Liver Imaging in HCC after locoregional and systemic therapies

Dr. Comșa Mihai

RECIST 1.1, mRECIST and other response assessment systems

Introduction

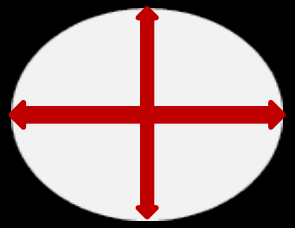
- Goal of anticancer treatment
  - Improve patient survival
- Ethical considerations
  - Balancing toxicity, adverse events, and quality of life
- Importance of detecting lack of treatment response
  - Oncological, ethical, and socio-economic perspectives

Tumour Burden and Survival

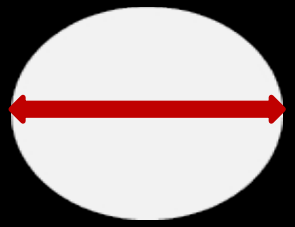
- Assumption: Tumour burden correlates with survival
- Monitoring tumour progression as a surrogate for survival
- Tumour response as a proxy for increased survival

History

- 1978 WHO criteria for response



- 2000 RECIST 1.0



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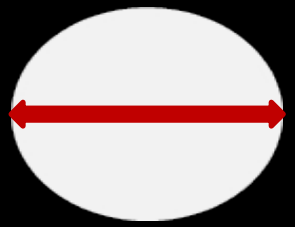
Less target lesions

Rules about Lymph nodes and bones



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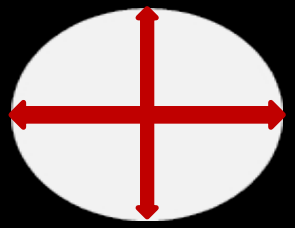

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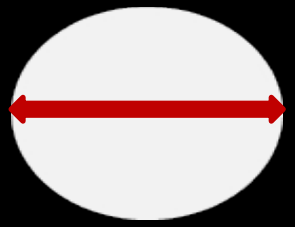

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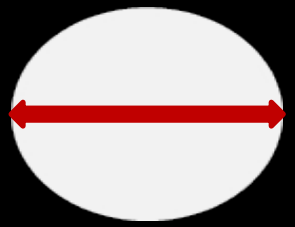


Evolution of Assessment Criteria

- WHO Criteria
  - Developed based on tumour burden assumption
- RECIST 1.1
  - Addressing limitations of WHO criteria
  - Widely accepted and validated worldwide

RECIST 1.1

Target and non- target

- Target lesion- something you can measure

  Maximum 2 lesions per organ

  Maximum 5 lesions total

- Not-Target

  Can t measure OR

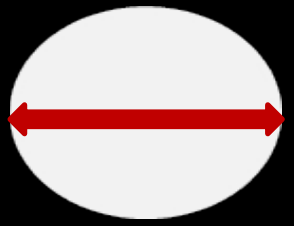
  Measurable but non selected as target

Maximum size measurable lesions

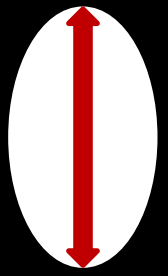
- Non-lymph nodes LONG AXIS

Lesion on CT> 10 mm

Longest dimension



You can change the axis if lesion changes shape



Maximum size measurable lesions

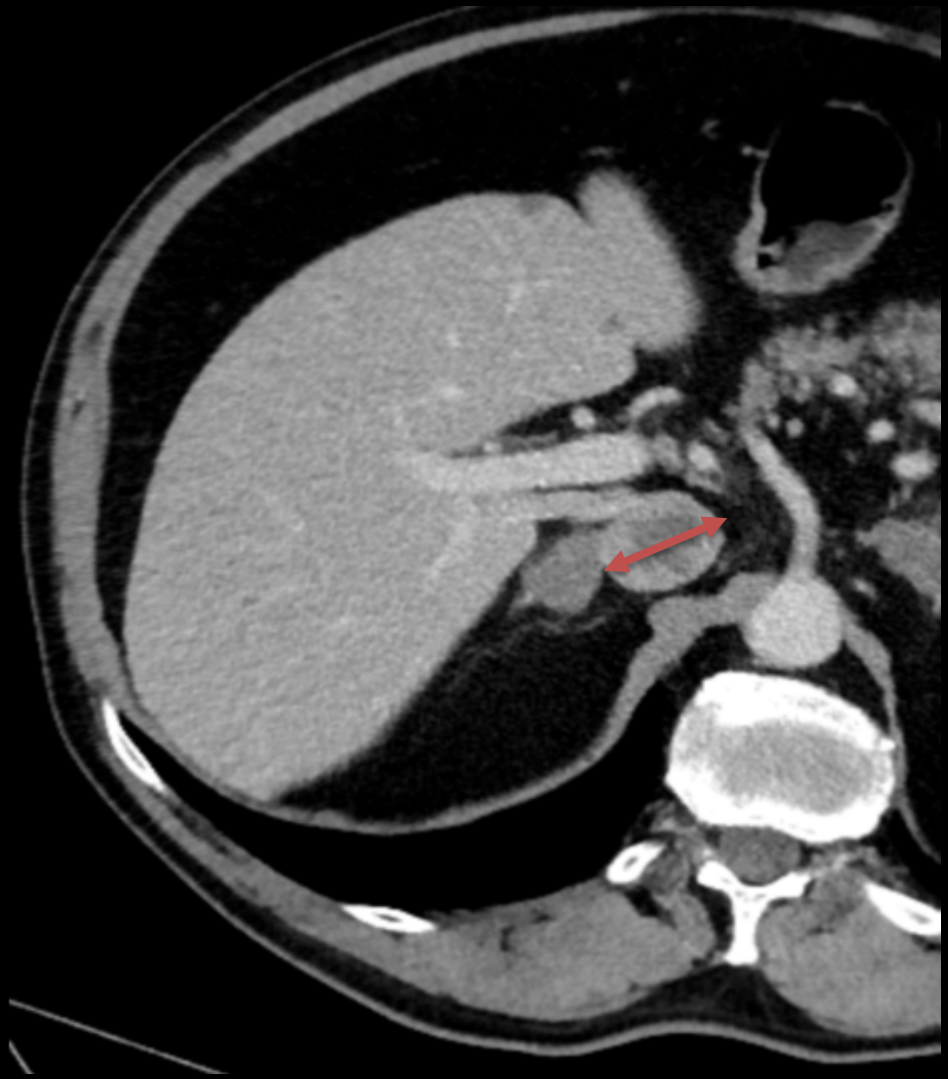
Lymph nodes
Measure *short axis*

1 Longest diameter

2 The longest perpendicular

Target?
Has to be more than 15 mm

Non target
Can be 10 to 15 mm



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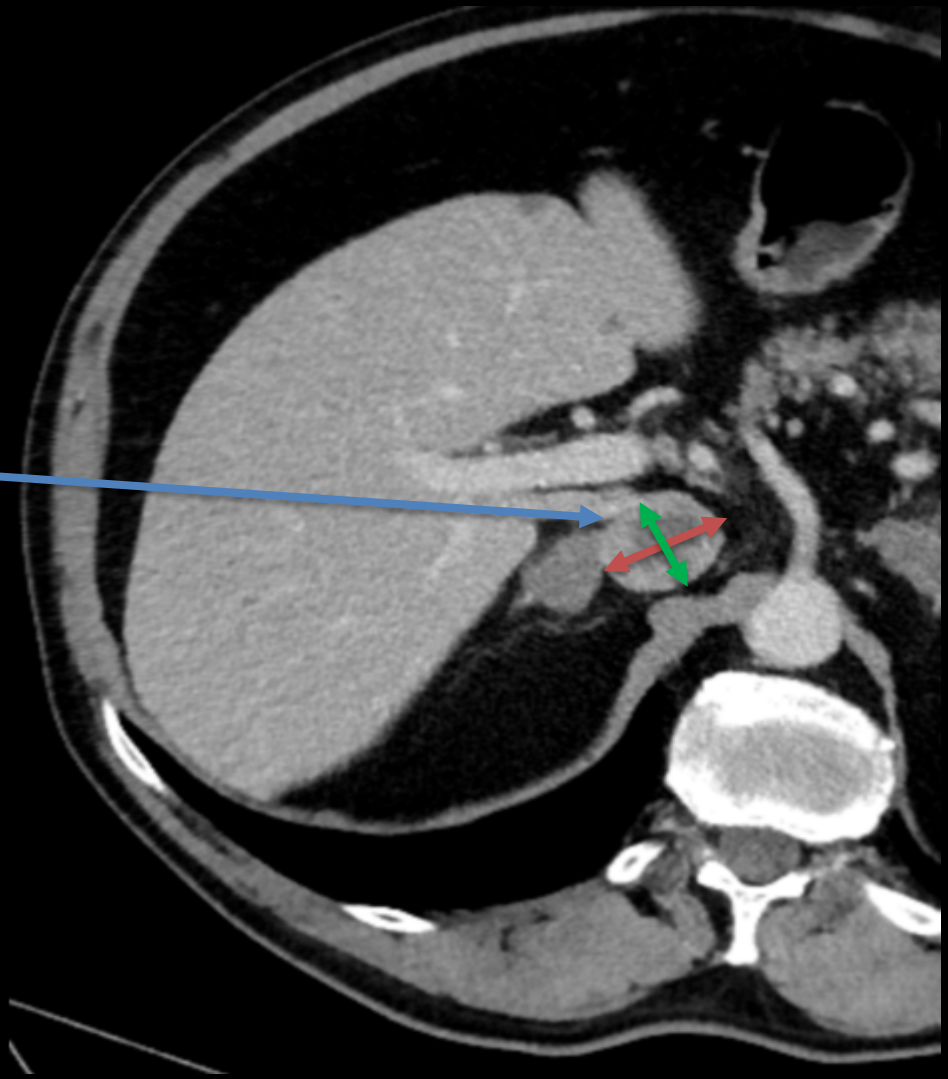

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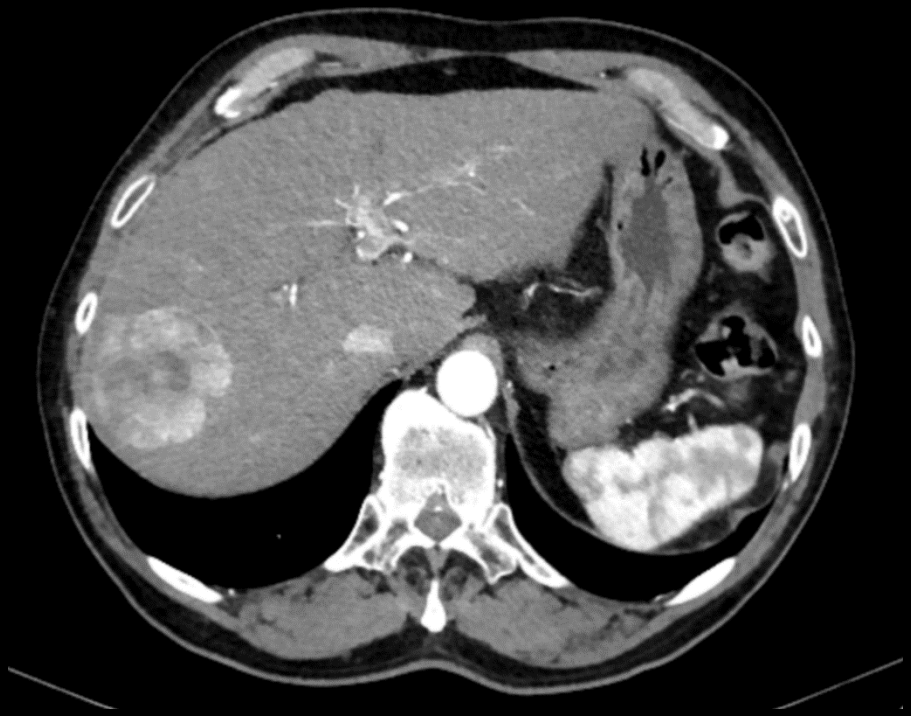
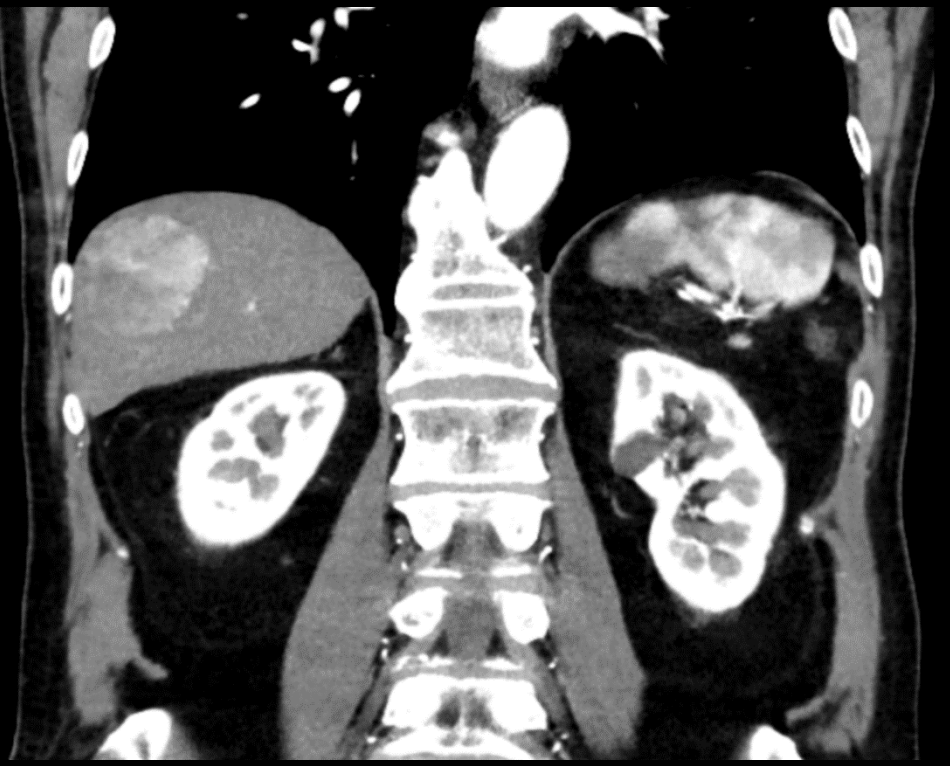
Use axial images





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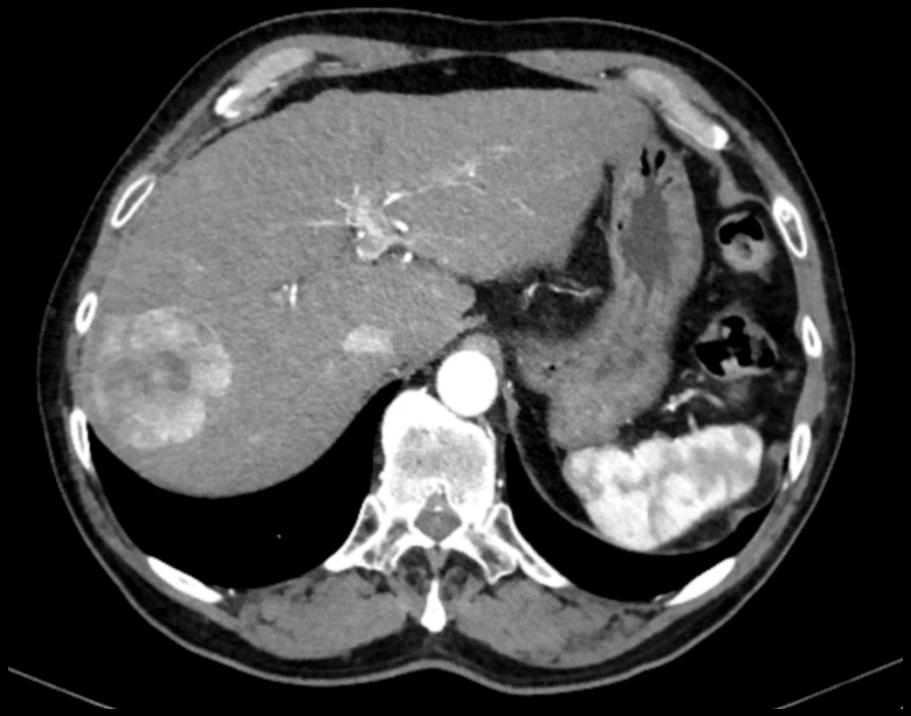

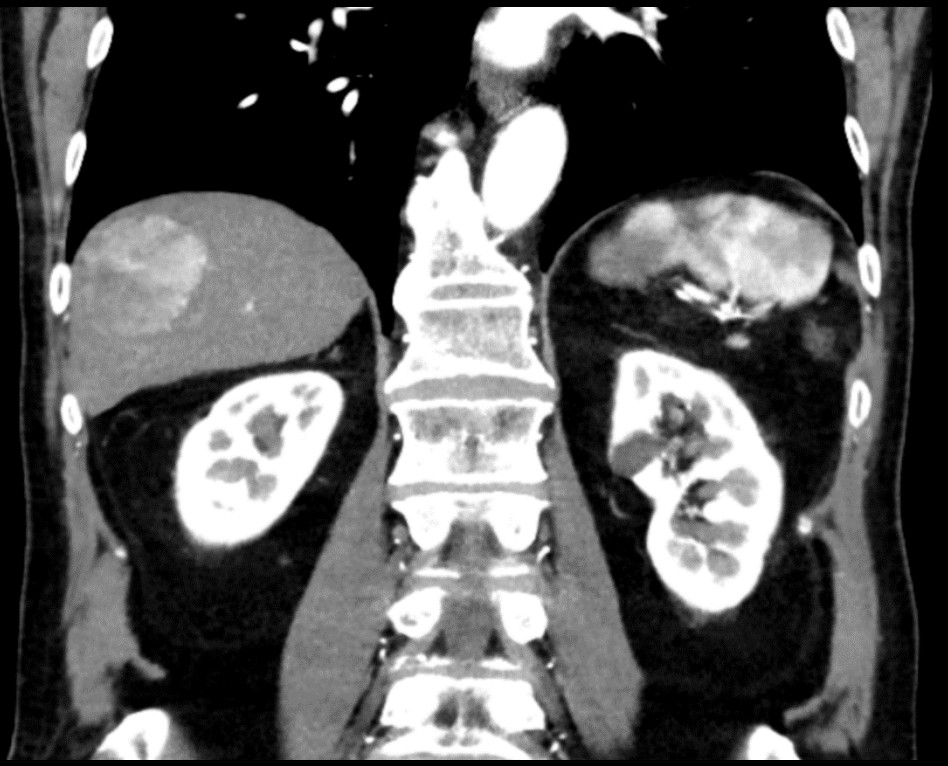

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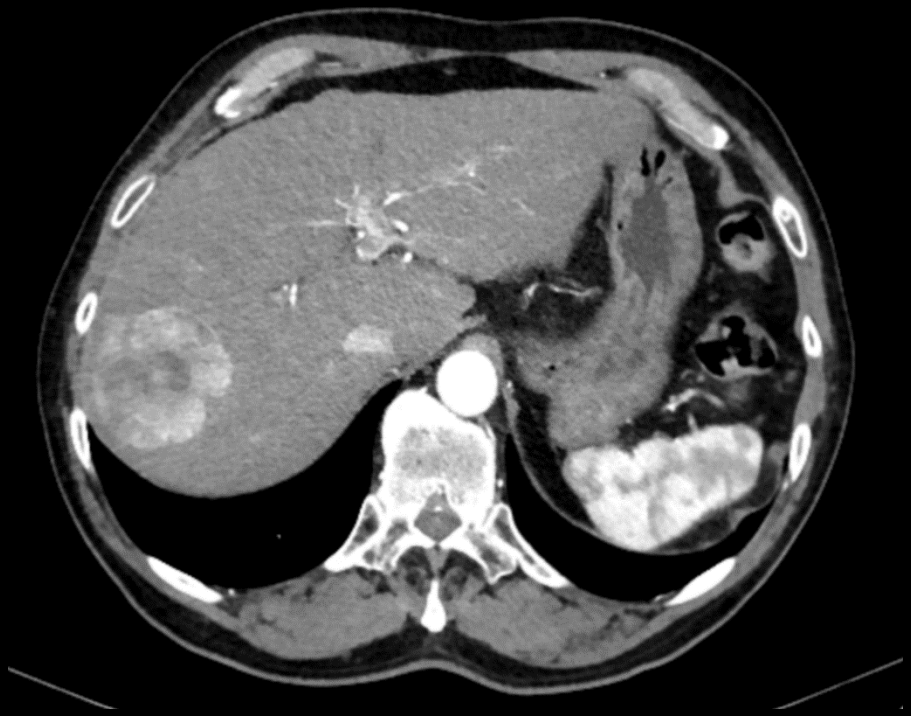

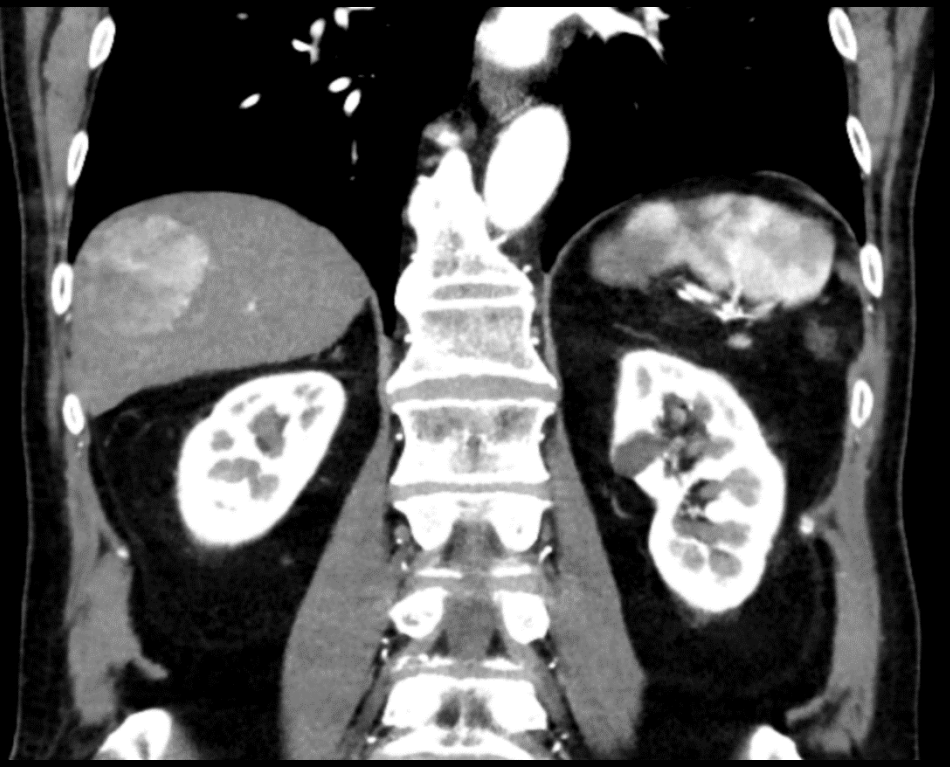

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Baseline

Choose target lesions

- Need to be measurable
- Max 2 per organ
- Max 5 total
- Lesions over 10 mm
- Nodes over 15 mm

Baseline

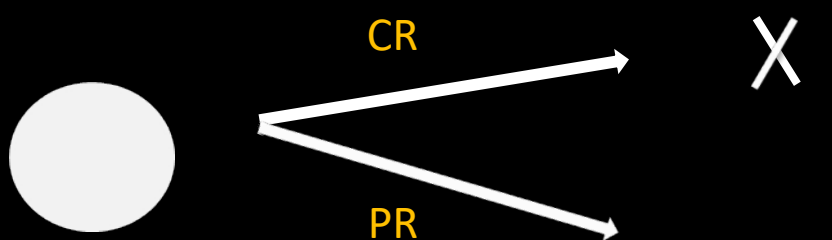
Calculate sum of diameters

- Nodes - short axis
- Non-nodes –Longest axis

Non target lesions

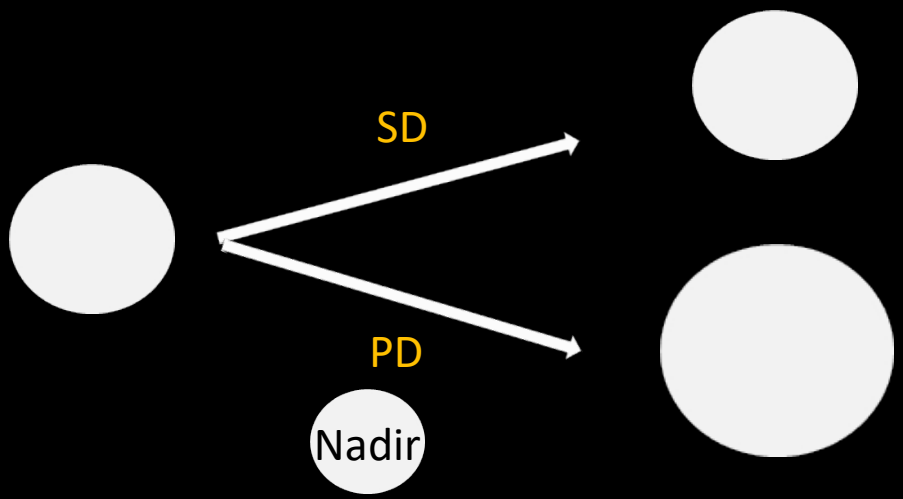
- Everything else that is cancer.

RECIST 1.1 Assessing Tumor Response



Complete response (CR)

Partial response (PR)
More than 30% decrease of SLD (Relative to baseline)



Stable disease(SD)
Neither PR nor PD

Progressive disease (PD)
More than 20% increase of SLD (Relative to Nadir – the time when the tumor burden was the smallest)

Limitations of RECIST Criteria

- Applicability in Conventional Chemotherapy
- Specific Challenges in Liver Tumours
  - Rich network of hepatic vessels
  - Rationale for locoregional therapies
- General limitations (uniform size assumptions, absence of necrosis consideration)
- Liver-specific limitations (rich arterial network, arterial phase hyperenhancement)

Challenge Posed by New Treatments

- Locoregional treatments and targeted therapies' impact on tumour necrosis
- Underestimation of response by RECIST criteria
- Need for improved assessment methods

Viable Tumour Appearance-Based Criteria

- Evaluating treatment efficacy based on viable tumour appearance
- Improving response assessment for locoregional and targeted therapies

Viable Tumour Appearance-Based Criteria

- Mechanisms differ from traditional chemotherapy
- Inducing apoptosis or targeting cell signaling pathways
- Impact on imaging findings compared to cytotoxic therapies

New Generation Criteria

- Viable Tumour Concept
  - Visualization of enhancement after contrast injection
- Size-Based Criteria (mRECIST and EASL)
- Quantification of Inner Changes (LI RADS and Choi Criteria)

- Better Identification of Responders

Focus on Liver Tumours

- Hepatocellular Carcinoma (HCC)
- Hepatic Metastases
- Cholangiocarcinoma

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mRECIST

Modified RECIST

- mRECIST incorporates the viable tumor concept and is a formal modification of RECIST 1.1
- Integrates RECIST definitions of response categories and target lesion selection into EASL

- CR: disappearance of all intratumoral arterial enhancement in all lesions
- PR: ≥ 30% decrease in sum of diameters of target lesions
- SD: not CR, PR or PD
- PD: ≥ 20% increase in sum of diameters

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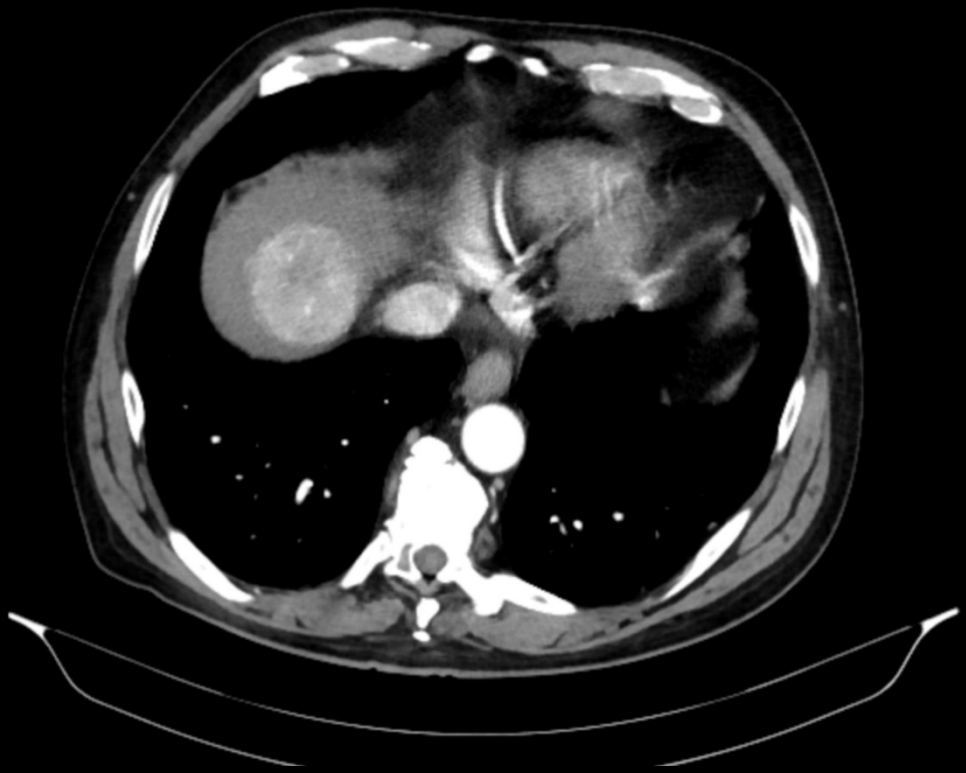
Modified RECIST

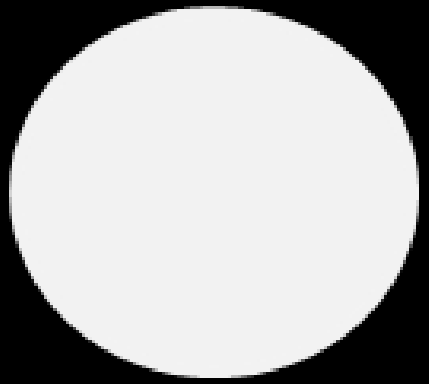
- Target lesion

- Can be accurately measured in at least one dimension
- Diameter more than 1 cm
- Suitable for repeat measurment
- Shows intratumoral arterial enhancement on CT and MRI

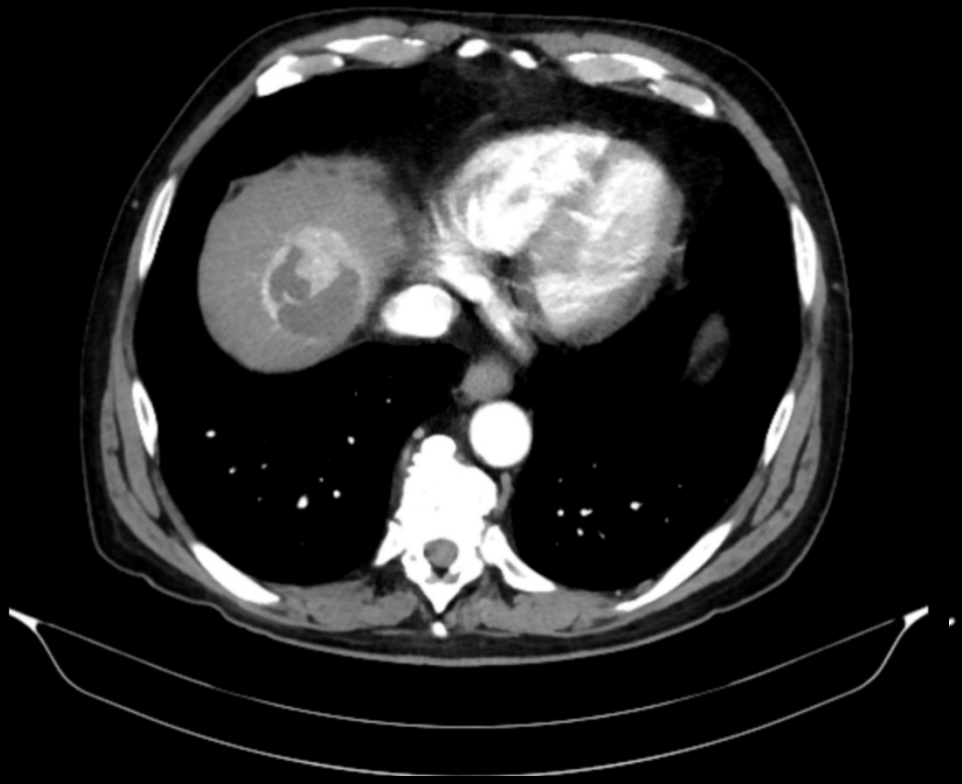
Non-target lesions: all other cancerous lesions

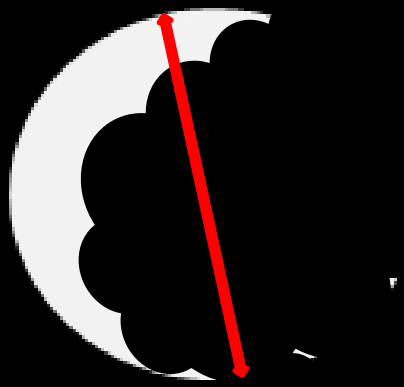
Measurments





Measurments after treatment





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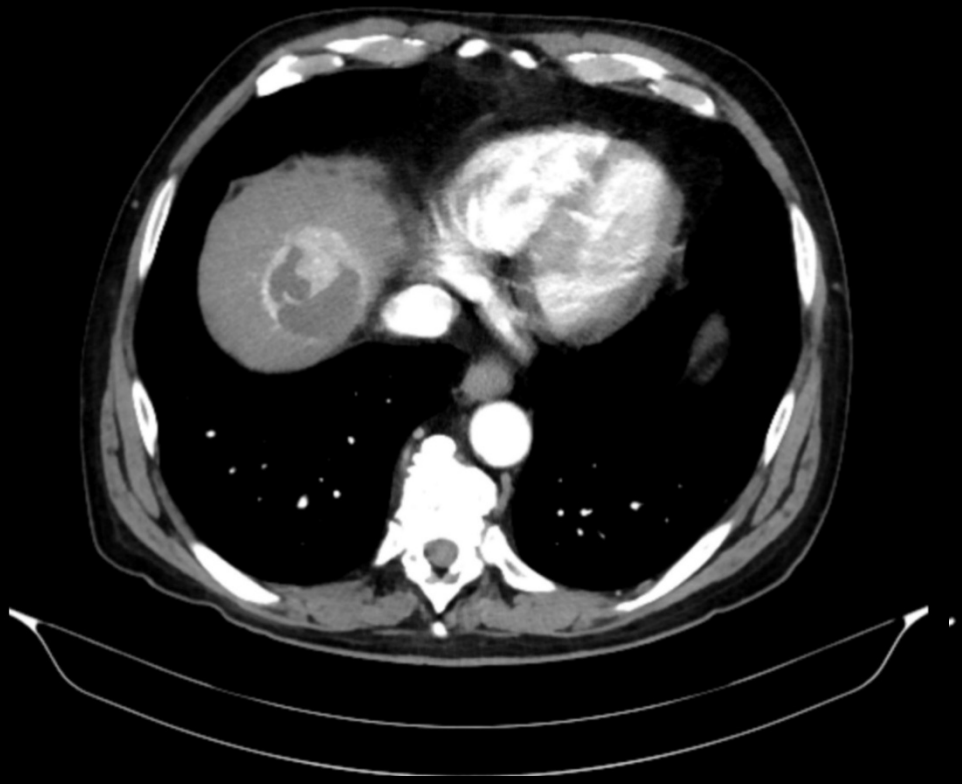
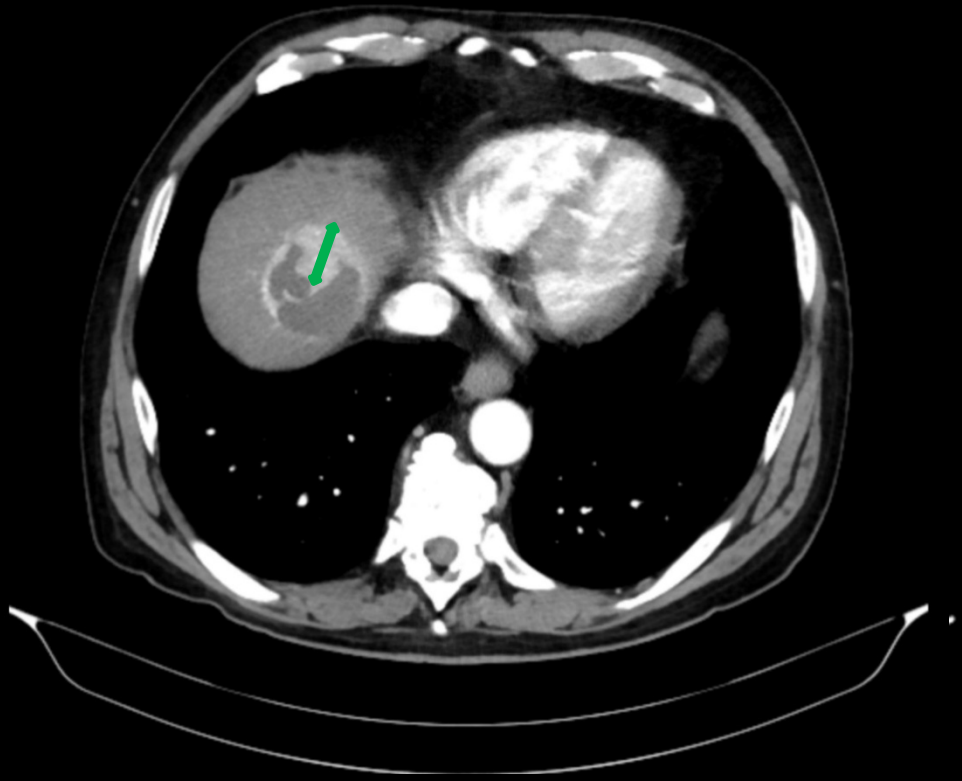
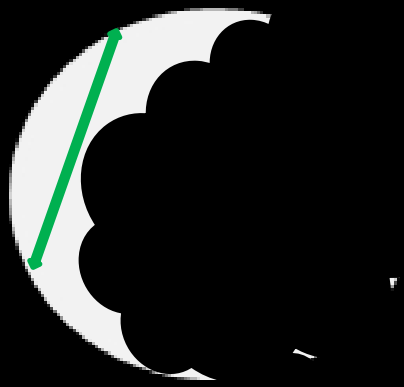


Measurments after treatment

The measurement of viable tumor diameter should not include any major intervening areas of necrosis.





Challenges to mRECIST

- Provide criteria to assess overall patient response in clinical trials
- Used in retrospective studies assessing treatment response for HCC patients
- Not typically used for assessing individual tumors in routine clinical practice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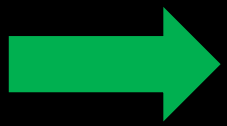


LI RADS TRA 2024

LI-RADS® CT/MRI Nonradiation TRA
v2024 Core

LI-RADS CT/MRI Treatment Response Algorithm

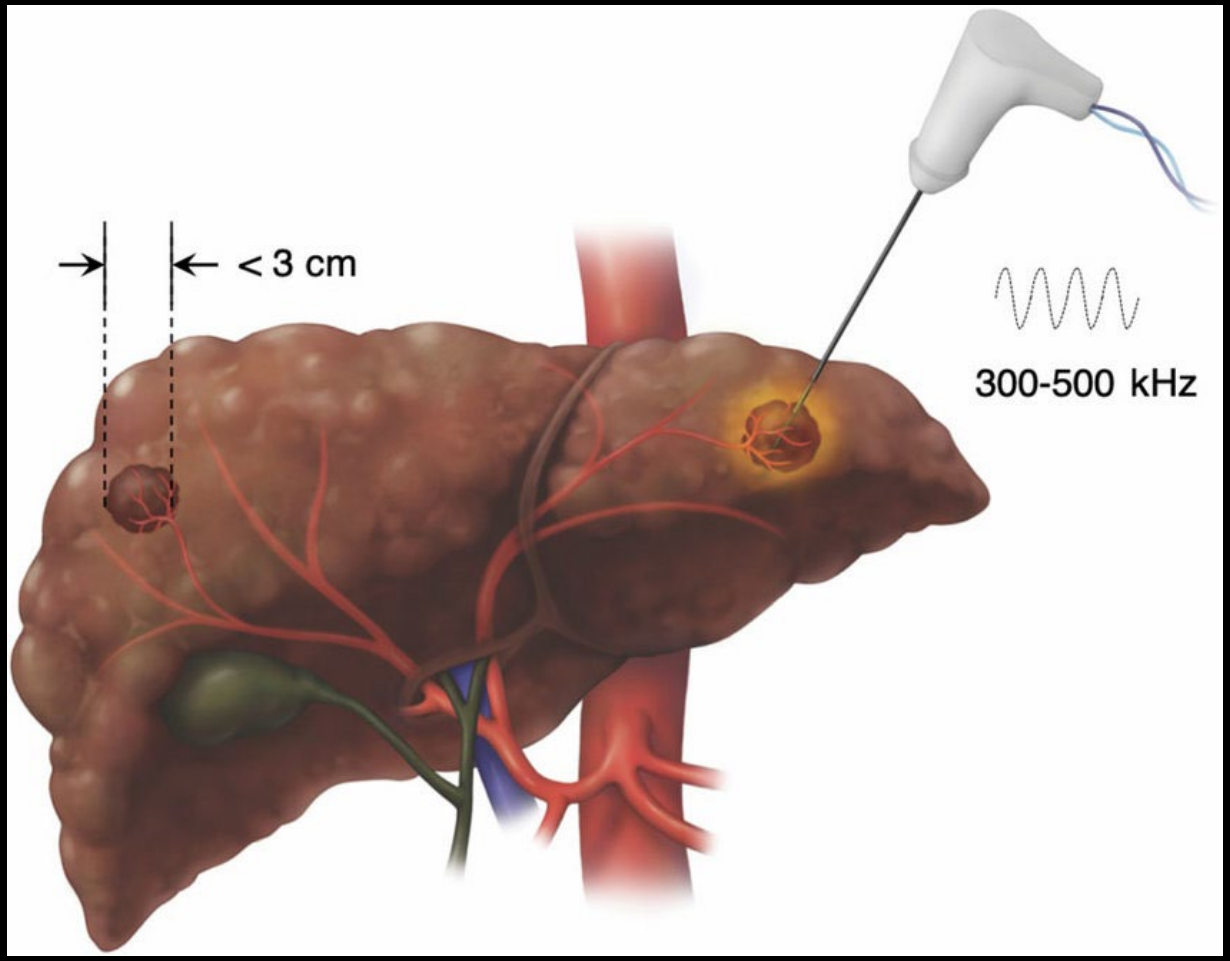
- Standardizes liver imaging terminology, technique, and interpretation.
- Assesses tumor viability post-ablation, intra-arterial therapies, or radiation therapy.
- Differentiates viable and non-viable tumors visually.
- Used for single or limited multifocal HCC and repeated treatments.
- Fills clinical gap in reporting HCC treated by LRT.
- Reproducible treatment response categories; further research needed for TARE and SBRT

Findings after local recurrences post RFA/MWA

Physical Principles of Thermal Ablation

- Definition: Tumor ablation involves the destruction of tissue through direct application of physical or chemical processes.
- Thermal Ablation: Refers to tissue destruction through heat treatment.
- Techniques: Mainly, Radiofrequency Ablation (RFA) and Microwave Ablation (MWA) are utilized in liver oncology.

Radiofrequency Ablation (RFA)

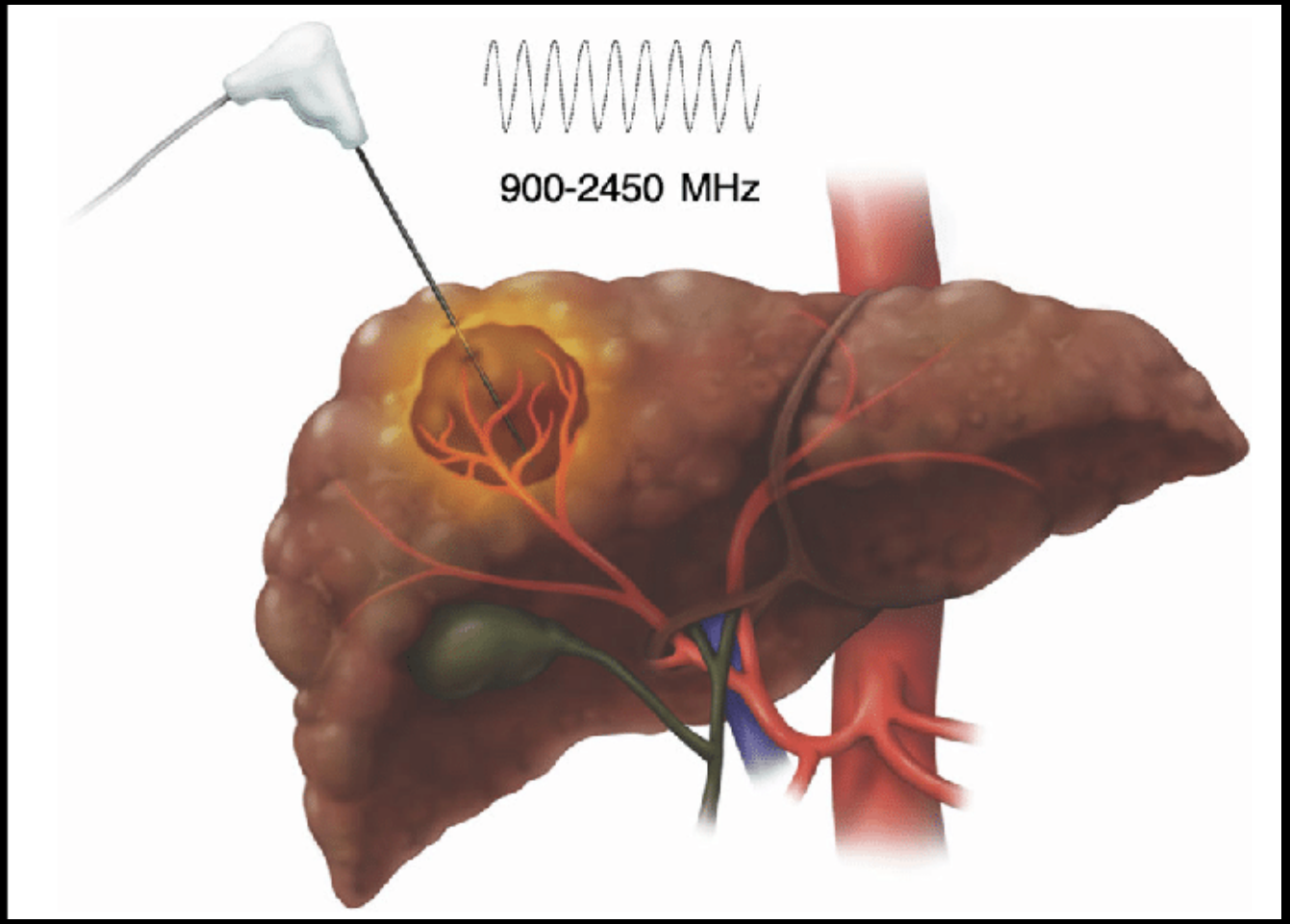


Radiofrequency Ablation (RFA)

- Mechanism: Utilizes an alternating electric field between a needle electrode and a ground pad, inducing ionic agitation, friction, and heat in surrounding tissue.

- Goal: Increase tissue temperature above cytotoxic threshold (50–100C) for 4–6 minutes

Microwave Ablation (MWA)



Microwave Ablation (MWA)

- Mechanism: Employs an antenna that produces electromagnetic waves interacting with water molecules, resulting in temperature elevation.

- Speed and Efficiency: MWA generates higher tissue temperatures more rapidly compared to RFA, creating larger ablations that may be less affected by tissue perfusion from large vessels.

RFA vs. MWA

- Comparison: Available data suggests that MWA exhibits similar technical success, efficacy rates, and oncologic outcomes as RFA for treating very early or early stage HCC.
- Note: No direct human comparisons between the two techniques have been published to date.

Follow-up Imaging after Ablation: How and When?

- **Role of Imaging**: Essential for post-ablation follow-up in HCC.
- **Objectives of Imaging**:

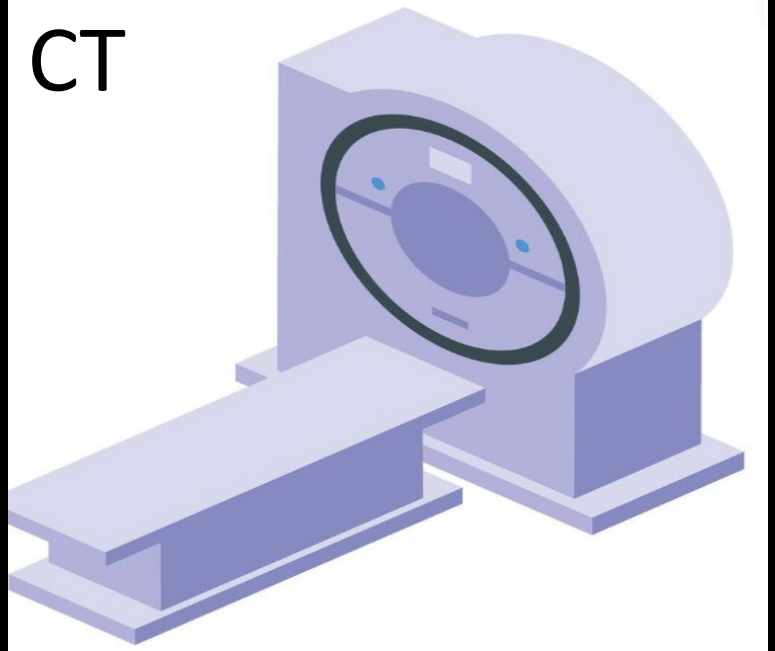
1) Assess technical success and identify complications;

2) Accurately identify tumor progression, intrahepatic recurrence, and distant extrahepatic recurrence.

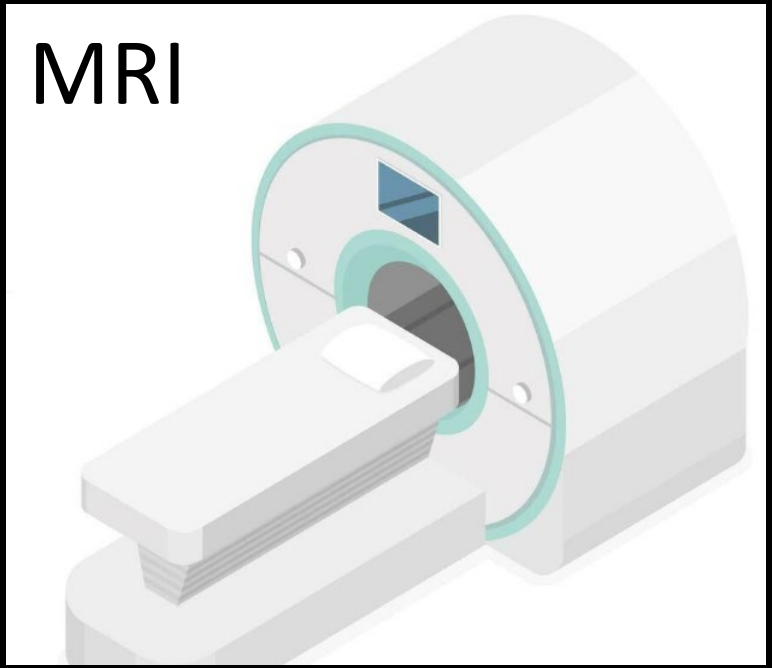
How do we assess HCC treatment response?

Contrast enhanced cross-sectional imaging - multiparametric

CT

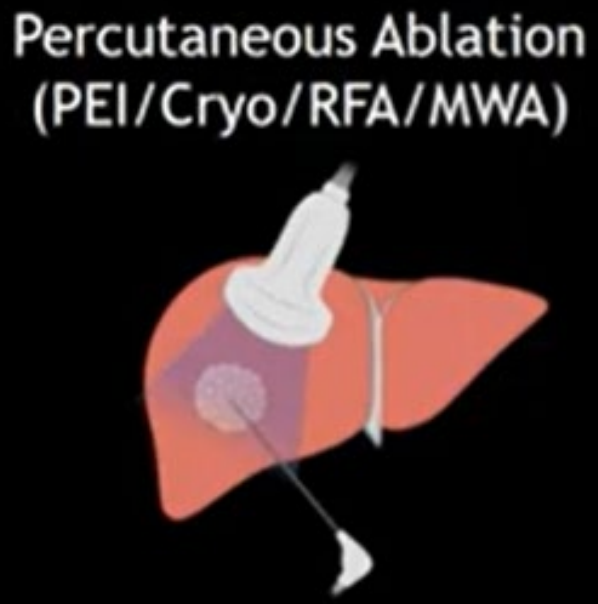


MRI



Post-LRT Imaging Timing Varies per institution

Regular follow-up aids in differentiation of progression from postablation changes



- imediately post treatment
- 1 month
- every 3 months

How do we assess HCC Treatment response?

- Understand pretreatment enhancement characteristics in order to accurately interpret response post- LRT.

Diagnostic enhancement pattern for HCC pre-treatment

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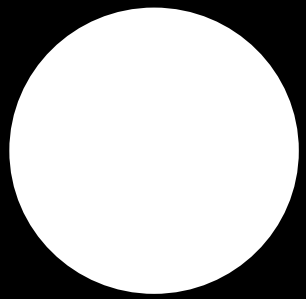

Arterial enhancement

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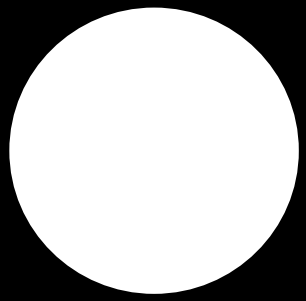

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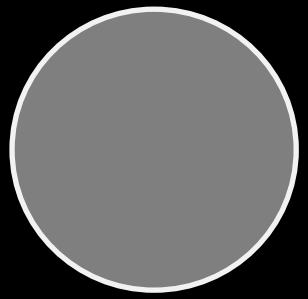

Portal venous wash-out +/- capsule, threshold growth

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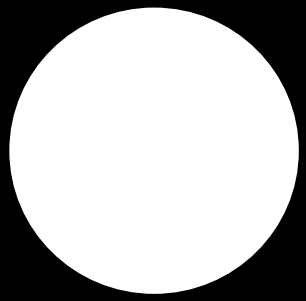

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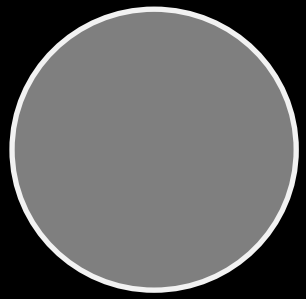

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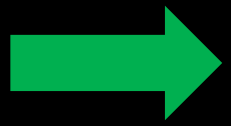

LR-5

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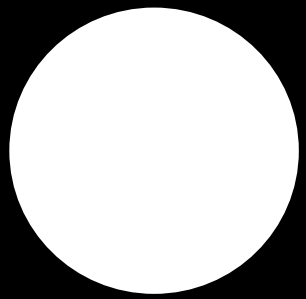

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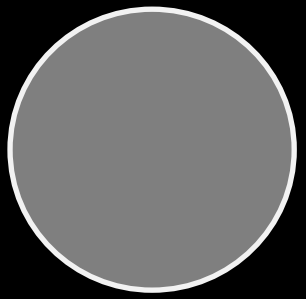

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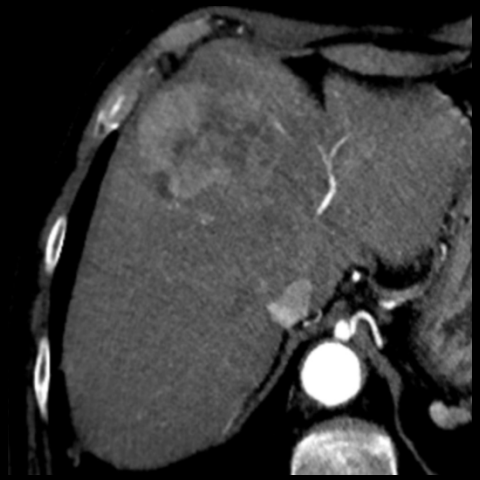
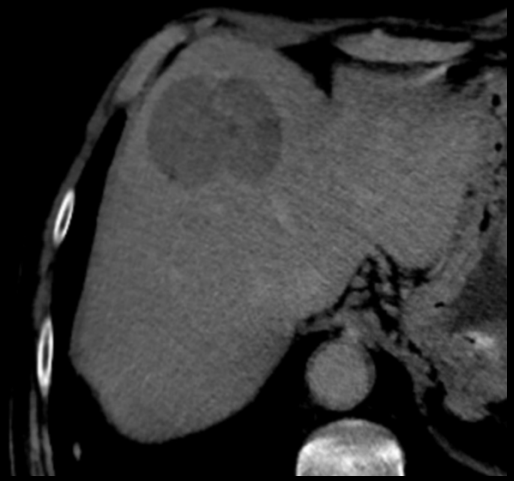
LR-5





How do we assess HCC Treatment responsa?

- Understand pretreatment enhancement characteristics in order to accurately interpret response post- LRT.

Other HCC enhancement pattern pre-treatment

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Arterial rim enhancement

LR-M

How do we assess HCC Treatment responsa?

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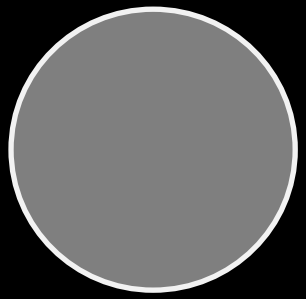
Other HCC enhancement pattern pre-treatment

Or



Arterial rim enhancement

Portal venous wash-out

LR-M

LR-4

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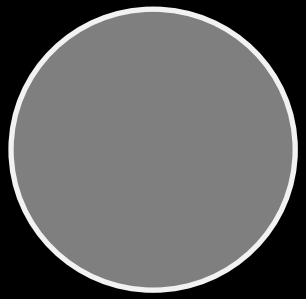
Other HCC enhancement pattern pre-treatment

Or



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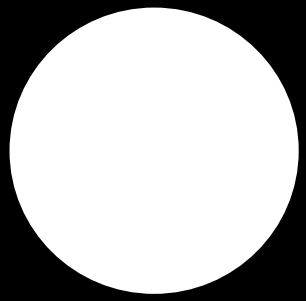

Arterial rim enhancement

LR-M

Portal venous wash-out

LR-4

Arterial enhancement + ancillary features

LR-4

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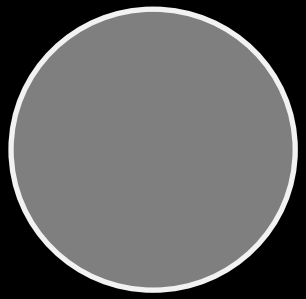
Other HCC enhancement pattern pre-treatment

Or



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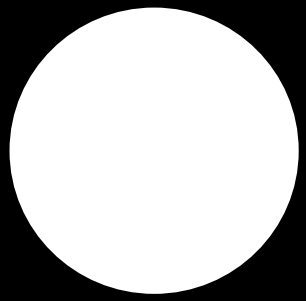


Arterial rim enhancement

LR-M

Portal venous wash-out

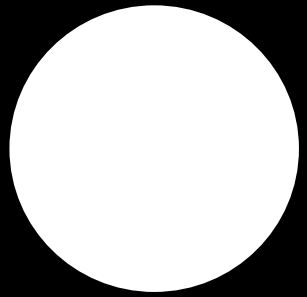
LR-4

Arterial enhancement + ancillary features

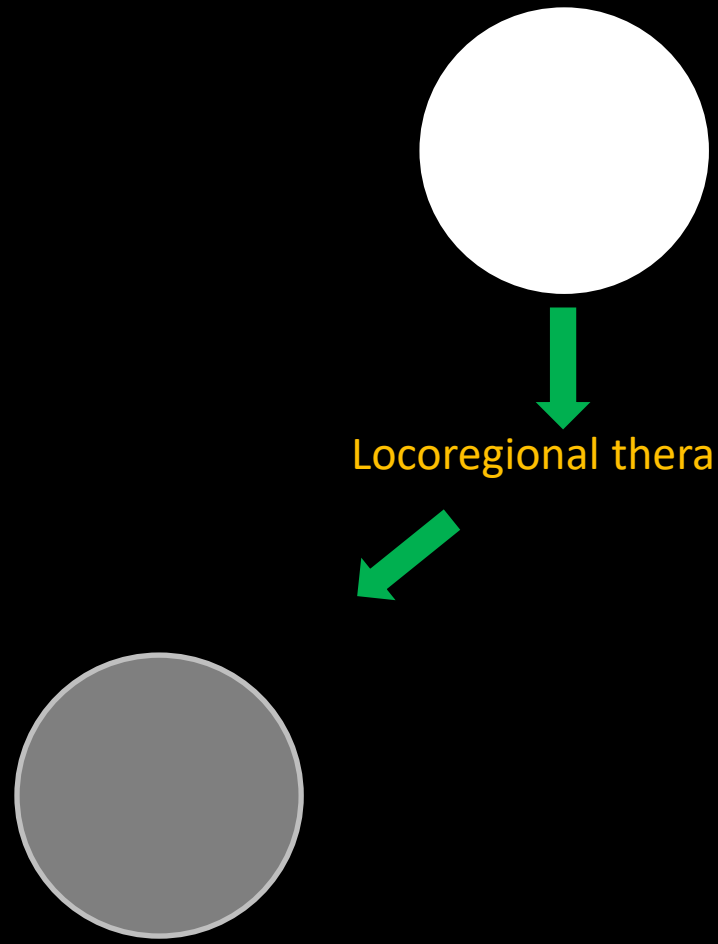
LR-4

Usually biopsy proven

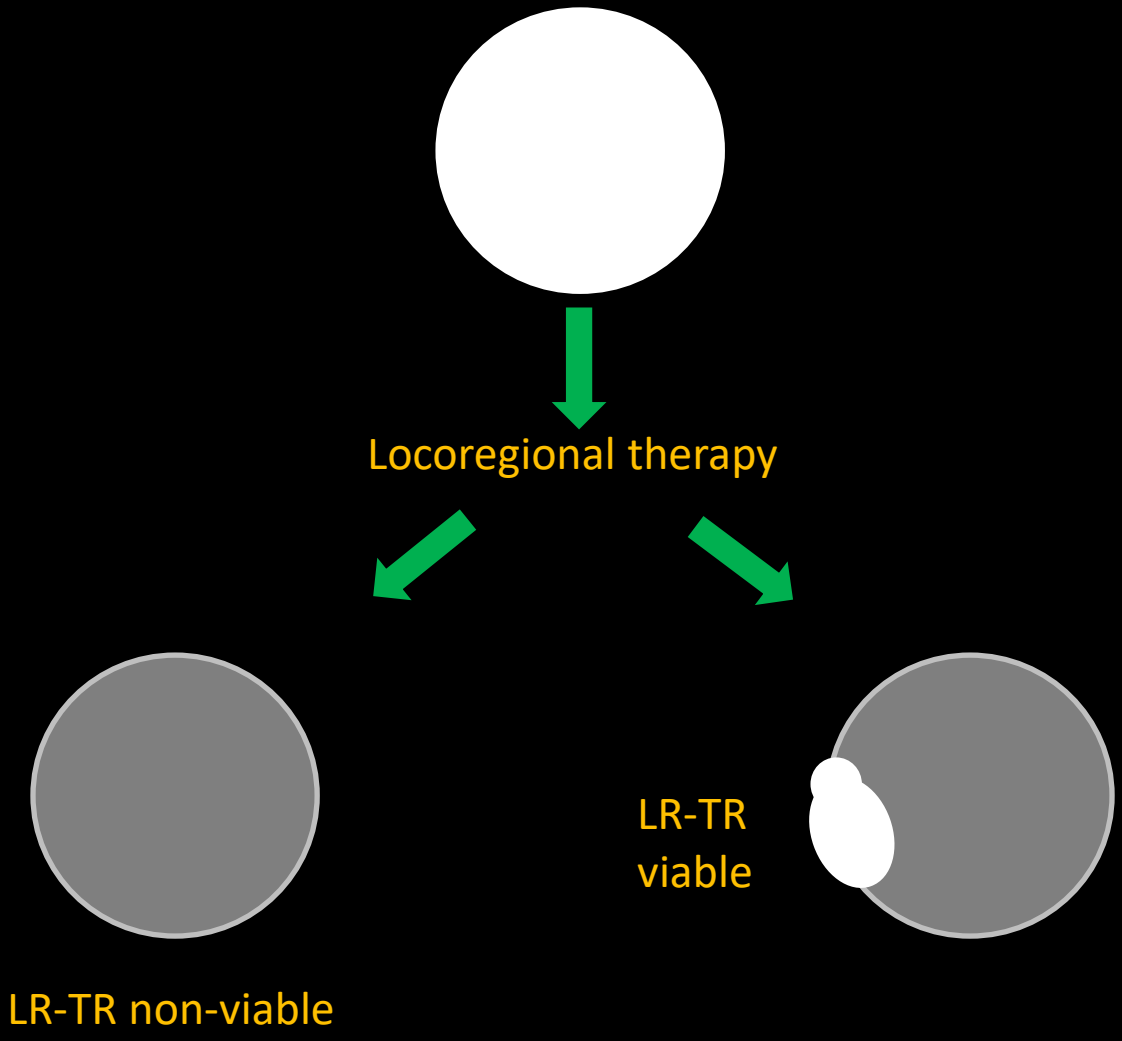
Li-RADS treatment response classification



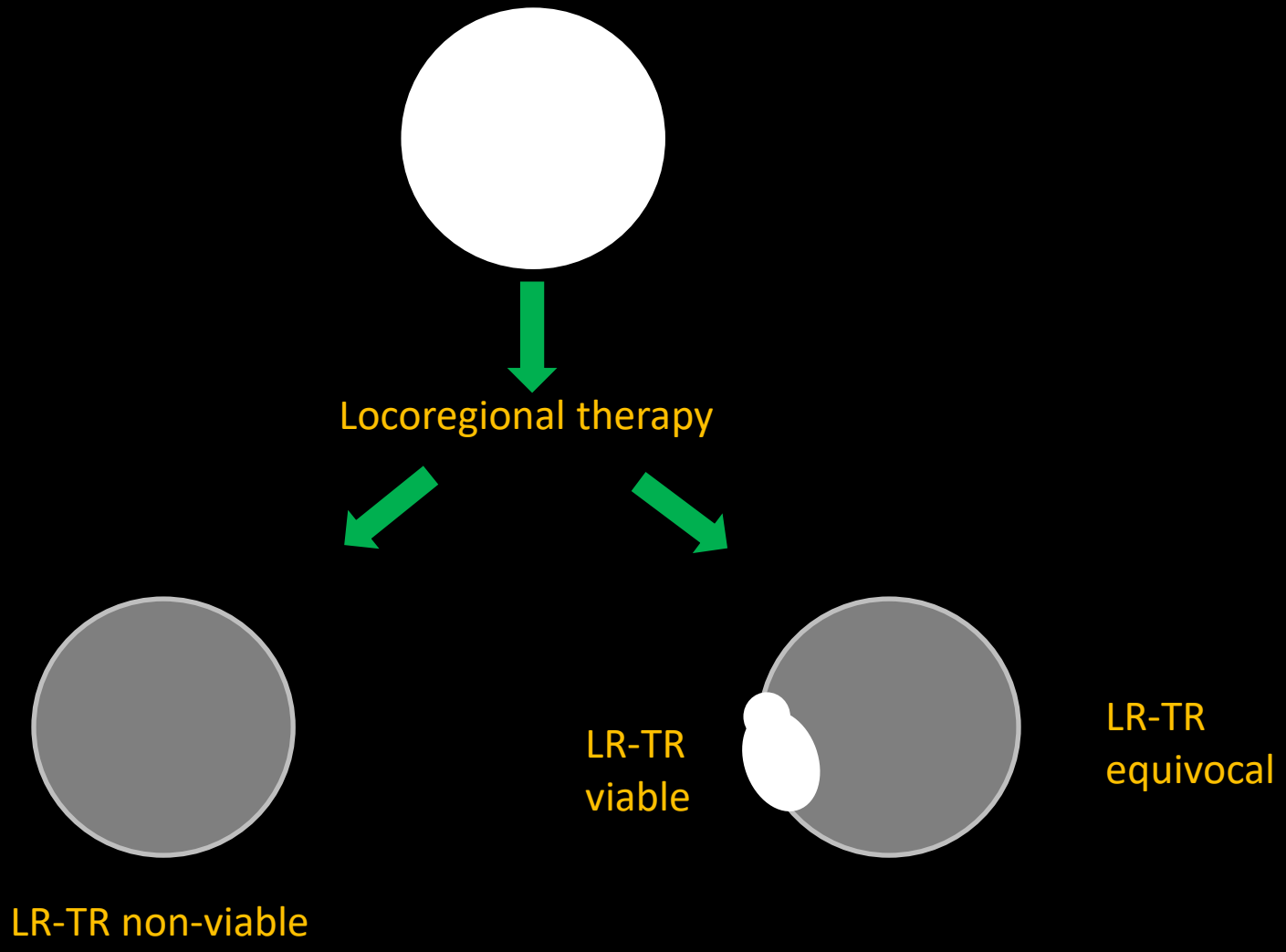
Li-RADS treatment response classification



Li-RADS treatment response classification



LI-RADS treatment response classification



LI-RADS

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 no meeting criteria for probably or definitely viable
LR-TR VIABLE	•Nodular, masslike, or thik irregular tissue in or along the treated lesion with any of the folowing: •Arterial phase hyperenhancemet OR •Washout appearance OR •Enhancement similar to pretreatment

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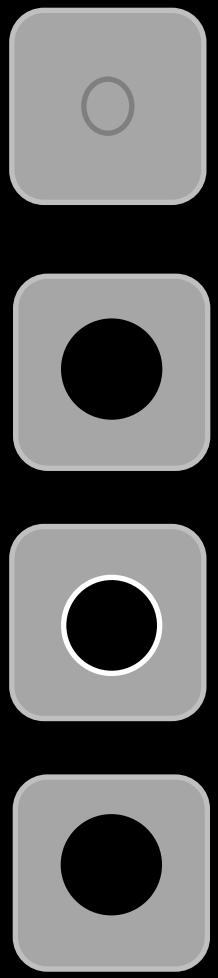
Must be familiar with common post treatment appearances for each locoregional therapy

LR-TR NONVIABLE



Complete lesion disappearance

No lesional enhancement

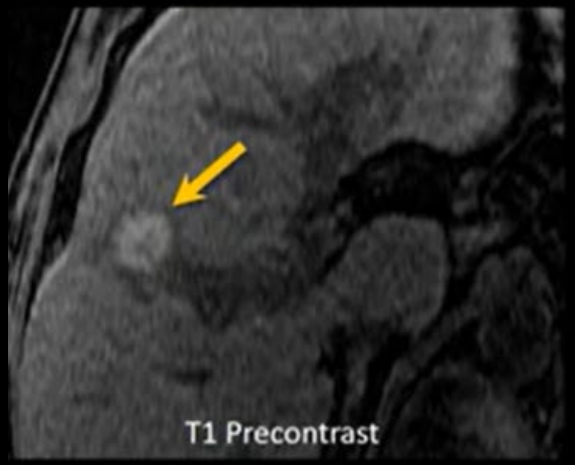
Smooth perilesional enhancement

Parenchymal perfusional changes

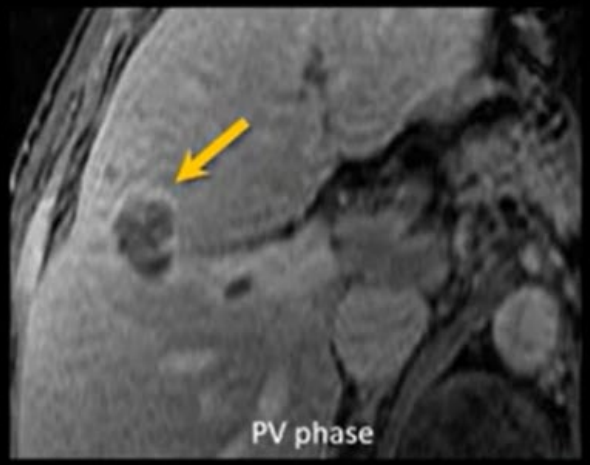
Expected post treatment imaging findings

- There should be NO residual APHE within the treated tumor

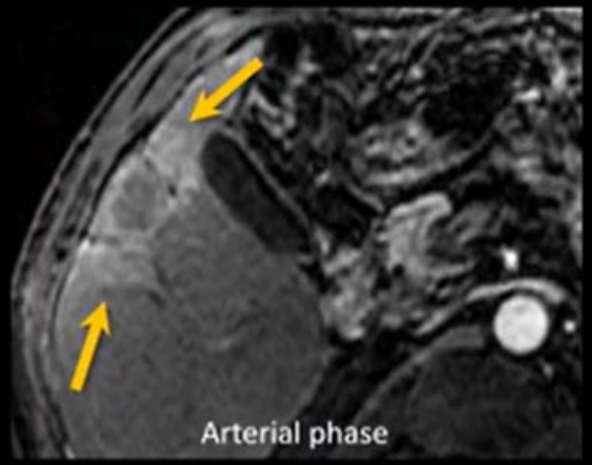
Expected post treatment imaging findings MRI



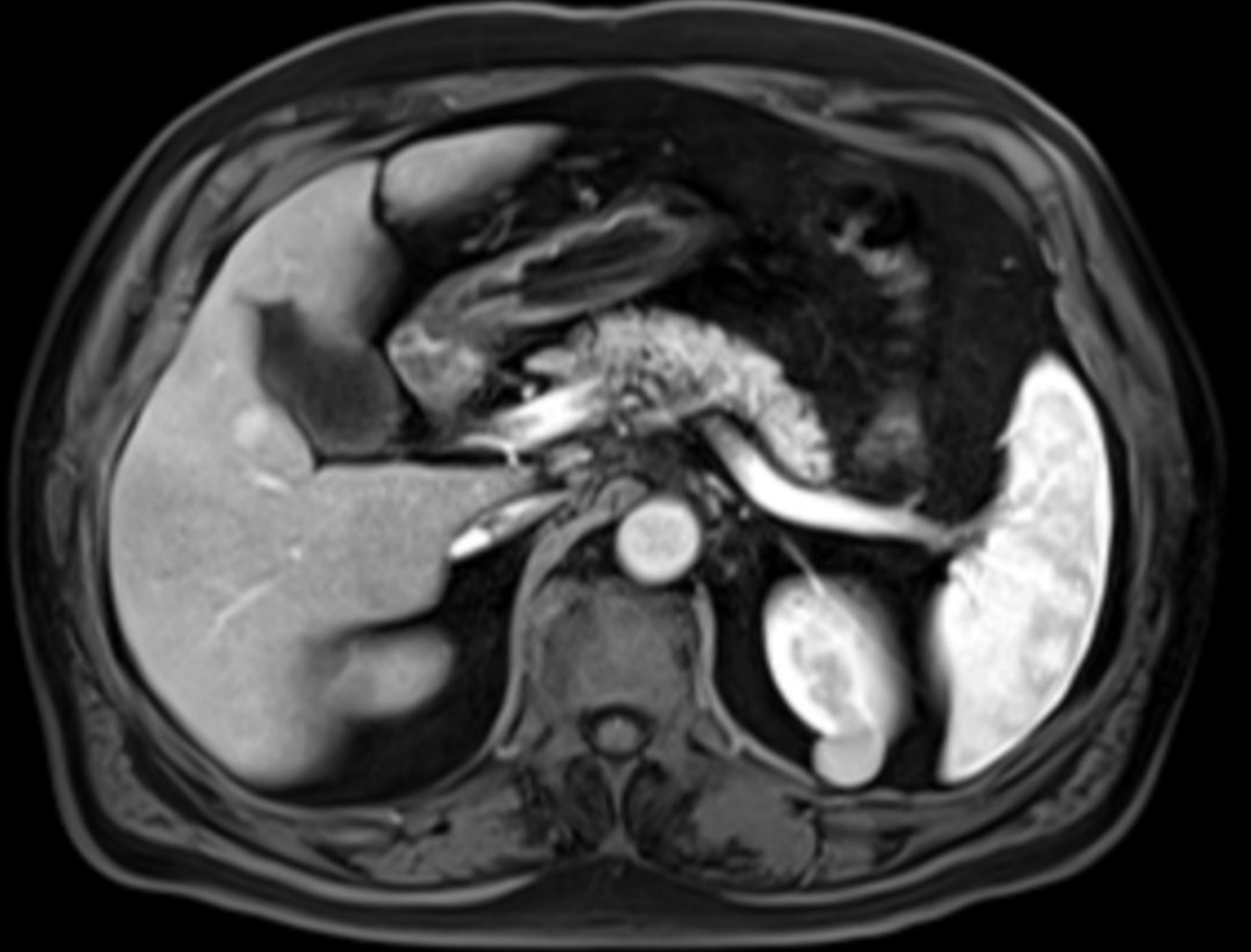
Central nonenhancing hyperdensity/hyperintensity within the center of the treatment cavity- coagulation necrosis

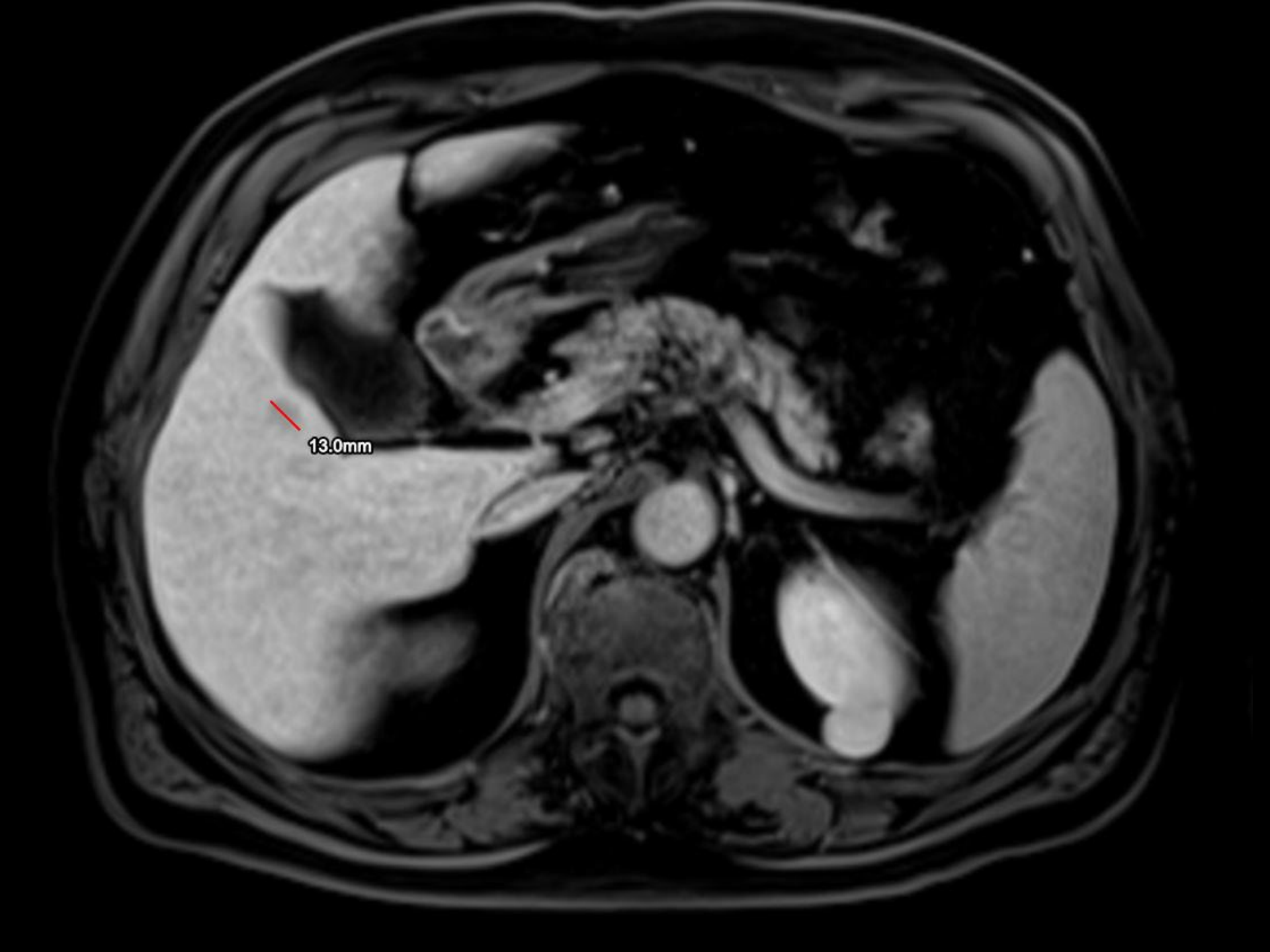


Thin continuous smooth rim enhancement

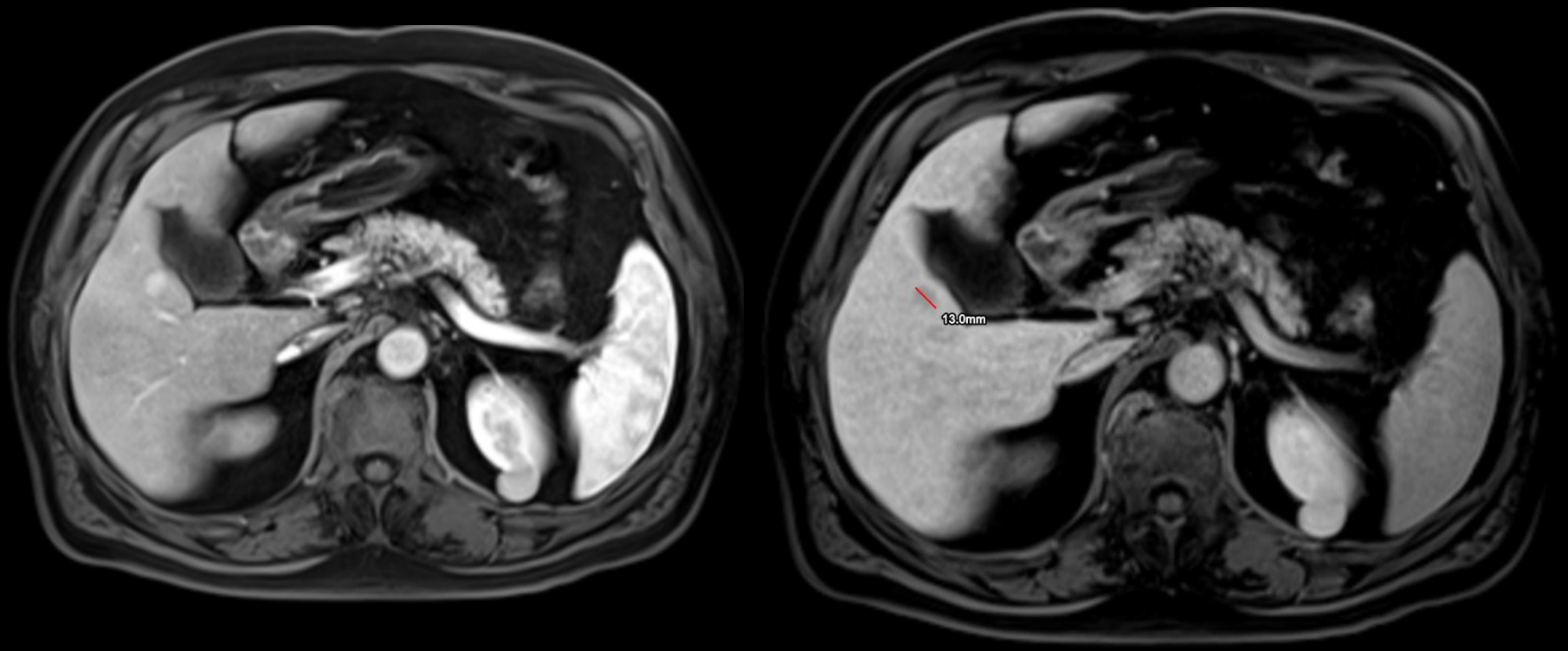


Mild peri-tumoral; ill-defined geographic areas of APHE within the parenchyma adjacent to the treatment cavity.

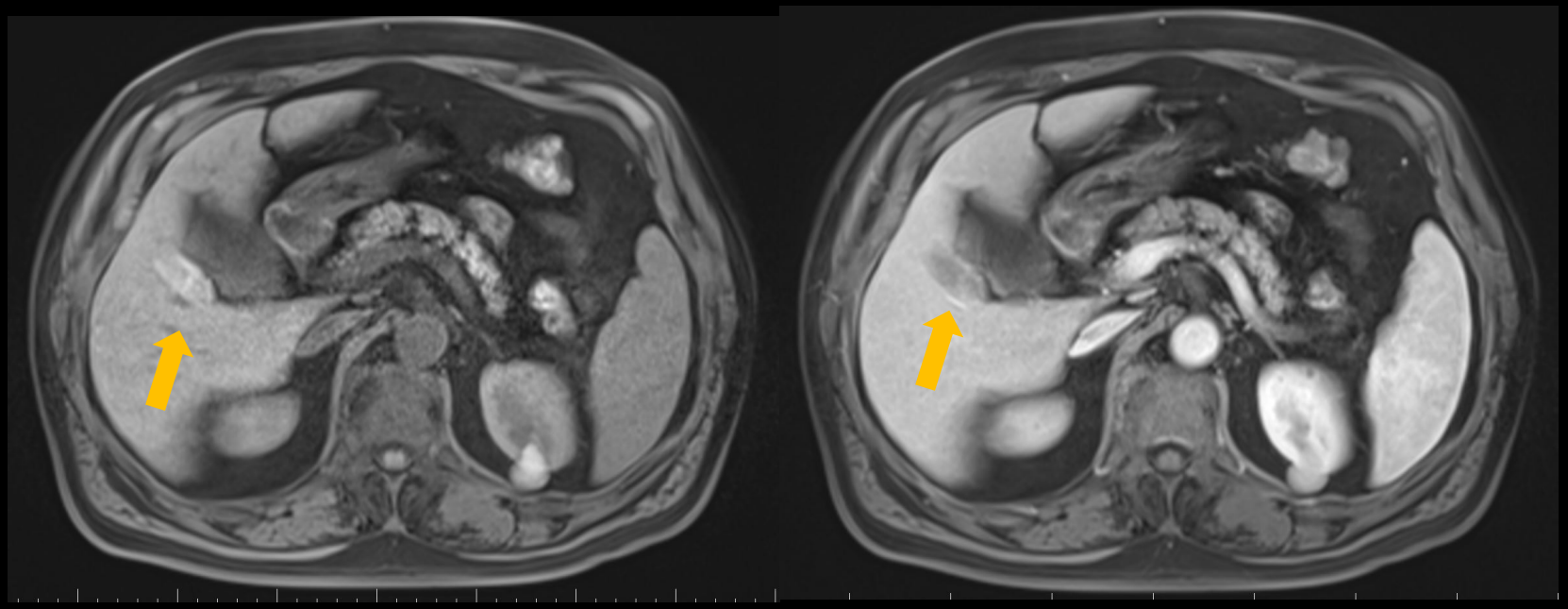



13.0mm

Initial
LR 5 HCC



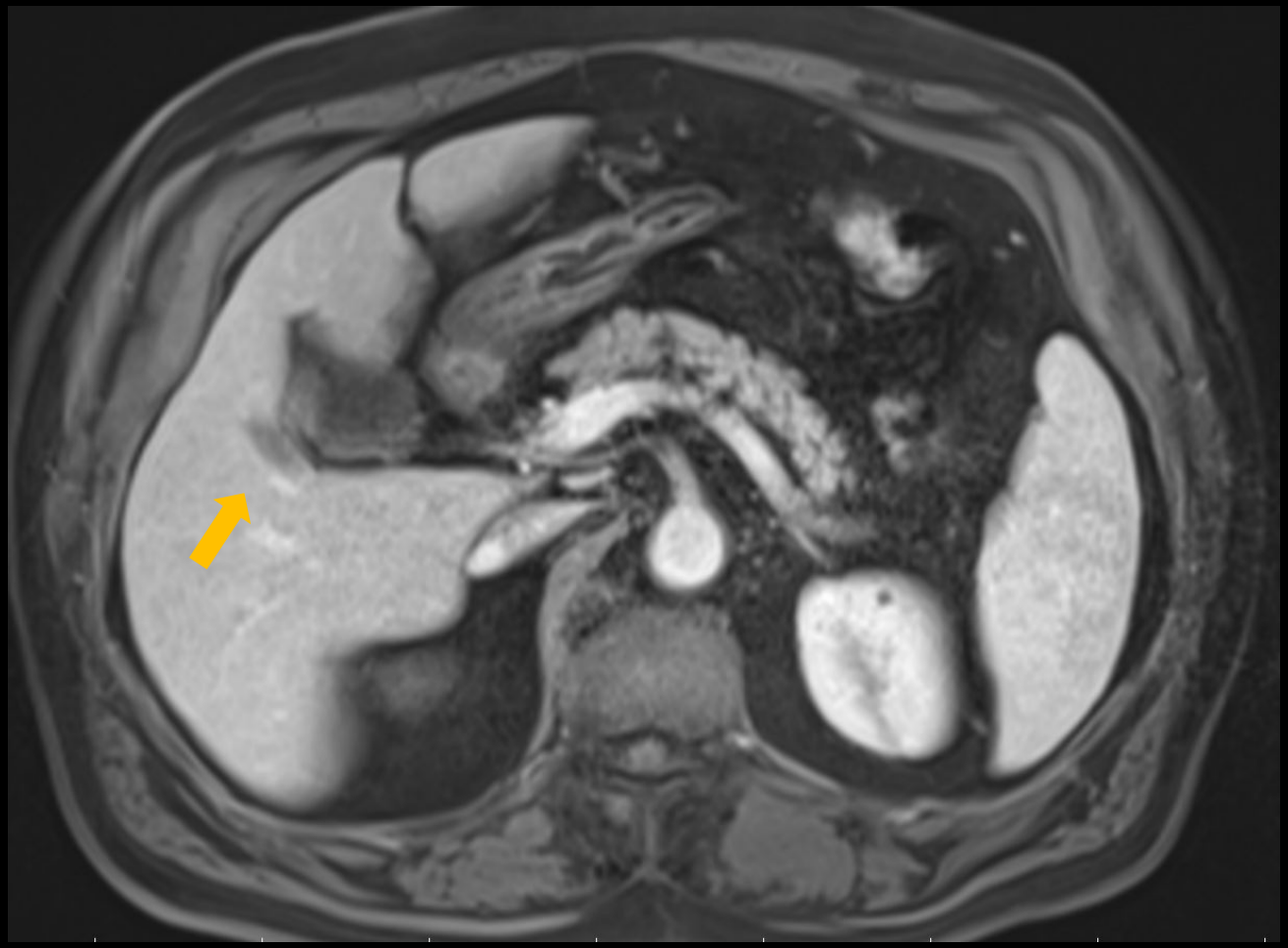
One month
LR TR Nonviable



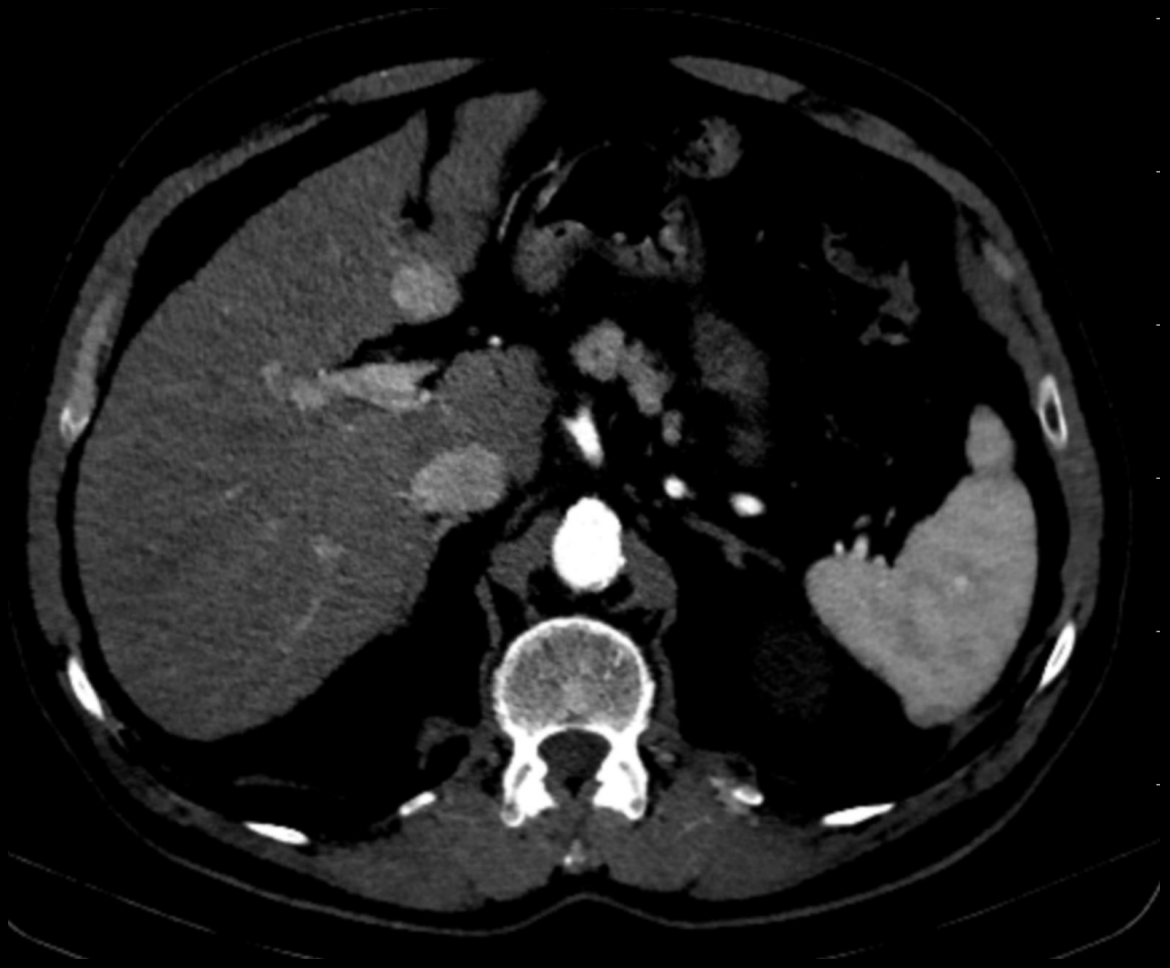
Ablation Zone Evolution

- *Long-Term Changes:* Size gradually decreases, possible capsular retraction.
- *Bile Duct Dilatation:* Well depicted after 3 months.

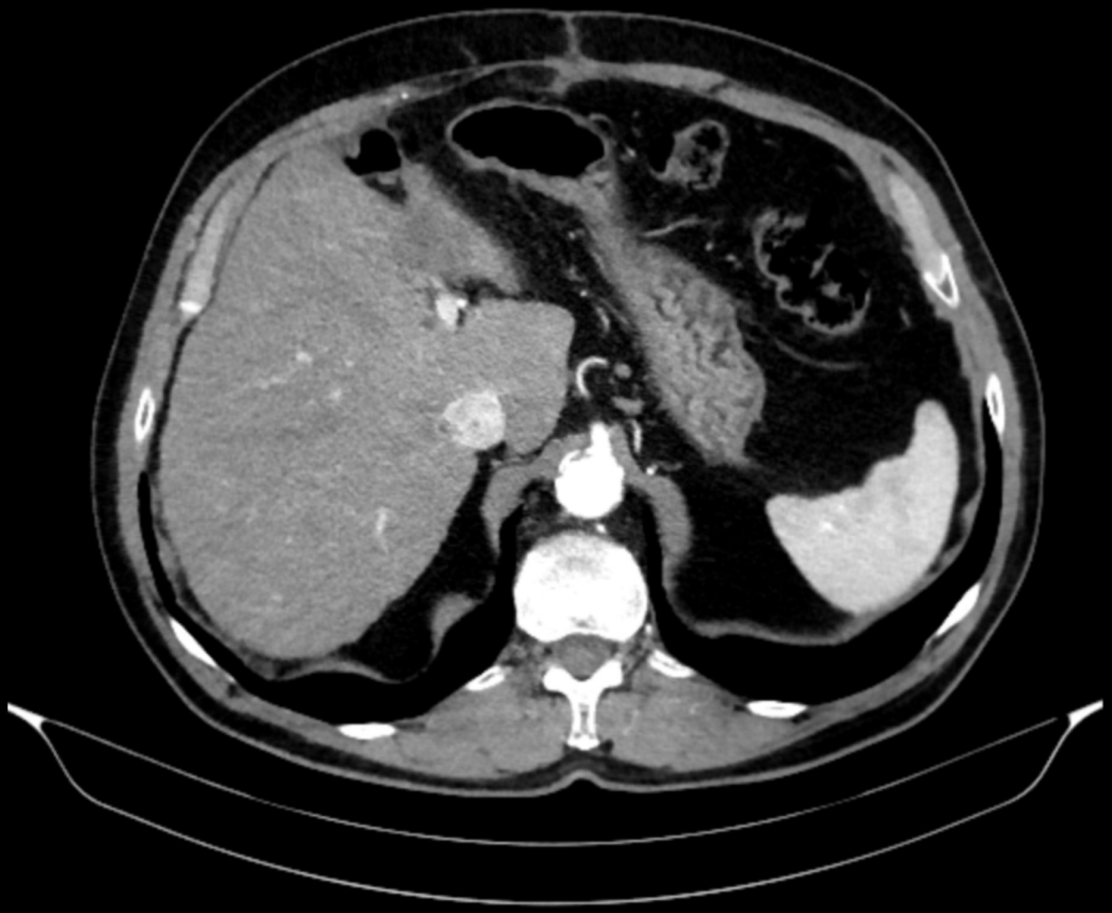
Two Years



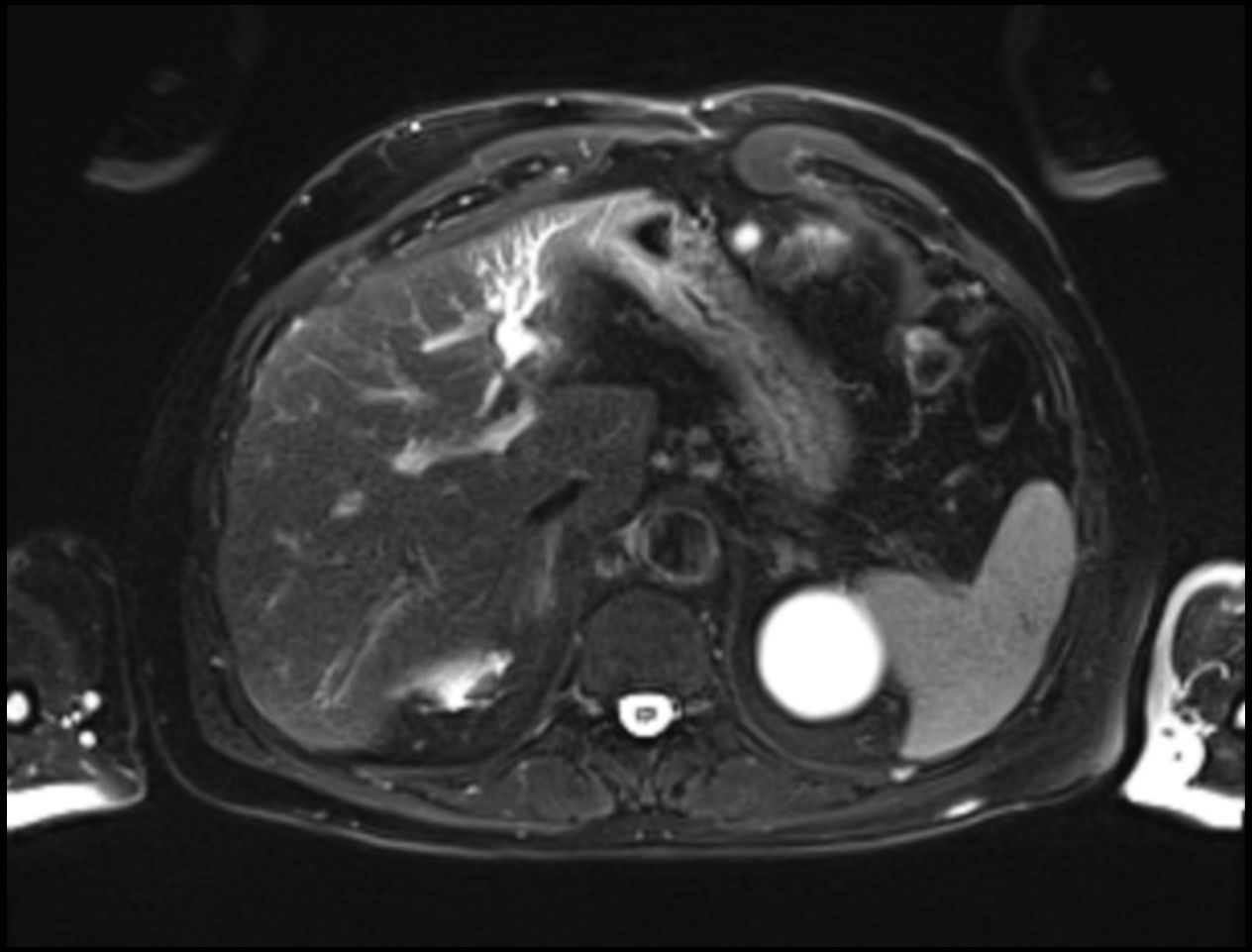
LR 5



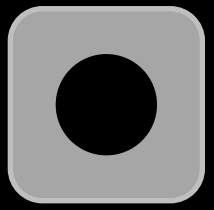
LR TR Nonviable



Left bile duct complications



LR-TR EQUIVOCAL



Uncertain likelihood of clinically significant viable tumor after treatment with non radiation-based LRT

Uncertain about mass like enhancement in treated lesion or along treated lesion margin

Equivocal is a unique response category

- LRT targets tumor and and adjacent hepatic parenchima.
- Geographic and/or amorphous APHE around the treated tumor from altered parenchymal perfusion – mimics viable disease- LR-TR Equivocal

Equivocal is a unique response category

- Results in posible untreated viable tumor
- HCC is slow growing with doubling times of 85-117 days
- Wait and watch approach prevents pacients with tenous liver function from being re-treated to early

LR-TR VIABLE

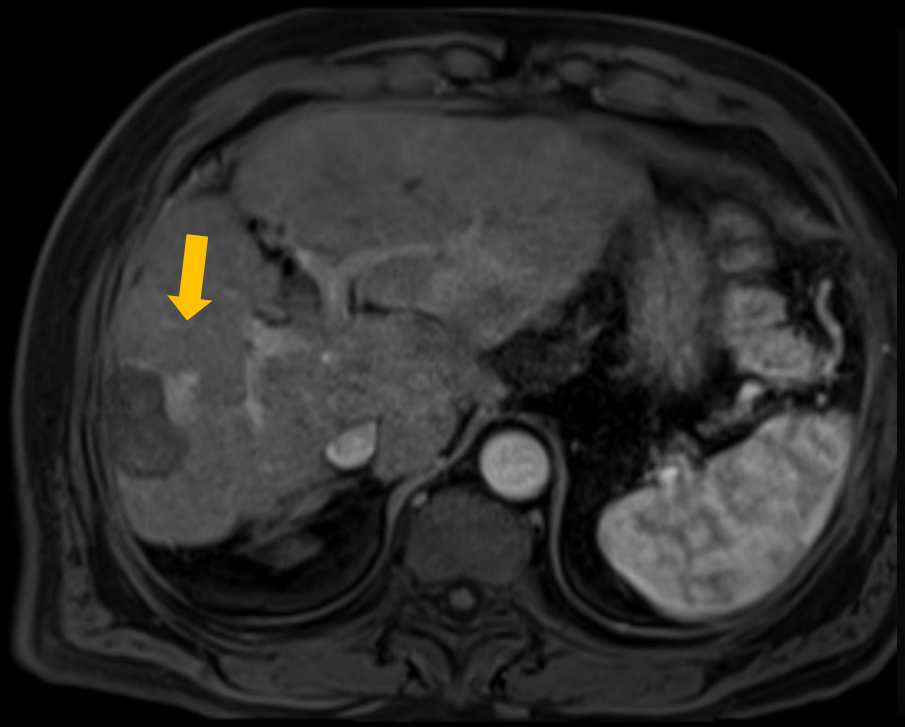
High likelihood of clinically viable tumor after treatment

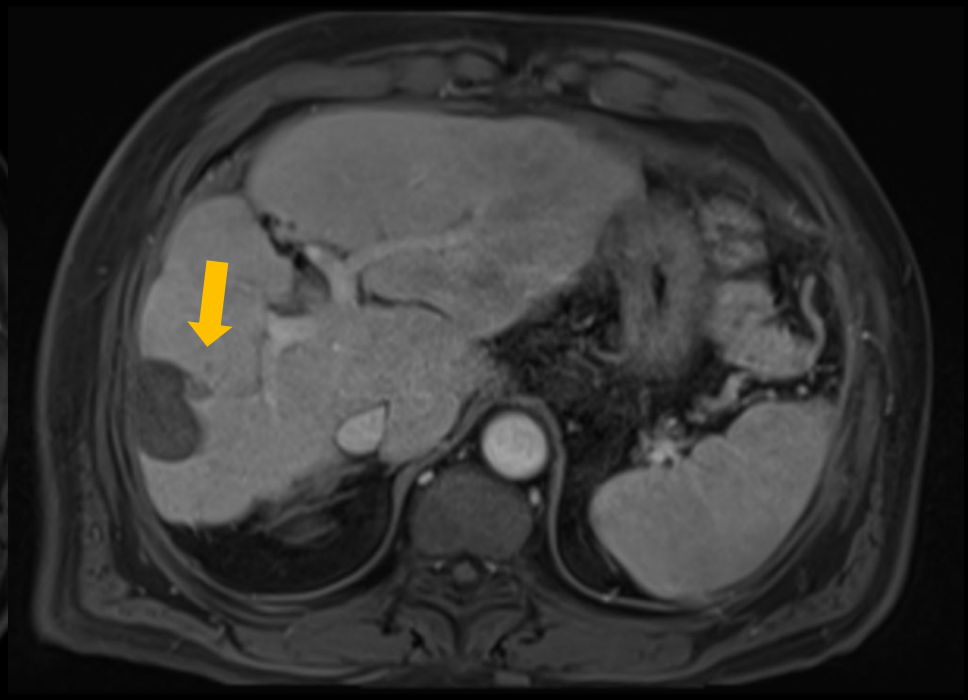
After non-radiation LRT

- Masslike enhancement (any degree, any phase) in treated leasion or along treated lesion margins OR

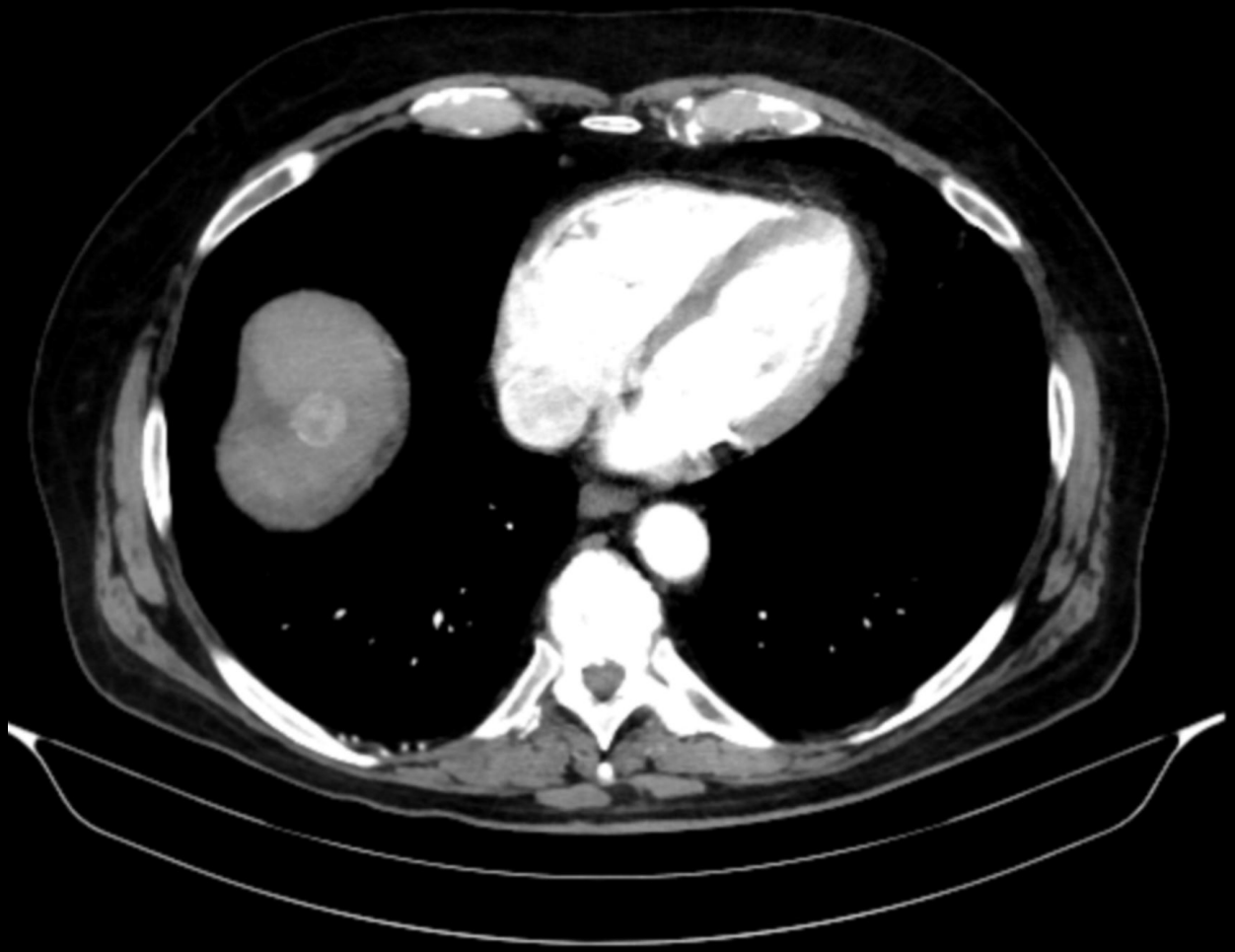
- Uncertain masslike enhancement plus mild-moderate T2 hyperintensity or diffusion restriction (any degree) in area of uncertain masslike enhancement

LR-TR viable

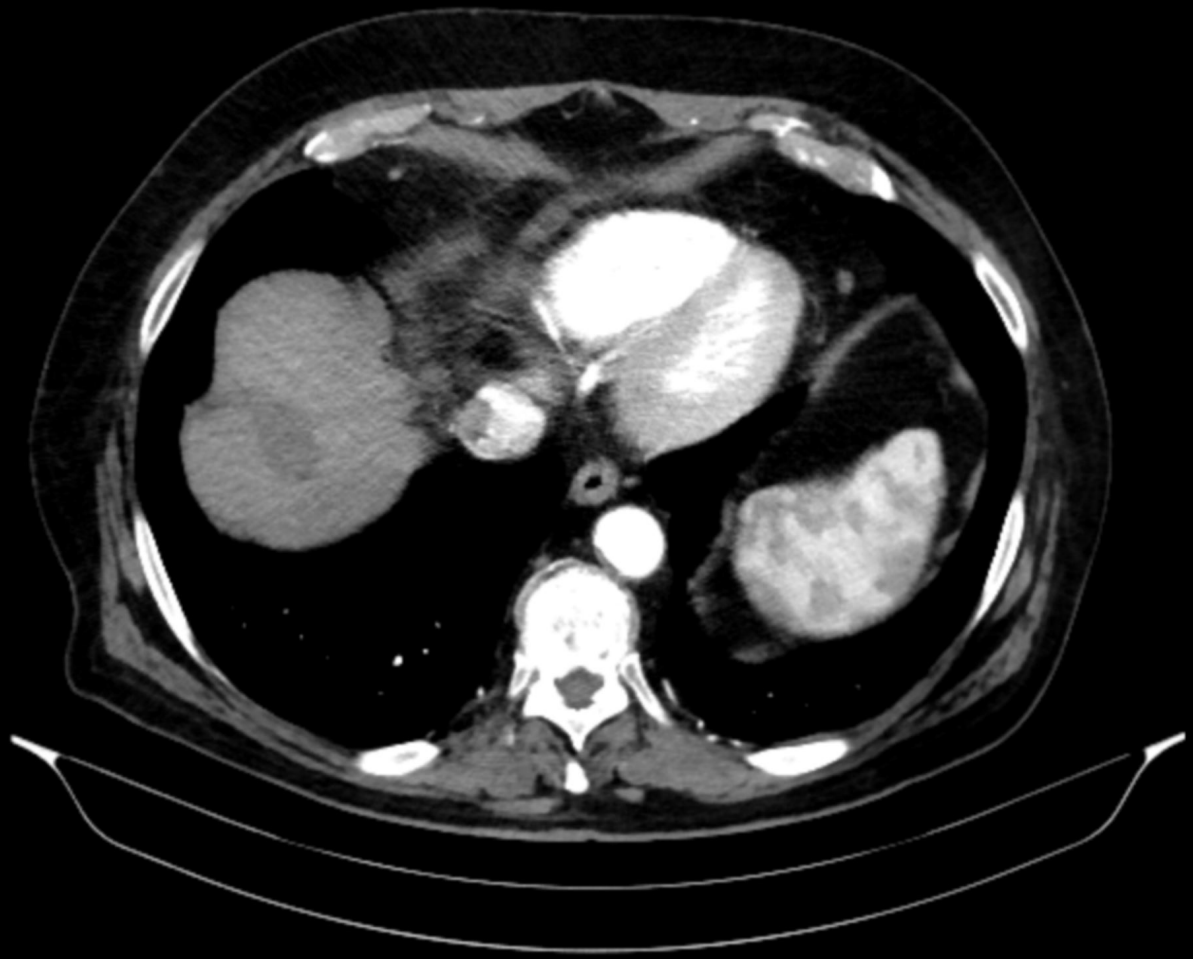




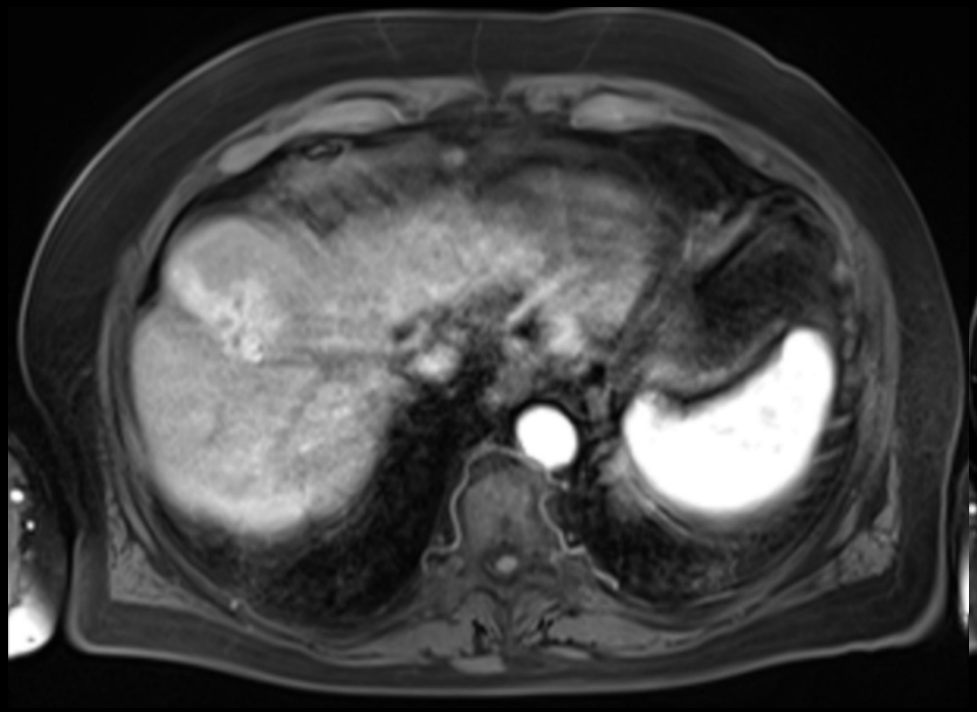
Recurrence post surgery

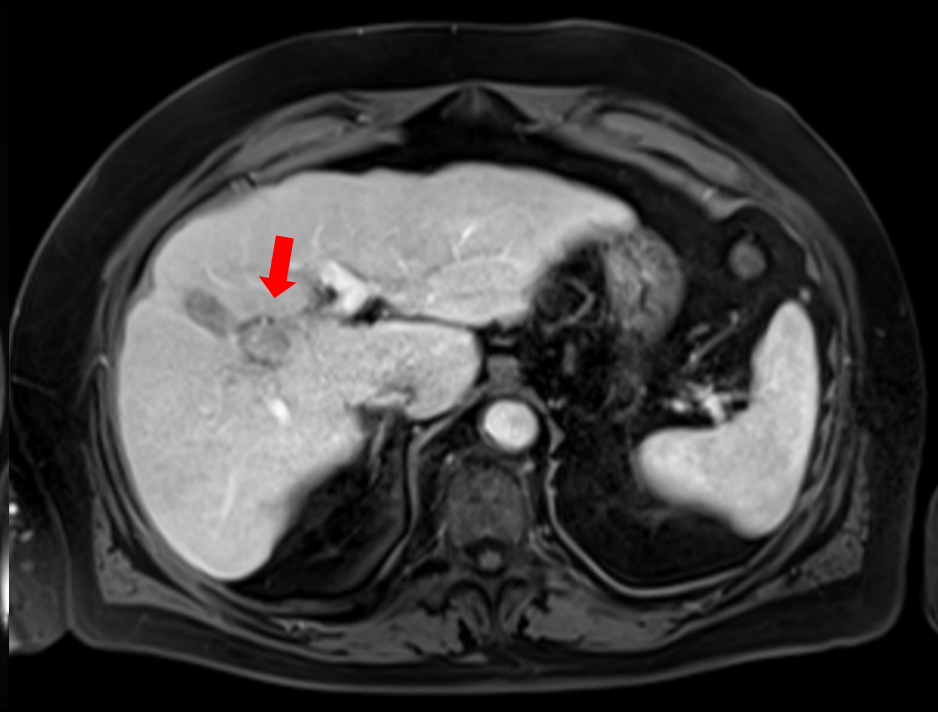


One month
LR TR Nonviable

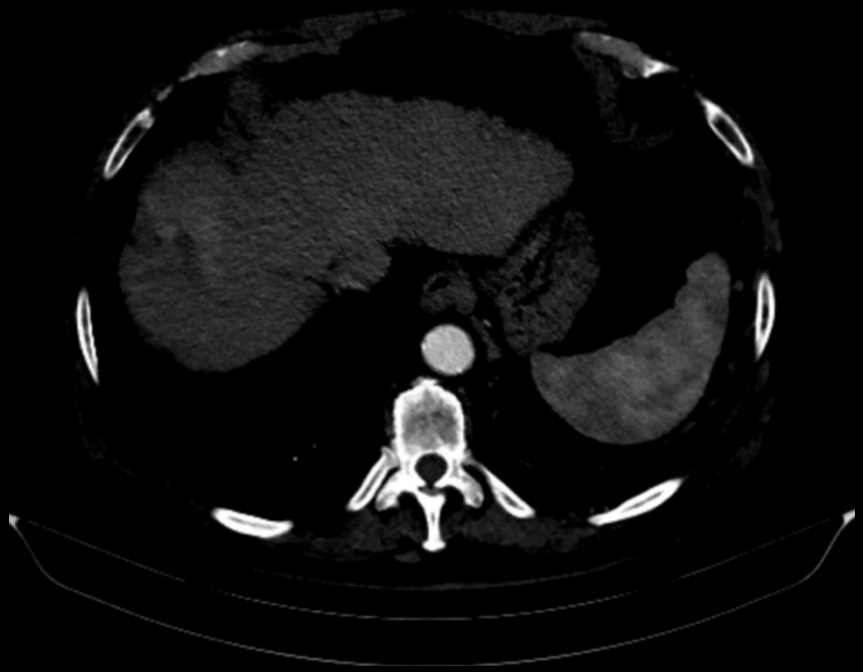


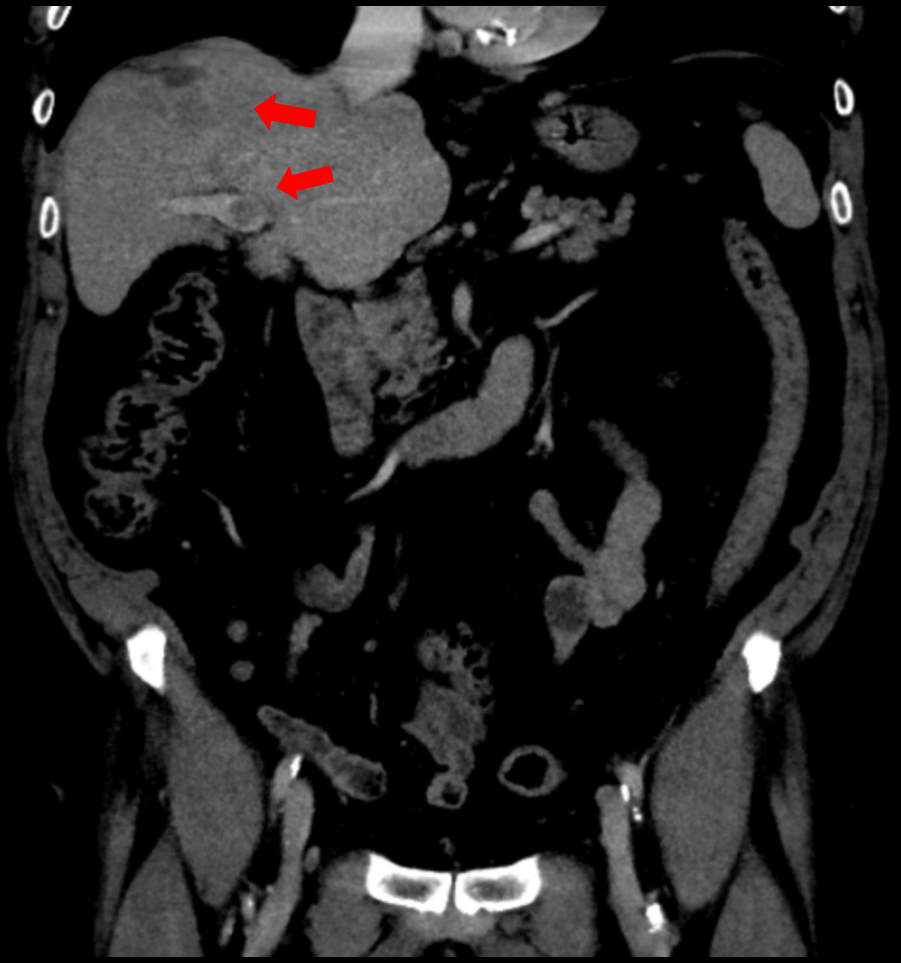
Two years
LR TR Viable
TIV





TIV CT





Bening liver changes post chemotherapy/Pseudopro gression

Introduction

- The Liver: Major organ for drug metabolism and detoxification.
- Liver Damage: Can be caused by various mechanisms, commonly resulting in inflammation, oxidative stress, and necrosis.
- Key Radiological Findings: Vascular alterations and structural changes

Chemotherapy and Liver Injury

- Evolution of Chemotherapy: From cytotoxic drugs to biological drugs.
- Increased liver damage due to multidrug regimens and prolonged therapies.
- Importance of Early Detection: Crucial to avoid severe complications.

Historical Context

- First case of chemotherapy-associated liver injury (CALI): Reported in the 1950s in children with acute leukemia.

- Modern Challenges: Newer therapies such as immune checkpoint inhibitors increase the incidence of CALI.

Symptoms and Diagnostic Challenges

- Nonspecific Symptoms: Abdominal discomfort, hepatomegaly, elevated liver function tests.

- Diagnostic Dilemma: Symptoms may be unrelated to chemotherapy.

Imaging in Chemotherapy-Associated Liver Injury

- Role of Imaging: Detecting pseudocirrhosis, “yellow liver,” and “blue liver.”

- Importance for Oncologists: Helps in the early recognition of therapy-induced liver changes.

Chemotherapy-associated liver injury

- Acute hepatic necrosis: Caused by antineoplastic agents.
- Sinusoidal Obstructive Syndrome (SOS): From myeloablative and alkylating agents.
- Immune-Mediated Injury: Increasing with immunomodulatory agents and checkpoint inhibitors.

CALI Overview

Two main types:

Vascular changes

Fatty changes

- Caused by ROS (reactive oxygen species)

- Leads to cellular damage and activates apoptosis pathways

- Prevalence increases with chemotherapy duration

- No convincing data on the reversibility of CALI

Immune checkpoint inhibitors

- Hepatocellular biochemical pattern

- Occurs in 2%-30% of patients

- Increased risk with multiple inhibitors and other immune-related adverse events

Yellow Liver

- Macroscopic feature due to increased parenchymal lipid content

- Includes hepatic steatosis and steatohepatitis (CASH)

CASH:

- Associated with chemotherapy agents like 5-fluorouracil, irinotecan, oxaliplatin, etc.

- Can lead to fibrosis and atrophy if not detected early

Imaging Techniques

Ultrasound: Subjective estimation using liver brightness and contrast with the kidney

CT Scan:

- Diffuse steatosis: Liver attenuation at least 10 HU less than the spleen

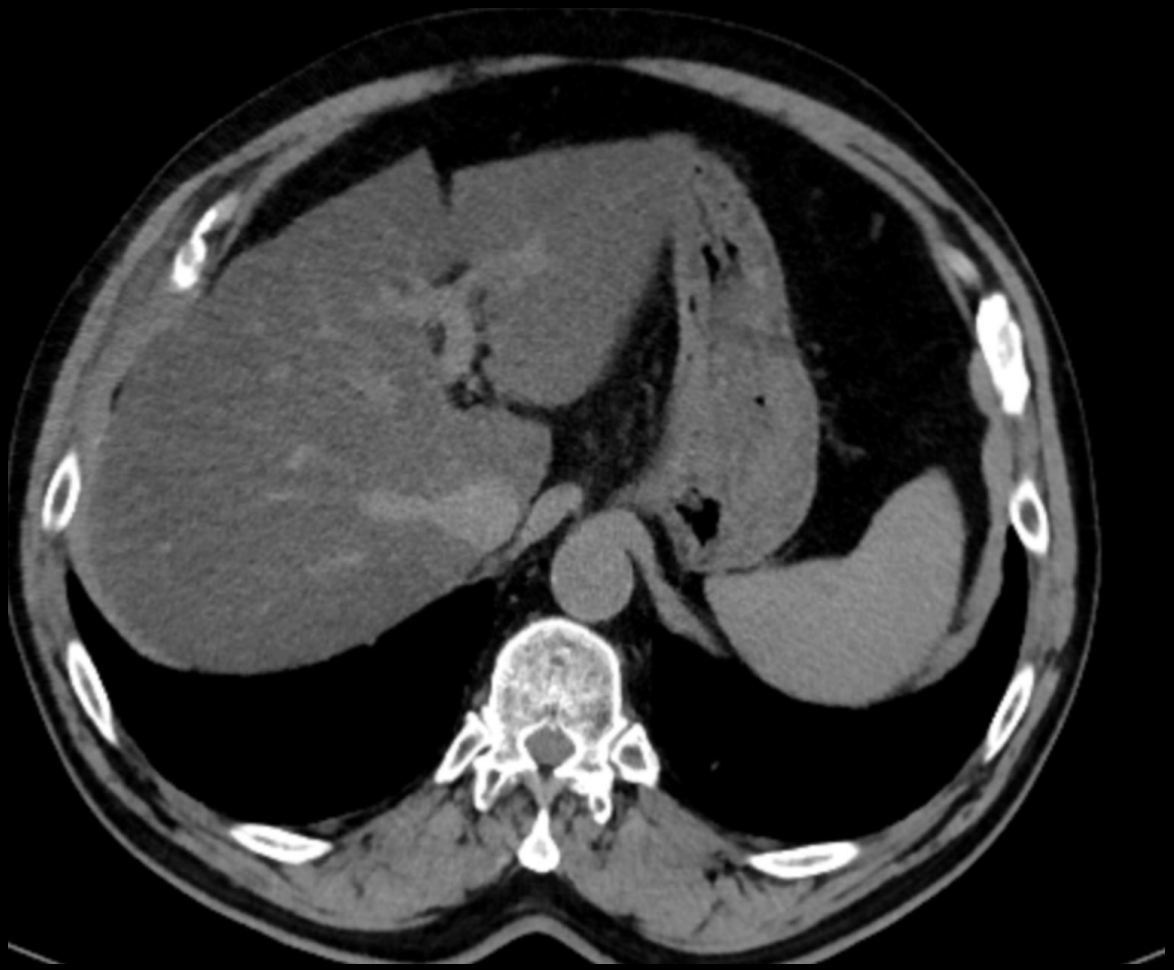
- Severe cases: Hyperdense intrahepatic vessels

MRI:

- Chemical shift gradient-echo imaging (in-phase and out-of-phase)

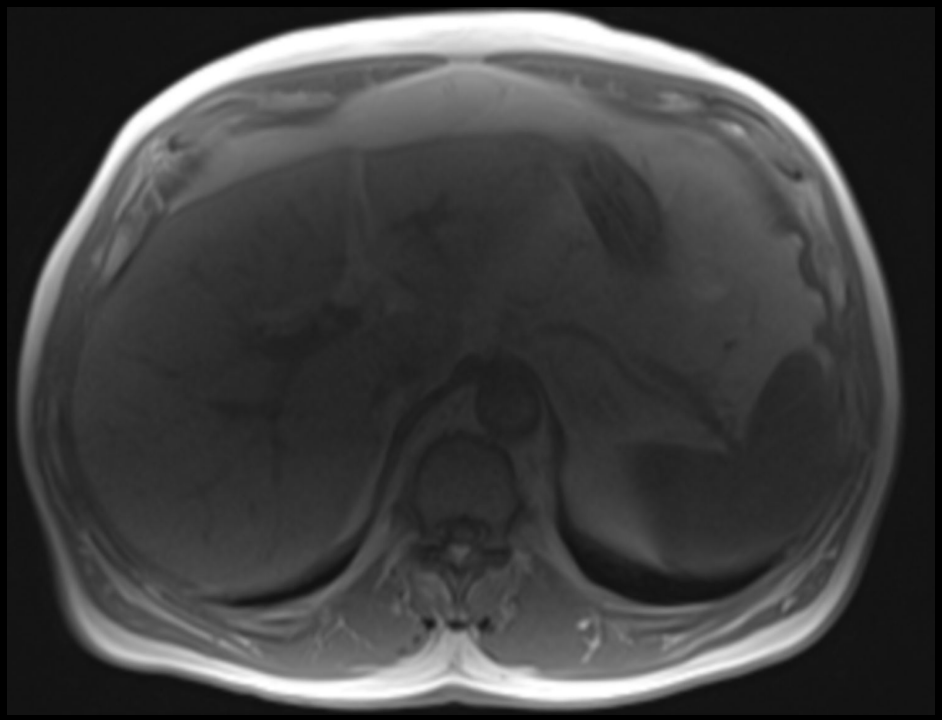
- Out-of-phase images show signal intensity loss

CT

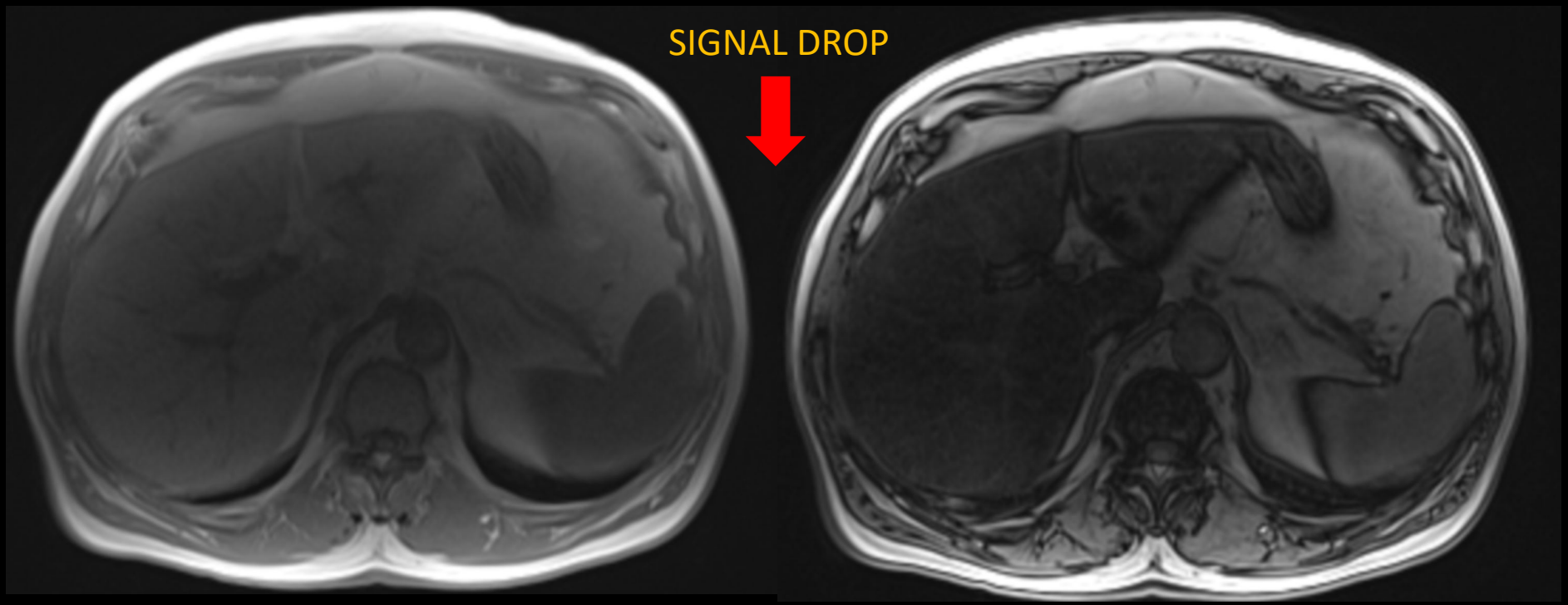


MRI

T1 IN PHASE



MRI



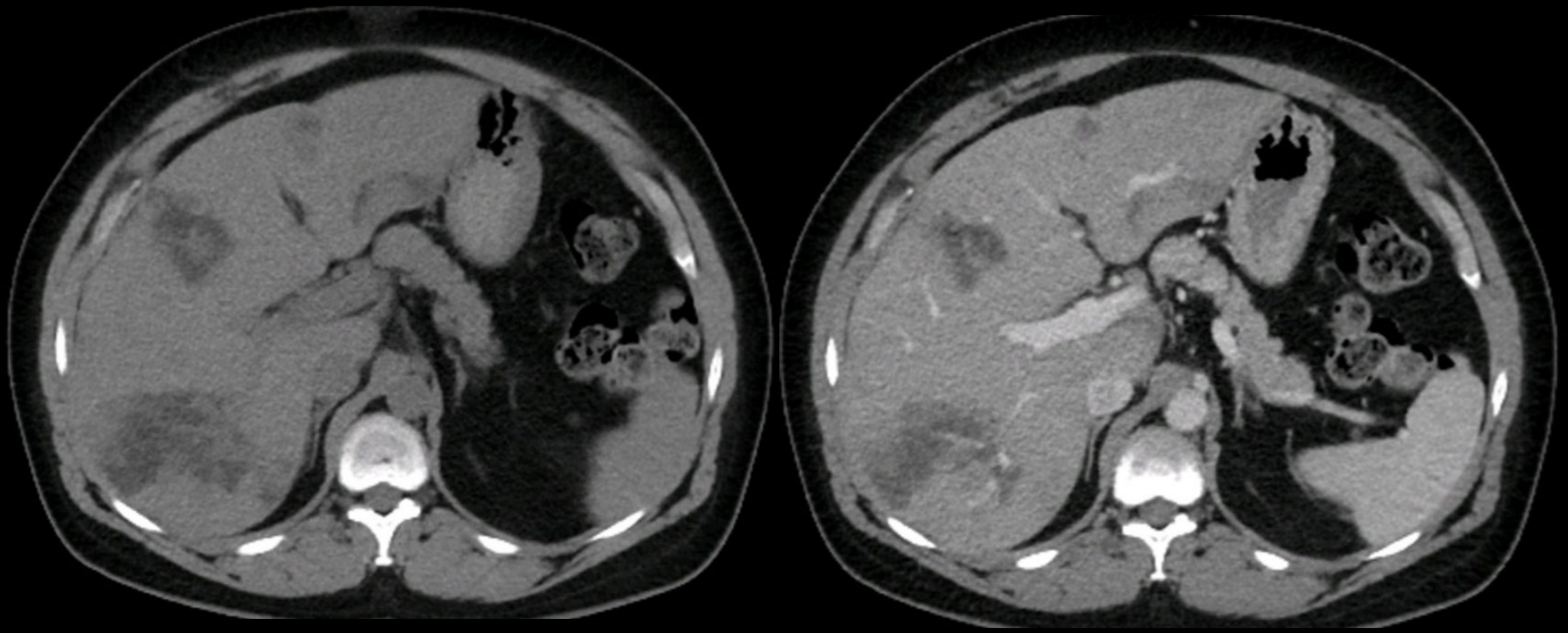
Focal fat deposition

- Can mimic hepatic mass or metastatic disease

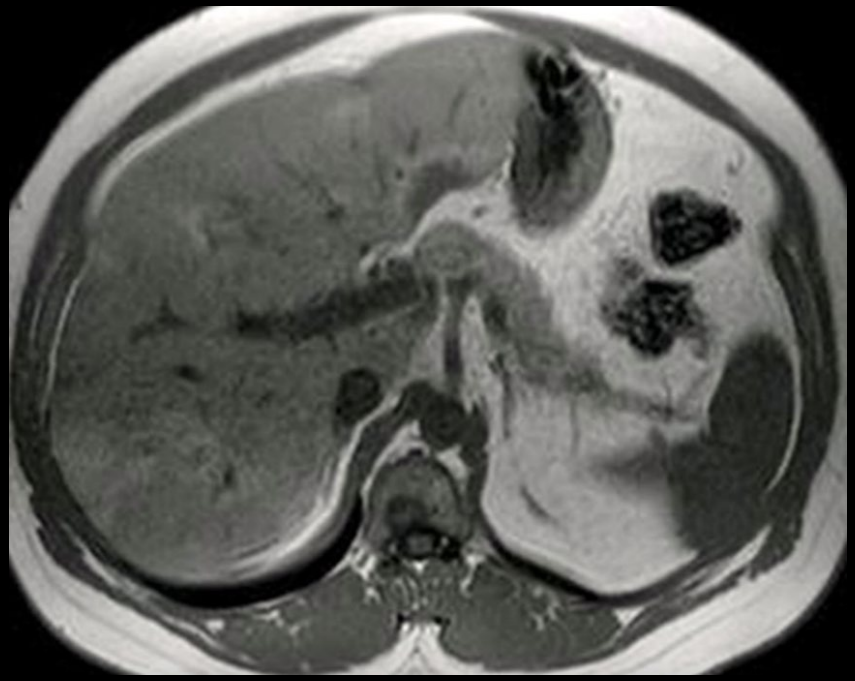
- Recognized by characteristic location, geographic pattern, absence of mass effect, and contrast enhancement

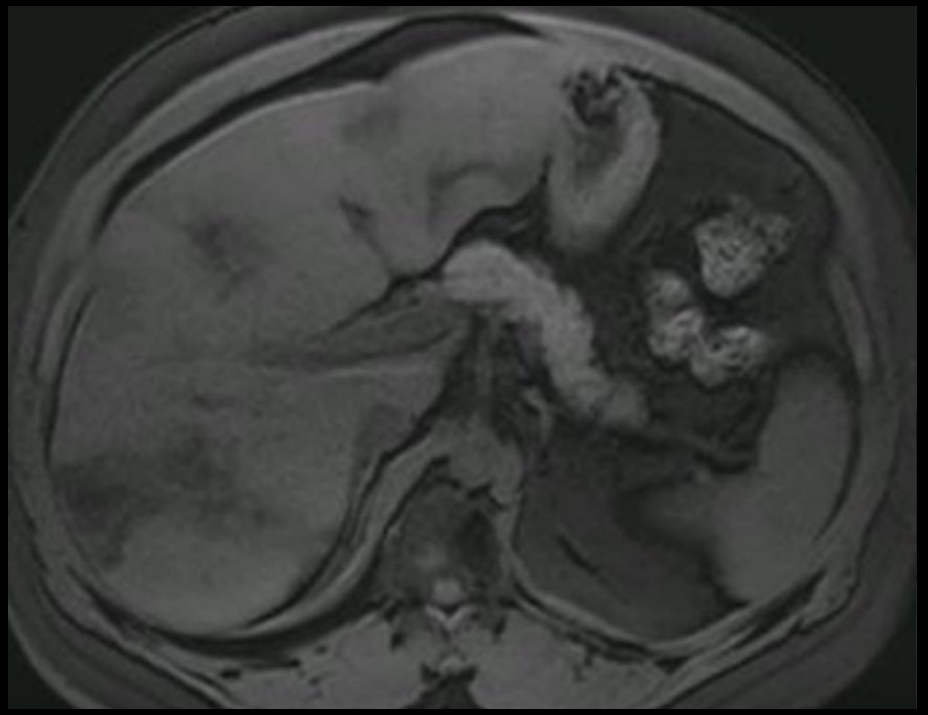
- MRI: Signal loss on out-of-phase T1-weighted images

Focal fat deposition CT



Focal fat deposition MR





Clinical considerations

Preoperative Assessment:

- Detecting CALI in future liver remnants is crucial

- Steatosis and steatohepatitis can be obstacles to surgical planning

- Patients with steatosis have higher postoperative morbidity and mortality

Blue Liver

Toxic injury to liver sinusoids causes sloughing of endothelial cells that embolize to hepatic venules and cause eventual fibrosis of the venules. This results in hepatic congestion (similar to Budd-Chiari syndrome) and post-sinusoidal portal hypertension.

Chemotherapeutics

- gemtuzumab, inotuzumab ozogomicin
- bleomycin, carmustine
- 6-thioguanine, vincristine
- oxaliplatin, carboplatin

Histological features of Blue Liver

- Early vascular alterations
- Progression to fibrosis
- Hepatocyte disruption and nodular regenerative hyperplasia NRH)

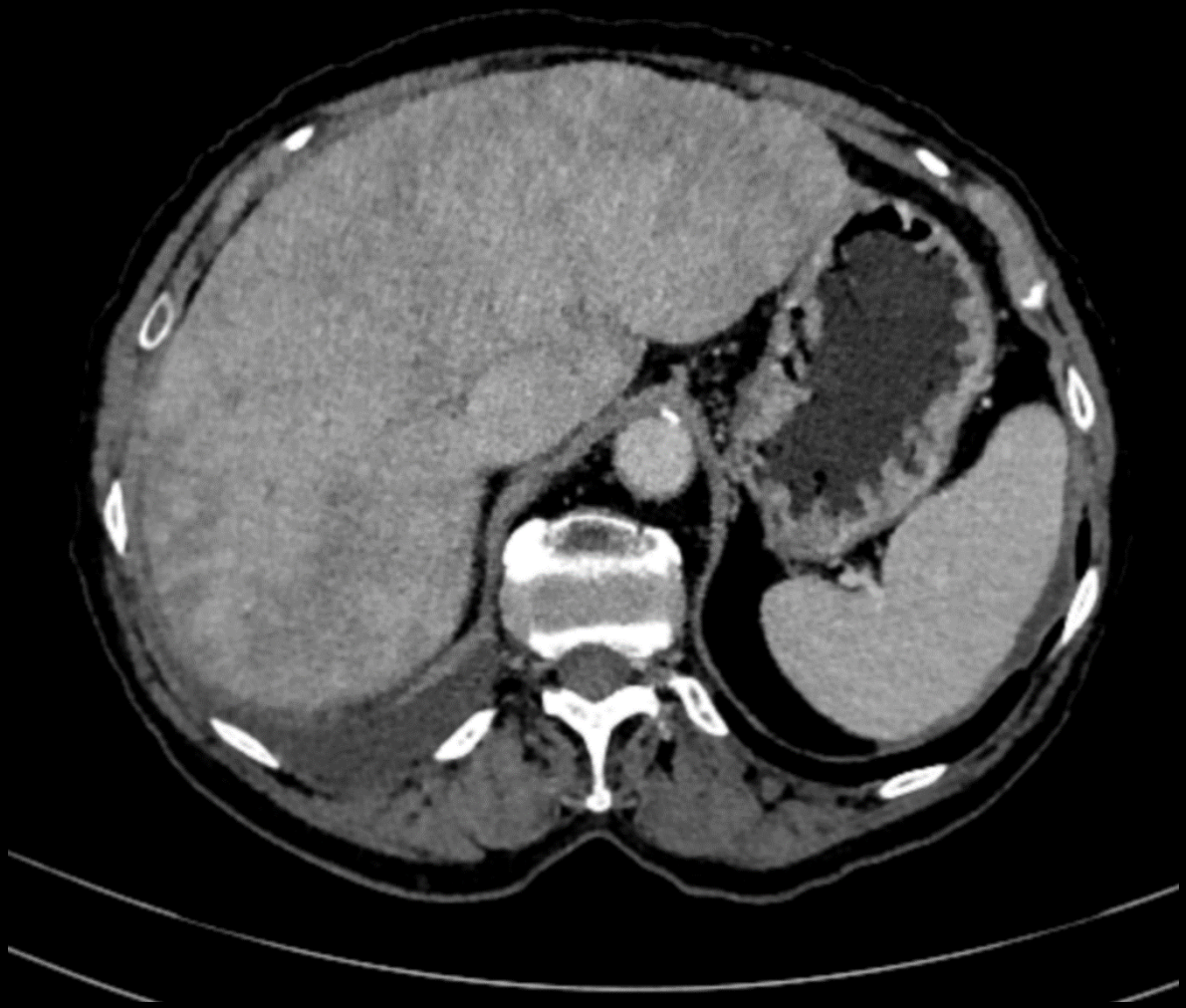
CT

- Hepatomegaly
- Nutmeg liver
- Portal vein dilatation
- Ascites

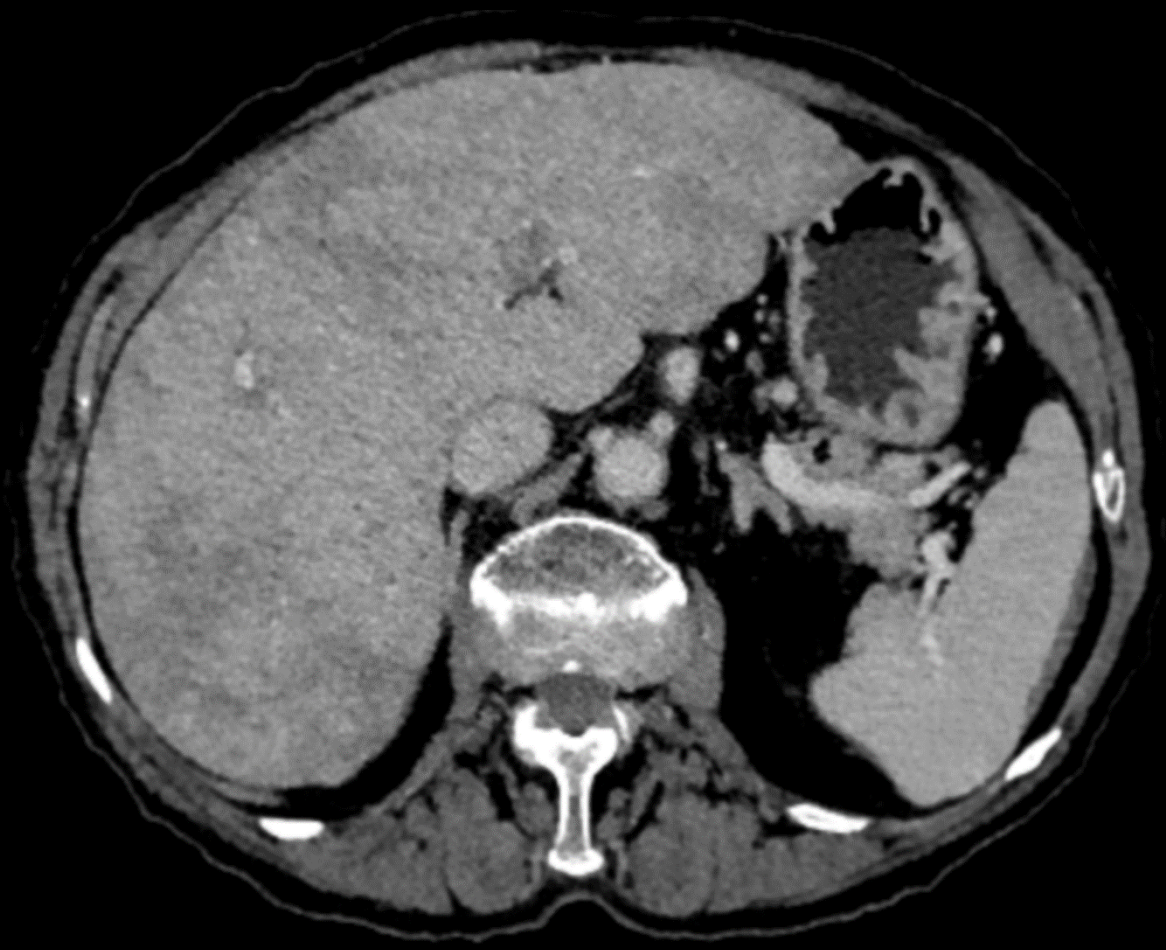
CT

- Hepatomegaly
- Nutmeg liver
- Portal vein dilatation
- Ascites

Imaging findings



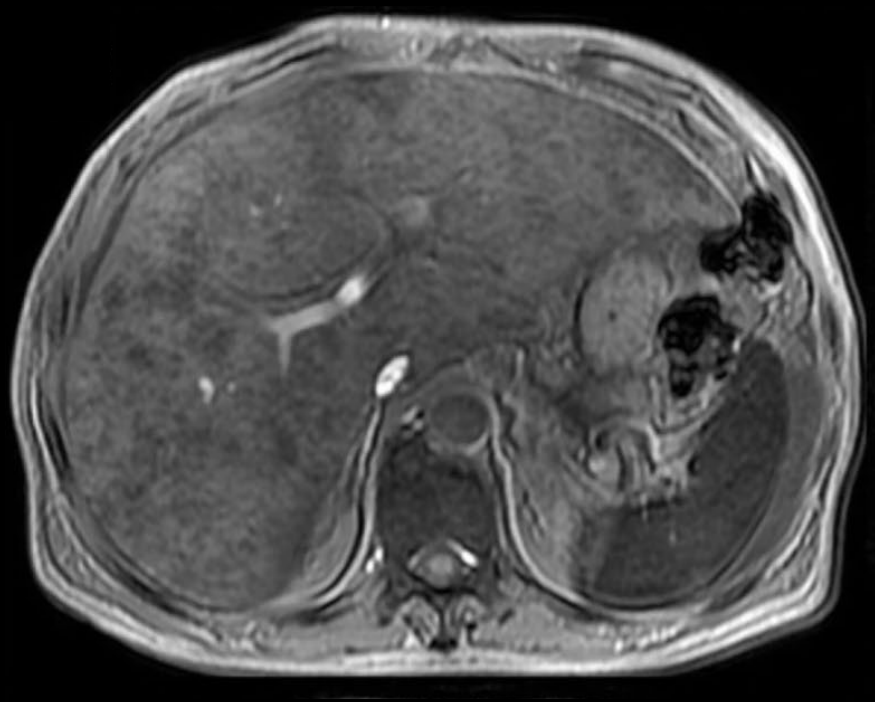
Imaging findings



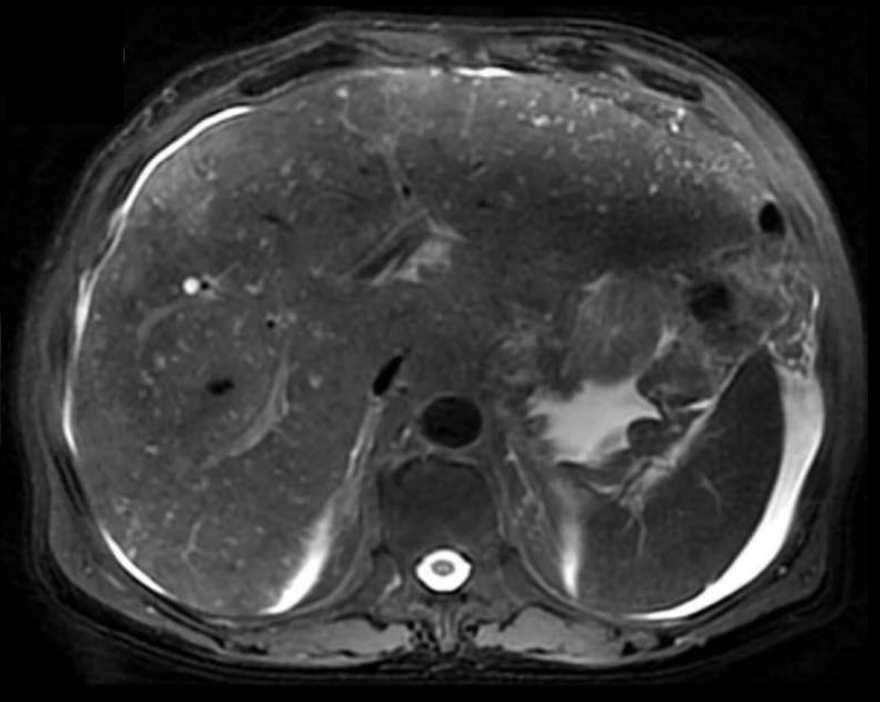
MRI

MRI studies with hepatocyte-specific contrast agent show a diffuse hypointense reticular pattern on post-contrast T1 delayed hepatobiliary phase as a highly specific sign for the diagnosis.

Unenhanced

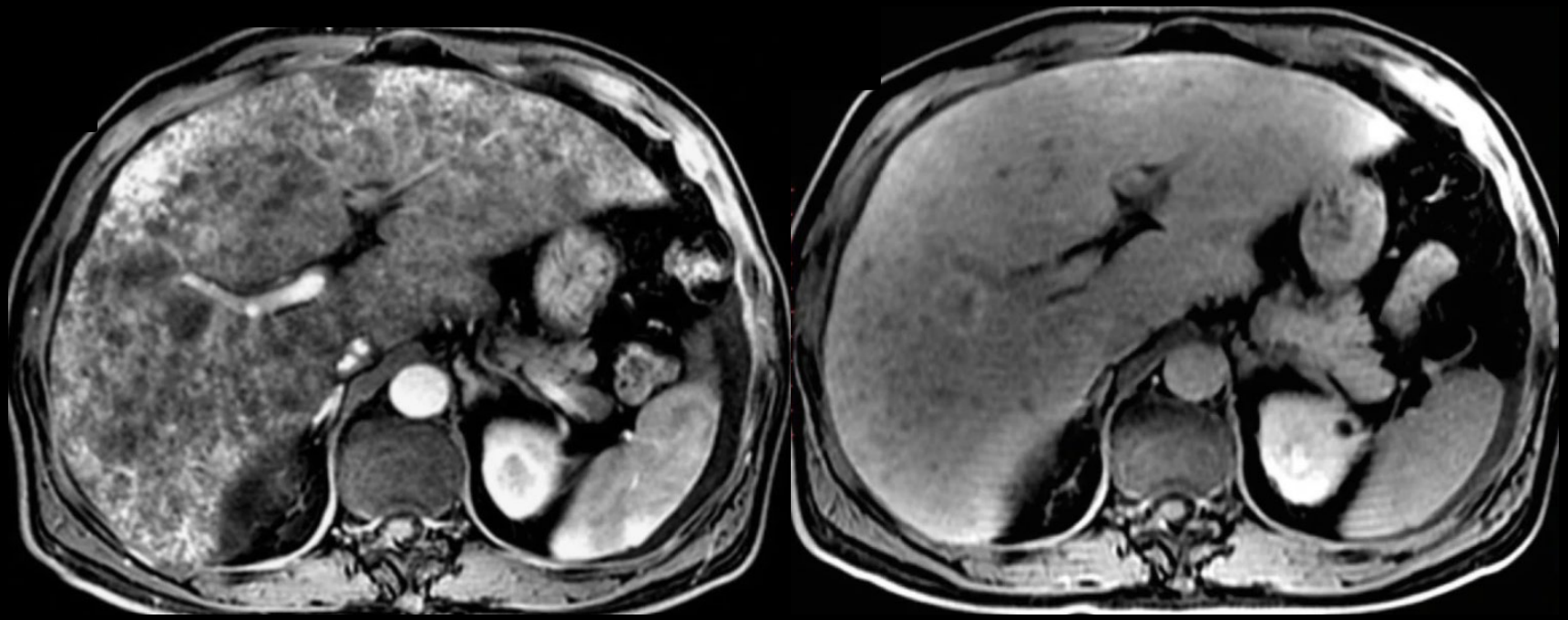


The T1-weighted image (T1WI) shows hepatomegaly, a non-uniform intensity of liver parenchyma with a patchy and nodular low-signal intensity of the liver.



The T2-weighted image (T2WI) shows a non-uniform signal intensity of liver parenchyma with a patchy and nodular high-signal intensity of the liver and ascites.

Portal and delayed



Portal phase contrast-enhanced MRI scan shows a significant heterogeneous enhancement of liver parenchyma with patchy and nodular lesions with decreased enhancement.

HBP of gadoxetic acid-enhanced MRI shows the signal intensity of liver parenchyma is slightly decreased and accompanied by the nodular lesions with lower-signal intensity.

Pseudoprogression

- Initial increased size of tumor lesions followed by a delayed partial response
- Biologic explanations:

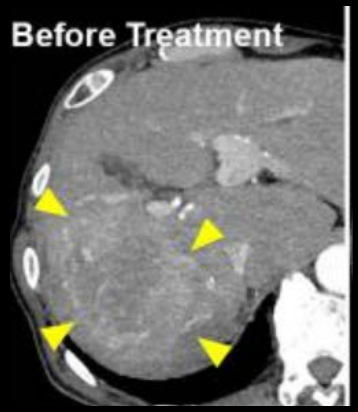
- Time required to mount an adaptive immune response
- Transient immune-cell infiltrate in the tumor bed

Pseudoprogression

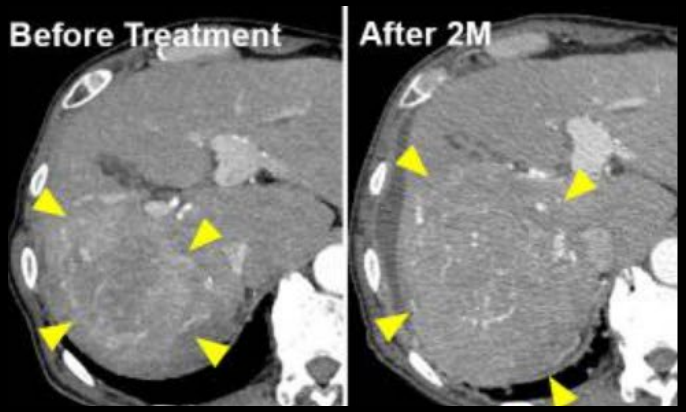
- Any time afterthe initiation of imunotherapy treatment, especially at around 12 weeks:

- Also observed much later, even after 15 cycles
- Some cases apear after cesation of imunotherapy treatment

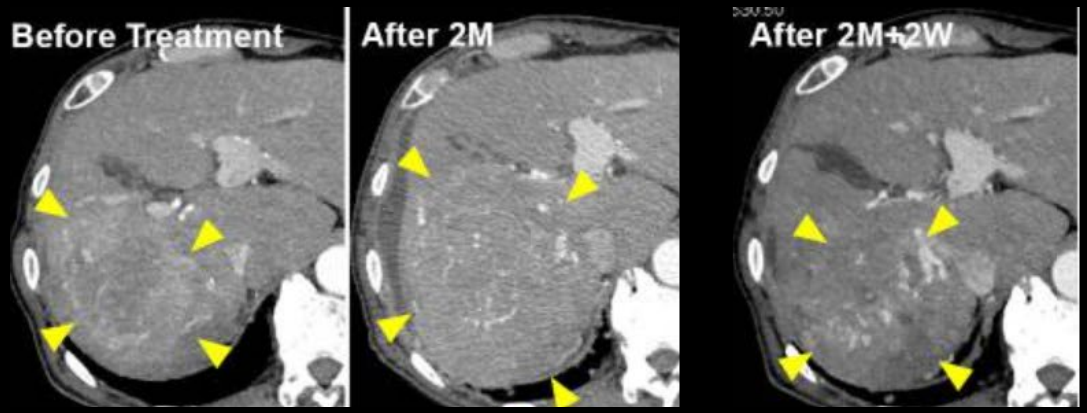
Pseudoprogression



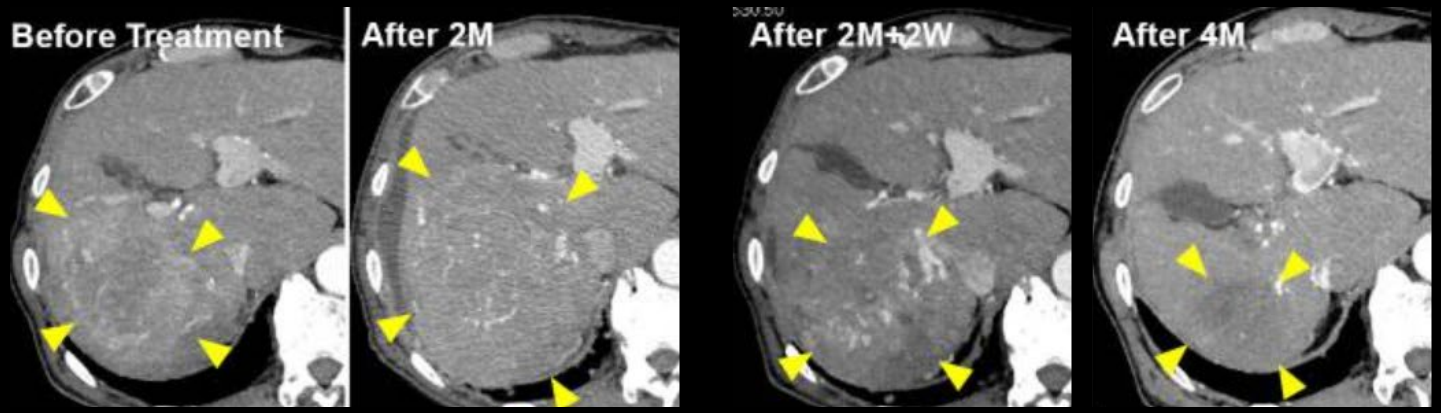
Pseudoprogression



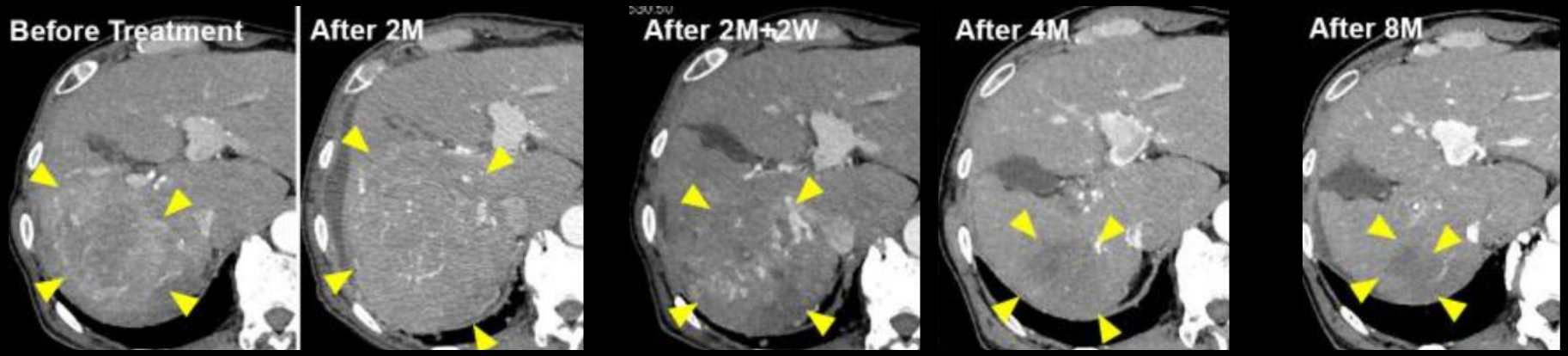
Pseudoprogression



Pseudoprogression



Pseudoprogression



Conclusion

- RECIST 1.1 is the gold standard for clinicians and researchers, guiding patient care and clinical trial endpoints. It remains crucial across all stages of anticancer therapy.
- mRECIST, focusing on tumor viability, is gaining recognition and could become a viable alternative to RECIST.
- Imaging is essential in HCC tumor ablation, helping recognize features essential for proper management.
- Radiologists play a key role in identifying imaging patterns, supporting therapeutic decisions, and preventing severe complications in patients with chemotherapy-associated liver injury.

THANK YOU