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Review

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Multidisciplinary assessment of tumor response after internal and external radiation therapy for hepatocellular carcinoma

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Abstract

Treatment of hepatocellular carcinoma with both internal and external radiation therapy is becoming more common, with the recent incorporation of internal radiation therapy (transarterial radioembolization) into the Barcelona Clinic Liver guidelines. With the increasing use of radiation therapy for the treatment of liver cancer, it is essential to understand the expected imaging findings after therapy and establish a consensus on the management of these patients. Recent insights into the unique post-treatment imaging features of HCC treated with radiation have prompted updates to treatment response algorithms to improve inter-reader response assessment. One must understand the type of locoregional treatment, the time interval of post-treatment imaging and the sequence of the treatment strategy to provide an accurate treatment response assessment. Although imaging response systems attempt to predict treatment efficacy, many of these complex cases should be discussed in a multidisciplinary setting for management recommendations.

Keywords: Hepatocellular carcinoma, radiation, LI-RADS, LIRADS-TRA, treatment response

INTRODUCTION

Radiation therapy is emerging as an effective treatment option for hepatocellular carcinoma (HCC) in

patients who are not candidates for conventional interventional locoregional treatment (LRT) such as ablation and intraarterial embolic therapy [conventional transarterial chemoembolization (cTACE), transarterial embolization (TAE)][1-3]. In recent years, transarterial radioembolization (TARE), stereotactic body radiation[4], and hypofractionated ablative radiation have been shown to play roles in treating unresectable HCC with excellent local control, for downstaging of disease prior to resection, and as a bridge to transplant[5-8].

Accurate assessment of tumor response is critical post radiotherapy to appropriately guide clinical management. Traditional treatment response algorithms such as mRECIST and EASL evaluate changes in the enhancement of the treated tumor to categorize treatment response. A newer treatment response algorithm, the CT/MRI Liver Imaging Reporting and Data System (LI-RADS) treatment response assessment (TRA) (LR-TRA), was created in 2017 to provide standardization and reporting guidelines for the evaluation of HCC treated with LRT at a lesion level. However, treatment response assessment using LR-TRA criteria also uses enhancement of the post-treatment lesion as the primary assessment of viability. The inherent limitation of these treatment response algorithms is their lack of accounting for differences in expected post-treatment appearance based on the type of LRT.

Multiple studies have shown that the post-treatment appearance of radiation-treated HCC is unique compared to HCC treated with other LRTs, such as thermal ablation and intraarterial embolic therapies[9,10]. Therefore, there is a need for an updated treatment response algorithm to improve treatment response assessment after both internal (TARE/y90) and external (SBRT/EBRT) radiation therapy for HCC. In addition, the importance of multidisciplinary discussion and collaboration for the management of radiation-treated HCC cannot be understated.

PATTERNS OF TUMOR RESPONSE POST RADIATION

To understand the post-treatment imaging appearance of tumors treated with radiation (internal or external), it is important to understand the mechanism of action of radiation-induced cell death. Radiation results in cell death via two mechanisms: immediate cell death by direct DNA destruction or the induction of cellular senescence. In the latter pathway, the cells are metabolically active without the ability to replicate and, therefore, eventually undergo cell death[11]. Understanding this concept is crucial for accurately assessing treatment response in radiation-treated HCC. In addition, there is a dose-related effect, as higher doses (ablative dose TARE) tend to result in immediate cell death and lower doses are more likely to result in cellular senescence. Finally, internal radiation (TARE) is administered intra-arterially, and therefore, its distribution follows arterial blood flow in a wedge-shaped distribution, whereas external (EBRT/SBRT) radiation tends to be more symmetric surrounding the treated lesion.

As a result of the biology of radiation-associated cell death, the post-radiation (TARE and EBRT/SBRT) appearance of HCC can vary. Often, radiation-treated HCC can demonstrate persistent mass-like lesional enhancement with delayed necrosis and is stable or decreases in size over time[3,9,10,12,13]. The timing of changes in enhancement and size of HCC after radiation treatment is not well documented; however, these findings are usually seen for at least 3-6 months or longer after treatment and then slowly start resolving. In some situations, particularly after segmental or ablative radiation doses with TARE, there can be complete necrosis and lack of tumoral enhancement immediately post-treatment[14].

Imaging findings are corroborated by radiology-pathology studies, which have demonstrated that persistent enhancement was seen in approximately 45% of completely necrotic tumors on explant in HCCs treated with SBRT[15]. Additionally, SBRT-treated tumors with a longer time to transplant showed greater loss of

arterial phase hyperenhancement (APHE) on imaging (OR 0.68; 95%CI: 0.45- 0.91; $P = 0.03$) with increasing necrosis on explant pathology (OR: 0.2; 95%CI: 0.04- 0.79; $P = 0.03$)[15]. These findings suggest that persistent enhancement after external beam radiation treatment is likely an expected finding that changes over time after treatment. Similarly, radiology-pathology studies on TARE-treated HCC have shown that decreasing tumor size on imaging corresponds to increasing pathologic necrosis over time, suggesting that tumor necrosis is not always immediate, even after internal radiation therapy[16]. Some studies also suggest that a higher dose of radiation (in the brachytherapy setting) can lead to persistent peritumoral enhancement and that this could also correlate with improved response based on explant specimens post radiotherapy[17].

This persistent enhancement often confounds conventional assessments of tumor response based on percutaneous ablation or transarterial embolization techniques. T2-weighted hyperintensity are historically associated with persistent or progressive disease post percutaneous ablation techniques per mRECIST criteria[18,19]. This can be very confusing when there is an increased enhancement or APHE in the first 6-12 months post radiation delivery[9,10]. The original EASL guidelines, as well as qEASL (quantitative volumetric evaluation of enhancement), are predicated on a reduction in contrast uptake and were originally designed to assess response post TACE[20]. However, these criteria are unlikely to apply in the radiotherapy setting, as a recent study demonstrated that they could not be reproducibly applied, nor were they predictive of response or overall survival in patients treated with radioembolization[21]. Similarly, changes in arterial perfusion (2D and 3D mapping) were also promising tools for response in the setting of TACE[22,23]. As noted above, there is often APHE that would make this type of mapping very difficult and inconclusive in the setting of radiotherapy.

More sophisticated methods using MR diffusion-weighted imaging have tried to circumvent some of these challenges[24,25]. Studies using diffusion metrics such as apparent diffusion coefficient (ADC) have been mixed due to a lack of standardization of MR techniques and inconsistent correlation between responders and non-responders[26,27]. Iodine-enhanced CT and MR mapping have been described for the diagnosis of HCC, but there are limited data on their use in evaluating response to radiotherapy with some published post TARE[28-31]. Finally, the use of hepatobiliary agents has been difficult to reproduce, as the hypointense appearance of treated tumors and viable tumors can be confusing for treatment response assessment.

As a result of the above-described expected post-radiation imaging findings of HCC, a watch-and-wait approach for persistently enhancing HCC after radiation treatment should be the preferred management as opposed to immediate retreatment, particularly in cases where enhancement and size of the treated tumor remain stable or decreases. It is well known that successful nonradiation-LRT of HCC results in immediate tumoral necrosis, characterized by a lack of enhancement of the treated lesion on post-treatment CT or MRI[13]. Conversely, as mentioned above, HCC successfully treated with radiation often demonstrates persistent mass-like enhancement on post-treatment imaging. Therefore, caution should be taken when applying existing treatment response algorithms to assess post-treatment viability since the current TRAs use persistent enhancement as the surrogate imaging biomarker for viability. For example, an SBRT-treated HCC demonstrating mass-like enhancement with minimal decrease in size post-radiation would be categorized as a stable disease when using mRECIST and LR-TR Viable when using LR-TRA, based on the criteria for response categorization. Unfortunately, incorrect treatment response categorization can result in unnecessary retreatment of radiation-treated HCC. Unlike nonradiation-LRT, which requires immediate retreatment in the setting of post-treatment mass-like enhancement, persistently enhancing radiation-treated HCC should be managed with imaging surveillance and retreatment should be considered only after discussion at a multidisciplinary conference [Figure 1]. In fact, persistently enhancing HCC after radiation treatment is the expected imaging finding, as long as the degree or size of enhancement is not increasing, in

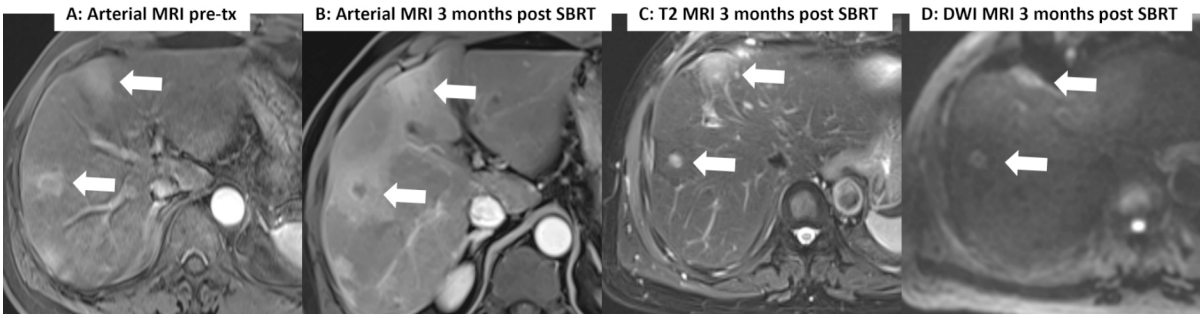

Figure 1. A 70-year-old male with hepatitis C cirrhosis presenting with two new lesions. Segment 4a LR 5 and Seg 8 LR-M biopsy proven HCC (A). Multidisciplinary decision was made to treat both lesions with SBRT. 3 months post SBRT, the lesion in segment 4a demonstrates persistent mass-like intralesional enhancement (B) and is stable in size, with residual T2 hyperintense signal (C) and restricted diffusion (D), LR-TR Nonprogressing. The lesion in segment 8 demonstrates irregular peripheral rim enhancement with central necrosis and is smaller in size (B), with residual T2 hyperintense signal (C) and restricted diffusion (D), LR-TR Nonprogressing. Note the surrounding parenchymal arterial phase hyperenhancement secondary to radiation changes in the radiation field. No further treatment is required and the patient should return for 3-month follow-up imaging. HCC: hepatocellular carcinoma;

which case the tumor can be categorized as viable.

These data highlight the need to revise the current treatment response algorithms for the assessment of treatment response after radiation therapy for HCC. As a result, the Liver Imaging and Reporting Data System (LI-RADS) treatment response algorithm (LR-TRA) has developed a new algorithm, v2024, which includes a new diagnostic algorithm and a new response assessment category unique for radiation-treated HCC[15,32].

UPDATED LI-RADS TREATMENT RESPONSE ALGORITHM

The new radiation algorithm takes into consideration evidence-based and consensus recommendations to address limitations in treatment response assessment after both internal and external radiation. The new algorithm has revised criteria and a new category for radiation-treated HCC, LR-TR Nonviable, LR-TR Viable, and LR-TR Nonprogressing. Additionally, the new algorithm uses enhancement and change in the size of the radiation-treated tumor as imaging biomarkers to evaluate treatment response. Please refer to the ACR website for full details on the new radiation treatment response algorithm, which can be found at https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/LI-RADS.

Criteria for *LR-TR Nonviable category*: No mass-like enhancement (complete lesion disappearance, no intralesional enhancement, smooth perilesional enhancement, parenchymal perfusional changes) in the treated lesion, along treated lesion margin, or along surgical margin. Size-based criteria are not used for Nonviable categorization since the tumor is not enhancing [Figure 2]. This category is often seen after ablative dose TARE segmentectomies or over time after EBRT.

LR-TR Viable criteria: mass-like enhancement (any degree, any phase), in treated lesion or along its margin, which is new or increased in size over time after LRT [Figures 2 and 3]. When intra-procedural imaging during TARE or simulation imaging for SBRT is available, they could be more accurate for comparison of tumor size at or close to the treatment session to provide accurate post-treatment assessment since size is now a criterion for assessment of viability.

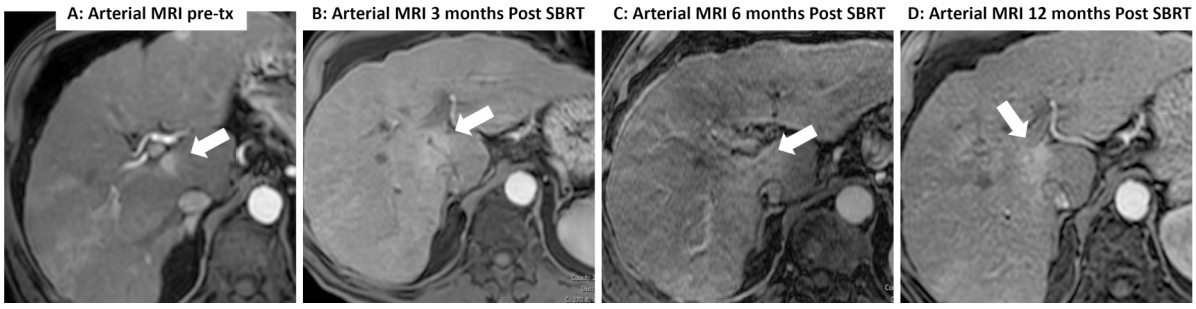

Figure 2. A 72-year-old female with alcohol-related cirrhosis presenting with a 1.2 cm LR 5 observation in the caudate lobe (A). The patient underwent SBRT after a multidisciplinary discussion. 3 months post SBRT, there is a small focal area of nonenhancement centrally, LR TR Nonviable (B). Note the surrounding arterial phase hyperenhancment in the parenchyma, compatible with radiation changes. 6 months post SBRT, there is no enhancement, LR-TR Nonviable (C). In addition, there are improving geographic radiation changes within the surrounding parenchyma. At 12 months post SBRT, there is a new mass-like area of enhancement along the margin, LR-TR Viable (D).

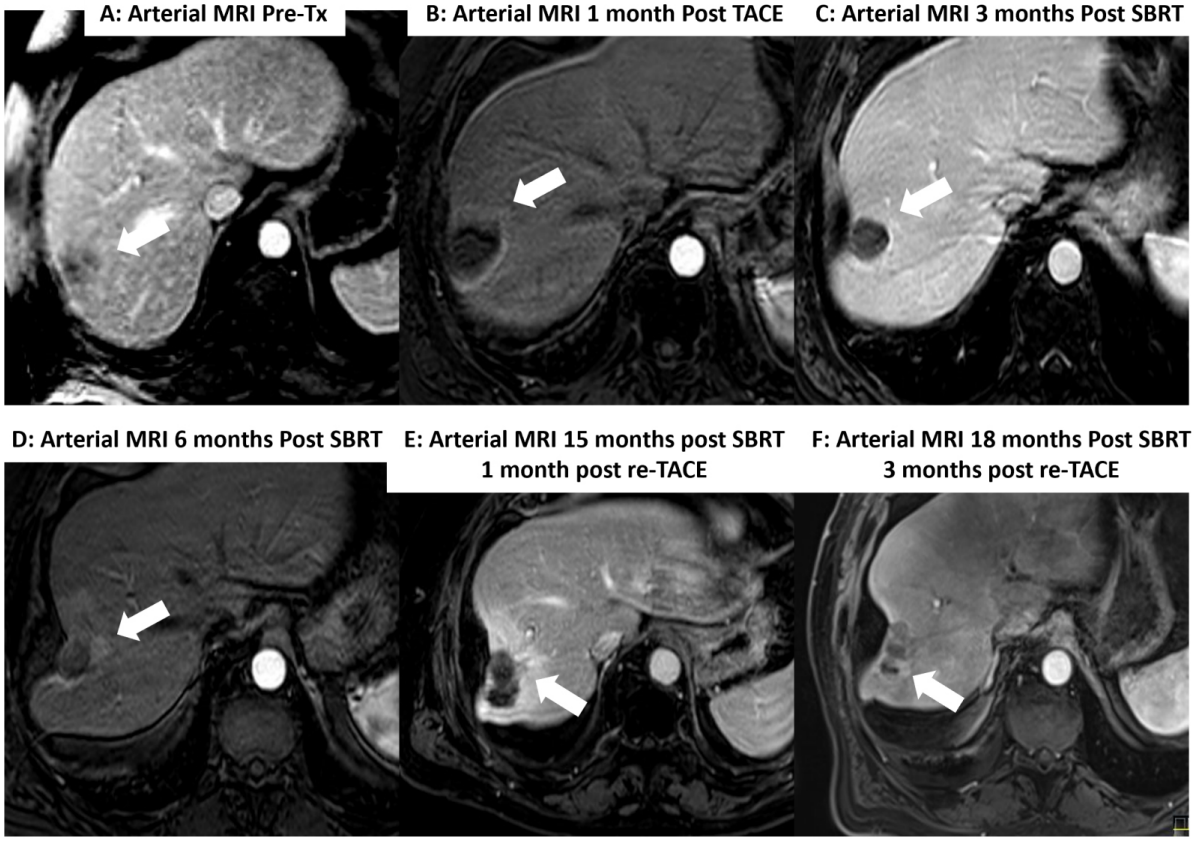

Figure 3. A 67-year-old male with hepatitis B cirrhosis presents with LR M observation (A). Biopsy revealed poorly differentiated HCC. After a multidisciplinary discussion, a decision was made to treat with the combination of TACE + SBRT. One month after TACE (B), there is no residual intralesional enhancement with smooth perilesional enhancement from the 2 o'clock to 7 o'clock position, although there is mild irregularity along the anterior margin, LR-TR Equivocal. SBRT was then performed, and 3 months after SBRT, there was no residual enhancement and there was a circumferential smooth rim of perilesional enhancement, LR-TR Nonviable. This was re-treated with TACE after a multidisciplinary discussion. 1-month post repeat TACE, there is no residual enhancement of the nodular area of recurrence, LR-TR Nonviable (E). 3 months post-repeat TACE and 18 months post initial SBRT, there is a new nodular area of enhancement along the 5 o'clock margin, LR-TR Viable.

LR-TR Nonprogressing criteria: mass-like enhancement (any degree, any phase), in treated lesion or along its

margin, which is stable or decreased in size over time after LRT. There are no time criteria for the LR-TR Nonprogressing categorization and it is used as long as the radiation-treated HCC demonstrates residual enhancement [Figure 1].

LR-TR Equivocal is no longer a category used for radiation-treated HCC. If there is questionable viable disease on imaging, the LR-TR Nonprogressing category should be used, prompting a 3-month follow-up imaging study. *Optional* use of ancillary MR imaging features can be employed for category adjustment to upgrade from LR-TR Nonprogressing to LR-TR Viable. The ancillary features used for upgrade include presence of mild-moderate T2-hyperintensity or diffusion restriction which must correspond to the area of stable or decreasing mass-like enhancement, at any time after radiation-based LRT.

PATTERNS OF PARENCHYMAL CHANGES POST EXTERNAL BEAM RADIATION THERAPY

EBRT of liver lesions not only results in changes to the targeted tumor, but also results in off-target effects in the parenchyma surrounding the targeted tumor. With external beam radiation, this tends to be geographic and surrounds the targeted tumor almost evenly on all sides, based on the planning volumes [Figures 1 and 2]. With internal radiation (transarterial radioembolization), this tends to be in a vascular distribution, often wedge-shaped. When interpreting imaging of radiation-treated HCC, it is critical not to confuse radiation-induced parenchymal enhancement with suspicious new or increasing tumoral enhancement. Careful comparison of pre-treatment and post-treatment imaging must be performed to accurately delineate radiation-induced parenchymal enhancement from tumoral enhancement. Radiation-induced perilesional parenchymal enhancement is an expected post-treatment imaging finding and should not be categorized as LR-TR Nonprogressing.

Studies have shown that off-target parenchymal enhancement secondary to radiation usually demonstrates arterial phase hyperenhancment (APHE) in the first 3-6 months post treatment in over 80% of patients, with slow conversion to delayed-phase hyperenhancement, seen in over 80% at 12 months post-treatment[9]. Additional radiation-induced parenchymal changes include gradual volume loss and increasing capsular retraction of the liver over time (37% at 6 months and 78% at 12 months) and increasing intrahepatic biliary ductal dilatation distal to the treated lesion[9].

TREATMENT RESPONSE EVALUATION AFTER COMBINATION THERAPY

There is increasing use of combination therapies to treat liver tumors, which have independent antitumor effects, but are administered in conjunction to induce a synergistic effect[33]. Frequent combinations with internal or external radiation therapy can be with intra-arterial embolic therapy, systemic immunotherapy, or thermal ablation. In fact, recent studies evaluating outcomes of SBRT + TACE have shown improved overall survival and progression-free survival with combination therapy compared to monotherapy[34,35]. Another recent study comparing immune checkpoint inhibitor therapy alone or in combination with SBRT showed improved survival outcomes in the combination therapy group, with an overall objective response of 24% versus 76%, respectively[36]. Results of studies such as these will result in more frequent treatment of patients with combination therapies, and therefore, it is important to understand expected imaging findings in order to accurately assess response.

Treatment response assessment after combination therapy requires an understanding of the type of therapies used, the timing of imaging after therapy, and the sequence of the treatments. It is also important to understand the expected post-treatment imaging appearances of the employed treatments. Given the complexity of these treatment regimens and the complexity in interpretation of post-treatment imaging, a multidisciplinary discussion of these cases may be warranted to ensure appropriate management in this

patient cohort.

In cases where TACE or microwave ablation (MWA) is the latter treatment in a combined TACE or MWA + SBRT regimen, the imaging findings predicting viability should follow nonradiation criteria. Thus, no mass-like enhancement of the treated lesion would be characterized as nonviable. However, if there is a presence of mass-like enhancement in or around the TACE- or MWA-treated tumor, LR-TR Viable categorization should be applied [Figures 3 and 4].

On the other hand, when TACE or MWA is performed prior to SBRT, the imaging findings predicting viability versus nonviability should follow expected post-radiation findings. Therefore, any areas of mass-like enhancement with stability or decrease in size from pre-treatment tumor should be categorized as LR-TR Nonprogressing. If, at any time, there is an increase in mass-like enhancement of the treated lesion, then the LR-TR Viable category should be applied. Once SBRT is completed, geographic or patchy regional parenchymal enhancement, surrounding the targeted tumor, will also be present.

THE ROLE OF RADIOMICS IN PREDICTING LIVER RADIOTHERAPY RESPONSE

The next frontier after physical imaging evaluation for tumor response and outcomes is radiomics. There have been a number of models integrating imaging and biomarkers post liver radiation for HCC. Cozzi et al. evaluated 138 patients, analyzing their non-contrast planning CTs for various imaging features in addition to the incorporation of BCLC staging[37]. Their model showed that a single textural feature (compacity, a measure of textural compactness) was correlated with overall survival[37].

One of the largest radiomics analyses post SBRT for HCC comes from Korea, where 409 patients were analyzed[38]. This study evaluated tri-phase contrast-enhanced CT scans and built models for prediction based on both tumoral and peritumoral imaging characteristics[38]. Their model was better able to predict clinical outcomes (objective response rate and failure-free survival) with the addition of portal venous phase imaging features to clinical characteristics such as BED > 62.5 Gy, multiple tumors, tumor size, and AFP[38]. Interestingly, the inclusion of a peritumoral zone (1 cm expansion on the treated lesion) also improved prediction of survival[38]. The University of Michigan has also alluded to the importance of analyzing the liver texture outside of the gross tumor volume (GTV), as they published a model noting that liver-GTV and critical voxels in the normal liver may also be important in predicting outcomes[39].

Recently, Wang *et al.* developed a radiomics-based nomogram for the prediction of overall survival post SBRT for HCC based on BED > 70 or < 70 Gy, Rad-score (integration of various imaging/radiomics features), tumor size, and baseline Child-Pugh score[40]. There have also been radiomic nomograms developed specifically for survival post radiation in patients with portal tumor vein thrombosis (PVTT) to guide the selection of patients who may benefit the most from radiotherapy[41].

In addition to the evaluation of the treated lesion, radiomics is also being assessed as a tool to predict hepatic decompensation post SBRT. Shen *et al.* utilized CT simulation scans and incorporated imaging characteristics with dose-volume histogram data and clinical data. The final model was a combination of ALBI, imaging, and V5 and V30 liver dose and evaluated its sensitivity and specificity for both traditional radiation-induced liver disease[42] defined as elevated liver enzymes and non-traditional RILD (worsening Child-Pugh score of 2 at 3 months)[43].

While radiomics is an exciting tool, the difficulty lies in the heterogeneity of imaging features as well as a lack of synchrony for many models. There is a lack of external validation and equivocation over whether

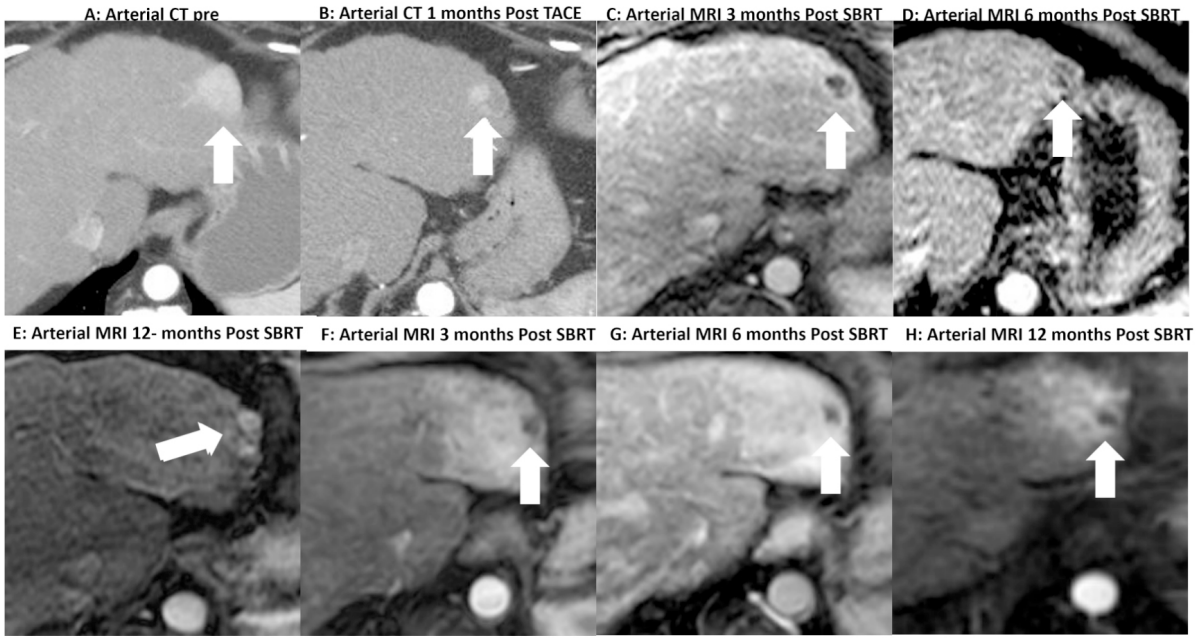

Figure 4. A 54-year-old female with hepatitis C cirrhosis presenting with an LR 5 observation in segment 2 of the liver on arterial phase contrast-enhanced CT (A). After a multidisciplinary discussion, the patient was treated with TACE. CT performed 1 month post TACE shows partial necrosis of the tumor with residual mass-like nodular enhancement along the margin of the lesion, LR-TR Viable (B). The patient was again presented at a multidisciplinary liver tumor board, and the decision was made for SBRT. Arterial phase MRI 3 months post SBRT reveals a decrease in the size of the targeted lesion with residual linear areas of intralesional enhancement, LR-TR Nonprogressing (C). Note that since SBRT was performed after TACE, the post-treatment imaging findings after radiation should dominate treatment response assessment. Therefore, the presence of mass-like intralesional enhancement, although a small septation, with decreasing size, is considered LR-TR Nonprogressing. Arterial phase MRI 6 months post SBRT shows an increasing area of intralesional enhancement (D). Because this was not mass-like or nodular, the reader believed it was "Equivocal"; however, since Equivocal is no longer terminology for radiation-treated HCC, LR-TR Nonprogressing category should be given instead. Arterial phase MRI performed 12 months post SBRT (E) demonstrates increasing size of mass-like enhancement along the margin of the treated lesion, LR-TR Viable. The patient was presented at a multidisciplinary liver tumor board again, with the decision for repeat SBRT. Arterial phase CT 3-, 6-, and 12 months (F, G, and H, receptively) post repeat SBRT demonstrates no intralesional enhancement, LR-TR Nonviable. Note the surrounding parenchymal enhancement from the nontarget effects of radiation. Over time, there is progressive atrophy of the left lobe of the liver secondary to radiation fibrosis.

MR-based imaging or CT imaging is best. The sensitivity and specificity of models vary widely and most studies are single institution experiences. Future studies will need cross-validation and collaboration among many centers to overcome these challenges and develop more robust prediction models.

FUTURE DIRECTIONS

The advent of the LR-TRA system may address some of the equivocations over the evaluation of response post liver radiotherapy. The standardization of response criteria for the burgeoning use of external beam radiation, SBRT, and TARE will aid in evaluating and comparing outcomes, especially in multimodality therapy. The use of antiangiogenic agents and immunotherapy can cause perfusional changes in the liver independent of any locoregional therapy[44]. With the addition of varying persistent enhancement post liver-directed radiation, it will be important to develop tools that can holistically evaluate response.

There has been growing interest in using radiotherapy as a bridge to transplant or as a neoadjuvant treatment prior to surgery. This is where response assessment will be critical[5,45-49]. Furthermore, multidisciplinary discussion and improved imaging tools will be needed. While LR-TRA only assesses each individual lesions, the updated version provides a key step in the right direction to accurately evaluate

response to radiation. Research is needed in a more holistic approach that enables evaluation of the entire liver, at all treated sites, taking into account all modalities of treatment.

CONCLUSION

Recent insights into the imaging features of HCC treated with radiation have prompted updates to treatment response algorithms to improve response assessment. With the increasing use of radiation monotherapy and combination LRT for liver cancer, accurate treatment response assessment is essential for patient management and transplant allocation. One must understand the type of locoregional treatment, the time interval of post-treatment imaging, and the sequence of the treatment strategy to provide accurate treatment response assessment. Although imaging response systems such as LI-RADS TRA attempt to provide a comprehensive approach to predict treatment efficacy, many of these complex cases should be discussed in a multidisciplinary setting for management recommendations.

DECLARATION

Authors' contributions

Made substantial contributions to the conception and design of the study, as well as the writing and editing of the manuscript: Mendiratta-Lala M, Owen D

Made substantial contributions to the writing of the manuscript: Batra S, Lala K, Kohn M

All authors have made substantial contributions to the manuscript.

Availability of data and materials

Not applicable.

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None.

Conflicts of interest

Not applicable.

Ethical approval and consent to participate

Approval was provided by the institutional review board of the University of Michigan (HUM00220689). Given that this was retrospective image analysis, the IRB approved a waiver for consent. All participants provided verbal informed consent prior to participation.

Consent for publication

Not applicable.

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