Chapter 9

LI-RADS® Treatment Response

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Table of Contents

LI-RADS® Treatment Response

LI-RADS Treatment Response Assessment is:

- A system for standardizing the image acquisition, interpretation, reporting, and data collection for HCC and other malignant lesions treated with locoregional therapy in high-risk patients .
- Intended for routine clinical practice, education, and research.
- A dynamic document, to be expanded and refined as knowledge accrues and in response to user feedback.
- Supported and endorsed by the ACR.
- Developed by an international and multidisciplinary LI-RADS Treatment Response Working Group of diagnostic and interventional radiologists, hepatologists, and radiation oncologists through literature review and expert consensus.

Why is LI-RADS Treatment Response Assessment important?

- Enables clear communication between radiologists and other specialists caring for patients after locoregional therapy.
- Provides standardized terminology to facilitate data collection, quality assurance, and research.
- Provides a simple, practical system suitable for routine clinical practice for assessing treatment response in individual lesions.
- Prior systems (see below) were developed for clinical trials, emphasize overall patient response, and are not as well suited for routine clinical practice.

What are prior treatment response systems?

- RECIST (Response Evaluation Criteria in Solid Tumors), modified RECIST (mRECIST), and EASL (European Association for the Study of Liver Disease) provide criteria to assess overall patient response in clinical trials and retrospective studies assessing treatment response for HCC patients, rather than to assess individual tumors in routine clinical practice.
- Concepts from mRECIST were adapted into the LI-RADS Treatment Response Algorithm for assessment of viability and tumor size measurements following treatment.

Why is LI-RADS Treatment Response Algorithm needed?

- Earlier versions of LI-RADS used LR-Treated as a placeholder; this category indicated whether a treatment had been applied but did not attempt to categorize the response. The new LI-RADS Treatment Response Algorithm provides standardized terminology as well as a comprehensive but simple system to assess treatment response, suitable for routine clinical practice.

LI-RADS® CT/MRI Treatment Response: Populations

Apply in patients to assess response for path-proven or presumed (e.g. LR-4, LR-5, LR-M) malignancy after locoregional treatment:

- Locoablative **OR**
- Transcatheter **OR**
- External radiation

Locoablative therapies: radiofrequency, microwave, ethanol ablations and cryoablation.

Transcatheter therapies: bland embolization, chemoembolization with or without drug-eluting beads, and radioembolization.

Do not apply for treatment response assessment after:

- Systemic therapy

Future versions of LI-RADS may address treatment response after systemic therapy.

Apply with caution for treatment response assessment after:

- Surgical resection
- Locoregional treatment in combination with systemic therapy

May apply with caution for postsurgical patients when assessing recurrence at the surgical margin, or in patients who undergo combined locoregional and systemic therapy.

Apply for multiphase exams performed with:

- CT or MRI with extracellular contrast agents (ECA) **OR**
- MRI with hepatobiliary contrast agents (HBA)

Do not apply to:

- CEUS

- CEUS remains an area of active investigation for treatment response, and may be included in future iterations of LI-RADS Treatment Response Assessment.

Pretreatment vs Posttreatment Imaging

Pretreatment Imaging

The roles of pretreatment imaging are to help:

- Diagnose and stage patients (see *Chapter 10*)
- Inform patient prognosis and management (see *Chapter 11*)

Some pretreatment imaging findings influence therapy selection, especially the number, size, location (e.g., proximity to major vessels and bile ducts) and appearance of tumors.

In most centers performing locoregional therapy for HCC, a multidisciplinary group (e.g. tumor board) helps select the most appropriate treatment option for a particular patient.

Posttreatment imaging

The roles of posttreatment imaging are to help:

- Assess treatment response, including residual tumor viability.
- Diagnose and stage untreated tumors elsewhere in the liver.
- Inform patient prognosis and management, including need for retreatment with same therapy or alternative therapy.

Posttreatment imaging usually is performed with CT or MRI (see *Chapter 12*).

- Centers with the requisite expertise may assess treatment response with CEUS.
- CEUS LI-RADS Treatment Response Assessment algorithm is in development.

Follow-up posttreatment imaging may vary, depending on institution protocol, but is generally performed at: 1 month, 3 months, 6 months, 9 months and 12 months, and about every 3 - 6 months thereafter.

Optimal imaging follow-up depends on the therapy used, planned future treatments (e.g. right followed by left hepatic radioembolization), and multidisciplinary discussion.

The interpretation of posttreatment imaging depends on the locoregional therapy used and the time interval since treatment. These issues are discussed in the remainder of this section.

Locoablative Therapies

What should the radiologist know?

Tumor ablation is defined as the direct application of tissue-destroying chemical material (i.e. non-energy) or energy to eradicate focal tumors.

LI-RADS has adopted the unified terminology of ablative therapies released in 2014 by the International Working Group on Image guided Tumor Ablation, Interventional Oncology Sans Frontières Expert Panel, Technology Assessment Committee of the Society of Interventional Radiology, and the Standard of Practice Committee of the Cardiovascular and Interventional Radiological Society of Europe.

- Energy-based locoablative therapies apply energy to destroy tissue:
  - Heat: i.e., radiofrequency ablation (RFA), microwave ablation (MWA)
  - Cold: i.e., cryoablation
  - Other forms of energy under investigation:
    - irreversible electroporation (IRE): high-voltage, low energy DC current to create nanopores in the cell membrane, inducing cell death by initiating apoptosis.
    - ultrasound
    - laser
- Chemical-based therapy: e.g. percutaneous ethanol ablation (PEA).

Definitions of energy-based therapies	
Radiofrequency Ablation (RFA)	Thermal ablative technique that creates heat with medium frequency alternating current (~350–500 kHz) to kill cells.
Microwave Ablation (MWA)	Thermal ablative technique using electromagnetic waves (~900-2450 mHz). Repeated short-duration high-voltage electrical pulses injure the cell membrane to kill cells.
Cryoablation	Thermal ablative technique in which rapid gas expansion by inserted cryoprobes generate subzero cytotoxic temperatures to kill cells.
Percutaneous Ethanol Ablation (PEA)	Image-guided injection of ethanol into a mass to cause chemically-induced coagulation necrosis *in situ.*

Locoablative Therapies

Complications relevant to radiologists

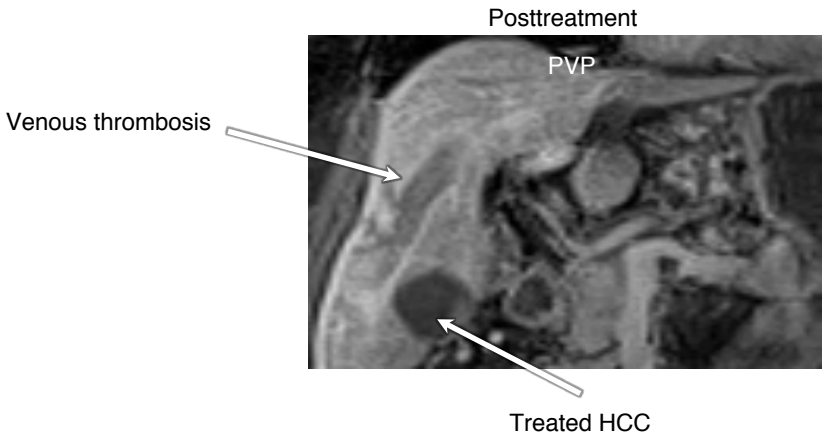
Thermal ablation-induced damage to adjacent structures within the ablation zone, including biliary injury and bowel perforation.

Abscess can form in the ablation zone. Note that gas may be seen in the absence of infection for days or sometimes weeks post ablation.

Arteriovenous shunt can develop along the probe tract.

Thrombosis of vessels, such as portal vein branches, can occur with RFA, MWA and PEA - more frequently with MWA compared to RFA due to higher power used. When both portal vein and hepatic artery are thrombosed, segmental or lobar infarction can occur.

Liver “cracking” causing catastrophic hemorrhage can occur during cryoablation.



Transcatheter Tumor Therapies

What should the radiologist know?

Transcatheter tumor therapy is defined as the intraarterial delivery of therapeutic agents via selective catheterization of arteries supplying the targeted lesion(s).

The unique dual blood supply of the liver and arterial dependence of HCC, as well as most liver metastases, provides the rationale for the use of transarterial embolization techniques. A transarterial approach allows for targeted therapy for malignant tumors that limits the impact of treatment on the remaining non-tumor bearing parenchyma.

The need for multiple treatment sessions is common and does not constitute treatment failure, particularly for bulky or bilobar disease, as well as for tumors with multiple feeding arteries.

Definitions of transcatheter tumor therapies	
Embolization (TAE)	Blockade of hepatic arterial flow with vascular occlusion particles (gelatin sponge, polyvinyl alcohol, or calibrated microspheres) to induce ischemia and necrosis. Ethiodized oil is no loger used.
Conventional Chemoembolization (TACE)	Transarterial infusion of single or multiple chemotherapeutic agents with or without ethiodized oil and with or without concurrent or tandem embolization with vascular occlusion particles (see TAE above).
Drug eluting beads chemoembolization (DEB-TACE)	Transarterial administration of microspheres onto which chemotherapeutic medication is loaded or adsorbed to provide sustained in-vivo drug release.
Ttransarterial embolization (TARE), sometimes known as radioembolization (RAE)	Transarterial infusion of radioactive substances such as microspheres containing yttrium-90 (^{90}Y), iodine-131 (^{131}I), or similar agents.

Transcatheter Tumor Therapies

Complications relevant to radiologists

With TAE, complications include post-embolization syndrome (including nausea, vomiting, pain, fever; seen in up to 80% of patients) and non-target embolization (including: pancreatitis, pulmonary emboli, and ischemic cholecystitis). Rare events include liver failure, liver abscess, bile duct injury and cardiac arrythmias.

With any transcatheter tumor therapy, patients with intratumor AV shunts or other vascular abnormalities are at risk for unintended drug delivery to extrahepatic structures. Shunts or other vascular abnormalities discovered during intraprocedural angiography may require embolization prior to treatment delivery.

For TARE, the potential harm of nontarget embolization of extrahepatic organs (lungs, GI tract) is particularly high. Hence, hepatic angiography mapping and intra-arterial ^{99m}Tc-MAA scintigraphy are performed routinely in advance to detect and quantify pulmonary and gastrointestinal shunting. When necessary, preemptive embolization of shunting vessels is performed.

External Beam Radiation Therapy

What should the radiologist know?

External beam radiotherapy (EBRT) delivers focused radiation beams from external sources to targeted tumor areas in the liver.

EBRT using image guidance and complex treatment planning is referred to as Stereotactic Body Radiotherapy (SBRT) or Stereotactic Ablative Radiotherapy (SABR).

SBRT/SABR provides an appealing alternative to other more invasive locoregional therapies for selected patients with liver-confined tumors. It can also be considered in patients with liver-confined tumors that are unsuitable or refractory to other locoregional therapies.

Complications relevant to radiologists

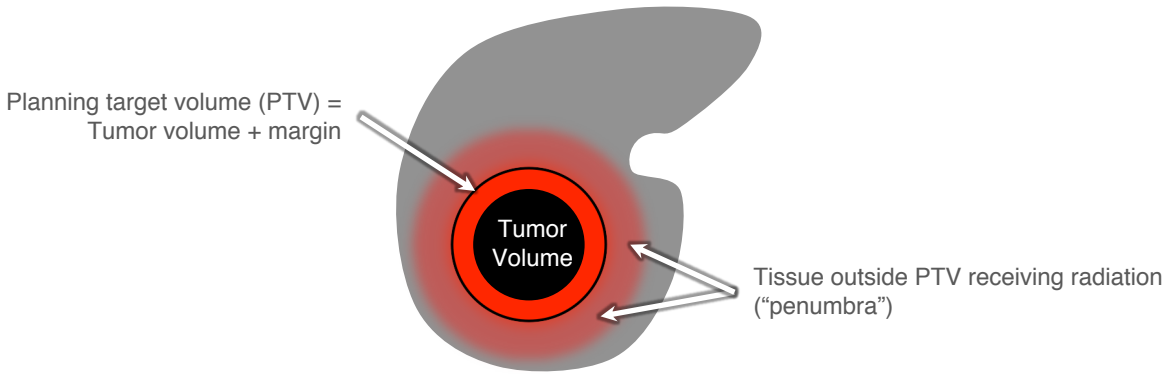
Normal liver tissue adjacent to a treated tumor may be injured by radiation, a process called radiation-induced liver injury (RILI).

Changes in the CT attenuation or MR signal intensity and enhancement pattern of the liver due to RILI may evolve over months.

Late complications from EBRT include parenchymal scarring, capsular retraction, and biliary dilation.

Key Technical Details

The planning target volume (PTV) is the the volume of tissue comprising the entire tumor volume (TV) plus a margin to account for uncertainties in tumor localization. Some tissue outside of the PTV ("penumbra") unavoidably receives low- and intermediate doses of radiation.



Local control is the absence of disease progression on imaging studies in the treated field, (e.g. stable disease, partial response, or complete response by RECIST and mRECIST).

Local progression or recurrence occurs when local control fails, i.e., with growth of targeted tumor or new tumor developing within or the PTV.

Imaging Techniques

What should the radiologist know?

Imaging is necessary after locoregional therapy to assess treatment response. The aim of imaging is to identify treatment success, complications, or presence of viable tumor, which may prompt retreatment or alternative therapeutic approaches.

The Treatment Response Algorithm is based on posttreatment contrast enhancement patterns. Treatment-related changes in parenchymal perfusion may resemble or obscure tumor enhancement, potentially leading to false-positive or false-negative assessment of viability.

Multiphase CT and MRI are currently accepted imaging modalities for response assessment, with contrast enhanced US (CEUS) still under investigation and reserved for select centers with the requisite expertise. Concepts relevant to each modality are described briefly below.

Contrast-enhanced CT (CECT)

In contrast to pretreatment imaging of HCC, noncontrast CT is helpful to identify the presence of iodized oil or hemorrhage and to more reliably characterize arterial phase hyperenhancement of viable tumor. Assessment of APHE on CECT can be challenging after therapies (e.g. TACE) that use iodized oil, which is hyperdense on precontrast CT and may obscure APHE.

MRI

Iodized oil is minimally seen on MRI, therefore, MRI is a potential alternative to CECT where hyperdense iodized oil limits the utility of CT.

LI-RADS ancillary features, such as T2 hyperintensity, diffusion restriction, and delayed hepatobiliary phase T1 hypointensity (with gadoxetate disodium), may help identify sites of suspected viable tumor on postcontrast imaging. However, these features themselves are not currently incorporated into the Treatment Response Algorithm, which is based entirely on vascular enhancement features.

Subtraction imaging can help assess arterial phase and later enhancement, when T1 hyperintense signal is present on pretreatment imaging. The use of subtraction imaging for assessing washout appearance has not been established and should be used with caution.

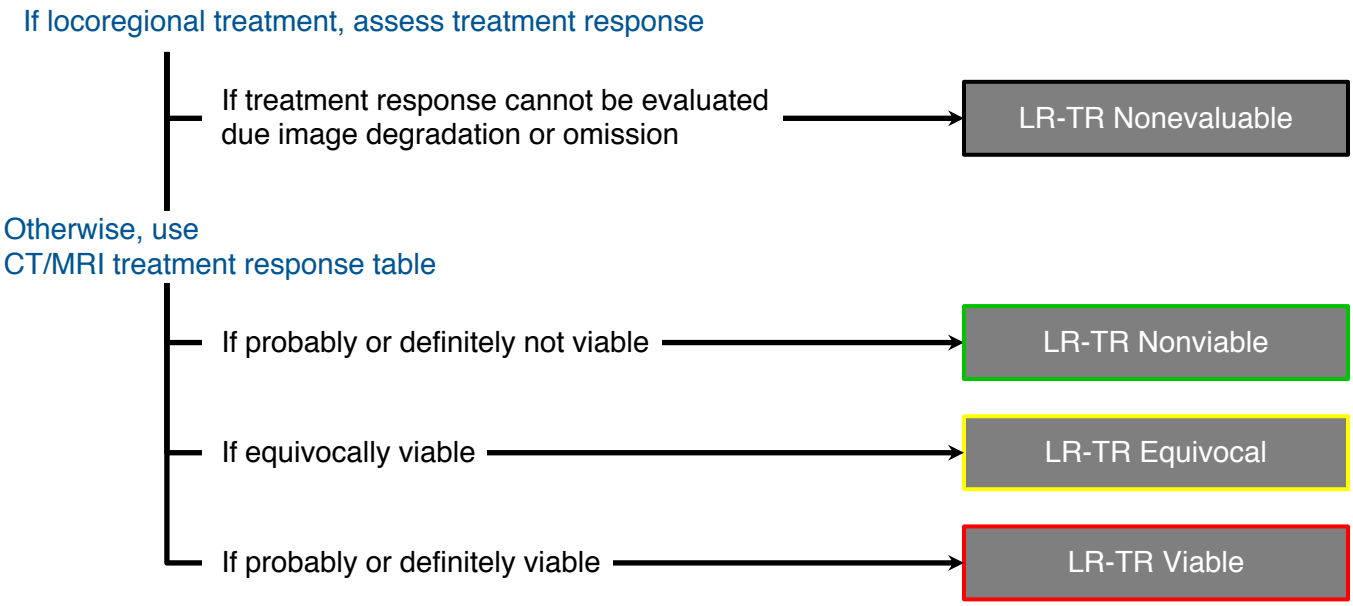
Contrast-enhanced US (CEUS)

CEUS can assess treatment effect in a single lesion immediately post ablation, and enables additional ablation in the same treatment session when indicated. Iodized oil is minimally seen on CEUS, therefore, CEUS is a potential alternative to CECT where hyperdense iodized oil limits the utility of CT.

Treatment Response Algorithm

The Treatment Response Algorithm was created to standardize the reporting of treated observations, regardless of the pretreatment LI-RADS category and varying enhancement patterns, subjected to any one or more locoregional therapy(ies).

The response algorithm is similar to mRECIST in that it is based mainly on imaging assessment of arterially enhancing tumor, but it expands upon the mRECIST definition of tumor viability.



If treatment response cannot be evaluated due to image artifacts or omission, the treated lesion is categorized **LR-TR Nonevaluable**. Otherwise, the CT/MRI Treatment Response Table (*page 9-11*) should be applied.

Treated lesions should be measured by following the measurement instructions (*page 9-13*).

The Treatment Response Algorithm is applied lesion by lesion. Thus, one lesion may be **LR-TR Nonevaluable** while another may be **LR-TR Nonviable**. However, multiple LR-TR Nonviable observations may be reported in aggregate at the discretion of the radiologist. Further guidance is available in the Reporting of Treated Observations (*page 9-15*) and in the *Chapter 14*.

Assessment of response at the patient level, or at the level of a hepatic lobe or segment for transcatheter therapy, is also performed at the discretion of the radiologist. Patient-level response may be addressed by using existing response criteria used in clinical trials, such as mRECIST, but is beyond the scope of the current version of LI-RADS.

CT/MRI Treatment Response Table

If a treated observation is evaluable, the treatment response criteria for Nonviable, Equivocal, or Viable disease should be applied:

Definitions of posttreatment response categories

Response Category	Criteria
LR-TR Nonviable	No lesional enhancement **OR** Treatment-specific expected enhancement pattern
LR-TR Equivocal	Enhancement atypical for treatment-specific expected enhancement pattern and not meeting criteria for probably or definitely viable.
LR-TR Viable	Nodular, mass-like, or thick irregular tissue in or along the treated lesion with any of the following: • Arterial phase hyperenhancement (APHE) **OR** • Washout appearance **OR** • Enhancement similar to pre treatment

CT/MRI Treatment Response Table

LR-TR Nonviable

Absence of lesional enhancement favors nonviability.

Terminology: Nonviable was chosen over ‘necrotic’ by the LI-RADS Tumor Response Working Group given that pathologic necrosis may not be present even in the absence of enhancement.

A few treatment-specific enhancement patterns may persist despite successful locoregional therapy, such as thin rim enhancement after embolization. These patterns should be recognized by the radiologist as LR-TR Nonviable. Examples are provided on the following pages.

LR-TR Viable

APHE in a nodular, mass-like, or thick irregular pattern is commonly recognized as viable disease after locoregional therapy.

Washout appearance alone can be seen in viable disease, including for tumors that do not have APHE before treatment.

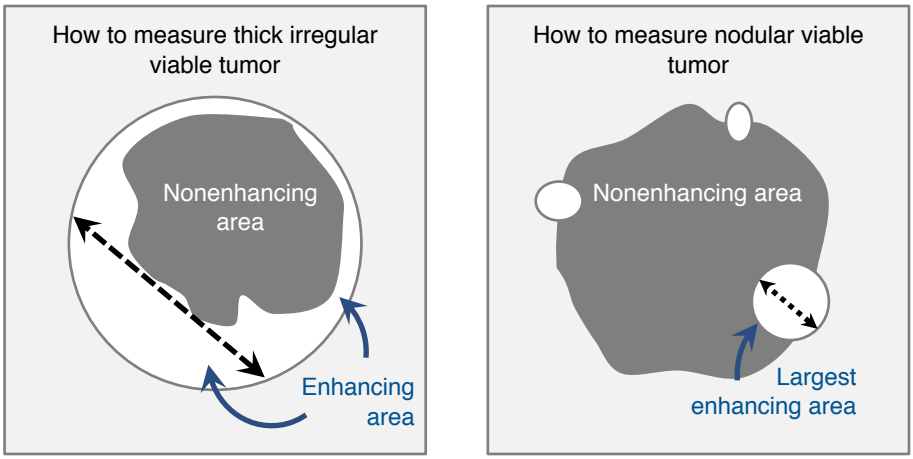
Some untreated tumors show atypical enhancement patterns, such as peripheral or rim-enhancement. Similar enhancement after treatment should be recognized as viable disease.

While growth of an enhancing portion of the tumor on follow up imaging is often interpreted as evidence of tumor viability, it does not supplant the criteria for LR-TR Viable. Growing lesions usually display more nodular or mass-like enhancement over time. Thus, there is no threshold growth criterion for LR-TR Viable.

Treatment Response Measurements

After applying the Treatment Response Algorithm, **LR-TR Viable** and **LR-TR Equivocal** tumors should be reported whenever possible with a single dimension measurement across the enhancing tumor, excluding intervening nonenhancing areas.

Measurements can be performed on the arterial phase (for lesions with APHE) or other phases (e.g. for lesions with washout appearance), in any standard orthogonal imaging plane.



The LI-RADS Treatment Response Algorithm and measurement guidelines are modeled after guidelines from mRECIST which specify that enhancing tumors should be measured on arterial phase. However, LI-RADS also allows measurement of tumors lacking APHE.

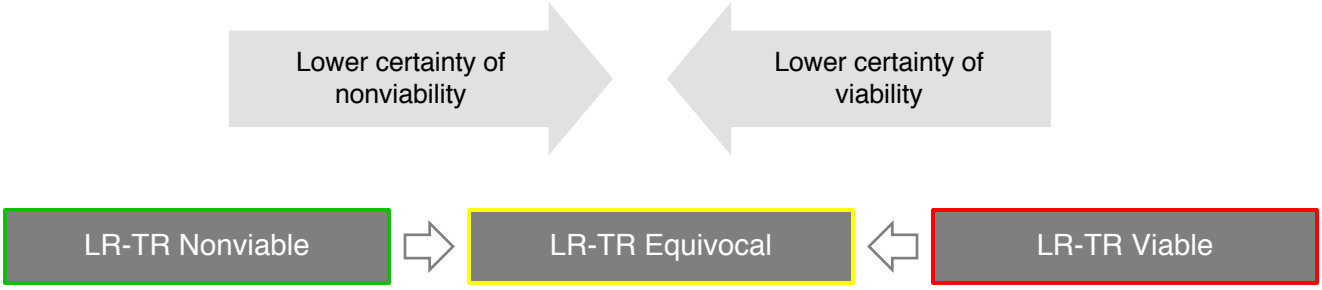
The use of a single dimension for viable tumor measurements has shown substantial to excellent agreement within the context of mRECIST.

When reporting a single dimension for viable tumor is deemed insufficient by the reporting radiologist, they are encouraged to provide additional information on the treated lesion in their report to help guide the referring physician, which is further expanded on *page 9-15*.

Reporting the pretreatment LR-category and size for comparison provides the referring physician an estimate of the magnitude of response, which is further expanded on *page 9-15*.

Treatment Response Tie-Breaking Rules

Apply **tiebreaking rules** if needed. In unsure between two categories, choose the one reflecting lower certainty, i.e. **LR-TR Equivocal**.



Reporting of Treated Observations

Overview

A full outline of posttreatment reporting is included in the reporting chapter (see *Chapter 14, page 14*). Briefly, for patients with limited disease, report each treated observation individually, and include the observation's pretreatment LI-RADS category and size for comparison. For example:

- LR-TR Nonviable (pretreatment LR-5, 22 mm)
- LR-TR Viable 20 mm (pretreatment, LR-5, 32 mm)

Providing the pretreatment category and size aids in identifying a patient's eligibility for transplantation after treatment. In combination with the pretreatment size, providing the posttreatment size of viable tumor succinctly summarizes the magnitude of response.

Local tumor progression

Local tumor progression consists of new foci of disease in tumors that were previously considered as completely treated. The distinction between locally recurrent tumor or new disease growing adjacent to the original targeted area is often impossible, with no clear guidelines to distinguish between the two. If the radiologist identifies new disease separate from the treated area, the LI-RADS CT/MRI Diagnostic Algorithm should be applied.

Downstaging

Downstaging refers to the application locoregional therapy to reduce the size and/or number of viable tumors. Patients downstaged from stage ≥ 3 to stage ≤ 2 may be eligible for liver transplantation exception points. Radiologists should report the number and size of viable tumors. Such patients should be discussed at multidisciplinary conference (tumor board).

Nonviable tumor detected only after treatment

Occasionally, a nonviable tumor is detected by imaging only after treatment, with no corresponding observation on pretreatment imaging. In this scenario, a pretreatment category should not be assigned. Instead, the report should indicate that a nonviable treated observation is visible posttreatment, that its current category is LR-TR Nonviable, and that it was not seen pretreatment.

Reporting of Treated Observations

Congruency with OPTN in transplant candidates

OPTN designates treated OPTN-5 lesions as OPTN-5T.

The (T) qualifier applies only to treated OPTN-5 lesions, including path-proven HCCs. It indicates that a treatment has been performed but does not reflect the presence or absence of viable tumor.

OPTN does not provide guidance on assessing treatment response. Thus, there are no OPTN classes analogous to LR-TR Nonevaluable, Nonviable, Equivocal, or Viable.

Patients who are awarded exception points for HCC are evaluated repeatedly (every ≤ 3 months) to determine if they remain within T2 stage. While treatment response is essential for directing management, the treatment response (LR-TR category) does not impact exception point status. Thus, an OPTN 5T lesion remains OPTN-5T regardless of lesion viability. Nevertheless, unequivocal progression of treated viable tumors to beyond Stage T2 may result in the patient's removal from the transplant list.

Patients with OPTN-5X observations do not qualify for automatic exception points as they are beyond T2 stage. These patients may still be considered for transplantation through regional review boards if they are downstaged successfully (see *prior page*).

Because OPTN is aimed at regulating MELD exception point status for transplantation eligibility, the system focuses only on definite HCC. OPTN does not provide guidance for treated or untreated observations that are probable or definite malignancies but that do not meet OPTN-5 criteria. These observations include LR-4, LR-M, and TIV. Most times these observations are managed through multidisciplinary discussion to establish T stage and transplant eligibility through pathological confirmation, additional or follow-up imaging, and/or correlation with serological tumor markers.

LR-TIV and OPTN-5X are not synonymous. LR-TIV definitely due to HCC is classified OPTN-5X, but OPTN-5X also applies to T3 stage or T4 stage disease without TIV. LR-TIV due to a non-HCC malignancy makes the patient ineligible for transplant but is not assigned an OPTN Class, since the malignancy is not a definite HCC.

Similarly, nonviable tumors detected at imaging only after treatment, with no corresponding observation on pretreatment imaging, do not count as OPTN 5T, unless they are biopsied and shown at microscopic examination to contain viable HCC cells.

Posttreatment Imaging Appearances

What should the radiologist know?

The radiologist should be aware of the type of locoablative therapy(ies) used and the intended targets: tumor(s), segment, or lobe. Discussion with the treating interventionalist is helpful when needed.

As previously discussed, posttreatment imaging is interpreted according to the Treatment Response Algorithm. Multiplanar reconstructions with CT and MRI can be helpful in evaluating for off-axial marginal residual tumor, for example at the superior rim of a treated cavity.

This chapter will illustrate the expected posttreatment appearances after locoregional therapy, for commonly used energy-based and transcatheter tumor therapies, as well as external radiation therapy. Familiarity with common posttreatment appearances specific to individual locoregional therapy is necessary to distinguish between expected posttreatment enhancement patterns that imply nonviable disease from enhancing treated observations consistent with viable disease.

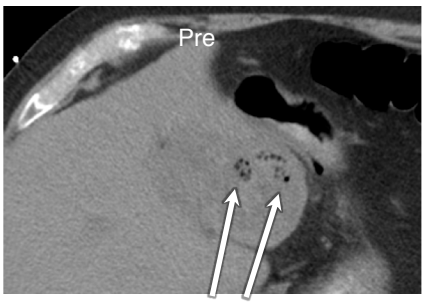
Common findings after locoregional therapy

Foci of gas can be seen for days or even weeks after locoablative and transcatheter tumor therapy. These are thought to represent nitrogen bubbles formed by negative pressure from contracting necrotic tumor, and should not be misinterpreted as gas from abscess or infection.

T1 and T2 signal intensity may be variable posttreatment due to the presence of blood products.

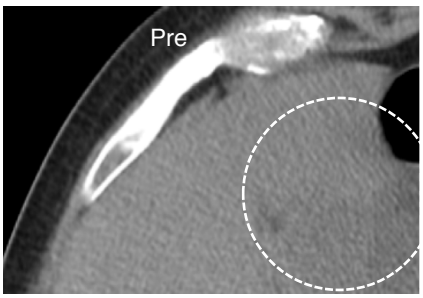
- Coagulation necrosis after MWA, RFA or PEA can cause T1 hyperintensity. Subtraction imaging on MRI may help to identify areas of enhancing tumor when T1 hyperintense signal is present.

3 days posttreatment after PEA



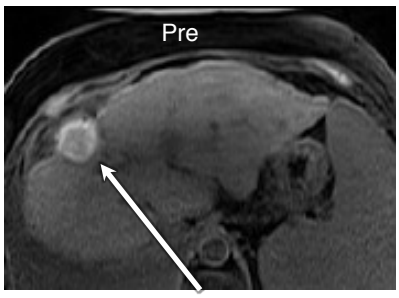
Gas bubbles

1 month posttreatment



Gas bubbles resolve over time

1 month posttreatment after RFA

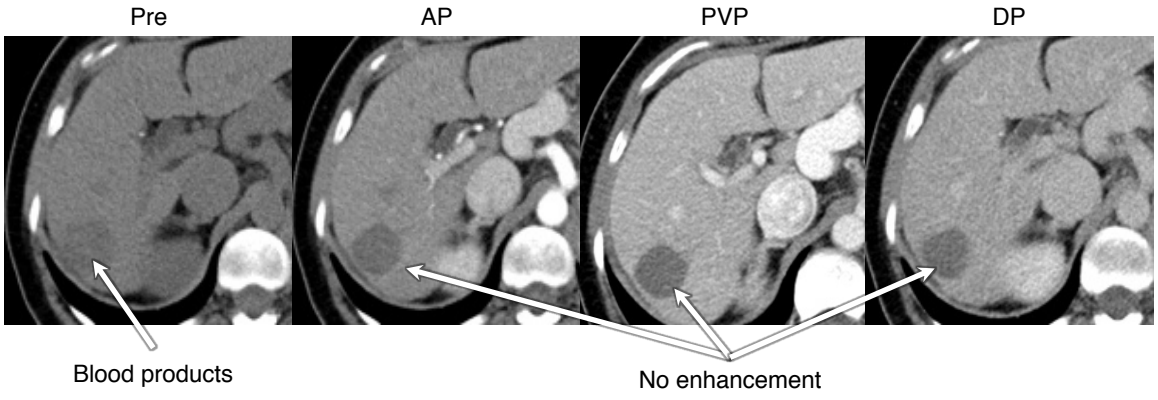


T1 hyperintensity due to coagulation necrosis

Posttreatment Imaging: RFA and MWA

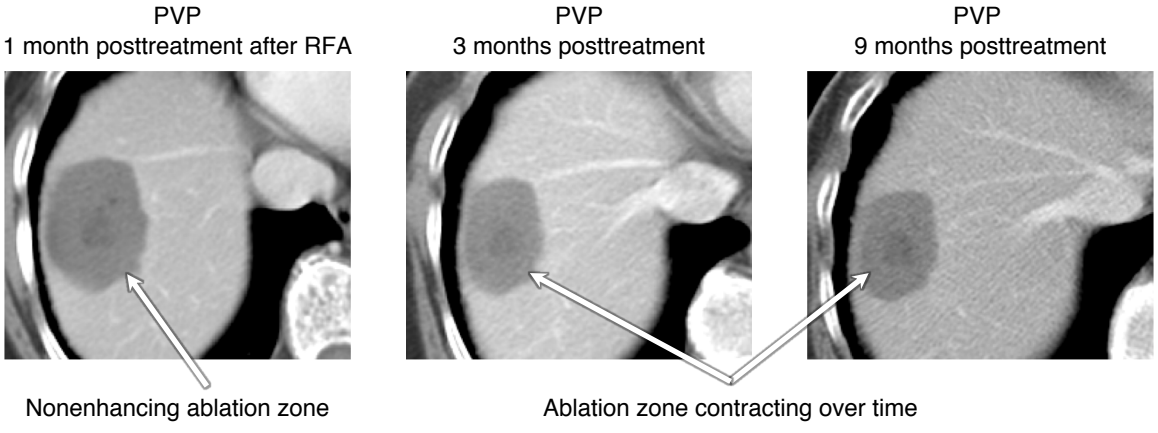
What should the radiologist know?

The RF or MW ablation zone typically goes beyond the pretreatment tumor border with a margin of at least 5 mm, which should not be confused with increased lesion size. Ideally, no residual enhancement should be present after treatment (**LR-TR Nonviable**)



LR-TR Nonviable

Reduction in size of the ablation zone begins around 6 months posttreatment, but the ablation zone may not disappear completely – a residual ablation zone can persist indefinitely



LR-TR Nonviable

A linear area of nonenhancement can be seen corresponding to an RFA or MWA electrode track that is often ablated during removal to reduce the risk of hemorrhage and seeding.

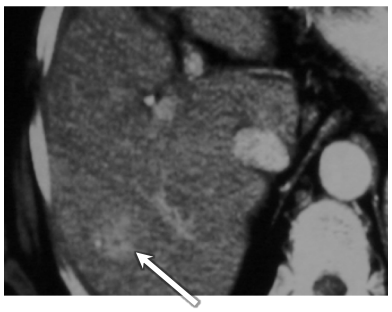
Posttreatment Imaging: RFA and MWA

What should the radiologist know? (Cont'd)

Perilesional hyperemia may be seen posttreatment, which resolves over time. When uncertain between perilesional hyperemia and residual viable tumor, assign a response of **LR-TR Equivocal**.

Pretreatment

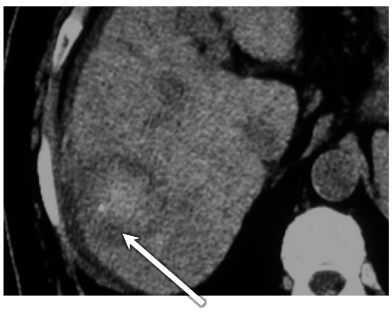
AP



APHE

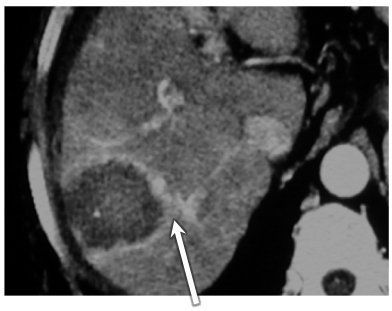
Posttreatment after ablation

Pre



Heterogeneous attenuation due to coagulation necrosis

AP



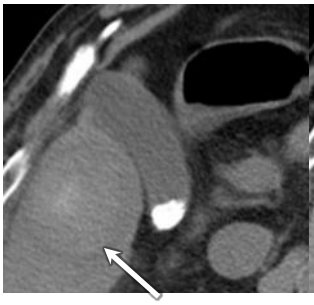
Perilesional irregular APHE

LR-TR Equivocal

Nodular or thick, rind-like area of enhancement is interpreted as **LR-TR Viable**.

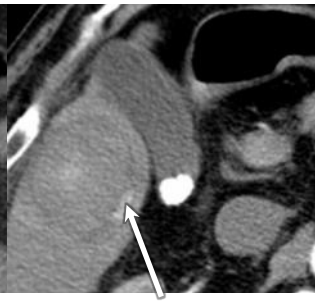
Posttreatment after RFA

Pre



Hyperdense coagulation necrosis in the ablation zone

AP

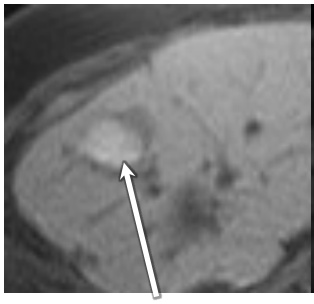


Nodular APHE

LR-TR Viable

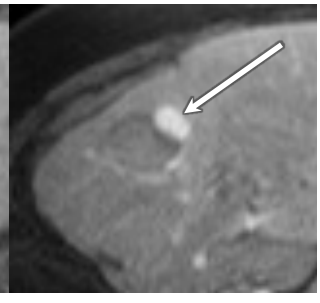
Posttreatment after MWA

Pre



T1 hyperintense coagulation necrosis

AP



Nodular APHE

LR-TR Viable

Posttreatment Imaging: Cryoablation

What should the radiologist know?

Ablation zones shrink over time and sometimes disappear completely, or result in focal hepatic atrophy, including capsular retraction or distortion of adjacent vessels.

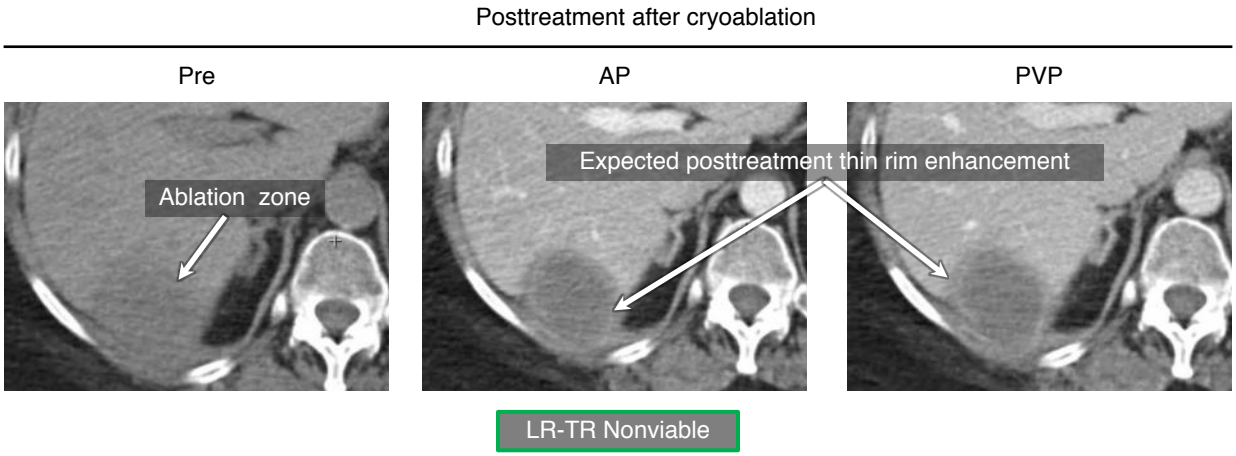
A thin rim of peripheral enhancement (reactive hyperemia) around the ablation zone immediately after cryoablation and can last for up to several months.

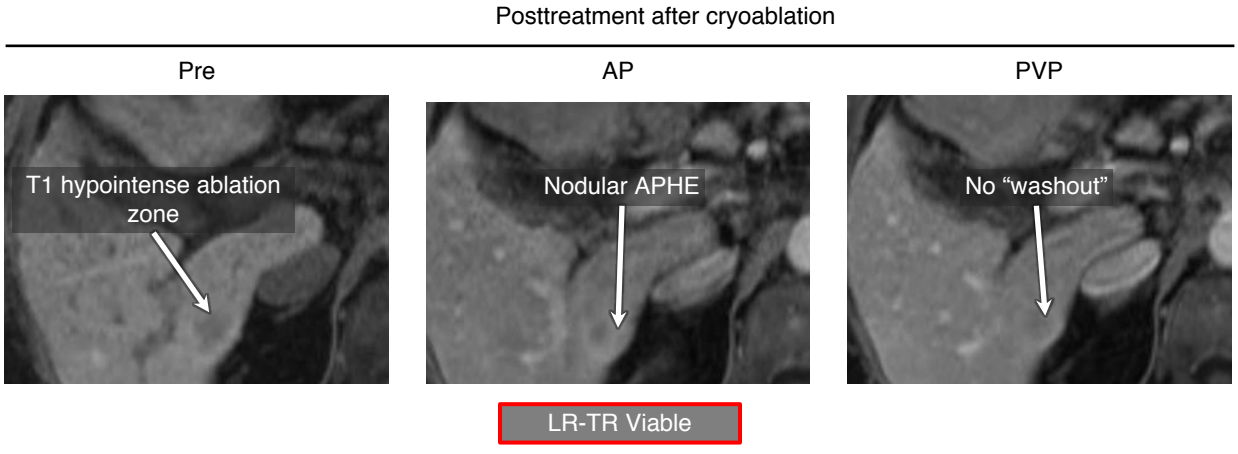
Small gas bubbles can be seen in the ablation zone immediately after treatment, can persist for up to several weeks, and should not be interpreted as abscess in asymptomatic patients.

Low signal on noncontrast T1W imaging in the ablation zone is common in contradistinction to increased signal after RFA or MWA.

Residual HCC may lack a washout appearance on the delayed phase images for up to 9 months after cryoablation; lack of this feature does not exclude viable tumor.

Biliary duct dilation is often seen after cryoablation, with damage to more central bile ducts, eventually resulting in segmental or lobar ductal dilation.





Posttreatment Imaging: PEA

What should the radiologist know?

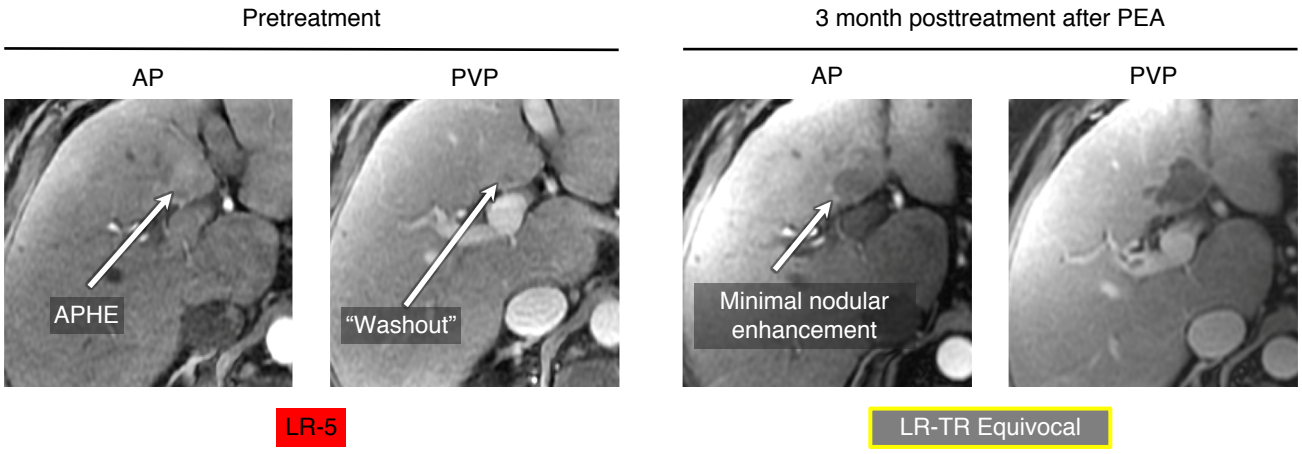
The treated area may be the same size or larger than the tumor before treatment initially.

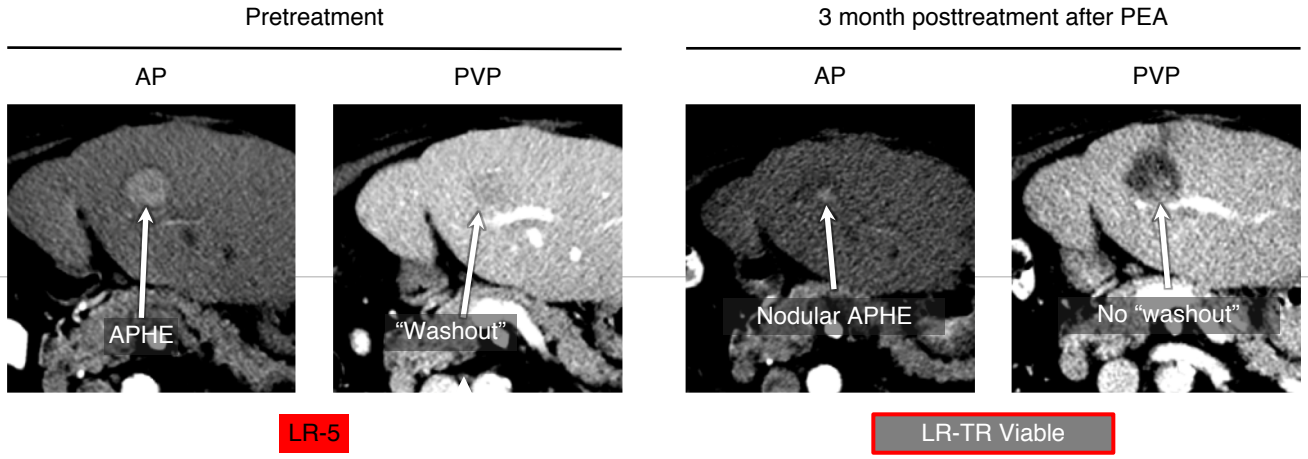
By several months after treatment, the ablation zone decreases in size due to fibrosis and retraction.

Areas of nodular or focal enhancement along the periphery or within the treated mass during the arterial or portal venous phases favors viable tumor.

On precontrast CT, a treated mass may demonstrate gas bubbles several days post treatment if the gas was introduced during instillation of ethanol and for up to a month post treatment if the gas is associated with tumor necrosis (particularly if PEA was used as an adjunct to MWA or RFA).

On precontrast MRI, treated areas may demonstrate low signal intensity on T2-weighted images and high signal intensity on T1-weighted images, reflecting coagulation necrosis.



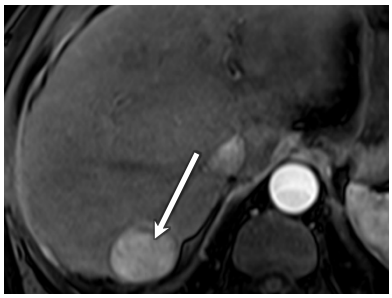


Posttreatment Imaging: TAE

What should the radiologist know? (Cont'd)

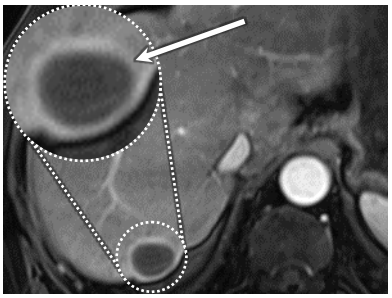
Thin linear rim enhancement of granulation tissue at the treated lesion's margin may persist for months to years. Ill-defined geographic enhancement surrounding a treated lesion may be a transient posttreatment perfusional alteration, but should be scrutinized on subsequent studies to exclude viable tumor .

AP: Pretreatment



APHE

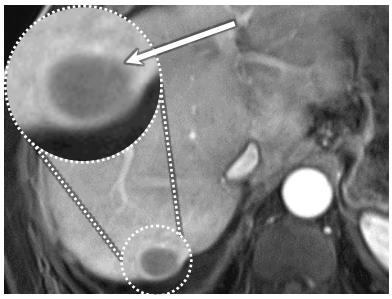
AP: 3 month posttreatment after TAE



Expected posttreatment thin enhancing rim

LR-TR Nonviable

AP: 6 month posttreatment

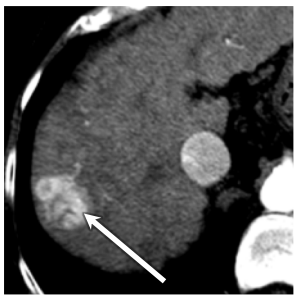


Thin rim of enhancement decreases over time

LR-TR Nonviable

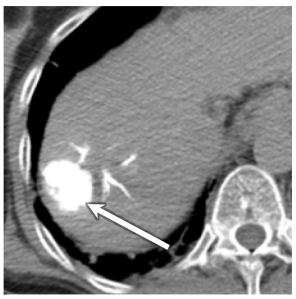
A noncontrast CT or cone beam CT can be performed within 20 minutes of treatment completion to evaluate as a marker technical success the distribution of retained contrast material administered during the procedure. Incomplete coverage of the tumor is associated with residual tumor and may prompt further intervention, such as percutaneous ablation.

AP: Pretreatment



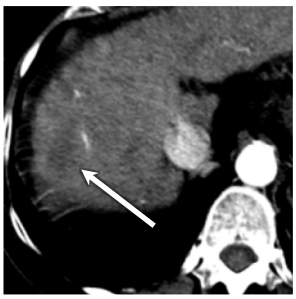
APHE

20 min posttreatment after TAE



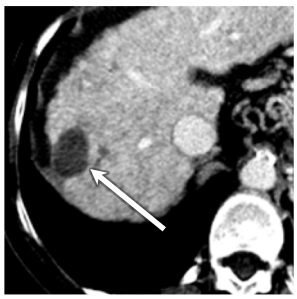
Ideal contrast retention posttreatment

AP: 3 month posttreatment



No enhancement

PVP: 6 month posttreatment



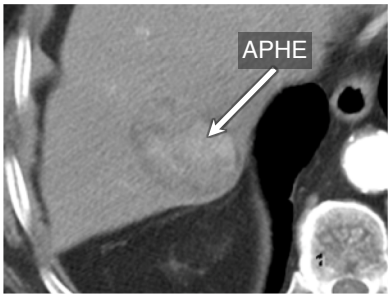
No enhancement

LR-TR Nonviable

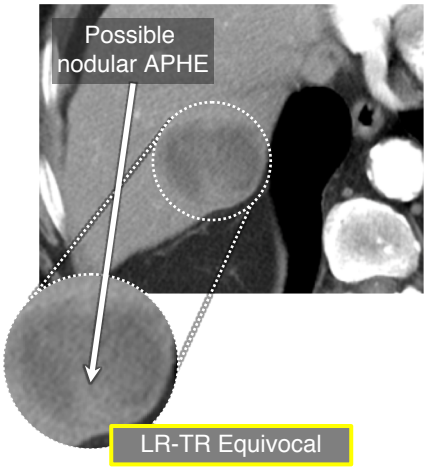
Posttreatment Imaging: TAE

What should the radiologist know? (Cont'd)

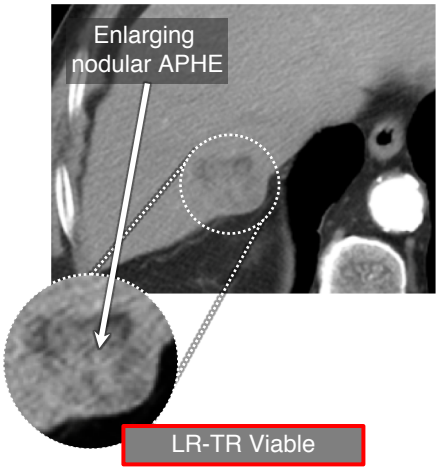
AP: Pretreatment



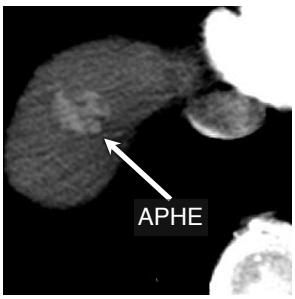
AP: 3 months posttreatment



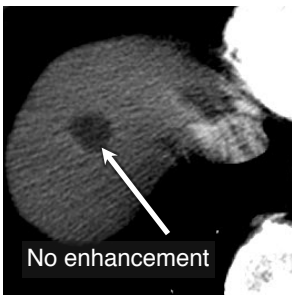
AP: 6 months posttreatment



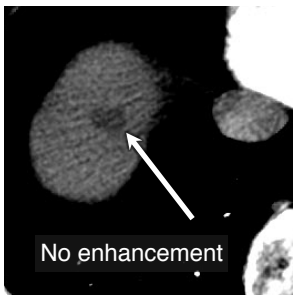
AP: Pretreatment



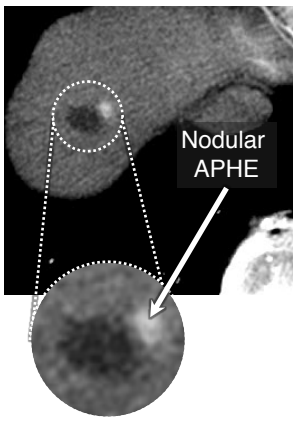
AP: 2 months posttreatment



AP: 12 months posttreatment



AP: 18 months posttreatment



Randomly dispersed foci of gas within the treated lesion may be seen on CT for 2 weeks posttreatment. Gas typically resolves within 2 weeks, but can be present for 4 weeks.

Posttreatment Imaging: TACE and DEB-TACE

What should the radiologist know?

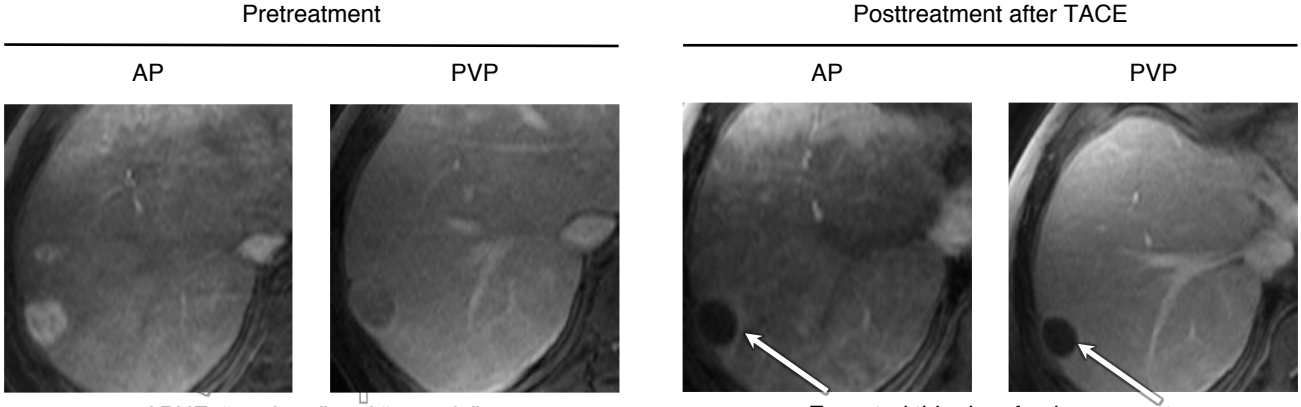
A thin, smooth, linear enhancing rim at the margin of the lesion may persist for months to years while ill-defined regional or geographic hyperenhancement surrounding the treated tumor may be a transient post-procedural perfusion alteration.

Other forms of arterial enhancement, particularly nodular enhancement or thick, irregular, or asymmetric rim enhancement within or along the margin of the treated lesion favors viable tumor. On portal venous and delayed phases, viable tumor may or may not show washout appearance.

With TACE, ethiodized oil uptake in the tumor is intrinsically hyperdense to surrounding parenchyma, making it challenging to assess APHE. On short-term posttreatment follow up (~4 weeks), more oil uptake by tumor is associated with higher technical success rates, but if the evaluation of tumoral enhancement is impaired on CT, the LR-TR Nonevaluable category should be applied.

With TACE, both tumor with ethiodized oil uptake and necrotic tumor have low signal intensity on post-gadolinium MRI with no enhancement on subtraction imaging.

There is no retention of iodinated contrast after successful treatment with DEB-TACE, and most treated tumors will hypoattenuating on noncontrast CT compared to adjacent parenchyma. Drug eluting beads are not visible on MRI.



APHE, “washout” and “capsule”

LR-5

Expected thin rim of enhancement

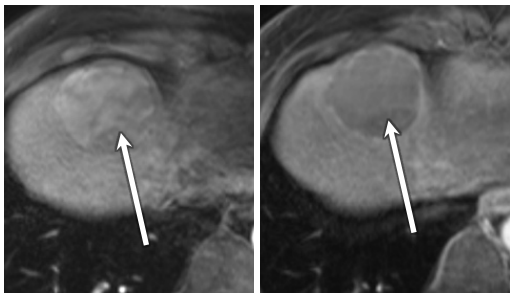
LR-TR Nonviable

Posttreatment Imaging: TACE and DEB-TACE

What should the radiologist know? (Cont'd)

Pretreatment

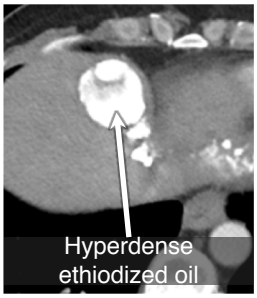
AP PVP



APHE, "washout" and "capsule"

Posttreatment CT 9 months

AP

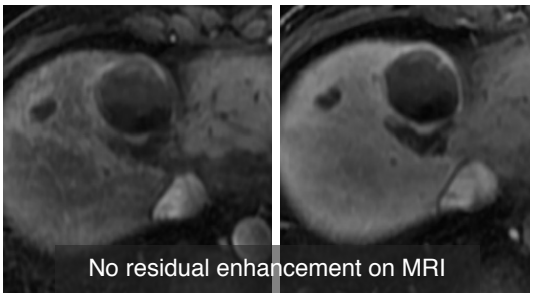


LR-TR Nonevaluable

While ethiodized oil uptake throughout the tumor is associated with a good response, it precludes assessment of posttreatment enhancement on CT

Posttreatment MRI 12 months after TACE

AP PVP

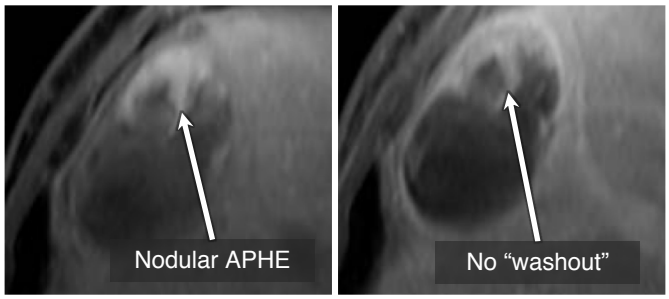


LR-TR Nonviable

Since ethiodized oil is barely or not visible on MRI, uptake of oil by tumor does not affect treatment response categorization on this modality

Posttreatment MRI after TACE

AP PVP

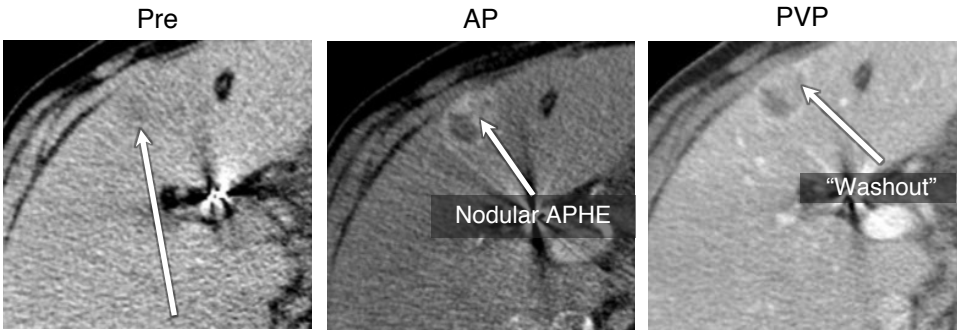


LR-TR Viable

Posttreatment Imaging: TACE and DEB-TACE

What should the radiologist know? (Cont'd)

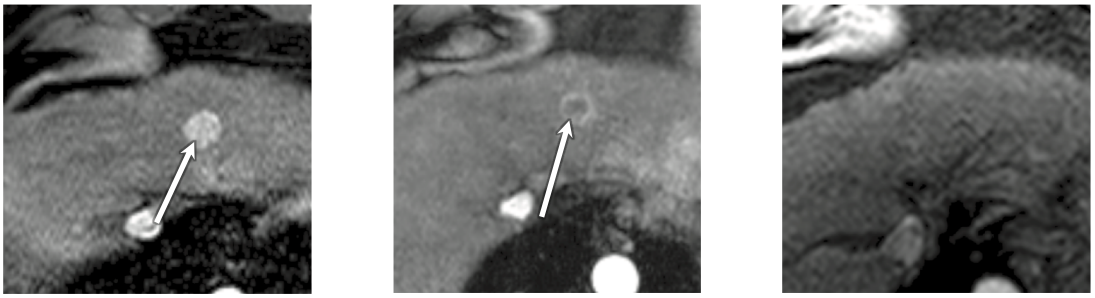
Posttreatment after DEB-TACE



No hyperdense ethiodized oil (compare to TACE)

LR-TR Viable

•



APHE

Thick but smooth and nonnodular rim enhancement

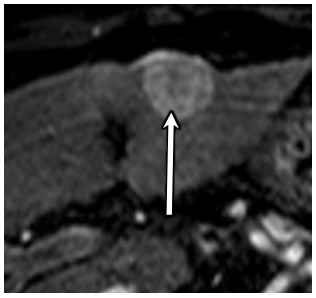
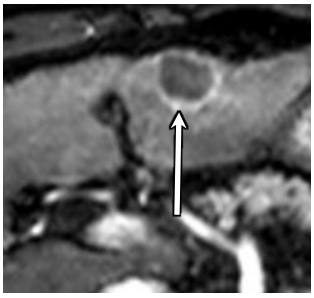
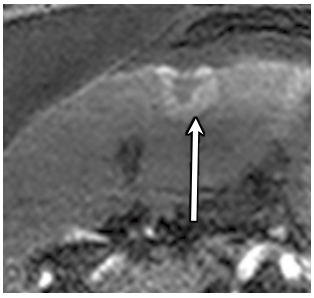
LR-TR Equivocal

No residual enhancement

LR-TR Nonviable

Posttreatment Imaging: TACE and DEB-TACE

What should the radiologist know? (Cont'd)

Pretreatment	1 month posttreatment after DEB-TACE	12 month posttreatments
AP	AP	AP
		
APHE	Equivocally asymmetric rim enhancement	Unequivocally irregular rim enhancement
	LR-TR Equivocal	LR-TR Nonviable

Posttreatment Imaging: TARE

What should the radiologist know?

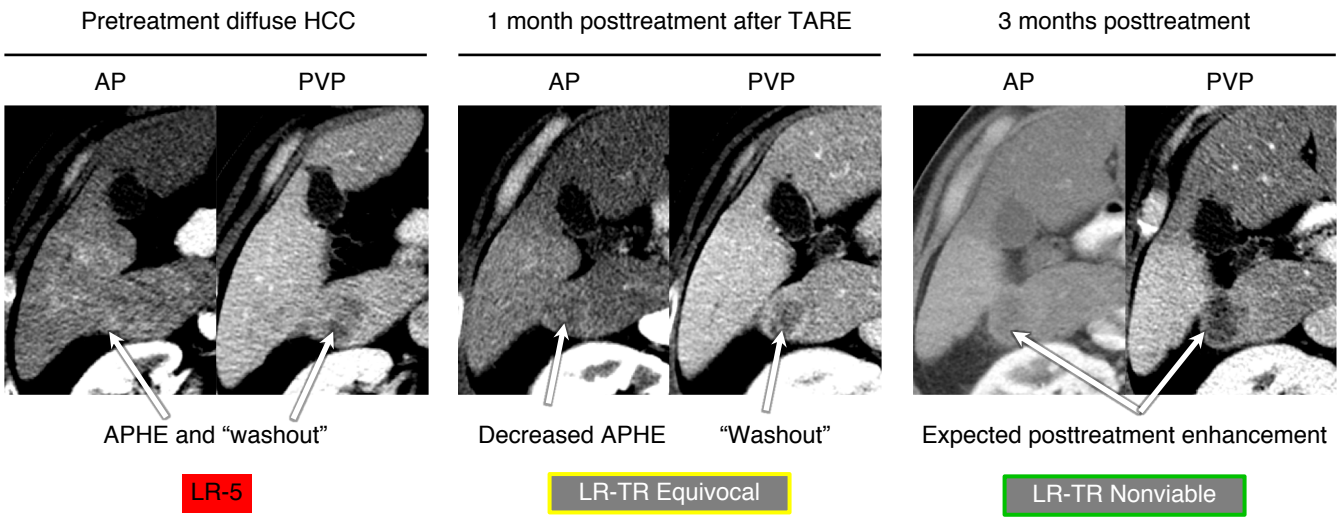
The embolic effect of TARE is less prominent compared to other transcatheter therapies. As a result, tumor enhancement can persist after TARE, even in a nodular pattern on early follow-up imaging, which may not indicate residual viable tumor. Imaging should be interpreted with caution during the first 6 months after treatment. Tumor necrosis after TARE is caused mainly by radiation, with delayed onset and slow time course.

Treated tumor is often stable at 1 month posttreatment, decreasing in size over several months. In some instances, edema and hemorrhage may produce transient mild increases in apparent tumor size early after treatment.

Necrotic tumors become nonenhancing, but can exhibit rim enhancement (inflammatory changes caused by the treatment).

Fibrosis can develop in the treated lobe, with volume reduction and capsular retraction, as well as compensatory hypertrophy of the contralateral hepatic lobe.

Patchy and ill-defined geographic regions of enhancement usually seen best on arterial phase can be seen in the treated vascular territory, mimicking diffuse heterogeneous tumor, but typically resolve over 1-5 months.

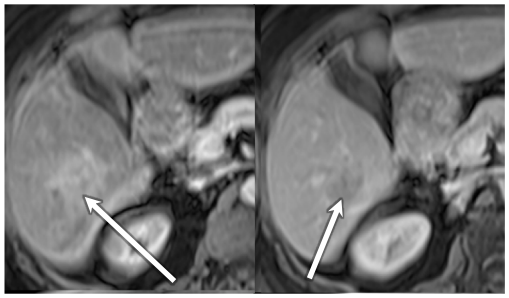


Posttreatment Imaging: TARE

What should the radiologist know? (Cont'd)

Pretreatment

AP PVP

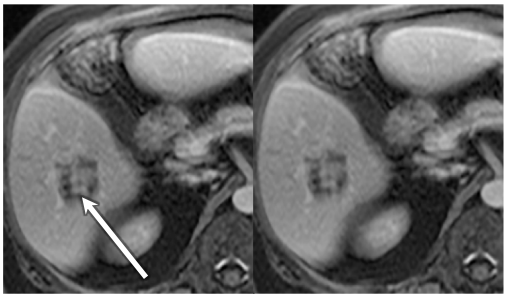


APHE and "washout"

LR-5

Posttreatment after TARE

AP PVP

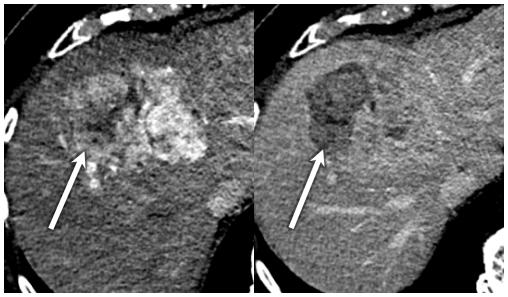


Nodular APHE

LR-TR Viable

Pretreatment

AP PVP

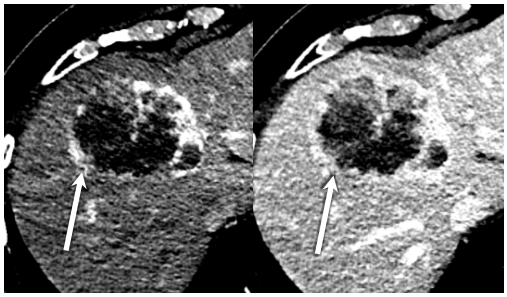


APHE and "washout"

LR-5

1 month posttreatment after TARE

AP PVP

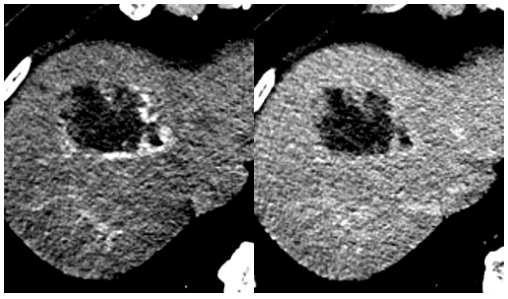


Irregular enhancement early after treatment

LR-TR Equivocal

3 months posttreatment

AP PVP

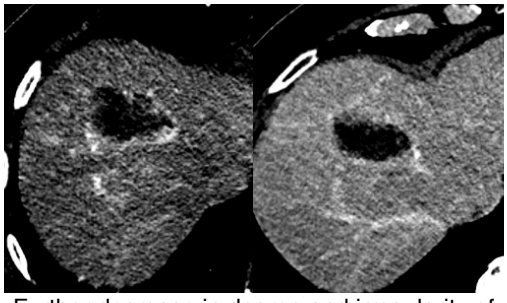


Decreased enhancement with persistent areas of irregular nodularity

LR-TR Equivocal

6 months posttreatment

AP PVP



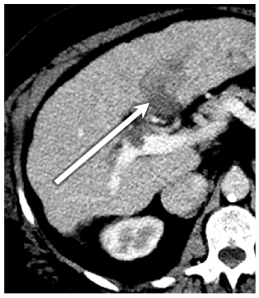
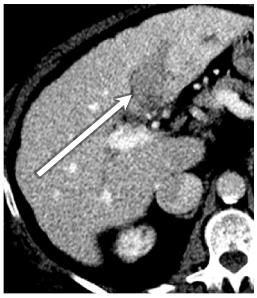
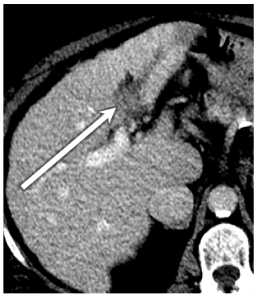
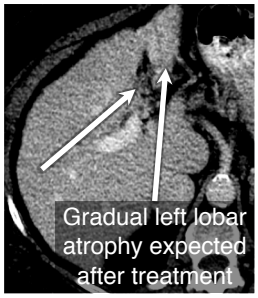
Further decrease in degree and irregularity of enhancement. Note isze reduction.

LR-TR Nonviable

Posttreatment Imaging: TARE

What should the radiologist know? (Cont'd)

Post TARE

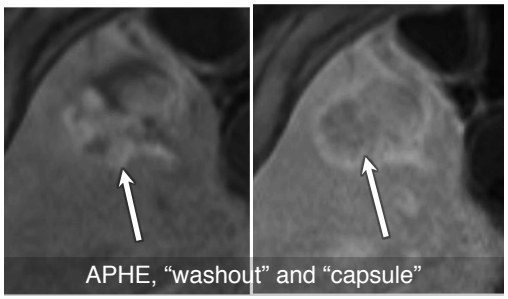
Pretreatment	1 month posttreatment	4 months posttreatment	11 months posttreatment
PVP	PVP	PVP	PVP
			
LR-TIV	Enhancement similar to pretreatment but only 1 mo post TARE	Enhancement decrease over time	
LR-TIV	LR-TR Equivocal	LR-TR Equivocal	LR-TR Equivocal

Posttreatment Imaging: TARE

What should the radiologist know? (Cont'd)

Pretreatment

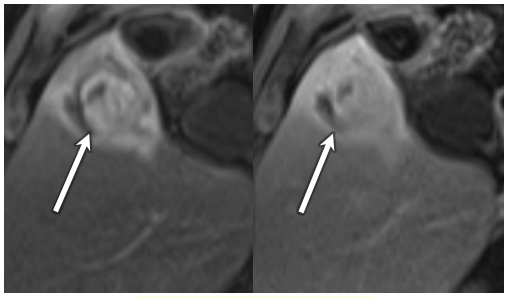
AP PVP



LR-5

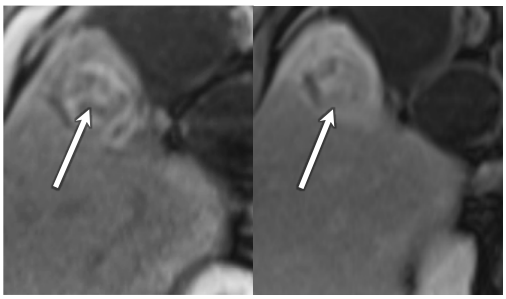
Post TARE

AP PVP



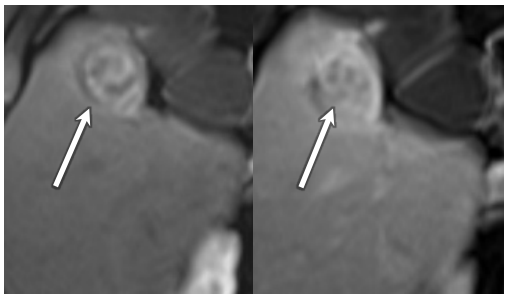
3 months

LR-TR Equivocal



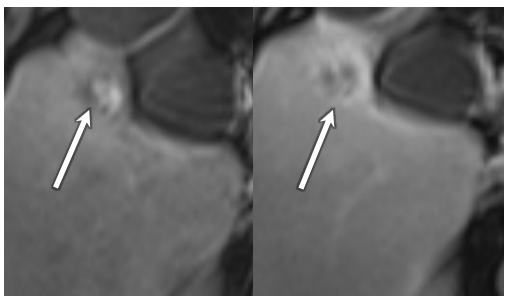
6 months

LR-TR Equivocal



12 months

LR-TR Equivocal



24 months

LR-TR Equivocal

Gradually diminishing size and arterial phase enhancement of treated lesion as well as gradually diminishing arterial enhancement of adjacent liver

Posttreatment Imaging: XRT

What should the radiologist know?

Tumor's response to radiation (***see Table below***) evolves over months and is attributable to damage to tumor DNA, damage to tumor stroma, and activation of pro-inflammatory and reparative pathways.

- Transient increase in tumor size and/or enhancement may be seen within the first 1-3 months (pseudo-progression) but tend to decrease thereafter.
- Reduction in tumor size may not occur for the first 3-6 months.
- Complete de-vascularization or necrosis is uncommon.

Expected imaging appearance of tumor	
Early post radiation period (< 3 months)	**Late post radiation period (> 6 months)**
• Persistence of arterial phase hyper-enhancement and washout common • May transiently increase in size and/or enhanacment (i.e. *pseudo-progression*)	• Gradual decrease in tumor size • Gradual decrease in APHE • May show capsule or halo on delayed phase • Complete de-vascularization or necrosis is uncommon

Posttreatment Imaging: XRT

What should the radiologist know? (Cont'd)

Surrounding liver's response to radiation (***see Table below***) also evolves over months and is attributable to the onset/resolution of

- microvascular veno-occlusion (microvascular thrombosis and sinusoidal outflow obstruction) and congestive edema (early post-treatment)
- chronic microhemorrhage and hemosiderosis (mid post-treatment)
- parenchymal fibrosis and architectural distortion (late post-treatment).

Diffuse parenchymal enhancement around treated tumor due to microvascular veno-occlusion (early) or fibrosis (late) could mimic diffuse tumor; review of treatment planning map may help in differentiation.

Evolving parenchymal abnormality surrounding treated tumor may confound the apparent attenuation/signal and enhancement characteristics of the treated tumor.

Treatment-related hepatocyte damage and/or fibrosis may impair parenchymal uptake of hepatobiliary agents, causing hypointensity of the treatmnent zone on HBP images. HBP phase images must be interpreted with other sequences to avoid misinterpretation of treatment zone as viable tumor.

Expected imaging appearance of surrounding liver

Early post radiation period (< 3 months)

- Reactive hyperemia: APHE
- Edema: pre-contrast low CT attenuation, low T1 signal, and high T2 signal
- Microvascular veno-occlusion: delayed liver enhancement
- Microhemorrhage: foci of T1 shortening (high signal) or susceptibility (low signal) on T1-weighted GRE images

Late post radiation period (> 6 months)

- Reactive hyperemia (APHE) resolves
- Fibrosis develops:
  - precontrast low CT attenuatation & low T1 signal
  - Progressive or delayed liver enhancement
- Evolution of microhemorrhages
- Structural changes: regional atrophy, architectural distortion, including biliary stricture and capsular retraction

Any post radiation period

- HBP hypointensity due to hepatocyte damage and/or fibrosis

Posttreatment Imaging: XRT

What should the radiologist know? (Cont'd)

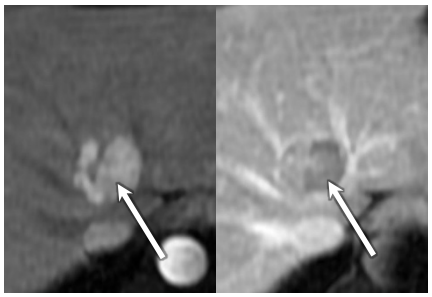
Image interpretation should emphasize serial imaging and trending of imaging features (i.e. using prior study as the internal control), rather than on imaging features at a single time point.

Uptrending in tumor size and/or increasing arterial enhancement after a period of favorable posttreatment response is concerning for recurrence.

Fiducial markers may be visible in or around treated lesion.

Pretreatment HCC

AP PVP

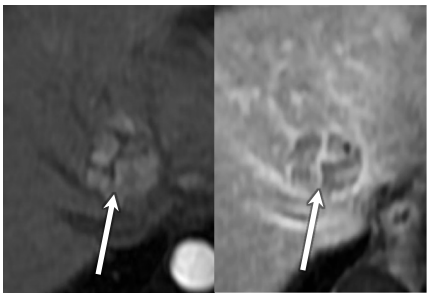


APHE and "washout"

LR-5

3 month posttreatment after XRT

AP PVP

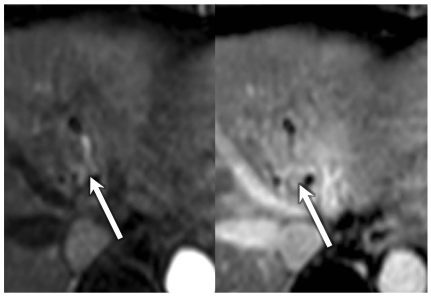


Persistent APHE and "washout"
No size reduction

LR-TR Equivocal

6 months posttreatment

AP PVP



Complete loss of APHE in the background of heterogeneous post-XRT liver parenchyma. No viable tumor in liver resection specimen. Foci of susceptibility are from fiducial markers.

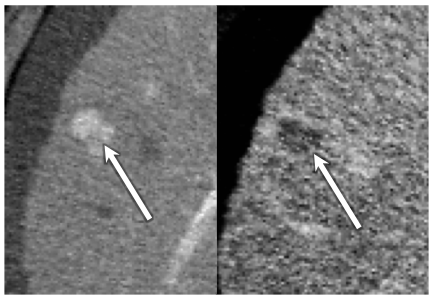
LR-TR Nonviable

Posttreatment Imaging: XRT

What should the radiologist know? (Cont'd)

Pretreatment HCC

AP PVP

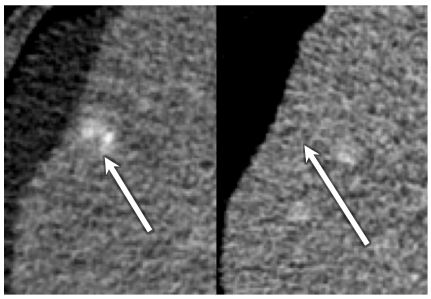


APHE and "washout"

LR-5

3 months posttreatment after XRT

AP PVP

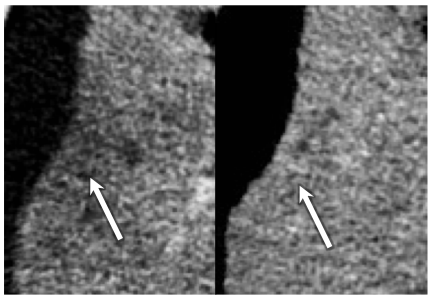


Persistent APHE in the early post-XRT period. Size is reduced. No "washout".

LR-TR Equivocal

6 months posttreatment

AP PVP

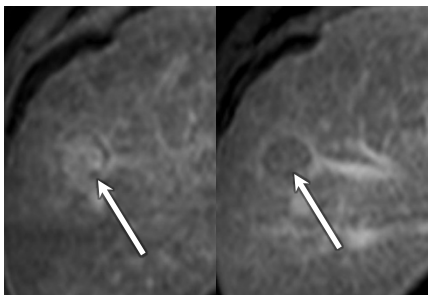


Complete loss of APHE in treated lesion.

LR-TR Nonviable

Pretreatment HCC

AP PVP

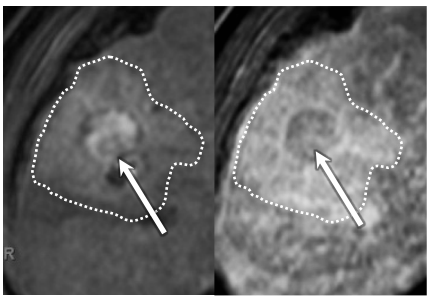


APHE, "washout" and "capsule"

LR-5

3 months posttreatment after XRT

AP PVP

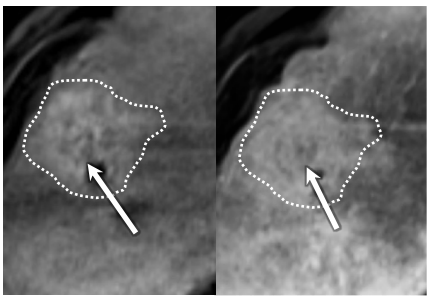


Persistent APHE and washout in treated lesion in early post-XRT period. Mild increase in tumor size (pseudo-progression). Post-XRT parenchymal changes bounded by dotted line.

LR-TR Equivocal

9 months posttreatment

AP PVP



Decreasing but persistent mild APHE in lesion and background liver. Equivocal for viability. Partially viable tumor was found on liver explant specimen.

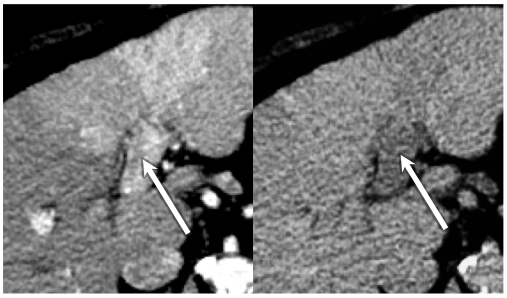
LR-TR Equivocal

Posttreatment Imaging: XRT

What should the radiologist know? (Cont'd)

Pretreatment TIV due to HCC

AP DP

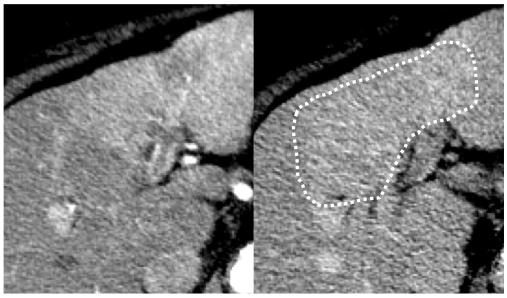


TIV, APHE and "washout"

LR-TIV

4 months posttreatment after XRT

AP DP



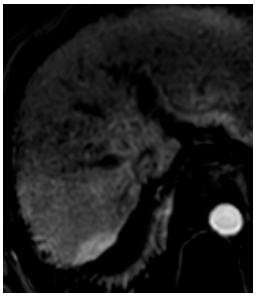
Slightly decreased APHE

Hyperenhancing post-XRT liver parenchyma

LR-TR Equivocal

9 months posttreatment

AP

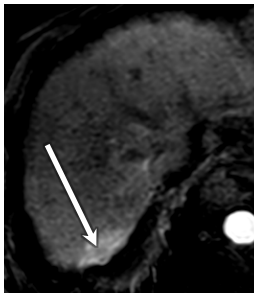


Residual parenchymal hyperenhancement in the XRT treatment zone without focal observation

LR-TR Nonviable

12 months posttreatment

AP

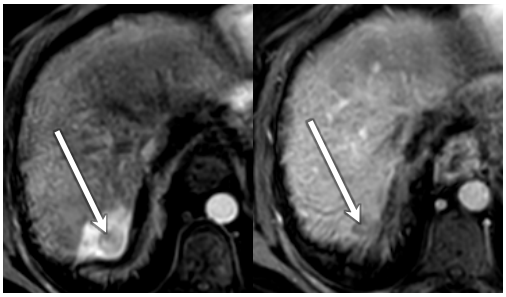


A questionable new subcentimeter observation (arrow) at the margin of XRT treatment zone.

LR-TR Equivocal

24 months posttreatment

AP PVP



Enlarging nodular observation with APHE compared to untreated parenchyma and washout in the portal venous phase compatible with marginal tumor recurrence.

LR-TR Viable

Systemic Therapy

What should the radiologist know?

Systemic therapy is usually reserved for advanced, unresectable HCC in whom surgical or locoregional therapy is not possible or has failed. The combination of systemic therapy with locoregional therapy may increase in use over time, and familiarity with the basics of HCC systemic treatment is important for radiologists.

Systemic therapy for HCC can consist of conventional chemotherapy, targeted therapy, immunotherapy, hormonal therapy and antiviral therapies.

- Conventional cytotoxic chemotherapy and hormonal agents have small or no long-term benefits.
- Targeted (molecular) therapies directed against specific molecular alterations in the pathophysiology of HCC have shown promise. Targeted therapies aim to prevent the growth and spread of disease by interfering in the signaling pathways for tumor progression and viability. These agents are geared towards increased efficacy and reduced toxicity.
    - Sorafenib, an oral multi-kinase inhibitor that targets both tumor cell viability and tumor angiogenesis, has been shown to improve survival when compared to placebo.
- Immunotherapy for HCC is being investigated and is based on the use of immune checkpoint inhibitors to harness the body's own immune system to generate a tumor-specific response. Radiologists should be aware of potential pitfalls in imaging interpretation after immunotherapy and be familiar with immune-related RECIST. With immunotherapy, it is not uncommon for new disease to be 'uncovered' by treatment or for existing disease to enlarge slightly before decreasing in size. Thus, early pseudoprogression may be misinterpreted as clinical progression if the radiologist is unaware that immunotherapy was administered or is unfamiliar with expected changes associated with immunotherapy.
- Approval of systemic therapies is rapidly evolving, with recent additions of Lenvatinib, Regorafenib, and Nivolumab, for example. Hormonal therapy, antiviral therapy and other investigational therapies are beyond the scope of this chapter.

Treatment response for systemic therapy has been based mainly on RECIST and mRECIST in clinical trial settings. Recent studies have shown that mRECIST identifies a greater number of patients with treatment response compared to RECIST during the course of treatment.

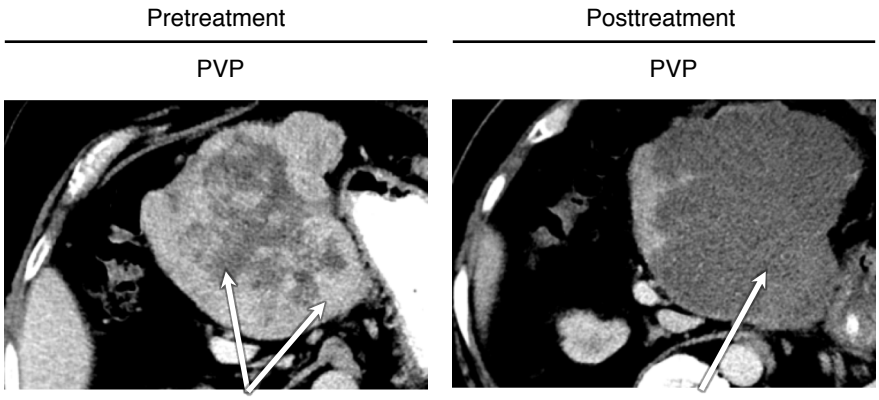
Combination of systemic therapy and locoregional therapy, including TACE and yttrium-90, are under active investigation in an effort to improve the outcomes of patients with unresectable or advanced HCC.

The LI-RADS Treatment Response Algorithm should be used with caution in patients undergoing locoregional therapy who are also treated concurrently with systemic therapy.

Systemic Therapy

Expected posttreatment appearance

- Decreased tumor enhancement can occur with response even without changes in size.

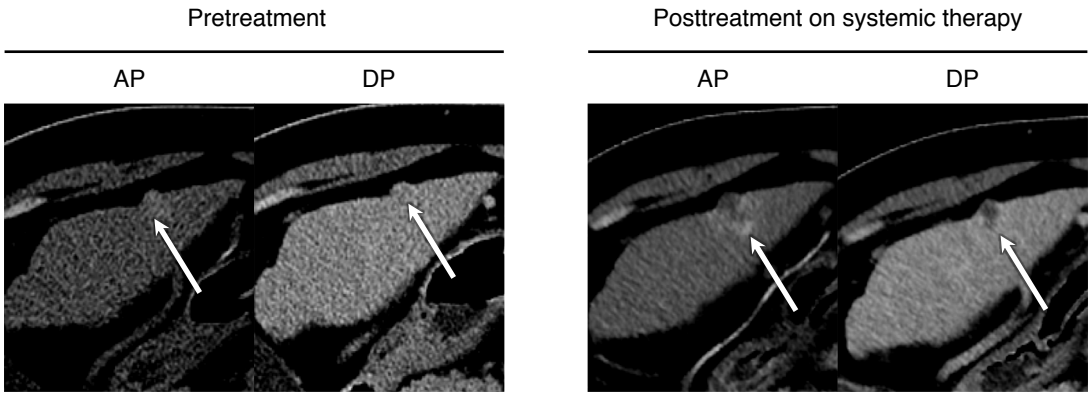


Heterogeneous enhancement

Decreased tumor enhancement

HCC may remain unchanged in size during therapy**.** Increase in tumor size early after therapy initiation may occur in the minority of patients, while decrease in tumor size is typically a late finding.

Similar to locoregional therapy, residual thick and nodular foci of arterial enhancement within HCC after systemic therapy favors residual viable tumor.



APHE and no “washout”

Nodular APHE without “washout”
Favors viable tumor.

LR-3

(Systemic therapy give for LR-5s elsewhere in liver)

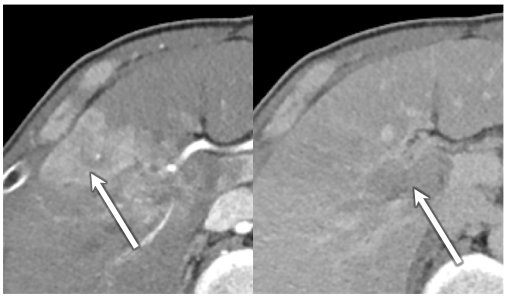
Treated by systemic therapy, probably viable

Posttreatment Imaging: Systemic Therapy

Advanced diffuse HCC can be challenging to measure both pretreatment and posttreatment during systemic therapy.

Pretreatment

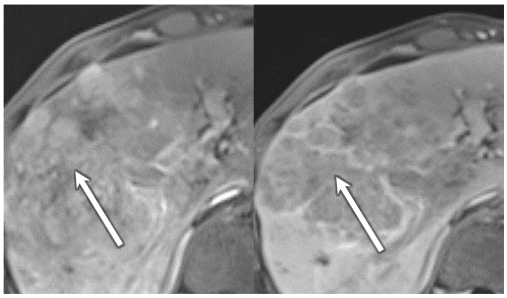
AP PVP



Heterogeneous APHE with Tumor in Vein

Posttreatment on systemic therapy

AP PVP



Increased nonmeasurable area of APHE with washout probably reflecting lack of response

Do not apply LR-TR criteria

The LI-RADS Treatment Response Algorithm was not designed for response assessment in HCC patients undergoing systemic therapy. This patient population may have diffuse or multifocal disease, and the changes in tumoral enhancement is often heterogeneous and challenging to measure. For patients undergoing combined locoregional therapy with systemic therapy, the Treatment Response Algorithm may be used with caution when the locoregional therapy effect is dominant.

Treatment Response: Patient-Level Criteria

Overview

Several radiologic response criteria exist for patients with multifocal or metastatic HCC, with the goal of standardizing assessment across sites for multi-center trials:

- World Health Organization (WHO)
- Response Evaluation Criteria in Solid Tumors (RECIST)
- EASL
- Modified RECIST (mRECIST)

EASL criteria and mRECIST take into account the cytostatic response related to many hepatic directed therapies (i.e. the tumor size does not change, but the enhancing component decreases).

- EASL criteria correlate better with survival than size-based methods (WHO and RECIST).

The choice between WHO, RECIST, EASL and mRECIST depends on the needs of the practitioner, department, institution, or clinical trial. While RECIST remains the predominant response criteria for clinical trials, mRECIST is increasingly used.

The LI-RADS Treatment Response Algorithm is in part adapted from concepts within mRECIST and can be applied at the patient level, but was not designed for use after systemic therapy.

Pitfalls and limitations of existing patient-level response systems

Optimal contrast phase or series to measure tumor:

- WHO and RECIST 1.1 do not provide guidance.

Measuring viable tumor in the setting of necrosis or partial response:

- EASL does not provide guidance; little correlation in literature with pathology.
- Reproducibility of measurements may be impacted by pattern of necrosis.

Assessing patient-level versus lesion-level response:

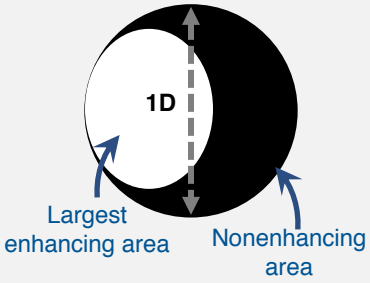
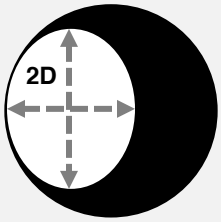
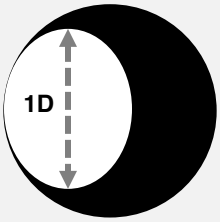
- Arterial embolic and ablation therapies are performed at staged intervals.
- Response assessment must take into account both treated and untreated disease.
- Creates complexity; definitions are lacking for time to progression and assessment of overall response following repeat embolizations.

Optimal timing of follow-up imaging and assessment of response evolution:

- Radiotherapy and TARE may require weeks to months to achieve response.
- Tumor enhancement may decrease following initial embolization, but not reflect necrosis.
- mRECIST ignores the mechanism of action and the time-dependence of response to treatment.

Atypical lesions may not be well represented by EASL criteria and mRECIST.

Treatment Response: Patient-Level Criteria

	RECIST	EASL	mRECIST
Definition	Response Evaluation Criteria in Solid Tumors (RECIST) Criteria based on 1D measurement of tumor size regardless of enhancement pattern. In 2009, RECIST was revised to RECIST version 1.1. 	The European Association for The Study of the Liver (EASL) Criteria based on 2D measurement of enhancing (viable) tumor. Developed by a panel of international experts in 2000 to measure response following TACE. 	Modified response evaluation criteria in solid tumors (modified RECIST) mRECIST incorporates the concept of viable tumor and is a formal modification of RECIST. It integrates the RECIST definitions of response categories and target lesion selection into EASL. 
Concepts	RECIST 1.1 classifies tumor lesions at baseline as “measurable” and “non-measurable” lesions. 1. Measurable lesions are defined as those lesions that can be accurately measured in at least one dimension as > 1 cm. 2. Non-measurable lesions refer to all other lesions, including small lesions (longest diameter <1cm) and truly non-measurable lesions. 3. Up to 5 Target Lesions are allowed (maximum of 2 lesions per organ). 4. Requires inclusion of the enhancing rim of the target lesion in the measurement. 5. Non-target lesions include all other sites of disease and should also be recorded at baseline.	EASL defines enhancing portion of tumor as viable and non-enhancing portions as necrotic. 1. Viable tumor: enhancing portion on arterial phase imaging. Two perpendicular measurements of greatest diameter of viable tumor are multiplied to produce an area of viable tumor. 2. Response: Percentage changes in tumor area on contrast enhanced CT or MR imaging studies performed 4 weeks following TACE. 3. Target Lesions: No definition of measurable disease is provided. All viable tumor areas are summed to give the total tumor burden.	mRECIST uses unidimensional measurements of the viable component of the tumor (on CT or MRI) in the arterial phase. Defines target lesions and non-target lesions. Target lesion: 1. Can be accurately measured in at least one dimension as 1 cm or more, 2. Is suitable for repeat measurement and 3. Shows intratumoral arterial enhancement on contrast-enhanced CT or MRI. Non-target lesions: All other measurable lesions (not included as target lesions) should be identified as non-target lesions and should also be recorded at baseline. Overall response is defined by combining the response of target and non-target lesions.

Frequently Asked Questions

What is a treated observation?

An observation that has been treated by locoregional therapies such as radiofrequency ablation, percutaneous ethanol ablation, cryoablation, microwave ablation, transarterial embolization or chemoembolization, transarterial doxorubicin-eluting bead chemoembolization, transarterial radioembolization, and external beam radiotherapy.

What about observations treated by systemic therapy?

LI-RADS v2017 does not address systemic treatment response assessment.

How do I determine if a treated observation is nonevaluable?

A category of LR-TR Nonevaluable should be assigned if treatment response cannot be meaningfully evaluated due to inappropriate imaging technique or inadequate imaging quality. Do not assign a response category of nonevaluable if image quality is adequate, even if imaging features are difficult to characterize or interpret.

What if the arterial phase is inadequate, but the portal venous phase shows unequivocal enhancement? Is that Nonevaluable or Equivocal?

Assign a response category of LR-TR Equivocal. Consider immediate repeat imaging or, if needed to ensure an adequate arterial phase, alternative imaging.

What is the optimal follow-up interval to assess treatment response?

Optimal follow-up intervals depend on the applied treatment, institutional guidelines, and reimbursement constraints. In general, follow-up CT or MRI is recommended every 3 months, although initial imaging at 1 month may be helpful after certain locoregional therapies.

Are there any pitfalls in assessing response too soon after treatment?

Treatment-related changes in parenchymal perfusion may resemble or obscure tumor enhancement, potentially leading to false positive or false negative assessment of viability.

What should I do if I am unsure about tumor viability versus expected posttreatment change?

Categorize as LR-TR Equivocal if image quality is adequate.

Frequently Asked Questions

Does LR-TR nonviable exclude microscopic viability?

No. LR-TR nonviable means there is no evidence of gross viable tumor, but small foci of live tumor cells cannot be excluded by noninvasive imaging.

How do I distinguish residual tumor from new tumor adjacent to a treated observation?

In contrast to new tumor in adjacent liver, residual tumor usually arises within or at the margin of the treated observation. No single threshold distance from the margin reliably distinguishes a new lesion from a marginal recurrence. Use your judgment to make the distinction and apply the corresponding LI-RADS algorithm (CT/MRI Treatment Response or Diagnostic). Example: a new observation has features indicating de novo origin (e.g., nodule in nodule) and/or excluding metastasis from the treated lesion (e.g., differences in fat, iron, HBP intensity): this should be considered a new tumor.

How do I assess the response of tumor in vein to treatment?

This can be challenging. Apply the LI-RADS treatment response criteria as best you can.

Do I need to assess response of each observation if the number of observations is large?

If there are a large number of treated observations with similar posttreatment imaging features and likely representing similar response, you may assess treatment response in aggregate.

Can I apply the treatment response algorithm to cholangiocarcinoma or LR-M?

The algorithm is also designed to be applicable to observations categorized as LR-M as these possibly represent cholangiocarcinoma (ICC) or HCC. There is limited literature for treatment response assessment of ICC subjected to locoregional therapies. The assessment of enhancing areas on delayed post contrast imaging is potentially helpful given that delayed enhancement is feature commonly seen in ICC. Thus, the treatment response algorithm may be applied with caution to observations that are pathologically proven to be ICC. The criteria for LR-TR Viable includes the pattern of enhancement ‘similar to pretreatment’ as a criterion, which can be applied to ICC.

Can I apply the treatment response algorithm after irreversible electroporation?

There is limited literature for treatment response assessment of HCC after irreversible electroporation (IRE). The treatment response algorithm should thus be applied with caution in these patients, or those who undergo other recently developed locoregional therapy.

Frequently Asked Questions

What should I apply for patients who undergo surgical resection?

Patients who undergo surgical resection with curative intent (excluding transplantation) may develop new lesions and HCC on follow-up imaging. The LI-RADS CT/MRI Diagnostic Algorithm is applicable to those with prior HCC, so it should be used to evaluate new lesions in the remnant liver. However, HCC recurrences at the surgical margin can appear atypical. If an enhancing lesion on follow-up is unequivocally at the surgical margin, the LI-RADS Treatment Response algorithm can be applied to guide the discussion in a multidisciplinary setting. Further evidence is needed to validate this approach.

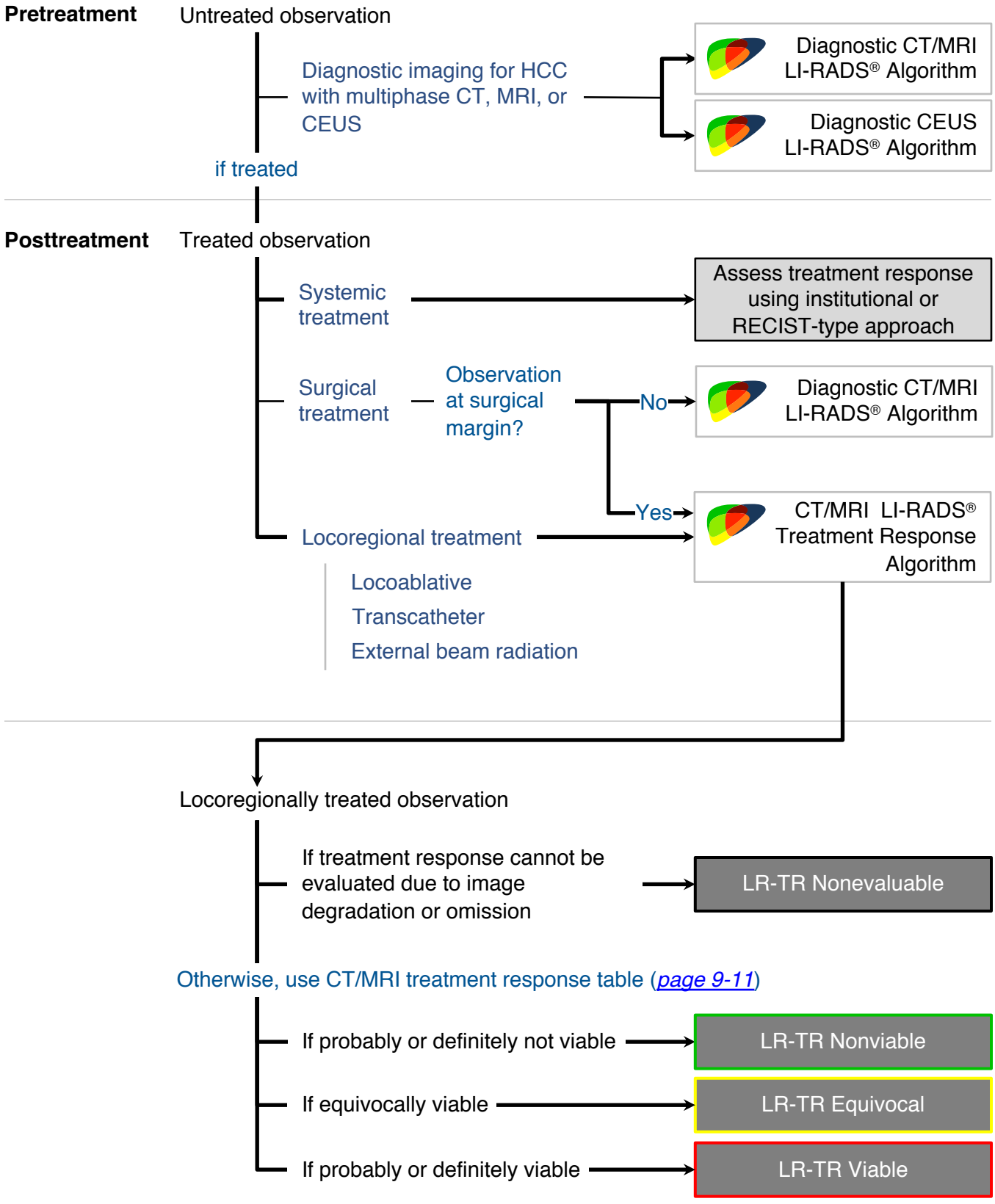
What should I apply for patients who undergo surgical resection?

Patients who undergo surgical resection with curative intent (excluding transplantation) may develop new lesions and HCC on follow-up imaging. The LI-RADS CT/MRI Diagnostic Algorithm is applicable to those with prior HCC, so it should be used to evaluate new lesions in the remnant liver. However, HCC recurrences at the surgical margin can appear atypical. If an enhancing lesion on follow-up is unequivocally at the surgical margin, the LI-RADS Treatment Response algorithm can be applied to guide the discussion in a multidisciplinary setting. Further evidence is needed to validate this approach.

Should I apply the Treatment Response Algorithm for patients who undergo combined locoregional therapy with systemic therapy?

An increasing number of patients who undergo locoregional therapy may receive concurrent or adjuvant systemic therapy. While the LI-RADS Treatment Response Algorithm was not designed for patients who undergo systemic therapy alone, it may be useful in assessing patients who have combined locoregional and systemic therapy. Radiologists are advised to use the Treatment Response Algorithm with caution, recognizing that systemic treatment can impact the posttreatment appearances in unpredictable ways.

LI-RADS® Treatment Response at a Glance



LI-RADS® Treatment Response Features

Viability	Presence of live tumor cells within or along the margin of a treated lesion. Radiologic viability is not synonymous with pathologic viability as imaging is not sensitive to microscopic or small foci of residual tumor.
Treatment-specific expected enhancement 	Expected temporal and spatial pattern of posttreatment enhancement attributable to treatment-related changes in parenchymal perfusion. For some treatments, early posttreatment enhancement patterns may not reliably differentiate viable from nonviable tumor. In the early postprocedural period for such treatments, the most appropriate response category may be LR-TR equivocal.
No lesional enhancement 	Absence of enhancement within or along the margin of a treated lesion.
Posttreatment APHE 	Nodular, mass-like, or thick and irregular APHE contained within or along the margin of a treated lesion suggests posttreatment tumor viability.
Posttreatment “washout” 	Nodular, mass-like, or thick and irregular washout appearance contained within or along the margin of a treated lesion suggests posttreatment tumor viability.
Posttreatment enhancement similar to pretreatment 	Nodular, mass-like, or thick and irregular enhancement similar to pretreatment enhancement in all postcontrast phases contained within or along the margin of a treated lesion suggests posttreatment tumor viability, even in the absence of APHE or washout appearance.

References

Ahmed M, Solbiati L, Brace CL, Breen DJ, Callstrom MR, Charboneau JW, et al. Image-guided tumor ablation: standardization of terminology and reporting criteria--a 10-year update. Radiology. 2014; 273(1): 241-60.

Atassi B, Bangash AK, Bahrani A, Pizzi G, Lewandowski RJ, Ryu RK, et al. Multimodality imaging following 90Y radioembolization: a comprehensive review and pictorial essay. Radiographics. 2008; 28(1): 81-99.

Avila MA, Berasain C, Sangro B, Prieto J. New therapies for hepatocellular carcinoma. Oncogene. 2006; 25(27): 3866-84.

Becker G, Allgaier HP, Olschewski M, Zähringer A, Blum HE; HECTOR Study Group. Long-acting octreotide versus placebo for treatment of advanced HCC: a randomized controlled double-blind study. Hepatology. 2007; 45(1): 9-15.

Benedict SH, Yenice KM, Followill D, Galvin JM, Hinson W, Kavanagh B, et al. Stereotactic body radiation therapy: the report of AAPM Task Group 101. Med Phys. 2010; 37(8): 4078-101.

Brook OR, Thornton E, Mendiratta-Lala M, Mahadevan A, Raptopoulos V, Brook A, et al. CT Imaging Findings after Stereotactic Radiotherapy for Liver Tumors. Gastroenterol Res Pract. 2015;15: 126245.

Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al., Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol. 2001; 35(3): 421-30.

Burak, KW and Kneteman NM. An evidence-based multidisciplinary approach to the management of hepatocellular carcinoma (HCC): the Alberta HCC algorithm. Can J Gastroenterol. 2010; 24(11): 643-50.

Camacho JC, Kokabi N, Xing M, Prajapati HJ, El-Rayes B, Kim HS. Modified response evaluation criteria in solid tumors and European Association for The Study of the Liver criteria using delayed-phase imaging at an early time point predict survival in patients with unresectable intrahepatic cholangiocarcinoma following yttrium-90 radioembolization. J Vasc Interv Radiol. 2014; Feb; 25(2):256-65.

Camacho JC, Kokabi N, Xing M, Prajapati HJ, El-Rayes B, Kim HS. Modified response evaluation criteria in solid tumors and European Association for The Study of the Liver criteria using delayed-phase imaging at an early time point predict survival in patients with unresectable intrahepatic cholangiocarcinoma following yttrium-90 radioembolization. J Vasc Interv Radiol. 2014; 25(2): 256-65.

Chow PK1, Tai BC, Tan CK, Machin D, Win KM, Johnson PJ, et al., High-dose tamoxifen in the treatment of inoperable hepatocellular carcinoma: A multicenter randomized controlled trial. Hepatology. 2002; 36(5): 1221-6.

References

Donati OF, Do RK, Hötker AM, Katz SS, Zheng J, Moskowitz CS, Beattie C, Brown KT. Interreader and inter-test agreement in assessing treatment response following transarterial embolization for hepatocellular carcinoma. Eur Radiol. 2015 Sep; 25(9): 2779-88.

Donati OF, Do RK, Hötker AM, Katz SS, Zheng J, Moskowitz CS, Beattie C, Brown KT. Interreader and inter-test agreement in assessing treatment response following transarterial embolization for hepatocellular carcinoma. Eur Radiol. 2015; 25(9): 2779-88.

Ebara M, Okabe S, Kita K, Sugiura N, Fukuda H, Yoshikawa M, Kondo F, Saisho H. Percutaneous ethanol injection for small hepatocellular carcinoma: therapeutic efficacy based on 20-year observation. J Hepatol. 2005; 43:458–464.

Edeline J, Boucher E, Rolland Y, Vauléon E, Pracht M, Perrin C, Le Roux C, Raoul JL. Comparison of tumor response by Response Evaluation Criteria in Solid Tumors (RECIST) and modified RECIST in patients treated with sorafenib for hepatocellular carcinoma. Cancer. 2012; 118(1): 147-56.

Edeline J, Boucher E, Rolland Y, Vauléon E, Pracht M, Perrin C, Le Roux C, Raoul JL. Comparison of tumor response by Response Evaluation Criteria in Solid Tumors (RECIST) and modified RECIST in patients treated with sorafenib for hepatocellular carcinoma. Cancer. 2012; 118(1): 147-56.

Ehman EC, Umetsu SE, Ohliger MA, Fidelman N, Ferrell LD, Yeh BM, Yee J, Hope TA. Imaging prediction of residual hepatocellular carcinoma after locoregional therapy in patients undergoing liver transplantation or partial hepatectomy. Abdom Radiol. 2016; 41(11): 2161-2168.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al., New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45(2): p. 228-47.

Furui S, Otomo K, Itai Y, Iio M. Hepatocellular carcinoma treated by transcatheter arterial embolization: progress evaluated by computed tomography. Radiology. 1984 Mar;150(3):773-8.

Gaba RC, Lewandowski RJ, Hickey R, Baerlocher MO, Cohen EI, Dariushnia SR, Janne d'Othée B, Padia SA, Salem R, Wang DS, Nikolic B, Brown DB; Society of Interventional Radiology Technology Assessment Committee. Transcatheter Therapy for Hepatic Malignancy: Standardization of Terminology and Reporting Criteria. J Vasc Interv Radiol. 2016; 27(4): 457-73.

Gaba RC, Lewandowski RJ, Hickey R, Baerlocher MO, Cohen EI, Dariushnia SR, Janne d'Othée B, Padia SA, Salem R, Wang DS, Nikolic B, Brown DB; Society of Interventional Radiology Technology Assessment Committee. Transcatheter Therapy for Hepatic Malignancy: Standardization of Terminology and Reporting Criteria. J Vasc Interv Radiol. 2016; 27(4): 457-73.

Galizia MS, Töre HG, Chalian H, McCarthy R, Salem R, Yaghmai V. MDCT necrosis quantification in the assessment of hepatocellular carcinoma response to yttrium 90 radioembolization therapy: comparison of two-dimensional and volumetric techniques. Acad Radiol. 2012; 19(1): 48-54.

References

Gavanier M, Ayav A, Sellal C, Orry X, Claudon M, Bronowicki JP, Laurent V. CT imaging findings in patients with advanced hepatocellular carcinoma treated with sorafenib: Alternative response criteria (Choi, European Association for the Study of the Liver, and modified Response Evaluation Criteria in Solid Tumor (mRECIST)) versus RECIST 1.1. Eur J Radiol. 2016; 85(1): 103-12.

Gavanier M, Ayav A, Sellal C, Orry X, Claudon M, Bronowicki JP, Laurent V. CT imaging findings in patients with advanced hepatocellular carcinoma treated with sorafenib: Alternative response criteria (Choi, European Association for the Study of the Liver, and modified Response Evaluation Criteria in Solid Tumor (mRECIST)) versus RECIST 1.1. Eur J Radiol. 2016; 85(1): 103-12.

Gazelle GS, Goldberg SN, Solbiati L, Livraghi T. Tumor ablation with radio-frequency energy. Radiology. 2000; 217(3): 633-46.

Gillmore R, Stuart S, Kirkwood A, Hameeduddin A, Woodward N, Burroughs AK, Meyer T. EASL and mRECIST responses are independent prognostic factors for survival in hepatocellular cancer patients treated with transarterial embolization. J Hepatol. 2011; 55(6): 1309-16.

Halperin EC, Brady LW, Perez CA, Wazer DE. Perez and Brady's Principles and Practice of Radiation Oncology. 6th ed. 2013: Lippincott Williams & Wilkins.

Halperin EC, Brady LW, Perez CA, Wazer DE. Perez and Brady's Principles and Practice of Radiation Oncology. 6th ed. 2013: Lippincott Williams & Wilkins.

Harding, JJ, El Dika I, Abou-Alfa, GK. Immunotherapy in hepatocellular carcinoma: Primed to make a difference? Cancer. 2016; 122(3): 367-77.

Herfarth KK, Hof H, Bahner ML, Lohr F, Höss A, van Kaick G, Wannenmacher M, Debus J. Assessment of focal liver reaction by multiphasic CT after stereotactic single-dose radiotherapy of liver tumors. Int J Radiat Oncol Biol Phys. 2003; 57: 444-51.

Hoppe, RT, Phillips TL, Roach M, Leibel and Phillips Textbook of Radiation Oncology. Third ed. 2010: Saunders Elsevier.

Ibrahim SM, Nikolaidis P, Miller FH, Lewandowski RJ, Ryu RK, Sato KT, et al. Radiologic findings following Y90 radioembolization for primary liver malignancies. Abdom Imaging. 2009; 34(5): 566-81.

Kim MJ, Choi JI, Lee JS, Park JW. Computed tomography findings of sorafenib-treated hepatic tumors in patients with advanced hepatocellular carcinoma. J Gastroenterol Hepatol. 2011; 26(7): 1201-6.

Kim SK, Lim HK, Kim YH, Lee WJ, Lee SJ, Kim SH, et al. Hepatocellular carcinoma treated with radio-frequency ablation: spectrum of imaging findings. Radiographics. 2003; 23(1):107-21.

Klein J and Dawson LA, Hepatocellular carcinoma radiation therapy: review of evidence and future opportunities. Int J Radiat Oncol Biol Phys, 2013; 87(1): 22-32.

References

Kubota K, Hisa N, Nishikawa T, Fujiwara Y, Murata Y, Itoh S, et al. Evaluation of hepatocellular carcinoma after treatment with transcatheter arterial chemoembolization: comparison of Lipiodol-CT, power Doppler sonography, and dynamic MRI. Abdom Imaging. 2001 Mar-Apr; 26(2): 184-90.

Kudo M, Ueshima K, Kubo S, Sakamoto M, Tanaka M, Ikai I, et al. Response Evaluation Criteria in Cancer of the Liver (RECICL) (2015 Revised version). Hepatol Res. 2016; 46(1): 3-9.

Lencioni, R and Llovet JM, Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010; 30(1): 52-60.

Liapi, E, Geschwind JF. Combination of local transcatheter arterial chemoembolization and systemic anti-angiogenic therapy for unresectable hepatocellular carcinoma. Liver Cancer. 2012; 1(3-4): 201-15.

Limanond P, Zimmerman P, Raman S, Kadell BM, Lu DS. Interpretation of CT and MRI after radiofrequency ablation of hepatic malignancies. AJR. 2003 Dec;181(6):1635-40.

Liu M, Lin MX, Lu MD, Xu ZF, Zheng KG, Wang W, Kuang M, Zhuang WQ, Xie XY. Comparison of contrast-enhanced ultrasound and contrast-enhanced computed tomography in evaluating the treatment response to transcatheter arterial chemoembolization of hepatocellular carcinoma using modified RECIST. Eur Radiol. 2015; 25(8): 2502-11.

Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al., Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008; 359(4): 378-90.

Llovet, JM, Bruix, J. Molecular targeted therapies in hepatocellular carcinoma. Hepatology. 2008; 48(4): 1312-27.

Lu DS, Raman SS, Vodopich DJ, Wang M, Sayre J, Lassman C. Effect of vessel size on creation of hepatic radiofrequency lesions in pigs: assessment of the "heat sink" effect. AJR. 2002; 178(1):47-51.

Lu JJ. and Brady LW, Radiation Oncology: An Evidence-Based Approach. 2008: Springer Berlin Heidelberg.

Marin D, Cappabianca S, Serra N, Sica A, Lassandro F, D'Angelo R, La Porta M, Fiore F, Somma F. CT Appearance of Hepatocellular Carcinoma after Locoregional Treatments: A Comprehensive Review. Gastroenterology Research and Practice. 2015; 2015:670965.

Mezhir JJ, Fong Y, Fleischer D, Seo SK, D'Amico F, Petre E, et al. Pyogenic abscess after hepatic artery embolization: a rare but potentially lethal complication. J Vasc Interv Radiol, 2011; 22(2): 177-82.

Miller FH, Keppke AL, Reddy D, Huang J, Jin J, Mulcahy MF, Salem R. Response of liver metastases after treatment with yttrium-90 microspheres: role of size, necrosis, and PET. AJR. 2007; 188(3): 776-83.

References

Narayanan G, Froud T, Suthar R, Barbery K. Irreversible electroporation of hepatic malignancy. Semin Intervent Radiol. 2013; 30(1): 67-73.

Olsen CC, Welsh J, Kavanagh BD, Franklin W, McCarter M, Cardenes HR, et al., Microscopic and macroscopic tumor and parenchymal effects of liver stereotactic body radiotherapy. Int J Radiat Oncol Biol Phys. 2009; 73(5): 1414-24.

Organization, WH, WHO handbook for reporting results of cancer treatment. 1979: Geneva : World Health Organization.

Orlando A, Leandro G, Olivo M, Andriulli A, Cottone M. Radiofrequency thermal ablation vs. percutaneous ethanol injection for small hepatocellular carcinoma in cirrhosis: meta-analysis of randomized controlled trials. Am J Gastroenterol. 2009; 104: 514–524.

Pan CC, Kavanagh BD, Dawson LA, Li XA, Das SK, Miften M, Ten Haken RK. Radiation-associated liver injury. Int J Radiat Oncol Biol Phys. 2010; 76(3 Suppl): S94-100.

Perks JR, Lehmann J, Chen AM, Yang CC, Stern RL, Purdy JA. Comparison of peripheral dose from image-guided radiation therapy (IGRT) using kV cone beam CT to intensity-modulated radiation therapy (IMRT). Radiother Oncol. 2008; 89(3): 304-10.

Prajapati HJ1, Spivey JR, Hanish SI, El-Rayes BF, Kauh JS, Chen Z, Kim HS. mRECIST and EASL responses at early time point by contrast-enhanced dynamic MRI predict survival in patients with unresectable hepatocellular carcinoma (HCC) treated by doxorubicin drug-eluting beads transarterial chemoembolization (DEB TACE). Ann Oncol. 2013; 24(4): 965-73.

Que JY, Lin LC, Lin KL, Lin CH, Lin YW, Yang CC. The efficacy of stereotactic body radiation therapy on huge hepatocellular carcinoma unsuitable for other local modalities. Radiat Oncol. 2014; 9: 120.

Riaz A, Miller FH, Kulik LM, Nikolaidis P, Yaghmai V, Lewandowski RJ, et al. Imaging response in the primary index lesion and clinical outcomes following transarterial locoregional therapy for hepatocellular carcinoma. JAMA. 2010; 303(11): 1062-1069.

Sanuki-Fujimoto N, Takeda A, Ohashi T, Kunieda E, Iwabuchi S, Takatsuka K, et al. CT evaluations of focal liver reactions following stereotactic body radiotherapy for small hepatocellular carcinoma with cirrhosis: relationship between imaging appearance and baseline liver function. Br J Radiol. 2010; 83: 1063-71.

Sato Y, Watanabe H, Sone M, Onaya H, Sakamoto N, Osuga K, et al. Tumor response evaluation criteria for HCC (hepatocellular carcinoma) treated using TACE (transcatheter arterial chemoembolization): RECIST (response evaluation criteria in solid tumors) version 1.1 and mRECIST (modified RECIST): JIVROSG-0602. Ups J Med Sci. 2013; 118(1): 16-22.

Seyal AR, Gonzalez-Guindalini FD, Arslanoglu A, Harmath CB, Lewandowski RJ, Salem R, Yaghmai V. Reproducibility of mRECIST in assessing response to transarterial radioembolization therapy in hepatocellular carcinoma. Hepatology. 2015; 62(4): 1111-21.

References

Shi W, He Y, Ding W, Gong S, Wang Y, Xiao J, He B. Contrast-enhanced ultrasonography used for post-treatment responses evaluation of radiofrequency ablations for hepatocellular carcinoma: a meta-analysis. Br J Radiol. 2016; 89(1064): 20150973.

Shim JH, Lee HC, Kim SO, Shin YM, Kim KM, Lim YS, Suh DJ. Which response criteria best help predict survival of patients with HCC following chemoembolization? A validation study of old and new models. Radiology. 2012; 262(2): 708-718.

Shim JH, Lee HC, Kim SO, Shin YM, Kim KM, Lim YS, Suh DJ. Which response criteria best help predict survival of patients with hepatocellular carcinoma following chemoembolization? A validation study of old and new models. Radiology. 2012; 262(2): 708-18.

Shim JH, Lee HC, Won HJ, Shin YM, Kim KM, Lim YS, Suh DJ. Maximum number of target lesions required to measure responses to transarterial chemoembolization using the enhancement criteria in patients with intrahepatic hepatocellular carcinoma. J Hepatol. 2012; 56(2): 406-11.

Shyn PB, Oliva MR, Shah SH, Tatli S, Catalano PJ, Silverman S. MRI contrast enhancement of malignant liver tumors following successful cryoablation. Eur Radiol. 2012; 22:398-403.

Siegel AB, Cohen EI, Ocean A, Lehrer D, Goldenberg A, Knox JJ, et al., Phase II trial evaluating the clinical and biologic effects of bevacizumab in unresectable hepatocellular carcinoma. J Clin Oncol. 2008; 26(18): 2992-8.

Spira D, Fenchel M, Lauer UM, Claussen CD, Gregor M, Bitzer M, Horger M. Comparison of different tumor response criteria in patients with hepatocellular carcinoma after systemic therapy with the multikinase inhibitor sorafenib. Acad Radiol. 2011; 18(1): 89-96.

Takizawa K, Numata K, Morimoto M, Kondo M, Nozaki A, Moriya S, et al. Use of contrast-enhanced ultrasonography with a perflubutane-based contrast agent performed one day after transarterial chemoembolization for the early assessment of residual viable hepatocellular carcinoma. Eur J Radiol. 2013; 82(9): 1471-80.

Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al., New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000; 92(3): 205-16.

Timmerman, RD, Herman J, Cho LC, Emergence of stereotactic body radiation therapy and its impact on current and future clinical practice. J Clin Oncol. 2014. 32(26): 2847-54.

Tsuda M, Majima K, Yamada T, Saitou H, Ishibashi T, Takahashi S. Hepatocellular carcinoma after radiofrequency ablation therapy: dynamic CT evaluation of treatment. Clin Imaging. 2001; 25(6): 409-15.

Wang X, Erinjeri JP, Jia X, Gonen M, Brown KT, Sofocleous CT, et al. Pattern of retained contrast on immediate postprocedure computed tomography (CT) after particle embolization of liver tumors predicts subsequent treatment response. Cardiovasc Intervent Radiol. 2013; 36(4): 1030-8.

References

Weintraub, JL, Salem R. Treatment of hepatocellular carcinoma combining sorafenib and transarterial locoregional therapy: state of the science. J Vasc Interv Radiol, 2013; 24(8): 1123-34.

Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé C, et al., Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res. 2009; 15(23): 7412-20.

Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé C, et al., Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res. 2009; 15(23): 7412-20.