Updates on LI-RADS Treatment Response Criteria for Hepatocellular Carcinoma: Focusing on MRI

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Abstract

As the incidence of hepatocellular carcinoma (HCC) and subsequent treatments with liver-directed therapies rise, the complexity of assessing lesion response has also increased. The Liver Imaging Reporting and Data Systems (LI-RADS) treatment response algorithm (LI-RADS TRA) was created to standardize assessment of response after locoregional therapy (LRT) on contrast-enhanced CT or MRI. Originally created based on expert opinion, these guidelines are currently undergoing revision based on emerging evidence. While many studies support the use of LR-TRA for evaluation of HCC response after thermal ablation and intra-arterial embolic therapy, data suggests a need for refinements to improve assessment after radiation therapy. In this manuscript, we review expected MR imaging findings after different forms of LRT, clarify how to apply the current LI-RADS TRA by type of LRT, explore emerging literature on LI-RADS TRA, and highlight future updates to the algorithm.

Keywords

Introduction

Hepatocellular carcinoma (HCC) is the fourth leading causes of cancer-related deaths worldwide [1]. Management of HCC is variable, and while hepatic transplant offers the best outcomes, limitations include organ availability and other patient-related factors (eg. tumor stage and non-candidates for transplant). Other treatment options for HCC include surgical resection and minimally invasive locoregional therapies (LRT) including ablation, intra-arterial embolic therapy, radiation therapy, and systemic chemotherapy or immunotherapy. These can also be used for curative intent, palliative intent, or bridging and downstaging to transplant[2]. Given the correlation between treatment response and patient prognosis, it is essential to provide an accurate response assessment after treatment to help guide clinical management[3].

Imaging surveillance after HCC treatment is usually performed every 3 months with multiphasic contrast-enhanced CT or MRI [4–6]. The LI-RADS treatment response algorithm (LI-RADS TRA) was created in 2017 based largely on expert opinion to provide a standardized approach for treatment response assessment and to help guide

clinical management. Emerging evidence on the validity of the LI-RADS TRA continues to accumulate, with several new publications reporting the diagnostic performance of the algorithm in predicting tumor viability on pathology, its correlation with patient survival, and inter-reader agreement when using LI-RADS TRA. In this review, we highlight expected MR imaging findings after different forms of LRT, clarify how to apply the current LI-RADS TRA based on the type of LRT, provide an update on the current LI-RADS TRA, highlight strengths and weaknesses of MRI for TRA after LRT for HCC, and suggest updates to improve future versions of the algorithm.

Review of LI-RADS TRA

The LI-RADS TRA provides a standardized approach for image acquisition, interpretation, reporting, and data collection for HCC treated with LRT. It is unique in providing a lesion-level assessment of treated observations while other treatment response systems provide a patient-level assessment (mRECIST, EASL). This is important for this high-risk patient population in which metachronous disease is common, particularly when patients may undergo several different types of LRT over time, based on patient factors, stage of disease, and tumor factors like size and location. Each treated lesion must be evaluated for treatment response to best assess tumor burden for the purposes of bridging and downstaging for liver transplant.

Currently, treatment response assessment is performed by evaluating treated lesions with multiphasic contrast-enhanced CT or MRI with either extracellular or hepatobiliary contrast agents. The key imaging feature used to categorize treatment response is the presence or absence of masslike arterial phase hyperenhancement (APHE). Based on the LI-RADS TRA, additional imaging features used for response assessment include washout and enhancement similar to pre-treatment[7]. [Figure 1] Regardless of the type of LRT used, LI-RADS TRA v2018 categorizes lesions as LI-RADS Treatment Response (LR-TR) Viable, Nonviable, or Equivocal. By strict application of LI-RADS criteria, lack of enhancement of the treated lesion is compatible with Nonviable categorization. However, the imaging appearances of treated HCC vary depending on the type of LRT performed, and it is therefore essential for the radiologist to understand not only the expected post-therapy imaging appearances after each type of LRT, but also the type of treatment each lesion has received in order to accurately characterize treated versus nontreated disease and ensure appropriate patient management.

Expected Imaging appearance of HCC treated with LRT

Broadly speaking, LRT can be divided into two main groups when assessing treatment response: non-radiation and radiation-based therapies. [Table 2] Non-radiation therapies include thermal ablation (ie., radiofrequency ablation (RFA), microwave ablation (MWA), and cryoablation), and intra-arterial embolic therapy (ie., transarterial embolization (TAE), conventional trans-arterial chemoembolization (cTACE), or drug eluting bead TACE (DEB-TACE))[8]. Radiation-based therapies include stereotactic body radiotherapy (SBRT) and transarterial radioembolization (TARE). To accurately assess the treatment response of HCC, radiologists must be aware that HCC appears different after treatment with non-

radiation-based therapies compared to radiation-based therapies, due to differences in pathophysiology of cell death between the different treatment modalities. In the first group, cell death is achieved by coagulation necrosis from thermal destruction or ischemic and/or cytotoxic mechanisms from arterial embolic therapies. On the other hand, radiation-induced cell death can occur via one of two pathways: direct DNA damage resulting in immediate apoptosis and cell death, or indirect damage to the DNA resulting in cellular senescence [9, 10]. In the second pathway, cellular senescence results in metabolically active cells without the capacity to replicate, and thus the cells eventually die without tumor progression [9, 10]. Thus, the imaging appearance of irradiated HCC will often differ from other more conventional forms of LRT, as the senescent cells remain metabolically active and maintain vascular perfusion, albeit are 'dead' in terms of clonogenicity, as they cannot replicate and will eventually undergo apoptosis[9, 10].

Expected imaging appearance of non-radiation treated HCC

After RFA, MWA, or cryoablation, tumor necrosis is instantly achieved, resulting in loss of intralesional perfusion and enhancement, which would be categorized as LR-TR Nonviable. [Figure 2] Other key imaging features expected after these treatment strategies include: a thin continuous rim of smooth peripheral enhancement secondary to inflammation[11], geographic APHE within the parenchyma surrounding the treatment zone which can be isoenhancing or hyperenhancing on portal venous and delayed phases of imaging [12], and coagulative necrosis centrally within the treated lesions resulting in hyperintense signal on pre-contrast T1-weighted images [5, 11]. Subtraction images may be used to confirm a lack of central enhancement, particularly when coagulative necrosis is present. [Figure 2] The presence of these key imaging findings allow categorization of the treated tumor as LR-TR Nonviable according to LI-RADS TRA v2018.

Early, transient apparent increase in the size of the treatment zone may occur post-treatment from intentional ablation of a zone larger than the tumor (after thermal ablation) or from underlying edema or hemorrhage (after arterial embolic therapy), typically followed by decreases in size over time on serial follow up exams[11]. Creation of an ablation margin at least 5–10 mm larger than the original tumor is essential to ensure adequate treatment margins encompassing any microscopic tumor to prevent early post-treatment recurrence[11]. Over time, the ablation cavity will slowly involute, although it usually does not completely resolves.

Following thermal ablation or intra-arterial embolic therapy, key imaging features of locally recurrent or residual viable HCC include irregular or masslike areas of APHE, APHE plus washout, washout alone, or enhancement similar to the pretreatment tumor. [11] Such cases are categorized as LR-TR Viable according to LI-RADS TRA v2018. [Figure 3] LR-TR Equivocal categorization is intended for lesions that do not have imaging criteria to suggest "probably viable" or "definitely viable" disease. LR-TR Equivocal is often used when there is subtle atypical enhancement in the hepatic parenchyma surrounding a treated lesion, which could reasonably represent either abnormal perfusion post-treatment versus true tumoral enhancement[11]. Equivocal categorization allows for a 'wait and watch' approach, during which subsequent reimaging can help to reassess the potential for viability.

Unlike in the LI-RADS diagnostic algorithm, use of ancillary features (diffusion restriction, mildly hyperintense T2-weighted signal and hepatobiliary phase hypointensity) is not part of LI-RADS TRA v2018.

CT and MRI are generally both regarded as acceptable for the follow-up of treated disease. However, one imaging pitfall after transarterial embolic therapy with iodized oil is that the embolic material appears hyperdense on non-contrast CT, which may obscure subtle areas of enhancement within and along the treatment zone, thus confounding evaluation for viable tumor[13] [Figure 4]. In these cases, MRI is a better imaging modality for treatment response assessment, as the iodized oil is not seen on MRI, and thus more accurate assessment of response can be provided[14]. On the other hand, an advantage of using iodized oil is that staining patterns within the targeted tumor can be a biomarker for treatment response by predicting lesion necrosis and outcomes in patients. Staining patterns within and around a targeted tumor, such as increased density of oil deposition within a targeted tumor, dense homogenous staining patterns, and a rim of ethiodized oil deposition surrounding the radiographically visible margin of the tumor are signs of excellent treatment response. [15–18] Such staining patterns have shown to be associated with lower rates of early post-treatment recurrence [15–18]. [Figure 4]

Expected imaging appearance of Radiation-treated HCC

In contrast, to ablation and embolic arterial therapy, lesions treated with radiation-based therapies (SBRT and TARE) have a distinct post-treatment imaging appearance based on the previously described complex mechanism of cell death. Some irradiated lesions exhibit immediate non-enhancement on MRI, compatible with an LR TR Nonviable categorization. However, a large proportion, greater than 50%, demonstrate irregular nodular or masslike APHE with or without washout, which can persist for a year or longer[19, 20]. [Figure 5] Emerging data suggests that enhancement and size of the treated lesion should gradually decrease over time if nonprogressing or nonviable, unlike viable tumors in which an increase in enhancement and/or size are imaging biomarkers for progression and should warrant discussion at multidisciplinary conference[21–23]. [Figure 6]

With strict application of LI-RADS TRA v2018 criteria, HCC treated with radiation-based therapy would be categorized as LR-TR Nonviable if there is no enhancement, LR-TR Equivocal if there is persistent post-treatment enhancement with stable to decreasing size, and LR-TR Viable if there is new or increasing enhancement and/or increasing size. Although LR-TR Equivocal lesions may harbor viable tumor after SBRT, they most often necrose over time. This natural history is different than LR-TR Equivocal categorization of lesions treated with non-radiation based treatment which frequently progress over time and often require retreatment [23–26]. This difference is likely a result of the different mechanisms of cell deathinduced by radiation versus non-radiation therapies.

Additional imaging findings commonly seen after radiation-based treatment include extensive perfusional changes within the liver parenchyma surrounding the treated tumor. Comparison of the pre-treatment imaging to the post-treatment imaging is essential to identify the margins and size of the treated tumor and distinguish peri-tumoral perfusional changes from viable tumor. Other findings that can help distinguish perfusional changes

from tumor include that perfusional changes tend to be geographic in shape, hyperenhancing on arterial phase and hyperenhancing or isoenhancing to background parenchyma on portal venous and delayed phases of imaging, instead of a washout[5, 20, 27] [Figure 5, 6]. In contradistinction, the radiation treated tumor can demonstrate persistent enhancement with washout, although, as mentioned above, persistent APHE and washout are expected post-radiation changes[19]. One way to distinguish clinically significant viable tumor from expected post radiation changes is to evaluate change and size of APHE over time, specifically, if the area of questionable APHE and washout are new when compared to pre-treatment or preceding post-treatment imaging. On MRI, new APHE or increasing intensity of enhancement over time on post-treatment imaging follow-up studies is an important feature suggesting local recurrence and should prompt classification of a lesion as LR-TR Viable [11, 20, 23]. [Figure 6]

Emerging Evidence Assessing the Diagnostic Performance of the LI-RADS TRA

To be clinically useful, any treatment response classification system must be assessed for validity and performance. The LI-RADS TRA is a relatively new algorithm based on expert opinion, and thus validation studies assessing performance and survival are important to support its use clinically. There is significant emerging data assessing diagnostic performance of the LI-RADS TRA via inter-reader reliability and radiologic-pathologic correlation, particularly for local ablative and intra-arterial embolic therapies. Usefulness of a treatment response algorithm requires the need for high inter-reader agreement since the final interpretation dictates patient management. Additionlly, the performance of LR-TR categories to predict outcomes data such as overall survival (OS), time to progression (TTP), and disease-free survival (DFS) is important from a clinical perspective for patient management.

Diagnostic Performance of Locoablative and Non-Radiation Arterial-based Therapies

Several recent metanalyses have evaluated the diagnostic performance of LI-RADS TRA in predicting incomplete necrosis based on pathology as the gold standard and have shown excellent performance after ablation and intra-arterial embolic therapy. Perhaps the most comprehensive analysis performed by Kim et al included 8 studies evaluating the diagnostic performance of LI-RADS TRA[28]. This metanalysis of 851 treated HCCs demonstrated an inter-rater reliability k of 0.55–0.94, with a pooled k of 0.70 (95% CI, 0.58–0.82) on CT and MRI. When evaluating inter-rater reliability of MRI alone as an imaging modality for TRA, pooled k was 0.71 (95% CI, 0.53–0.89), suggesting substantial inter-rater reliability for MRI to assess TRA after LRT for HCC [28]. [Table 1]

A more recent study systematically evaluated the LR-TR Viable category for detection of pathologically viable HCC after non-radiation LRT. For this category, the pooled sensitivity and specificity was 58% (95% CI, 45%–70%) and 93% (95% CI, 88%– 96) for pathologic detection of incomplete necrosis[29]. In another meta-analysis using similar studies as the

aforementioned study, they performed a subgroup analysis of LR-TR Viable categorization based on MRI as the imaging modality for detection of incomplete necrosis in 379 non-radiation treated HCCs and demonstrated sensitivity and specificity of 0.60 (0.46–0.74) and 0.90 (0.84–0.97), respectively[30]. Both of these studies evaluating radiology and pathology concordance of the current LR-TRA, suggest that the current LR-TRA is effective for detection of Viable HCC after non-radiation LRT. Furthermore, it has also been shown that interreader reliability for LR-TR categorization as a whole was moderate to substantial for MRI (k = 0.56–0.69), comparable to CT (k = 0.69)[29]. [Table 1] These findings suggest that readers with varying levels of experience can assign LI-RADS TRA categories on multiphase imaging with moderate to substantial agreement.

While most evidence suggests a high sensitivity of the LI-RADS TRA for detection of viable and nonviable disease, the data for the LR-TR Equivocal categorization remains less convincing. Most studies show higher sensitivities for predicting incomplete necrosis when the LR-TR Equivocal category is treated as viable rather than non-viable [24, 31]. For example, Chaudhry et al found a sensitivity of 81–87% for predicting incomplete necrosis when the equivocal category was considered viable versus 40–77% when considered nonviable, with little difference in specificity (81–85% versus 85–97%, respectively)[31]. Similarly, another study reported improved sensitivity, specificity, and positive predictive value (PPV) of 44%, 99% and 93% for predicting incomplete necrosis when the equivocal category was considered viable versus 30%, 86% and 67% when considered non-viable, respectively[32] A third study demonstrated that 71% of non-radiation treated HCC with LR TR Equivocal categorization had pathologically viable tumor on explant, thus increasing the evidence that LR TR Equivocal category warrants close follow-up because of the likelihood of persistent viable disease. [24].

A recent metanalysis by Kim et al. showed pooled sensitivities for the LR-TR Viable category alone for diagnostic detection of incomplete necrosis was 0.56 (95% CI 0.43–0.69) with a specificity of 0.91 (95% CI 0.84–0.96) and area under the curve of 0.86 (95% CI 0.82–0.88). However, when combining the LR-TR Viable and Equivocal categories for detection of incomplete necrosis on pathology, the pooled sensitivity and specificity was 0.73 (95% CI 0.60–0.84) and 0.82 (95% CI 0.74–0.88), respectively[30]. This is corroborated by a recent meta-analysis which reviewed TRA of HCC treated with ablation or embolic therapy and showed that the majority (70.5%) of LR TR Equivocal lesions were viable[33]

Based on the aforementioned data, most lesions categorized as equivocal after ablation or embolic therapy are likely incompletely necrotic following ablation and intra-arterial embolization. Low sensitivity is likely in part due to the challenges of conventional imaging to detect pathologic microscopic viable tumor. The LR-TR Equivocal category is most often applied in questionable areas of enhancement, and thus presumably represents small volumes of viable tumor with limited clinical impact, as HCC tumor doubling times are reported to be 70–180 days.[34] Therefore, we advocate for imaging surveillance intervals of 3 months after equivocal categorization, as viable tumor will eventually declare itself over time.

The above studies support the use of LI-RADS TRA v2018, but the agreement seen per feature of the LR-TR categories must also be evaluated to ensure the validity and clinical utility of the current algorithm. The key features of the LI-RADS TRA include APHE, washout, and enhancement similar to pretreatment, the latter two of which are novel features when evaluating treatment response as compared to other response classification systems (e.g. modified Response Evaluation Criteria in Solid Tumors (mRECIST) and European Association for the Study of Liver Disase (EASL)). Multiple studies show that APHE has the highest diagnostic accuracy for predicting incomplete necrosis (AUC 0.69, 95% CI: 0.58–0.80), whereas lack of APHE and decreased size have the highest accuracy for predicting complete necrosis (AUC 0.75, 95% CI: 0.62–0.88)[24, 31, 35, 36]. Studies evaluating LI-RADS TRA features show relatively high interreader agreement in APHE (κ = 0.71–0.80), washout (κ = 0.67–0.72), and enhancement similar to pretreatment (κ = 0.62 to 0.73)[25, 37, 38].

However, while interreader agreement on the presence of imaging features is high, the actual diagnostic performance of each individual imaging feature did not perform as well in terms of interreader agreement. In a metanalysis by Kim et al, they show that the pooled sensitivity for detection of incomplete necrosis was substantially higher using APHE (0.67 [95% CI 0.51–0.81]) than washout (0.43 [95% CI 0.26–0.62]) or enhancement similar to pretreatment (0.24 [95% CI 0.15–0.36]). Furthermore, in lesions with incomplete pathologic necrosis, the pooled proportion of lesions showing washout without APHE was 2%, enhancement similar to pretreatment without APHE was 1% and enhancement similar to pretreatment with neither APHE nor washout was 0%[30]. According to a metanalysis by Huh et al, pooled calculations of sensitivity for each LI-RADS TRA feature from 10 studies with a composite cohort of 971 patients and 1153 observations post-LRT showed that the presence of APHE provided the highest sensitivity (81%) for diagnosing viable HCC following LRT, while washout (55%) and enhancement similar to pretreatment (21%) demonstrated suboptimal performance; specificity amongst all 3 features was high (95–98%)[38]. This pooled analysis across a variety of post-LRT studies reinforces the singular importance of APHE in detection of viable tumor, which is the best indicator of incomplete necrosis, and the most agreed upon LI-RADS TRA feature. These data will be used for future modifications in the LI-RADS TRA.

Current evidence assessing diagnostic performance of LI-TRA with Radiation-based therapies

Studies have shown SBRT and TARE to be effective treatment options for downstaging or bridging to transplant[39–42]. While SBRT shows promising outcomes for HCC treatment, lack of prospective randomized comparative clinical trials for predicting survival outcomes limits widespread clinical adoption and inclusion of SBRT as a treatment modality in the updated Barcelona Clinic Liver Cancer (BCLC) staging system. However, strong evidence from the recent LEGACY (Local radioEmbolization using Glass Microspheres for the Assessment of Tumor Control with Y-90) trial has allowed for modification of the new BCLC 2022 staging system to incorporate TARE as a treatment option for HCC[43]. With

increasing use of radiation as a form of LRT for HCC, accurate assessment of post-treatment imaging is critical to ensure appropriate patient management.

As mentioned above, HCC treated with radiation therapy usually demonstrates post-treatment persistent APHE, a feature LR-TRA uses to categorize lesions as viable. Thus, this imaging feature confounds treatment response assessment after radiation using current response assessment systems (LI-RADS TRA, mRECIST) and can result in a high rate of potential misclassification of treated disease as LR-TR Viable, which could result in unnecessary retreatment of already successfully treated HCC. One challenge in validating response assessment systems after radiation therapy is the paucity of studies correlating post-radiation imaging findings with pathology. Additionally, the mechanism of radiation-induced cell death complicates the application of imaging features to determine a final LR category. Since radiation can induce cellular senescence, cell death is not always immediate and evolves over time[44]. Thus, strict application of the current LI-RADS TRA would suggest that 'viable' categorization may be appropriate when radiation-treated HCC demonstrates persistent APHE; however, the clinical implication is different than disease radiologically categorized as 'viable' after conventional LRT.

To date, there is only one study evaluating the diagnostic performance of the LI-RADS TRA in assessing HCC viability after SBRT using radiology-pathology concordance[23]. In this study, decreasing APHE after treatment highly correlated with complete pathologic necrosis, although persistent post-treatment APHE was still seen in 45% of tumors that were completely necrotic on pathology[23]. Inter-reader agreement was fair ($\kappa = 0.22$) for LR-TRA categorization of HCC treated with SBRT. Additionally, LI-RADS TRA was able to predict complete (sensitivity 71–86%, specificity 85–96%, NPV = 85–96%) and incomplete tumor necrosis (sensitivity 88–96%, specificity 71–93%, PPV = 88–92%, with LR-TR Equivocal lesions considered viable)[23]. 67% of lesions categorized as LR-TR Equivocal were found to be incompletely necrotic at histopathology, a finding which is not unexpected since SBRT-treated HCC demonstrating persistent APHE on imaging were categorized as LR-TR Equivocal by the readers. Concordant with other prior results, they also found that a longer time to transplant from treatment resulted in greater loss of APHE (OR 0.68) and increasing degree of necrosis (OR 0.2). These findings suggest that radiated lesions categorized as 'equivocal' should be followed rather than immediately retreated, as pathologically viable tumor will usually necrose over time, given the normal course and pathophysiology of radiation induced cell death.

The data supporting TARE for HCC is more robust because of several large clinical trials. Like SBRT-treated HCC, the appearance of HCC treated with TARE is variable, ranging from complete necrosis immediately after treatment to varying degrees of intralesional APHE which can persist for some time after treatment [45]. Riaz et al show that 61% of HCCs treated with TARE exhibited complete pathologic necrosis despite residual nodular APHE on post-treatment imaging [22]. King et al evaluated the performance of LI-RADS TRA versus mRECIST in predicting treatment response after TARE in 57 patients with 77 HCCs and found that LI-RADS TRA was a better predictor of pathologic necrosis and treatment response[46], a finding which was confirmed by Violi et al[47]. Few studies have

assessed the ability of LI-RADS TRA to predict overall survival following radiation-based therapies, and further longitudinal studies are needed.

Performance of Ancillary Features and Evidence Supporting the Use in LIRADS TRA

An emerging area of interest is the utility of ancillary features, including T2-weighted (T2W) signal abnormality, hepatobiliary phase (HBP) hypointensity, and restricted diffusion [48], in improving detection of viable tumor following LRT. Currently the LI-RADS TRA uses only major features (APHE and washout) for determining tumor viability after LRT. However, recent radiology-pathology studies demonstrate improved diagnostic performance for detection of viable tumor post-LRT using MRI-based ancillary features (AF), specifically mild T2 weighted hyperintensity, restricted diffusion and hepatobiliary phase hypointensity. Park et al evaluated the utility of adding MRI-based AF in category adjustment for detecting viable tumor as compared to LR-TR categorization using only major imaging features of APHE and washout on MRI[37]. They showed higher sensitivities of detecting tumor viability when using AFs (84% (91/108)) to upgrade to viable category as compared to enhancement alone on MRI (76% (82/108)) without differences in specificity[37]. Similarly, Kim et al showed an increase in the sensitivity for detecting viable tumor when using LI-RADS TRA with AF (sensitivity 64.5% without AF vs. 86.9% with AF) and no difference in specificity (98% vs. 97%)[49]. In both studies, the presence of AF corresponding to areas of questionable APHE allowed upgrading of the category from LR-TR Equivocal to LR-TR Viable, and had high concordance with pathologic viability. Both studies showed an overall decrease in use of LR-TR Equivocal categorization when adding AF to assess for tumor viability.

Additional smaller studies confirm improved detection of tumor viability with the addition of AFs. For example, in a radiology-pathology study of 181 HCCs, the presence of hepatobiliary phase hypointensity in a lesion categorized as LR-TR Viable or LR-TR Equivocal compared to LR-TR Viable alone demonstrated improved sensitivity for detection of viable tumor (65.6% versus 57%) with no significant difference in specificity (90.8% versus 94.3%)[50]. Another study showed that using restricted diffusion corresponding to equivocal areas of APHE improved sensitivity for detection of viable disease than when not using AF (92% versus 85%)[51] Overall, findings suggest that a modified TRA utilizing ancillary MR features may be superior to the LI-RADS TRA alone in detecting viable tumor and may result in lower use of 'equivocal' classification [52].

LIRADS TRA: Current Limitations and Future Directions

We have demonstrated a host of emerging data describing post-LRT imaging appearances, as well as supporting the validity of the LI-RADS TRA to predict necrosis. Most studies demonstrate excellent diagnostic performance of the LI-RADS TRA; however, emerging data also reveals key limitations. First, the current LI-RADS TRA must be modified to incorporate more accurate treatment response assessment after radiation therapy based on the unique pathophysiology of radiation induced cell death which results in persistent post-treatment APHE, a feature currently used to assign tumor viability based on all

treatment response systems. Second, studies continue to demonstrate the utility of AFs in improving the sensitivity of viable tumor detection. Improved post-treatment categorization will ultimately impact patient management. Third, further guidance on treatment response assessment for HCC treated with combination LRT and systemic and immunotherapies must be clarified since they are not part of the current algorithm. This will likely require longitudinal studies to obtain enough evidence to validate or update existing LI-RADS TRA. Fourth, improved guidance on structured template reporting and an updated lexicon for LI-RADS TRA will be critical to allow for improved standardization and concordance in image interpretation in this cohort of patients. Finally, treatment response assessment using contrast enhanced ultrasound is currently under investigation and future studies are necessary in order to develop its utility in TRA.

Conclusion

The expanding number of available LRTs has increased the complexity of treatment response assessment. Post-treatment imaging for treatment response assessment is essential to guide patient management. Understanding the various expected post-treatment imaging findings specific to each form of LRT is key to accurately categorizing treated lesions. LI-RADS TRA provides a framework to describe treatment response using a lesion-level approach with emerging evidence suggesting high validity and reliability in using this algorithm after non-radiation-based therapies. Emerging data also reveals that the LI-RADS TRA should be used cautiously when evaluating treatment response after radiation-based therapies since persistent APHE is common and expected after irradiation of HCC. Furthermore, emerging data suggests that the use of AFs improves sensitivity for detection of viable disease, although the impact on overall survival and time to progression is currently unknown. This constellation of evidence has resulted in modifications of the existing LI-RADS TRA v2018, with a separate categorization system for radiation-treated HCC and incorporation of AFs to allow category upgrades, similar to the LI-RADS diagnostic algorithm. This new algorithm is currently in the final stages of approval by the LI-RADS treatment response working group, steering committee, and the American College of Radiology, and will be released in 2023.

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Terminology:

HCC	hepatocellular carcinoma
LI-RADS	Liver Imaging Reporting and Data Systems
LI-RADS TRA	Treatment response algorithm
LRT	locoregional therapy

APHE	arterial phase hyperenhancement
LR-TR	LI-RADS Treatment Response
RFA	radiofrequency ablation
MWA	microwave ablation
TAE	transarterial embolization
cTACE	conventional trans-arterial chemoembolization
DEB-TACE	drug eluting bead TACE
SBRT	stereotactic body radiotherapy
TARE	transarterial radioembolization
OS	overall survival
TTP	time to progression
DFS	disease-free survival
PPV	positive predictive value
NPV	negative predictive value
mRECIST	modified Response Evaluation Criteria in Solid Tumors
EASL	European Association for the Study of Liver Disase
HBP	hepatobiliary phase
AF	ancillary features
BCLC	Barcelona Clinic Liver Cancer

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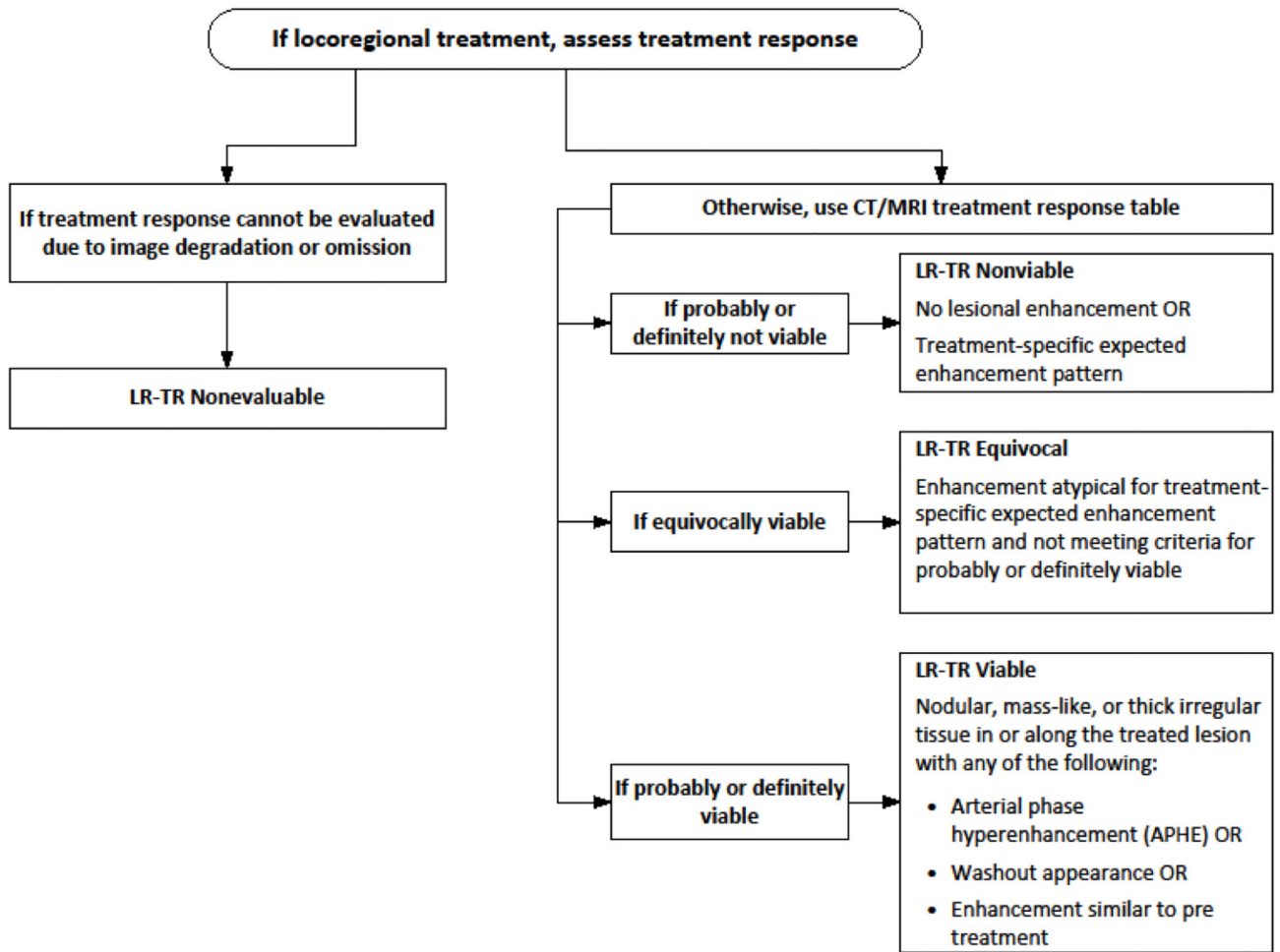
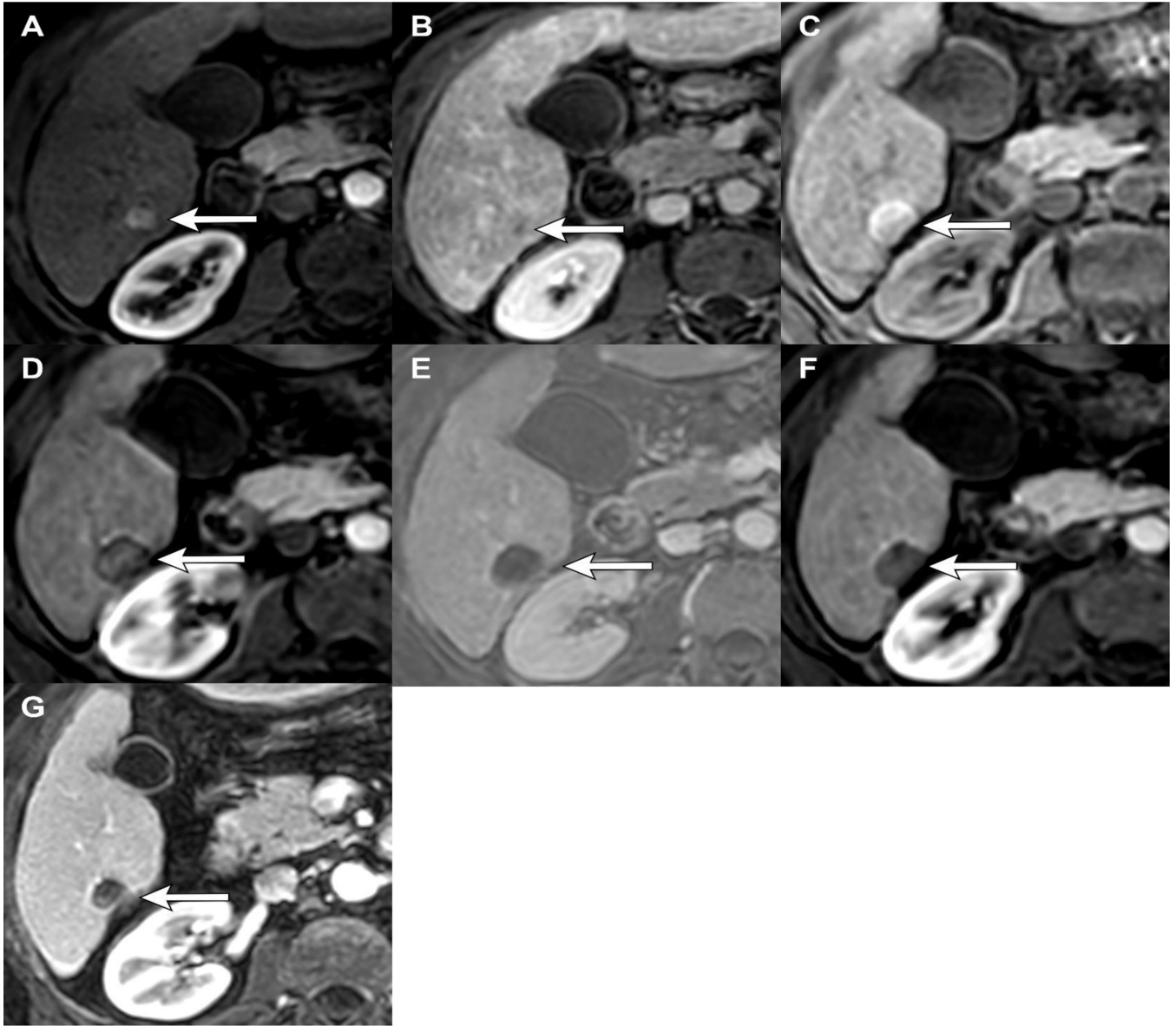**Figure 1:**
LI-RADS Treatment Response Algorithm

Figure 2.
LR-TR Nonviable after thermal ablation: 65-year-old male with HCV cirrhosis presenting with a 1.3cm LR 5 observation demonstrating APHE (A) and WO (B). 1-month post-MWA there is hyperintense signal within the treatment cavity seen on T1 pre-contrast MRI (C), compatible with coagulation necrosis. Arterial phase imaging demonstrates no enhancement (D), confirmed with subtraction images (E). Arterial (D) and portal venous phase of imaging (F) shows smooth peripheral rim enhancement which is an expected post-ablation finding, LR-TR Nonviable. Note, the treatment cavity is larger than the original tumor size, also an expected imaging finding which ensures adequate treatment of possible microscopic tumor along the treatment margin. 12 months post-MWA the lesion is smaller in size with no APHE (G), LR-TR Nonviable.
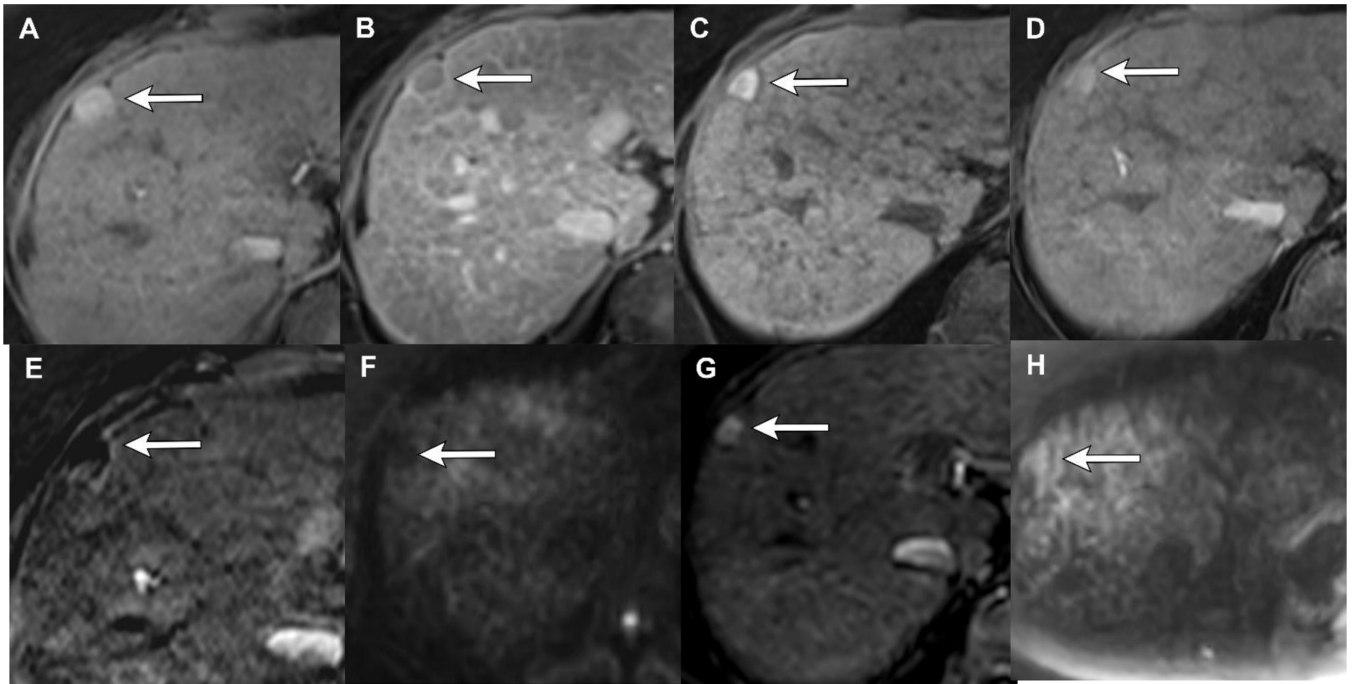
Figure 3.
LR-TR Viable after thermal ablation: Cirrhotic patient with 1.8 cm LR 5 HCC demonstrating APHE (A) and WO (B). 1-month post-MWA there is hyperintense signal on T1 pre-contrast MRI (C), compatible with coagulation necrosis. Arterial phase imaging demonstrates no enhancement (D), confirmed with subtraction images (E) and no restricted diffusion (F). 18 months post-MWA there is new mass-like nodular APHE along the margin of the treated lesion (G), LR-TR Viable. There is also new restricted diffusion corresponding to the area of nodular APHE (H).

Figure 4.
LR-TR Viable and Nonviable categorization after cTACE: 47 year old female with cirrhosis and LR 5 HCC demonstrating APHE (A) and washout (B) pre-treatment. Intraprocedural CT after cTACE with ethiodized oil shows incomplete and heterogeneous staining of the tumor (C, D). 1 month post cTACE, there is significant masslike intralesional APHE (E), compatible with LR-TR Viable category. A second lesion in the same patient treated at a different time shows dense homogeneous staining of ethiodized oil at the time of treatment (F). 1 month follow-up MRI after cTACE shows complete tumor necrosis with no APHE (G), LR-TR Nonviable. Note that the dense ethiodized oil is not seen on MRI, thus if there were subtle areas of masslike APHE along the margin of the tumor, it would not be obscured and could easily be identified.
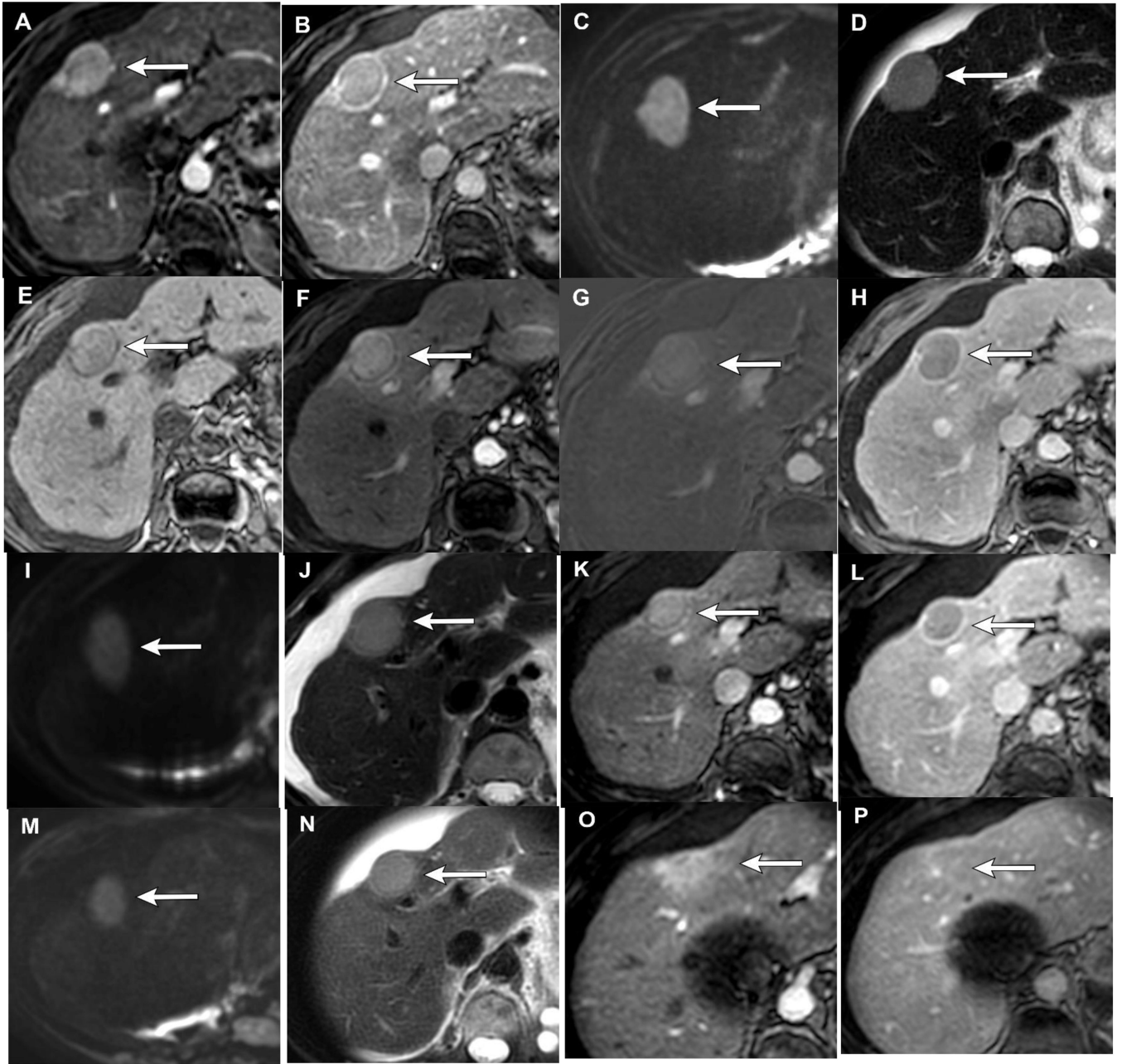
Figure 5.
Application of LI-RADS TRA v2018 after SBRT: 72-year-old female with alcohol induced cirrhosis presenting with a 3.3 cm LR 5 HCC with APHE (A), washout and capsule (B), restricted diffusion (C) and mild T2 hyperintense signal (D). 3 months post SBRT the treated lesion now measures 2.9 cm with T1 pre-contrast hyperintense signal (E), persistent APHE (F), confirmed with subtractions (G), washout and capsule (H), restricted diffusion (I) and mild T2 hyperintense signal (J), LR-TR Equivocal based on v2018, although nonprogressing. 10 months post-SBRT the treated observation measures 2.6 cm, with similar imaging features as the 3 month post-SBRT imaging, persistent APHE (K), washout and capsule (L), restricted diffusion (M) and mild T2 hyperintense signal (N), LR-TR Equivocal.

Note the geographic arterial phase hyperenhancement in the parenchyma surrounding the treatment cavity (O) which becomes isoenhancing on PV phase of imaging (P), findings related to radiation induced changes in the parenchyma, not tumor progression, which would likely demonstrate areas of washout.
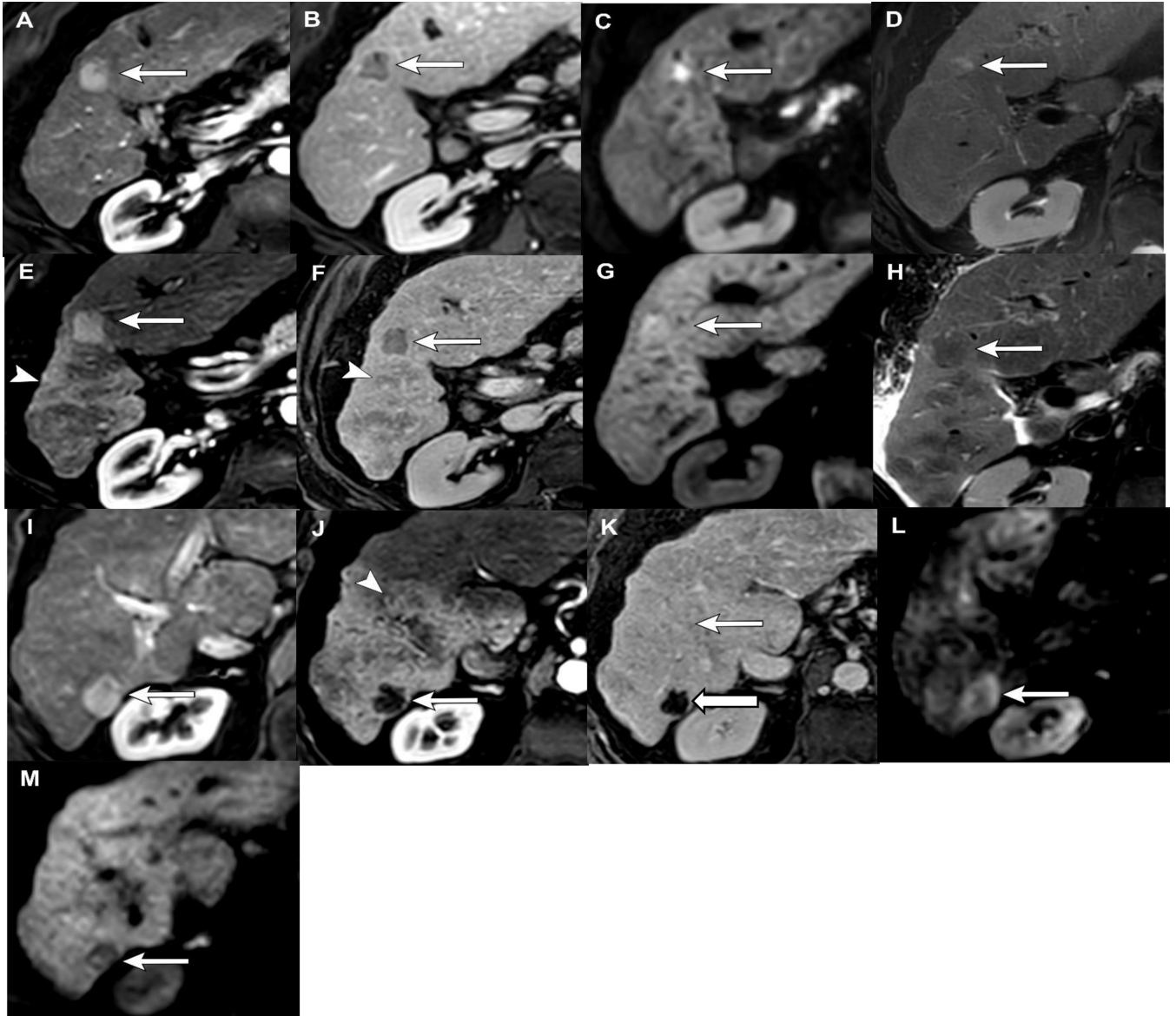
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Figure 6.
Application of LI-RADS TRA v2018 after TARE: 78-year old male with cirrhosis, presenting with multi-focal HCC. Lesion 1: There is a 1.9 cm segment 5 LR 5 observation with APHE (A), washout (B), restricted diffusion (C) and mild T2 hyperintense signal (D). 12 months post-TARE the tumor is now 2.6cm with persistent APHE (E), washout (F), increasing restricted diffusion (G) and resolution of T2 signal (H). The increasing size of the arterially enhancing component makes this LR-TR Viable. This patient was retreated with MWA. Note, the presence of new diffusion could be used as an ancillary feature for upgrading the category in the new algorithm (not yet released). Lesion 2: 2.4 cm LR 5 observation with APHE (I), washout (not shown), and restricted diffusion (J) pre-treatment. 12 months post-TARE there is no enhancement of the tumor on arterial (K) or PV phase (L), and the restricted diffusion has almost completely resolved (M). Note the extensive geographic perfusional changes within the surrounding parenchyma (E, J) which

becomes isoenhancing on PV/delayed phase of imaging (F, K), compatible with perfusional post-radiation changes, in contrast to viable tumor which would washout.

Table 1:

Studies evaluating diagnostic performance and reliability of LIRADS TRA

Study	Study Design	Publication year	# Of HCCs	# of total LRTs performed and analyzed	Imaging Modality	Interreader agreement (κ; 95CI)	Sensitivity (for LR TR Viable to detect incomplete necrosis) %	Specificity (for LR TR Viable to detect incomplete necrosis) %
Abdel Razek et al [53]	Prospective	2020	112	Ablation: 97 Arterial (cTACE): 25	MRI	0.94 (0.89–1)	N/A	N/A
Chaudhry et al[31]	Retrospective	2020	53	Ablation: 53	MRI	0.71 (0.59–0.84)	0.4–0.77	0.85–0.97
Cools KS et al[32]	Retrospective	2020	59	Ablation: 59	MRI	0.75 (SE±0.09)	0.30	1.0
Kim SW et al[49]	Retrospective	2020	183	Ablation: 42 Arterial (cTACE or DEB TACE): 137 Ablation + Arterial: 4	MRI	0.58 (0.49–0.67)	0.41–0.67	0.98
Park S et al[37]	Retrospective	2020	138	Ablation: 18 Arterial: 98 Ablation + Arterial: 22	CT or MRI	0.72 (0.61–0.83)	0.79	0.83
Seo N et al[25]	Retrospective	2020	206	Ablation: 34 Arterial: 168 Ablation + Arterial: 4	CT or MRI	0.56 (0.41–0.72)	0.56	0.92
Shropshire EL [24]et al	Retrospective	2019	63	Arterial: 63	CT or MRI	0.55 (0.47–0.67)	0.55	0.88
Kim Dh et al[29]	Meta-analysis (5 studies: retrospective)	2022	631	TARE: 1 TACE: 1 Combination: 3	MRI (3 studies) CT and MRI (2)	0.56–0.69	0.58[*]	0.93[**]
Kim TH et al[30]	Meta-analysis (6 studies: retrospective)	2021	534	Ablation and TACE	MRI and CT	N/A	0.56[*]	0.91[**]

LRT: Locoregional therapy, cTACE: conventional Transarterial chemoembolization, DEB TACE: Drug eluting beads TACE,

[*] pooled sensitivity,

[**] pooled specificity

Table 2:

Summary of imaging findings after LRT of HCC

	Expected post-treatment imaging appearance of successfully treated HCC	Imaging features suggestive of Viable Category
Thermal Ablation (Figure 2 and 3)	• No intralesional enhancement • Smooth perilesonal rim of enhancement and/or parenchymal perfusional changes **without** masslike area(s) of enhancement	Irregular **masslike** enhancement along the margin or intralesional (any degree, any phase)
Intra-arterial embolic therapy (TAE, cTACE, DEB-TACE) (Figure 4)	• No intralesional enhancement • Smooth perilesonal rim of enhancement and/or parenchymal perfusional changes **without** masslike area(s) of enhancement	Irregular **masslike** enhancement along the margin or intralesional (any degree, any phase)
SBRT (Figure 5)	• No intralesional enhancement • Smooth or geographic parenchymal perfusional changes **without** masslike area(s) of enhancement • Irregular intralesional masslike enhancement (any degree, any phase) any time after treatment **AND** definite stability or decrease in size and/or degree of intralesional enhancement	Irregular intralesional masslike enhancement (any degree, any phase) at any time after treatment with new or increased size or degree of intralesional enhancing component(s)
TARE/y90 (Figure 6)	• No intralesional enhancement • Smooth or geographic parenchymal perfusional changes **without** masslike area(s) of enhancement • Irregular intralesional masslike enhancement (any degree, any phase) any time after treatment **AND** definite stability or decrease in size and/or degree of intralesional enhancement	Irregular intralesional masslike enhancement (any degree, any phase) at any time after treatment with new or increased size or degree of intralesional enhancing component(s)