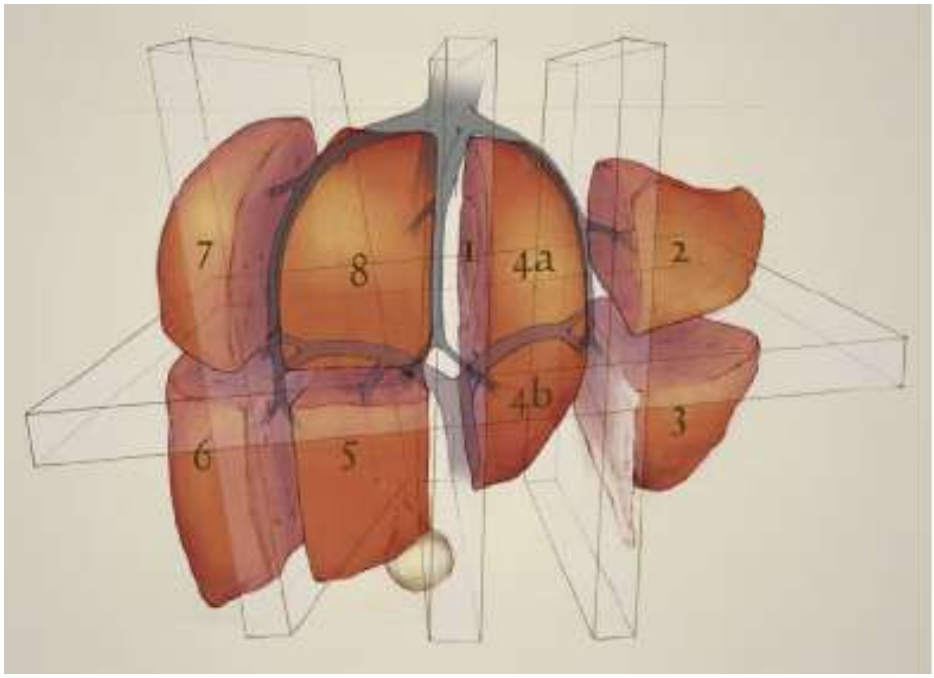

Figure (1): Segmental anatomy of the liver as originally described by Couinaud [1].

In these cases, locoregional therapies (LRTs), including transarterial chemoembolization (TACE), radiofrequency ablation (RFA), and microwave ablation (MWA), are widely employed either as bridge therapies or as primary modalities for local tumor control [2,3]. Assessing the response to these treatments is essential for decision-making regarding re-intervention, systemic therapy initiation, or consideration for transplantation.

Historically, treatment response was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST), which relies solely on changes in tumor diameter [4]. However, such criteria inadequately capture the complexity of HCC response, especially when necrosis occurs without significant size reduction. To address this, modified RECIST (mRECIST) was introduced, focusing on changes in arterial enhancement as a surrogate for viable tumor tissue [5].

Building upon this, the Liver Imaging Reporting and Data System (LI-RADS) introduced the Treatment Response (TR) algorithm, offering a standardized and structured imaging-based approach tailored to post-therapy HCC evaluation [6]. Despite the availability of these tools, variation in interpretation and limitations in cases of atypical enhancement patterns or small lesions remain challenges. Hence, understanding their strengths and shortcomings is critical for clinicians and radiologists managing HCC patients.

mRECIST: Principles, Criteria, and Clinical Utility

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The modified Response Evaluation Criteria in Solid Tumors (mRECIST) was developed to address the limitations of conventional RECIST in hepatocellular carcinoma (HCC) response evaluation. Unlike RECIST, which relies on measuring the overall tumor size regardless of viability, mRECIST targets viable tumor portions based on arterial phase hyperenhancement (APHE) observed on dynamic imaging [7].

The core concept of mRECIST is that viable HCC tissue continues to demonstrate arterial enhancement after locoregional therapy, while non-enhancing portions represent necrosis or fibrosis. Therefore, rather than measuring the longest tumor diameter, mRECIST focuses on the enhancing viable component [8]. Lesions are categorized into complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) based on changes in the sum of diameters of viable tumor regions. A CR corresponds to the disappearance of any arterial enhancement in all target lesions, while PR denotes at least a 30% reduction in the sum of enhancing areas [9].

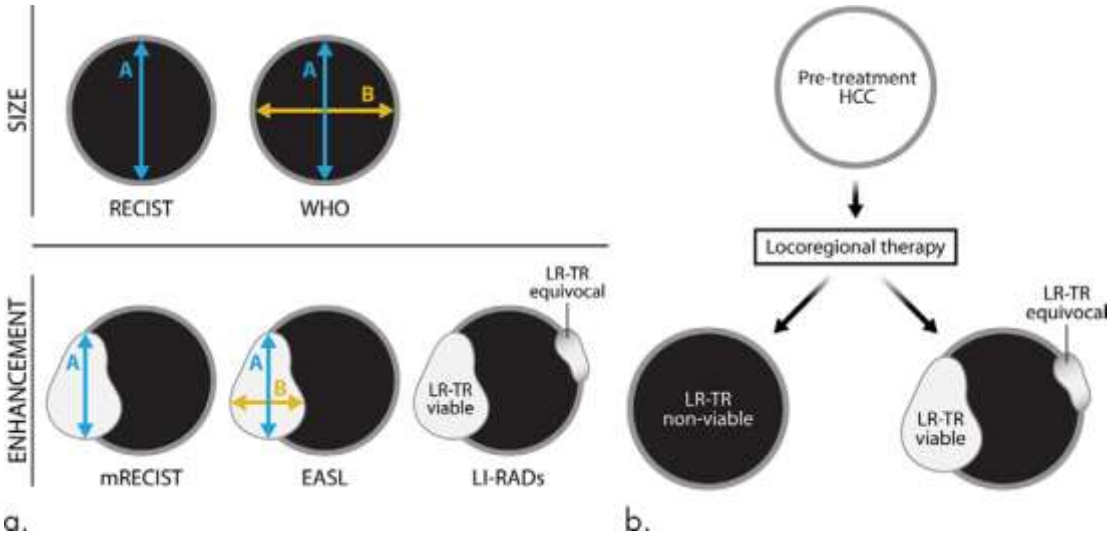

Figure (2) (a) Current tumor response classification systems used to report tumor response after treatment. Size-based classification systems include World Health Organization (WHO) criteria (bidimensional) and RECIST (unidimensional), where the size of the treated lesion is measured, regardless of enhancement. Enhancement-based classification systems include EASL (bidimensional), mRECIST (unidimensional), and more recently, LI-RADs (presence or absence of enhancement), where the size of the residual enhancing component is measured for the former two.

(b) The LI-RADS treatment response classification system is shown. EASL = European Association for the Study of Liver Diseases, HCC = hepatocellular carcinoma, LI-RAD = Liver Imaging and Reporting Data System, LR-TR = LI-RADS treatment response, mRECIST = modified RECIST, RECIST = Response Evaluation Criteria for Solid Tumors [7].

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Numerous studies have validated mRECIST's utility in predicting patient outcomes, showing a stronger correlation with overall survival and disease progression than size-based criteria [10]. For example, in patients undergoing TACE or ablation, mRECIST offers an improved ability to distinguish between responders and non-responders early in the course of therapy, allowing for timely therapeutic adjustments [11].

However, mRECIST is not without limitations. It can be challenging to apply in cases with irregular or heterogeneous enhancement, post-treatment hemorrhage, or when artifacts obscure imaging interpretation. Furthermore, small lesions or those near vascular structures may be difficult to assess reliably [12].

Despite these challenges, mRECIST remains a widely adopted and clinically validated method in both research and clinical settings for evaluating locoregional treatment response in HCC. It also serves as a foundation upon which other evaluation systems, such as LI-RADS Treatment Response (LR-TR), have been developed.

LI-RADS Treatment Response Algorithm (LR-TR): Evolution, Principles, and Classification

The Liver Imaging Reporting and Data System (LI-RADS) Treatment Response (LR-TR) algorithm was developed by the American College of Radiology to standardize imaging-based assessments of hepatocellular carcinoma (HCC) after locoregional therapy. It builds upon the limitations of RECIST and mRECIST by incorporating specific imaging features of tumor viability and offering a structured categorical interpretation [13].

Introduced formally in 2017 and updated in subsequent versions, including the 2024 iteration, LR-TR classifies treated HCC lesions into three primary categories: **nonviable**, **viable**, and **equivocal**. A “nonviable” lesion shows no arterial phase hyperenhancement (APHE), washout, or enhancement similar to pre-treatment patterns. “Viable” tumors are identified by nodular, mass-like, or irregular APHE, washout, or enhancement similar to untreated HCC. The “equivocal” category is applied when the imaging findings do not clearly indicate either viability or complete necrosis [14].

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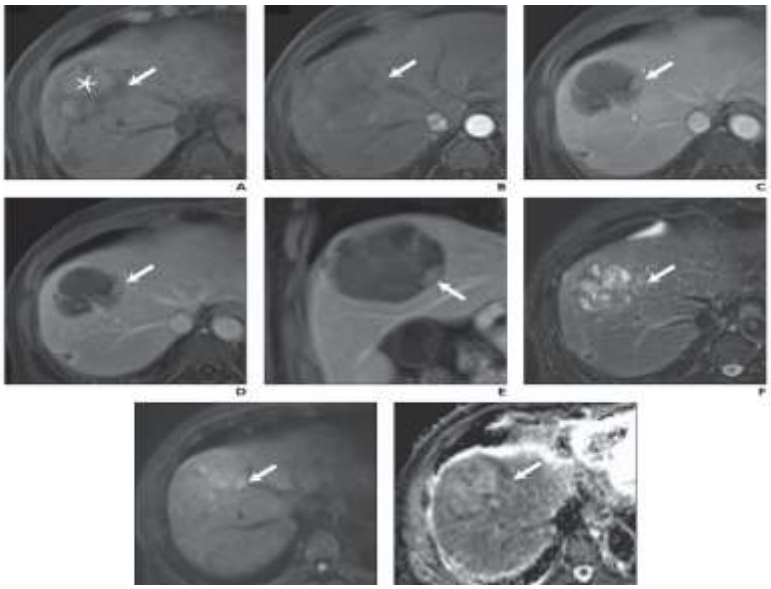

Fig.(3) 58-year-old man with segment VIII hepatocellular carcinoma treated with conventional transarterial chemoembolization (TACE). Treatment response was assessed by MRI; both study readers provided identical classifications of MRI findings and response assessment categories. A, Axial precontrast T1-weighted image shows treated lesion is predominantly hyperintense (asterisk) with smaller peripheral area of hypointensity (arrow). B, Axial late arterial phase postcontrast T1-weighted image shows masslike isoenhancement (arrow) in peripheral area. C–E, Axial portal venous phase postcontrast (C) and axial (D) and coronal (E) delayed phase postcontrast T1-weighted images show masslike hypoenhancement (arrow) in peripheral area. F, Axial fat-suppressed T2-weighted image shows mild-moderate T2 hyperintensity (arrow) in peripheral area. G and H, Axial DWI (b = 500 s/mm2) (G) and ADC map (H) show diffusion restriction (arrow) in peripheral area. Lesion was categorized by modified RECIST (mRECIST) as nonviable given absence of intratumoral arterial phase hyperenhancement. Lesion was categorized by LI-RADS Treatment Response Algorithm (TRA) version 2017 (v2017) as LR-TR Equivocal given that enhancement was atypical for treatment-specific expected enhancement, late arterial phase images did not show hyperenhancement, and portal venous and delayed phase postcontrast images did not show definitive washout. Lesion was categorized by LI-RADS Nonradiation TRA version 2024 (v2024) as LR-TR Viable given masslike enhancement of peripheral area with arterial phase isoenhancement. Lesion also showed both ancillary features in LI-RADS Nonradiation TRA v2024 (diffusion restriction and mild-moderate T2 hyperintensity). Lesion underwent surgical resection, which confirmed pathologic viability [14].

One of LR-TR's key strengths is its ability to integrate multiple post-treatment imaging characteristics from CT or MRI, including diffusion-weighted imaging and subtraction techniques. It is applicable across various treatment modalities, including transarterial chemoembolization (TACE), radiofrequency ablation (RFA), microwave ablation (MWA), and Y-90 radioembolization [15].

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LR-TR improves inter-reader agreement compared to mRECIST and has shown robust performance in predicting histopathologic viability, especially when paired with subtraction imaging or hepatobiliary contrast agents [16]. Moreover, LR-TR's integration into structured reports helps unify communication between radiologists, oncologists, and transplant teams [17].

Despite these advantages, LR-TR may still present challenges, particularly in distinguishing reactive hyperemia from residual viable tumor, especially in the early post-treatment period. Additionally, categorization into "equivocal" may lead to uncertainty in management decisions and often necessitates follow-up imaging or multidisciplinary discussion [18].

With continued refinements, including the 2024 update emphasizing ancillary features and perfusion alterations, LR-TR is increasingly becoming a cornerstone in assessing therapeutic outcomes in HCC management.

Comparative Analysis of mRECIST vs LI-RADS Treatment Response Algorithm

The evolution from RECIST to mRECIST, and more recently to LI-RADS Treatment Response (LR-TR), represents a critical advancement in evaluating hepatocellular carcinoma (HCC) response to locoregional therapies. Modified RECIST (mRECIST) remains a widely used guideline for assessing tumor response, focusing on viable tumor burden defined by enhancement in the arterial phase. However, mRECIST is limited by challenges in standardization, inter-observer variability, and applicability across various treatment modalities [19].

LI-RADS TR offers several advantages over mRECIST. While both systems recognize arterial phase hyperenhancement (APHE) as a marker of viability, LI-RADS incorporates additional features such as washout appearance, enhancement similar to pretreatment, and the option to classify findings as equivocal. This allows a more nuanced and accurate depiction of post-treatment changes, especially for ablative and transarterial therapies [20].

Furthermore, LI-RADS facilitates clearer communication among multidisciplinary teams by integrating structured templates and lexicons. Studies have demonstrated that LR-TR provides improved sensitivity and specificity for detecting viable tumor, particularly when using subtraction imaging or gadoxetic acid-enhanced MRI, compared to mRECIST [21].

Nonetheless, mRECIST still maintains clinical relevance, especially in systemic therapy trials, where quantifiable tumor burden is essential for response categorization. Some centers continue to use both systems in tandem, leveraging the quantitative strengths of mRECIST alongside the qualitative benefits of LI-RADS TR [22].

Recent meta-analyses comparing both systems found LI-RADS TR to be more accurate in identifying histopathologically confirmed viable tumors, with better inter-reader agreement [23]. However, the

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"equivocal" category in LR-TR can introduce ambiguity in management decisions, especially when used outside expert centers [24].

In summary, while mRECIST offers simplicity and quantitative assessment, LI-RADS TR provides a more detailed and flexible framework that aligns better with the complexity of locoregional HCC treatment response.

Role of Imaging Modalities in Post-Treatment Assessment

Accurate post-treatment imaging is vital for assessing therapeutic efficacy, detecting residual viable tumor, and guiding further clinical decisions in hepatocellular carcinoma (HCC) management. Magnetic resonance imaging (MRI), computed tomography (CT), and contrast-enhanced ultrasound (CEUS) are the most frequently used modalities for follow-up after locoregional therapies such as radiofrequency ablation (RFA), microwave ablation (MWA), and transarterial chemoembolization (TACE) [25].

MRI with extracellular or hepatobiliary contrast agents is widely regarded as the most sensitive imaging modality for detecting viable tumor, particularly in the context of the LI-RADS treatment response algorithm. Features such as arterial phase hyperenhancement (APHE), washout appearance, and capsule appearance are better appreciated with MRI, especially when subtraction imaging is applied to identify subtle APHE obscured by pre-existing hyperintensity on unenhanced images [26]. Diffusion-weighted imaging (DWI) also contributes by highlighting areas of restricted diffusion that may correspond to viable tumor [27].

CT, while more accessible and widely used, has limitations in detecting small foci of residual disease. However, it remains useful in many centers due to its availability, speed, and reproducibility. The timing and type of contrast injection critically impact diagnostic performance. For example, insufficient arterial enhancement can reduce sensitivity to APHE [28].

CEUS offers a real-time, cost-effective alternative, particularly useful in follow-up after ablation. Its utility is limited by operator dependency and inability to evaluate the entire liver in one examination, but it can be valuable in detecting local recurrence at the ablation margin [29].

The choice of imaging modality should be guided by available resources, patient factors (e.g., renal function, claustrophobia), and institutional experience. In general, MRI is preferred where available due to its superior sensitivity and compatibility with LI-RADS-based assessments.

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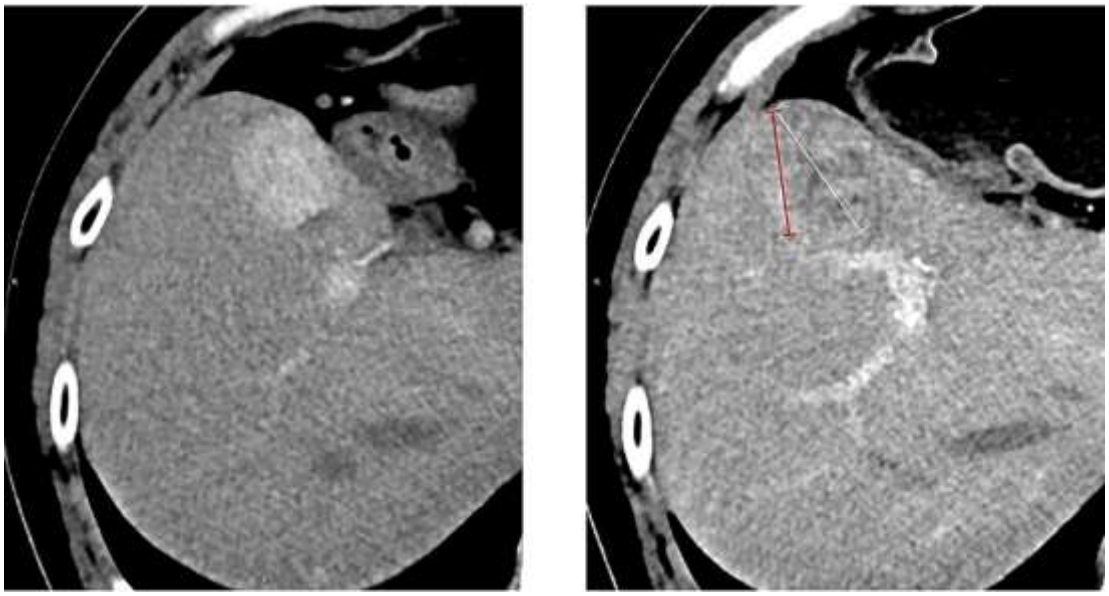

Figure (4): Measurement of the longest tumor diameter in a target hepatic lesion: mRECIST vs. RECIST 1.1. Arterial-phase CT scan obtained after immunotherapy. According to RECIST 1.1, the overall longest diameter of the tumor is captured (*white arrow*), regardless of the presence of a large area of intratumoral treatment-induced necrosis. In contrast, mRECIST measurement (*red arrow*) only includes the longest diameter of the viable portion of the tumor, as recognized by contrast enhancement. A 54-year-old man who had an arterial-phase CT examination before and after 27 cycles of immunotherapy. The baseline CT size of the target hepatic lesion was 30 mm (**left**). After immunotherapy, follow0up CT (**right**) showed treatment response of previous lesions. The response was assessed as PD according to RECIST 1.1 (47 mm) and SD based on mRECIST (34 mm) [26].

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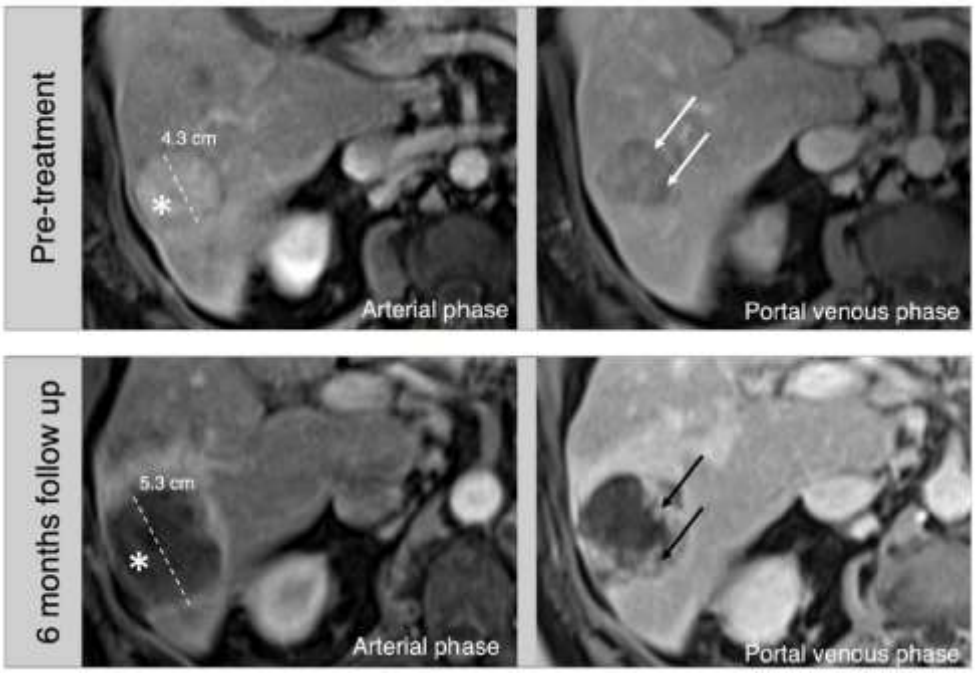

Figure (5): 76-year-old male, hepatitis C cirrhosis, MR images. On pretreatment images, a 4.3 cm arterial phase hyperenhancing (*asterisk*) observation with portal venous phase washout (*arrows*) in the right lobe is consistent with HCC (LR-5). Follow-up images 6 months after Y-90 radioembolization shows a larger appearance of the mass due to treatment changes. The lack of arterial phase hyperenhancement (*asterisk*) and irregular progressive enhancement on portal venous phase (*black arrows*) are consistent with posttreatment changes (LR-TR Nonviable) [27].

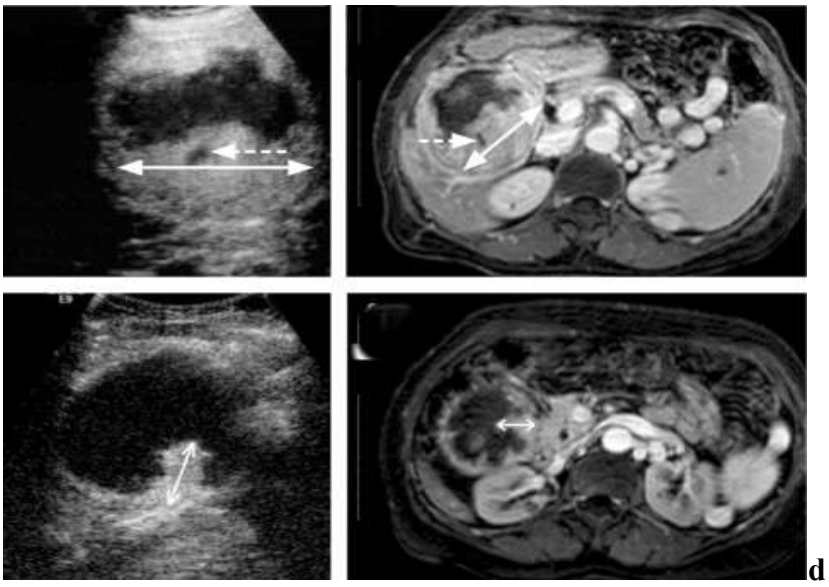

Figure (6): The contrast-enhanced ultrasonography (CEUS) images of the same tumor at baseline (**a**), and at follow-up, one month after the third session of TACE (**c**), show a significant decrease in the viable (enhancing) components of the tumor. Axial contrast-enhanced MR images of the tumor at baseline (**b**) and one month after the third session of TACE (**d**) confirm the decrease of tumoral enhancement. Double-headed arrows indicate the

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longest diameters of the enhancing parts of the tumors. In accordance with mRECIST guidelines, small necrotic areas (*dotted arrows*) and was diagnosed as a partial response [27].

Interpretation Pitfalls and Limitations of Response Criteria

While imaging-based criteria have significantly improved the standardized assessment of hepatocellular carcinoma (HCC) treatment response, several pitfalls and limitations must be considered to avoid misinterpretation and mismanagement.

One major challenge is the overlap in imaging features between post-treatment changes and residual viable tumor. For instance, hyperemia or reactive granulation tissue at the periphery of an ablation zone may mimic arterial phase hyperenhancement (APHE), leading to false-positive interpretations [30]. Similarly, coagulative necrosis after treatment may exhibit persistent hyperintensity on T1-weighted MRI or lack of contrast washout, confusing viable tumor with benign post-treatment tissue [31].

Timing of follow-up imaging is another critical factor. Performing imaging too early (e.g., within the first two weeks) after locoregional therapy may yield inconclusive results due to transient inflammatory changes, hemorrhage, or incomplete tumor necrosis [32]. Optimal imaging windows vary by modality and treatment type but are generally recommended between 4 to 6 weeks post-therapy.

Inter-reader variability is a recognized limitation, especially in borderline or equivocal cases. Despite the use of standardized systems like LI-RADS Treatment Response (LR-TR), interpretation can differ depending on reader experience and institutional protocols. Studies have reported moderate to substantial interobserver agreement, indicating room for improvement [33].

Moreover, current criteria such as LI-RADS TR and mRECIST primarily focus on enhancement characteristics, which may overlook infiltrative tumor components or extrahepatic spread that lack typical enhancement patterns [34]. In such cases, supplementary tools like diffusion-weighted imaging (DWI) or positron emission tomography (PET) may enhance diagnostic accuracy but are not yet standardized in guidelines.

Finally, limitations exist in evaluating lesions treated with radiation segmentectomy or stereotactic body radiotherapy (SBRT), where tumor necrosis evolves over a longer period, and enhancement patterns may not follow conventional criteria [35].

A comprehensive understanding of these limitations is essential for accurate assessment and to guide appropriate clinical decisions.

Conclusion

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Accurate and timely assessment of treatment response in hepatocellular carcinoma (HCC) is a cornerstone of effective disease management, particularly in patients undergoing locoregional therapies. While conventional criteria such as RECIST and mRECIST offer structured evaluation based on size and enhancement patterns, they are limited in capturing the complex biological behavior of treated lesions. LI-RADS, especially its treatment response algorithm (LI-RADS TRA), represents a major advancement by standardizing terminology and improving diagnostic confidence in interpreting post-therapeutic imaging.

Nonetheless, evolving challenges—including treatment-induced imaging artifacts, the presence of atypical enhancement patterns, and the difficulty of distinguishing viable tumor from necrotic or fibrotic tissue—necessitate the integration of advanced imaging modalities. Functional MRI, diffusion-weighted imaging, and emerging techniques such as radiomics and artificial intelligence are showing promise in refining assessment accuracy and predicting clinical outcomes.

Furthermore, the incorporation of serologic markers and multimodal imaging strategies is increasingly recognized as essential to a holistic evaluation framework. These approaches not only improve early detection of residual or recurrent disease but also facilitate personalized therapeutic decision-making, enhancing overall patient outcomes.

Looking forward, continued validation of emerging tools in large-scale, multicenter studies is needed to establish their role in routine clinical practice. With further technological advancement and integration of imaging biomarkers, the future of HCC treatment response assessment holds the potential for more precise, individualized, and adaptive management pathways.

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