2024 PARIS HEPATOLOGY CONFERENCE 16

Hybrid PHC 2024
Institut Pasteur - Paris
18 - 19 March

FHU MOSAIC

Tuesday March 19, 2024

HCC – SESSION 1: DIAGNOSIS AND STAGING

Towards multiscale imaging of HCC

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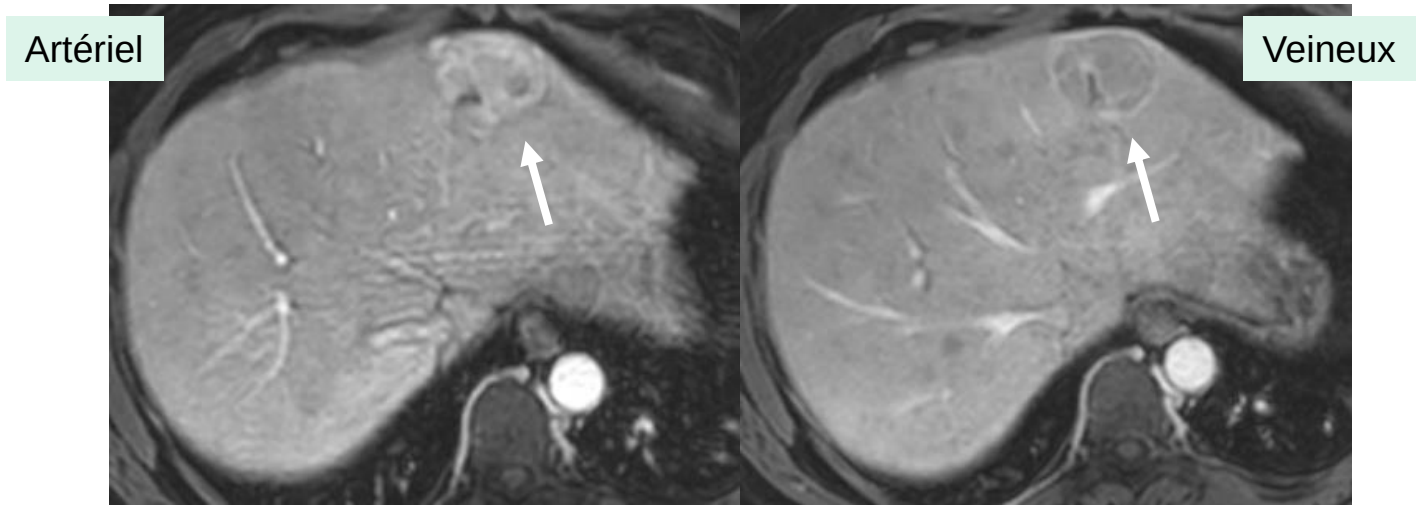
Radiology - Pathology
Hôpital Beaujon, Clichy, France

Hôpital Beaujon AP-HP

A debate? What debate?

Non-invasive diagnosis is the standard!



Untreated observation without pathologic proof in patient at high risk for HCC

- If cannot be categorized due to image degradation or omission → LR-NC
- If definite tumor in vein (TIV) → LR-TIV
- If definitely benign → LR-1
- If probably benign → LR-2
- If probably or definitely malignant but not HCC specific (e.g., if targetoid) → LR-M

Otherwise, use CT/MRI diagnostic table below

- If intermediate probability of malignancy → LR-3
- If probably HCC → LR-4
- If definitely HCC → LR-5

Arterial phase hyperenhancement (APHE)		No APHE		Nonrim APHE		
Observation size (mm)		< 20	≥ 20	< 10	10-19	≥ 20
Count additional major features: • Enhancing "capsule" • Nonperipheral "washout" • Threshold growth	None	LR-3	LR-3	LR-3	LR-3	LR-4
	One	LR-3	LR-4	LR-4	LR-4/LR-5	LR-5
	≥ Two	LR-4	LR-4	LR-4	LR-5	LR-5

LR-4/LR-5

Observations in this cell are categorized based on one additional major feature:
- LR-4 – if enhancing "capsule"
- LR-5 – if nonperipheral "washout" **OR** threshold growth

If unsure about the presence of any major feature: characterize that feature as absent

Applies to high-risk patients

✓

Applies to patients with

- Cirrhosis **OR**
- Chronic HBV infection **OR**
- History or current HCC

✗

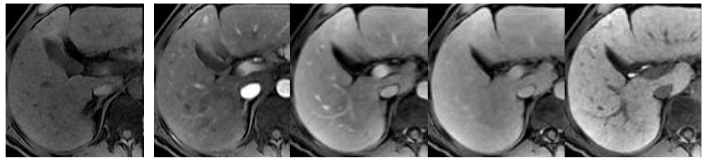
Does NOT apply to patients

- without risk factors
- < 18 years old
- Vascular / Malformative / Congenital Diseases

Standardisation

Standardisation

- **Terminology**
- **Technique**
- **Interpretation**
- **Reporting**
- **Data**



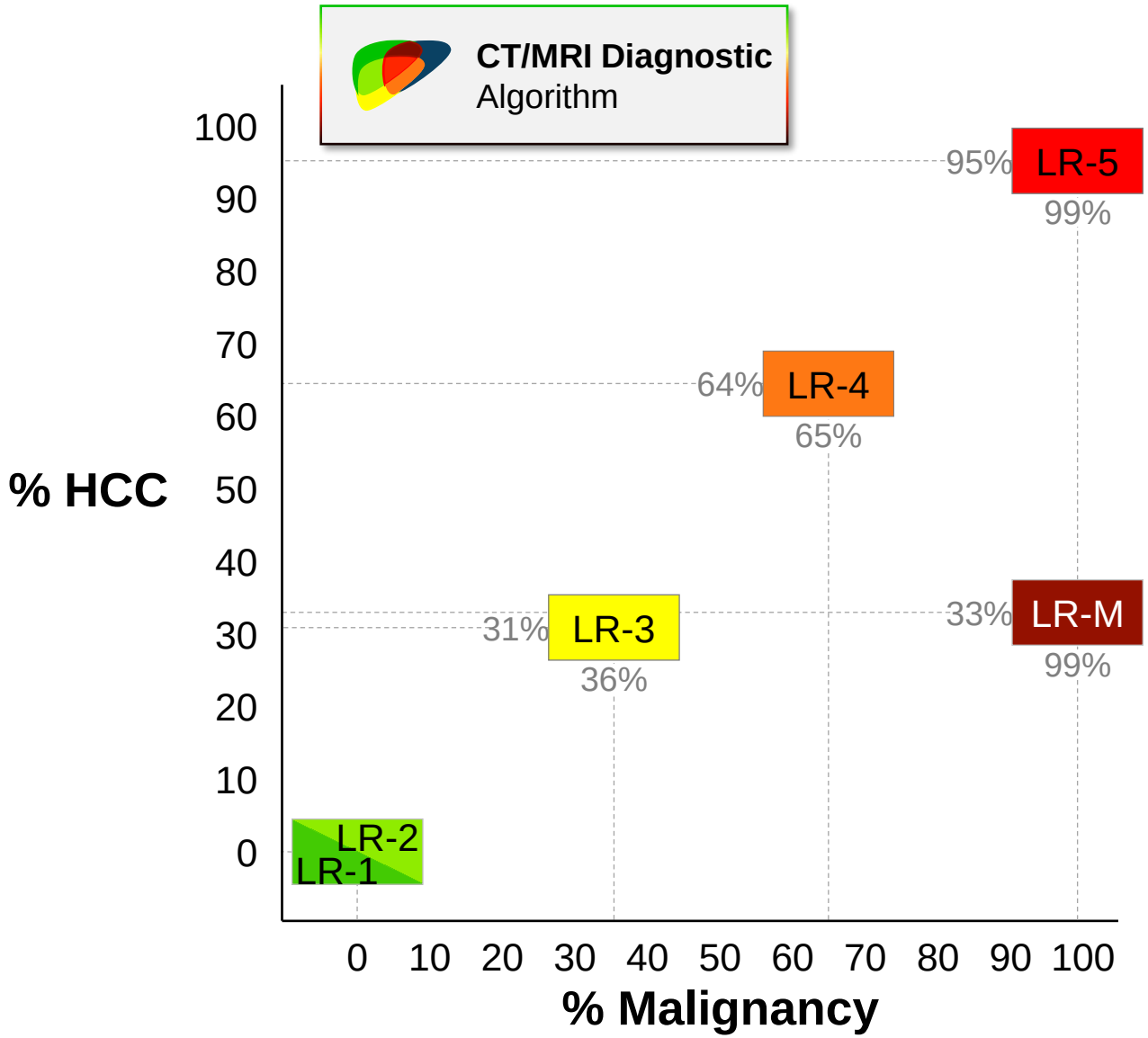
CT/MRI Diagnostic Table

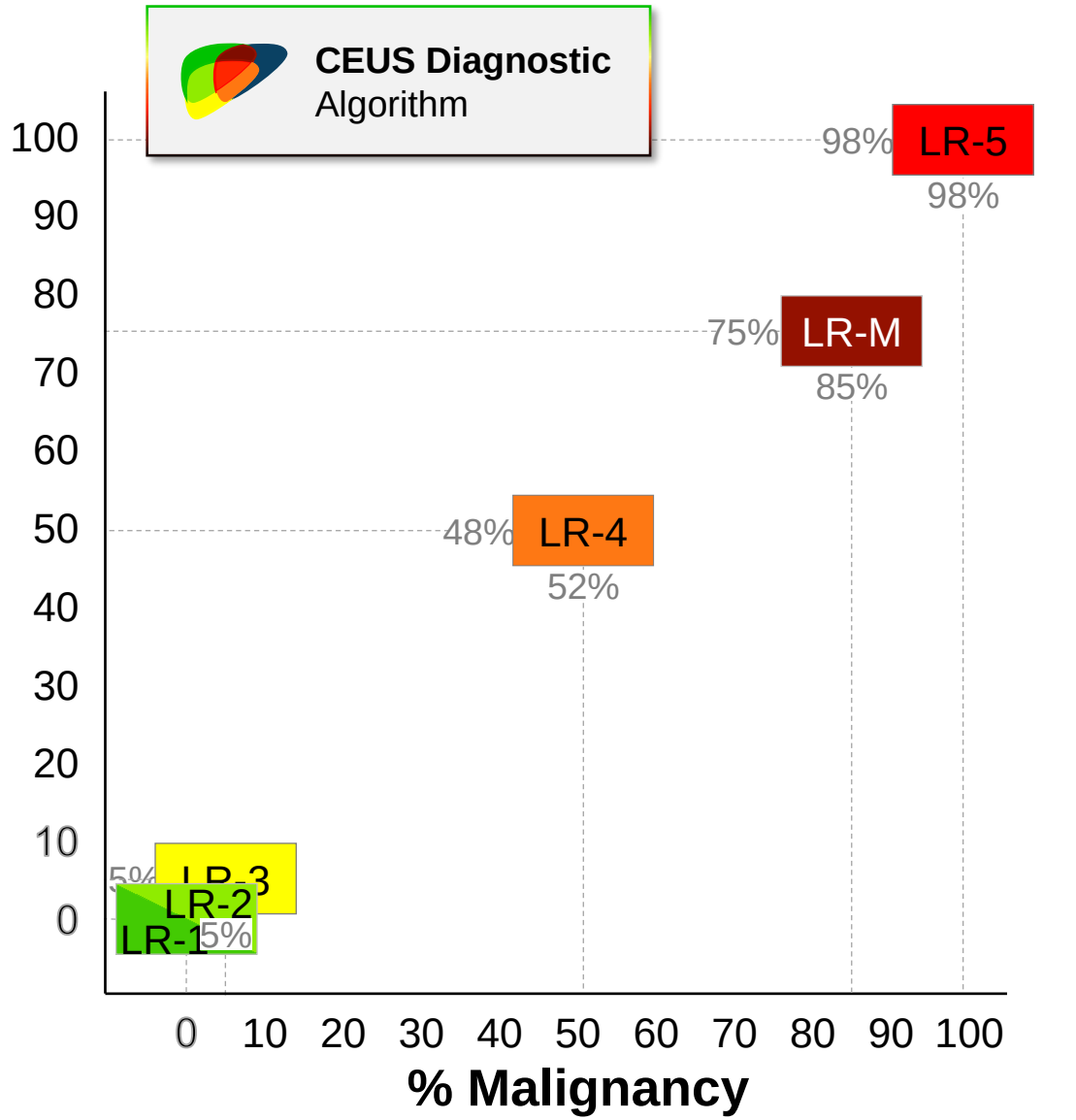
Arterial phase hyperenhancement (APHE)		No APHE		Nonrim APHE		
Observation size (mm)		< 20	≥ 20	< 10	10-19	≥ 20
Count additional major features:	None	LR-3	LR-3	LR-3	LR-3	LR-4
•Enhancing "capsule" •Nonperipheral "washout" •Threshold growth	One	LR-3	LR-4	LR-4	LR-4 / LR-5	LR-5
	≥ Two	LR-4	LR-4	LR-4	LR-5	LR-5

Observation #: 1/2/3/4/5
Location: Segment I/II/III/IVa/IVb/V/VI/VII/VIII
Size: [] x [] [mm/cm] (image # [], series [])
Tumor in Vein: [No/Yes (*describe the involved vessels*)]
LR-M Features: [None/*List all that apply*]
Nonrim AP hyperenhancement: [Yes/No]
Threshold growth: [Yes/No/Not applicable]
Nonperipheral washout appearance: [Yes/No]
Enhancing capsule appearance: [Yes/No]
Ancillary features:
Favoring benignity: [None/*List all that apply*]
Favoring malignancy: [None/*List all that apply*]
LI-RADS v2018 Category: [NC/1/2/3/4/5/TIV/M]

Lexicon

It works!





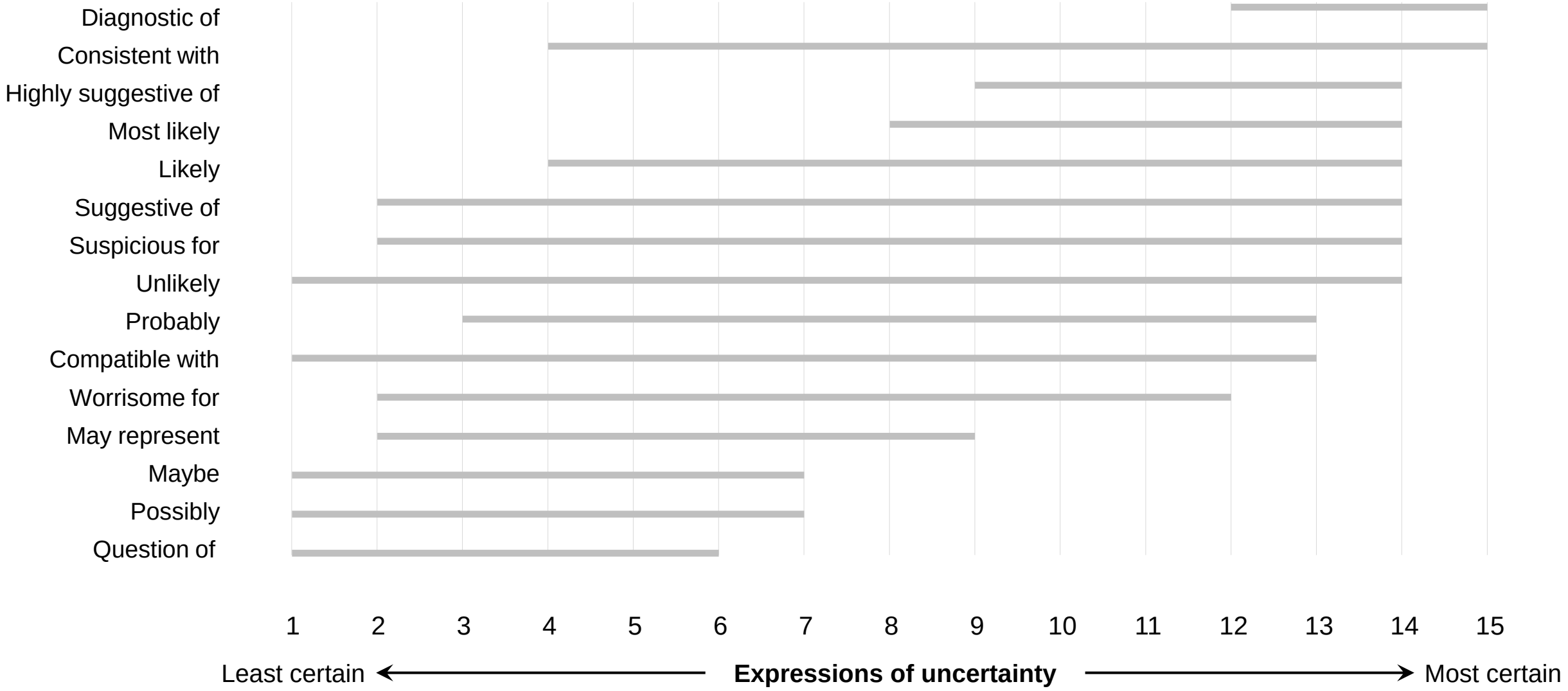
Lee et al *JACR* 2020 PMID 32640250

Huang Radiology 2020 31793849

It works!

	Sensitivity		Specificity	
	EASL	LI-RADS 5	EASL	LI-RADS 5
Clarke Clin Radiol 2021 PMID 33461746	44	45	86	89
Hwang Eur Radiol 2021 PMID 33409787	54	63	93	94
Park Eur Radiol 2021 PMID 33389037	68	71	94	94
Jeon Eur Radiol 2020 PMID 32333148	39	35	92	97
Byun Hepatol Int 2020 PMID 32314171	63	64	90	95
Lee Hepatol Int 2020 PMID 31802388	72	79	85	90
Erkan PLoS One 2019 PMID 31821360	88	90	86	89

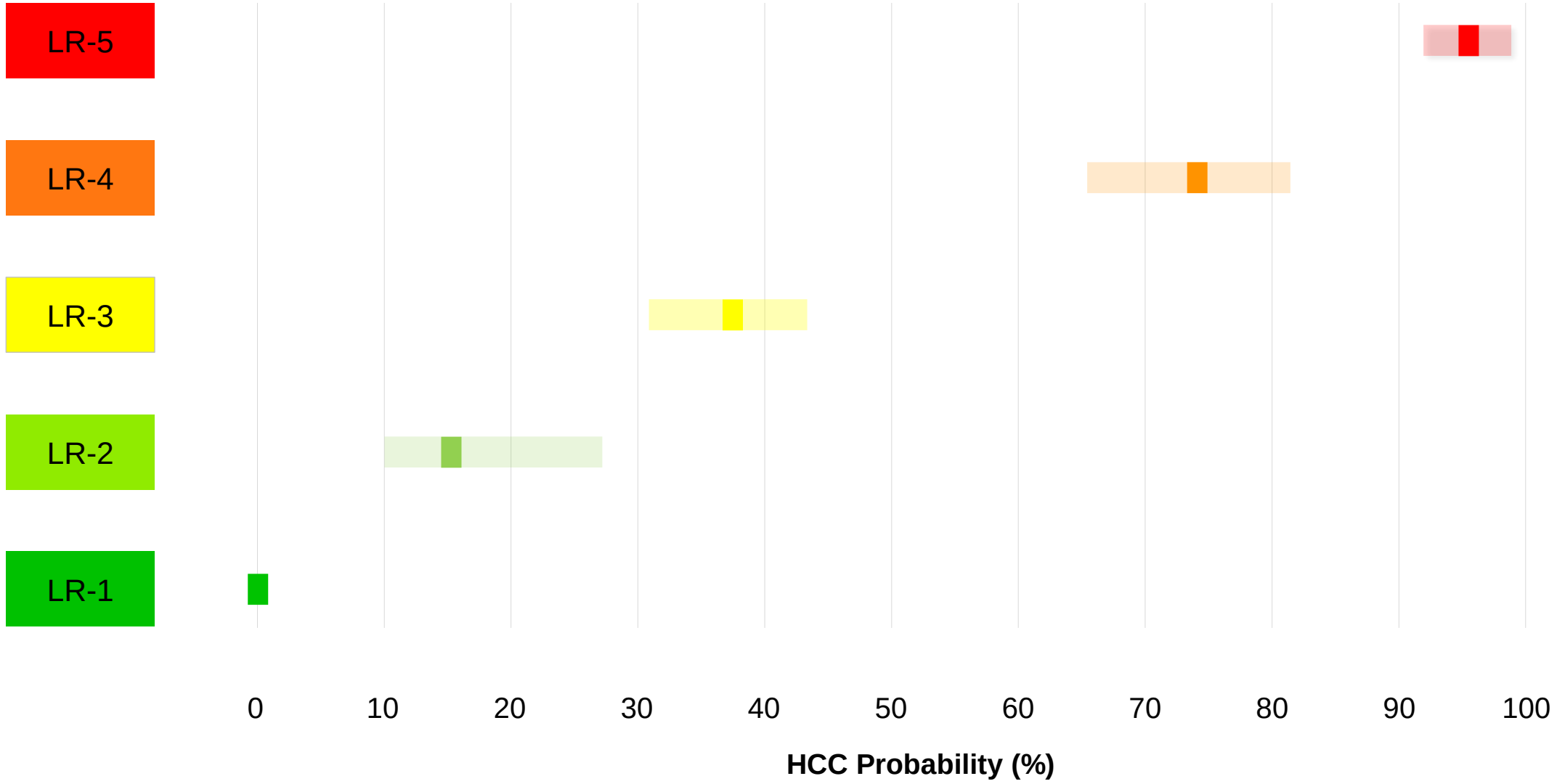
Less confusion



Slide courtesy of An Tang; Adapted from: Khorasani R Acad Radiol 2003

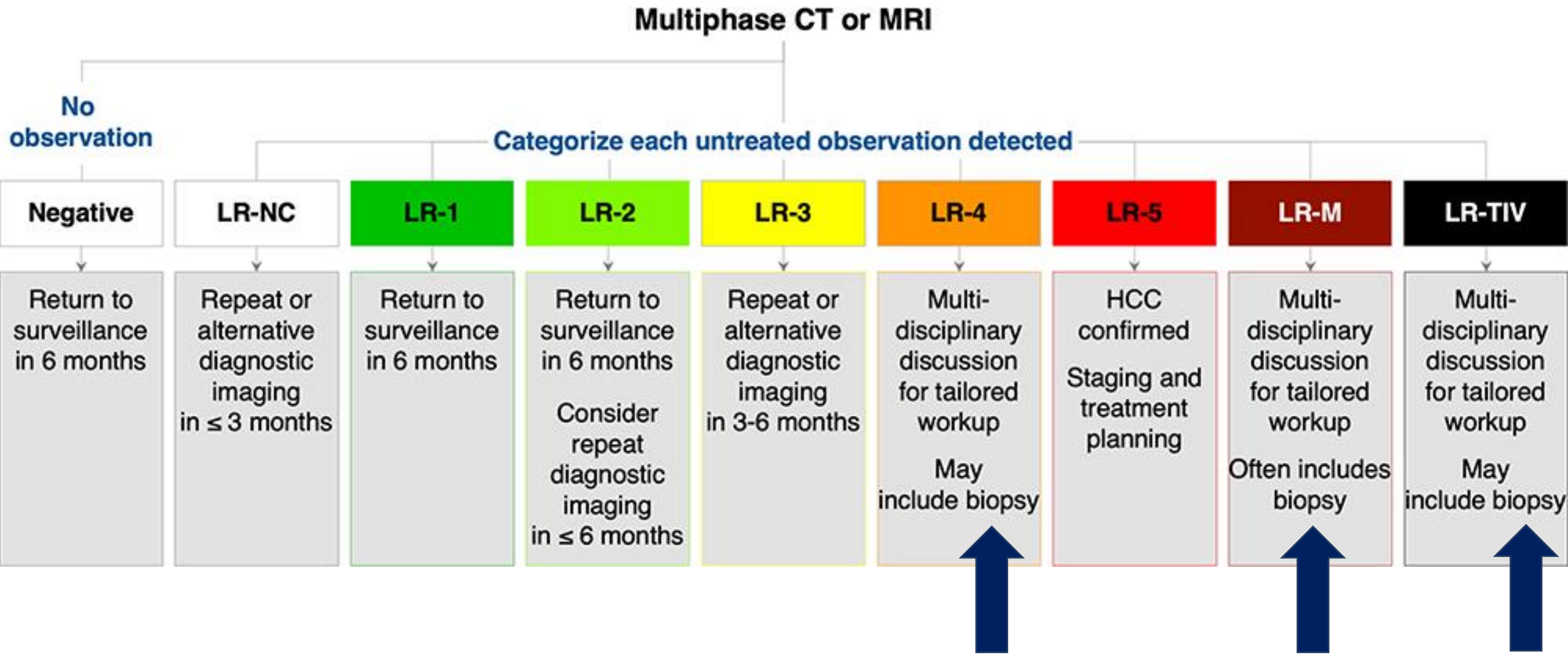
LI-RADS

Facilitates communication



Slide courtesy of An Tang

Biopsy for atypical cases!



Always biopsy!

How ? For what ?

≥ 19 Gauge
Image-based guidance

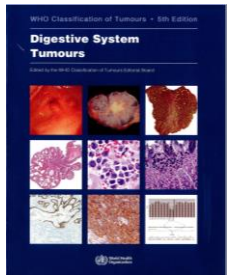
Tumor and non-tumoral liver

Standard stainings and
Immunohistochemistry

Not one but several HCCs !

Intertumoral heterogeneity

8 morphological subtypes

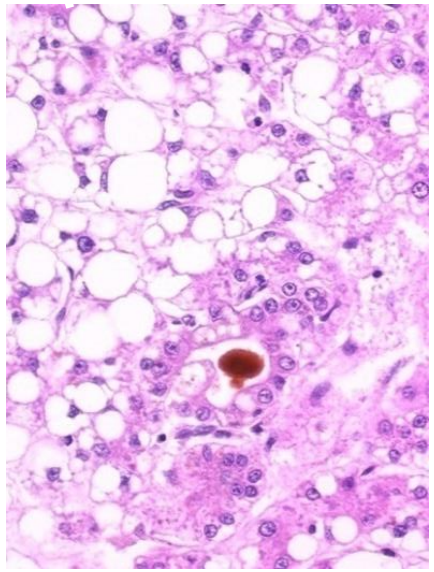


Always biopsy!

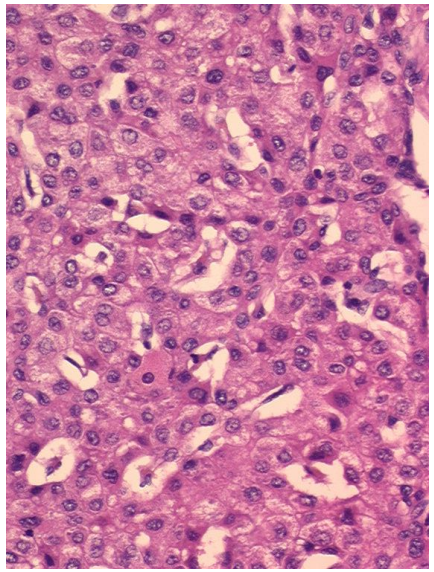
Biopsy is more than just diagnosis!

Tumor differentiation

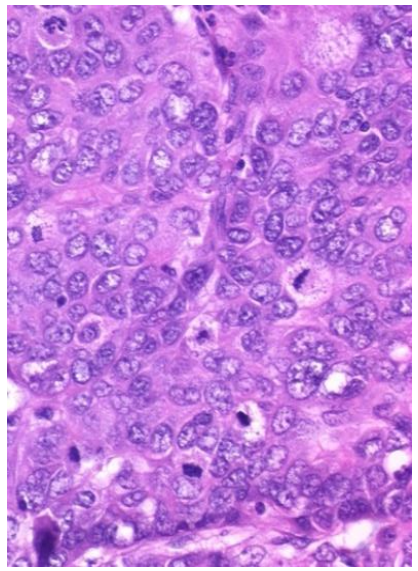
Well



Moderately



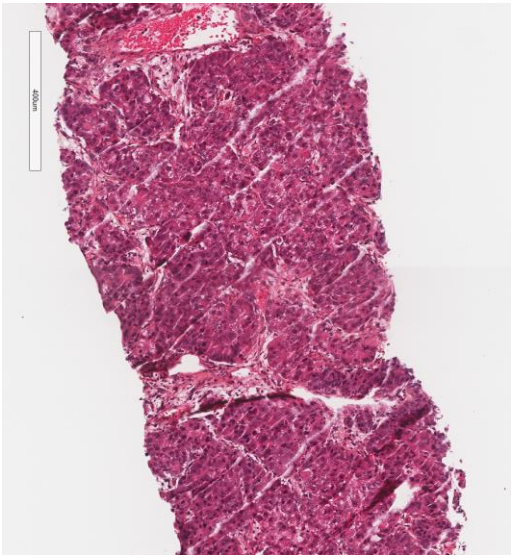
Pooly



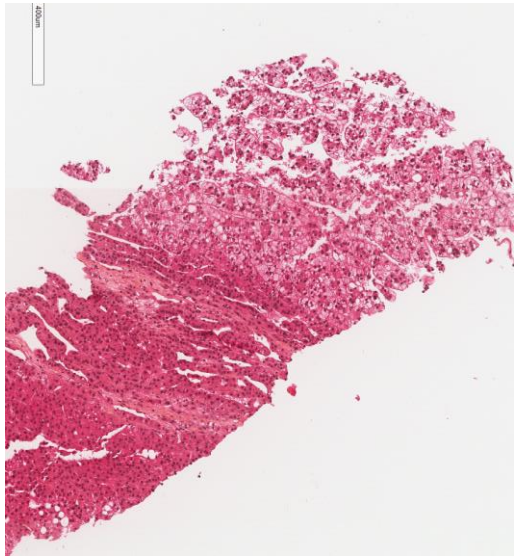
Prognosis

Intratumoral heterogeneity

Macrotrabecular architecture



Microtrabecular architecture & clear cells



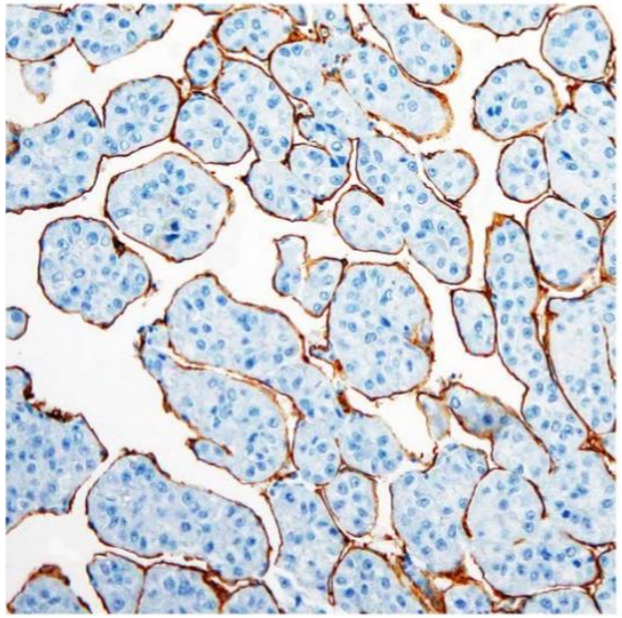
Prognosis

Always biopsy!

Biopsy is more than just diagnosis!

VETC (Vessels Encapsulating Tumor Clusters)

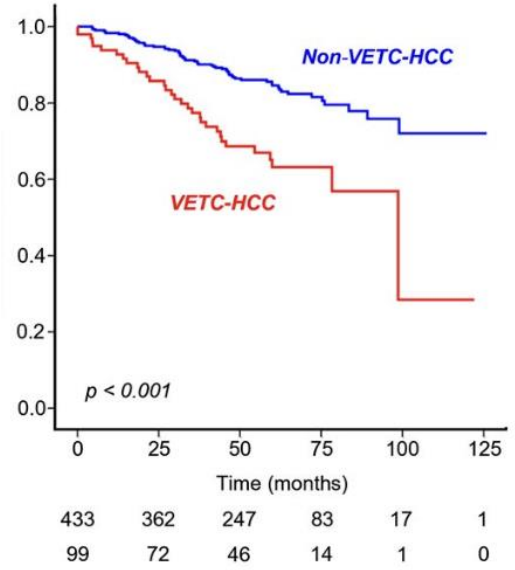
CD34



>55% of tumor area

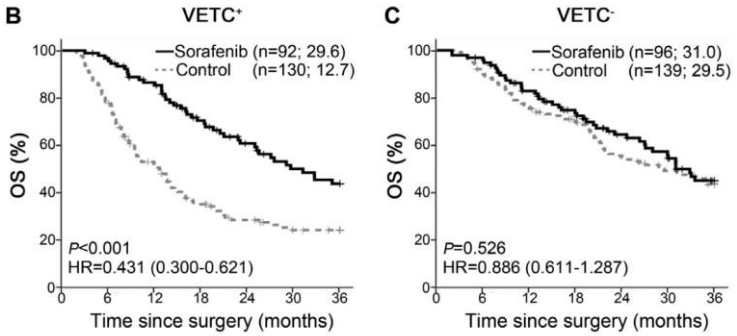
Vessels Encapsulating Tumor Clusters (VETC) Is a Powerful Predictor of Aggressive Hepatocellular Carcinoma

Overall survival



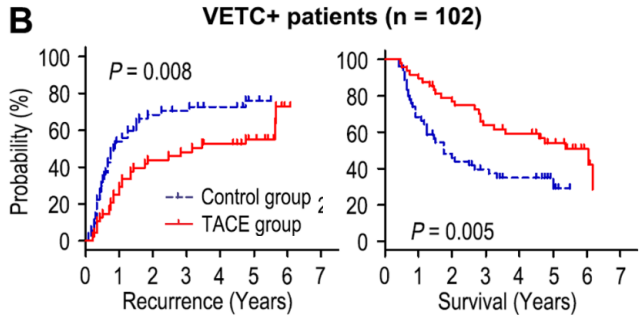
Renne SL Hepatology 2020

Vessels That Encapsulate Tumor Clusters (VETC) Pattern Is a Predictor of Sorafenib Benefit in Patients with Hepatocellular Carcinoma



Fang JH Hepatology 2019

Vessels that encapsulate tumor clusters (VETC) pattern predicts the efficacy of adjuvant TACE in hepatocellular carcinoma



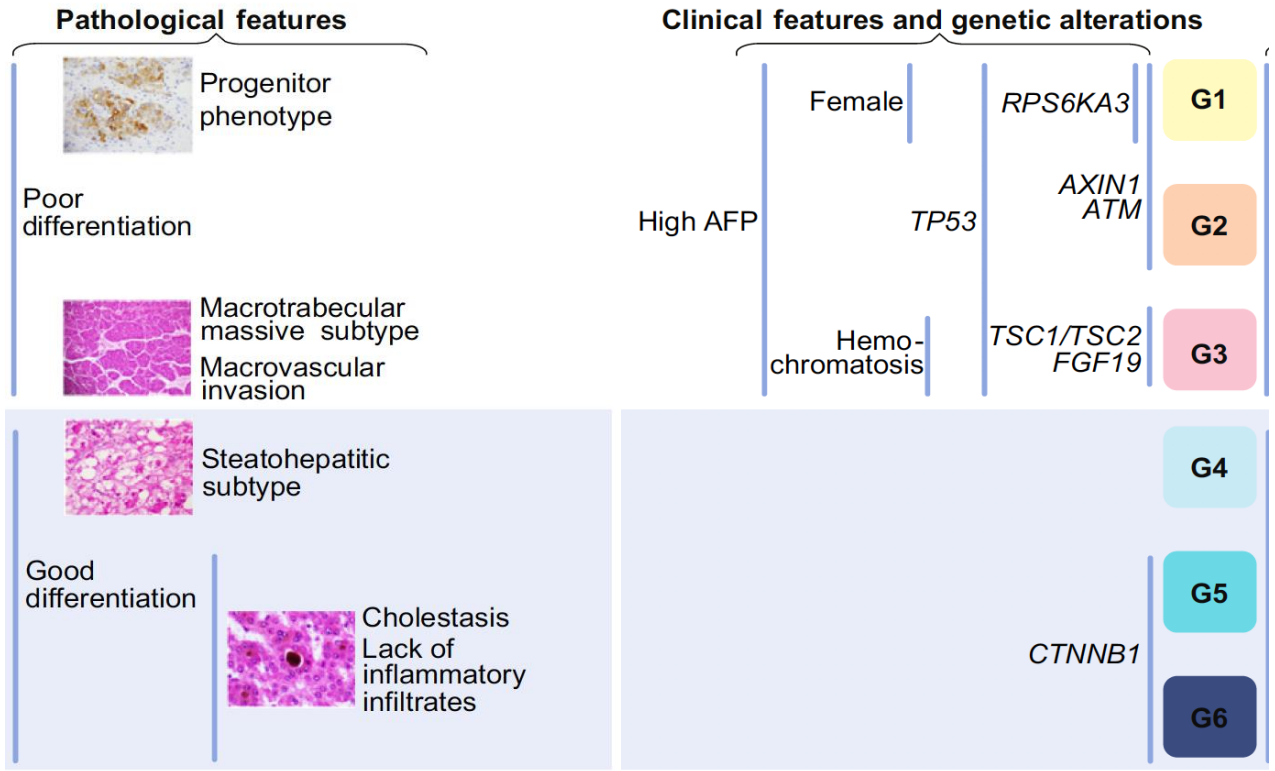
Wang JH J Cancer Res Clin Oncol 2022

Correlated with microvascular invasion, AFP, tumor size, Macrotrabecular HCC subtype

Always biopsy!

Pathomolecular Classification

Histological subtypes of hepatocellular carcinoma are related to gene mutations and molecular tumour classification☆

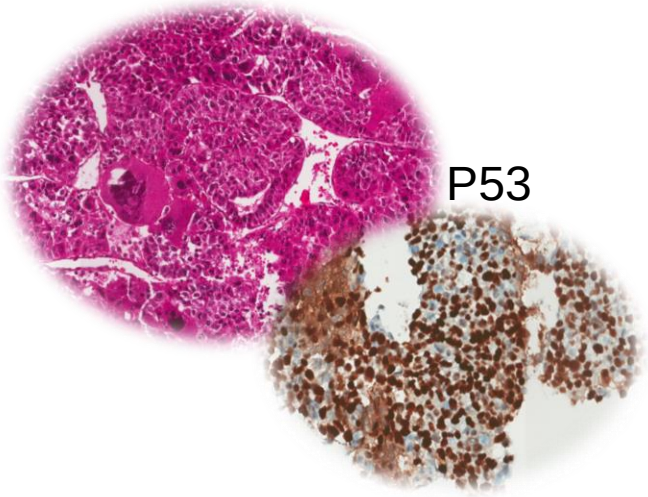


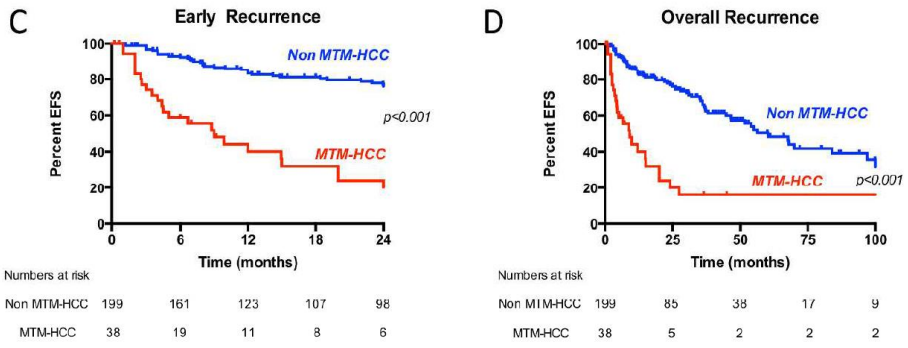
Calderaro J J Hepatol 2017

Always biopsy!

Different prognosis

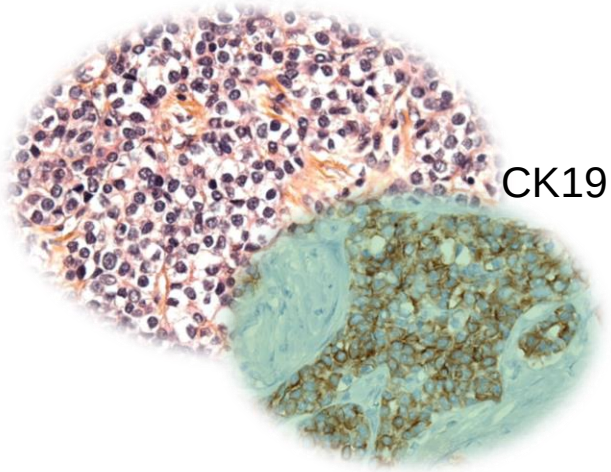
Macrotrabecular / Massive HCC

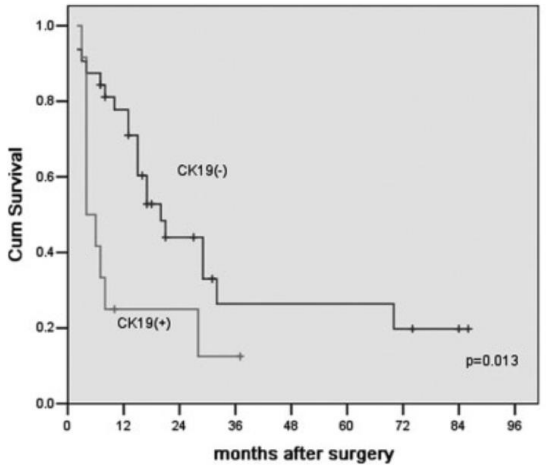




Ziol M Hepatology 2017

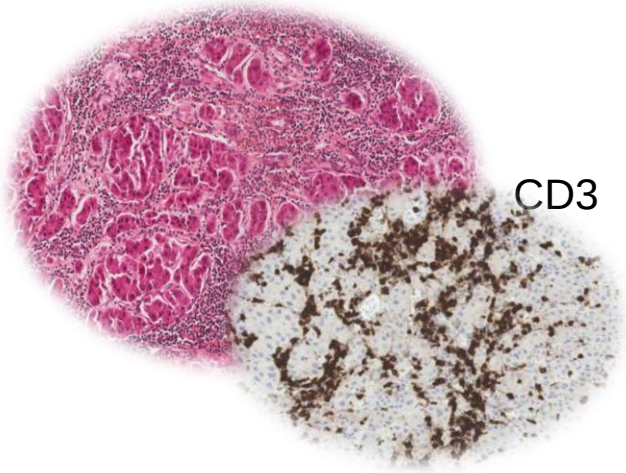
Progenitor HCC

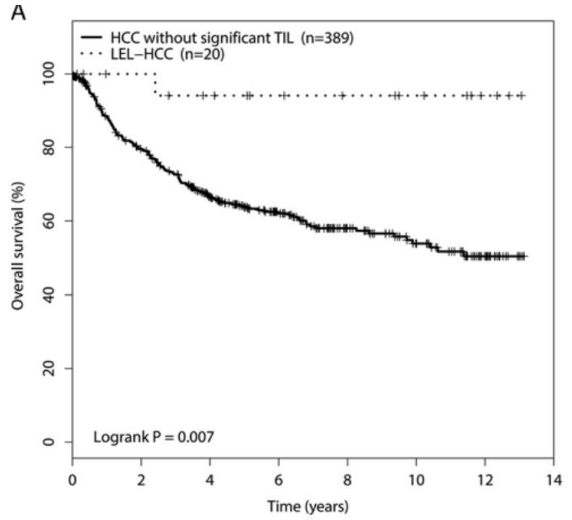




Durnez Histopathology 2006

Lymphoepithelioma-like HCC





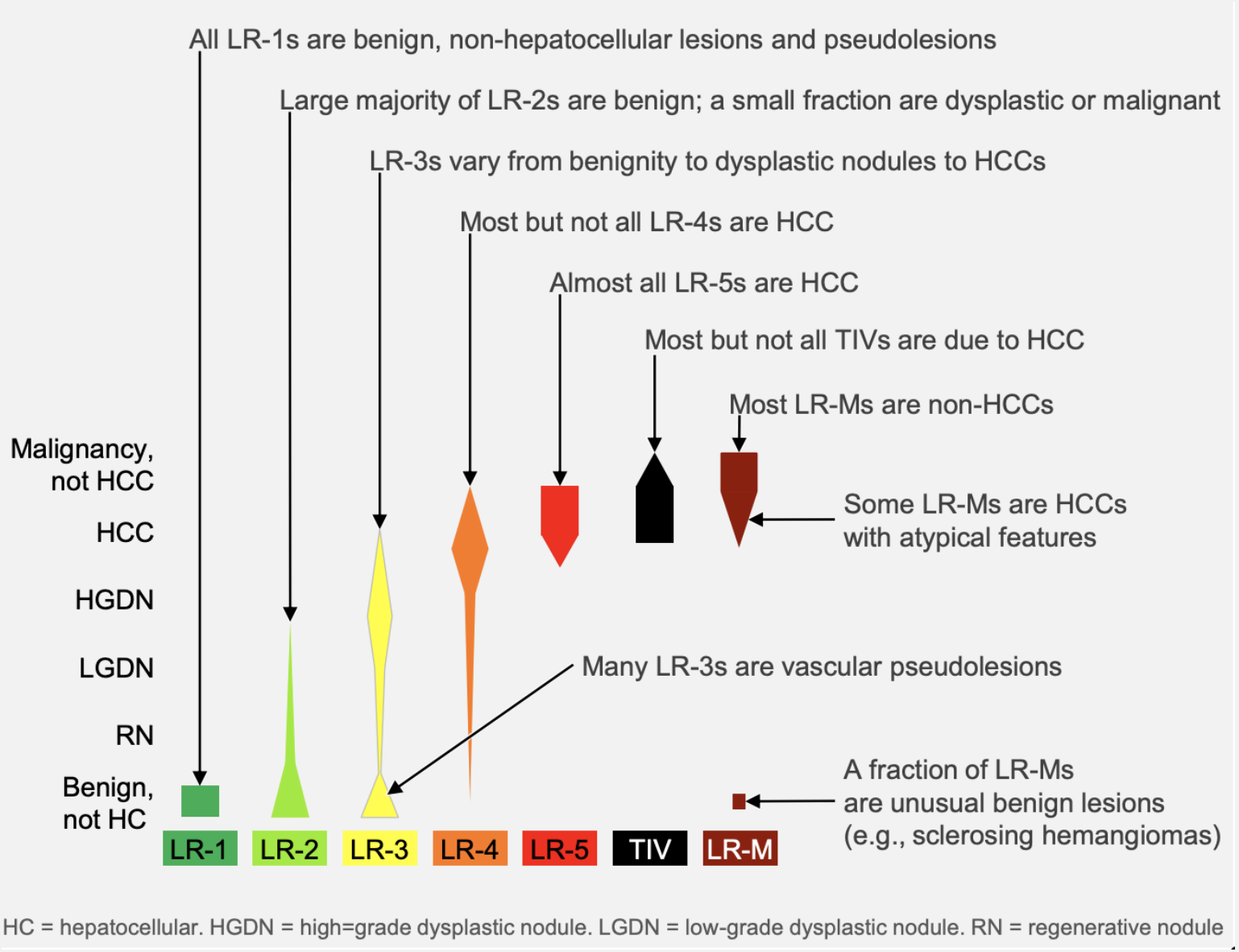
Chan AWH Am J Surg Pathol 2015

But …

Pathomolecular Classification

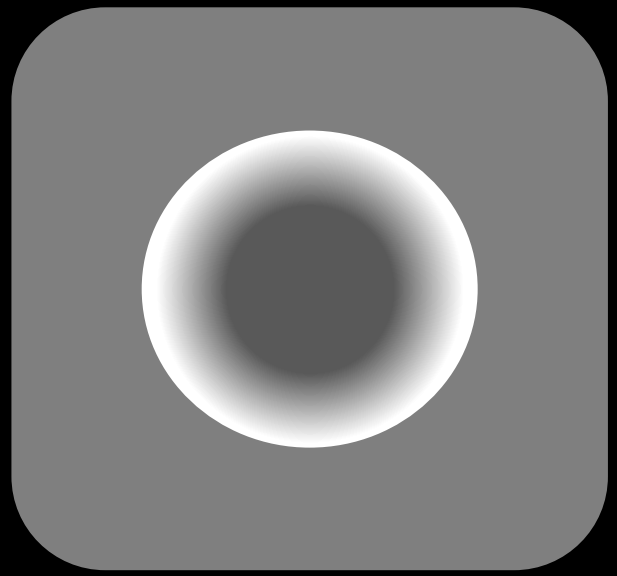
No actionable mutations

Heterogeneity underestimated in imaging?



https://www.acr.org/-/media/ACR/Files/RADS/LI-RADS/LI-RADS-2018-Core.pdf?%20la=en

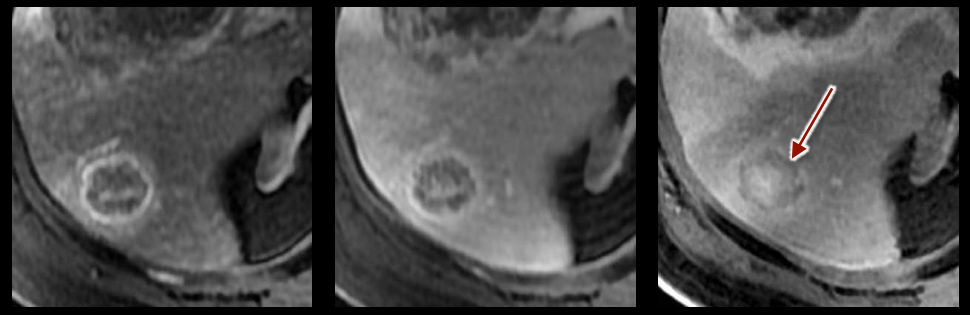
Proliferative forms



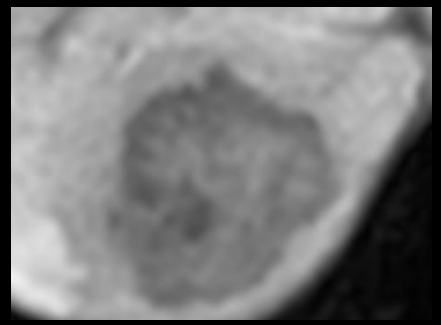
Targetoid

Arterial

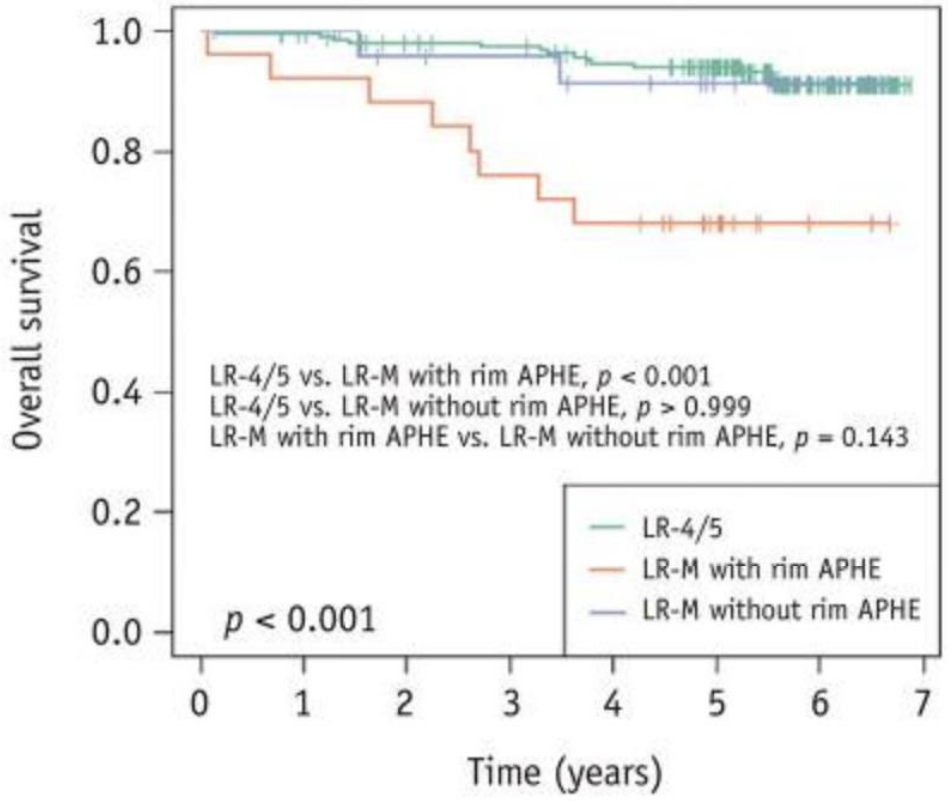
Venous



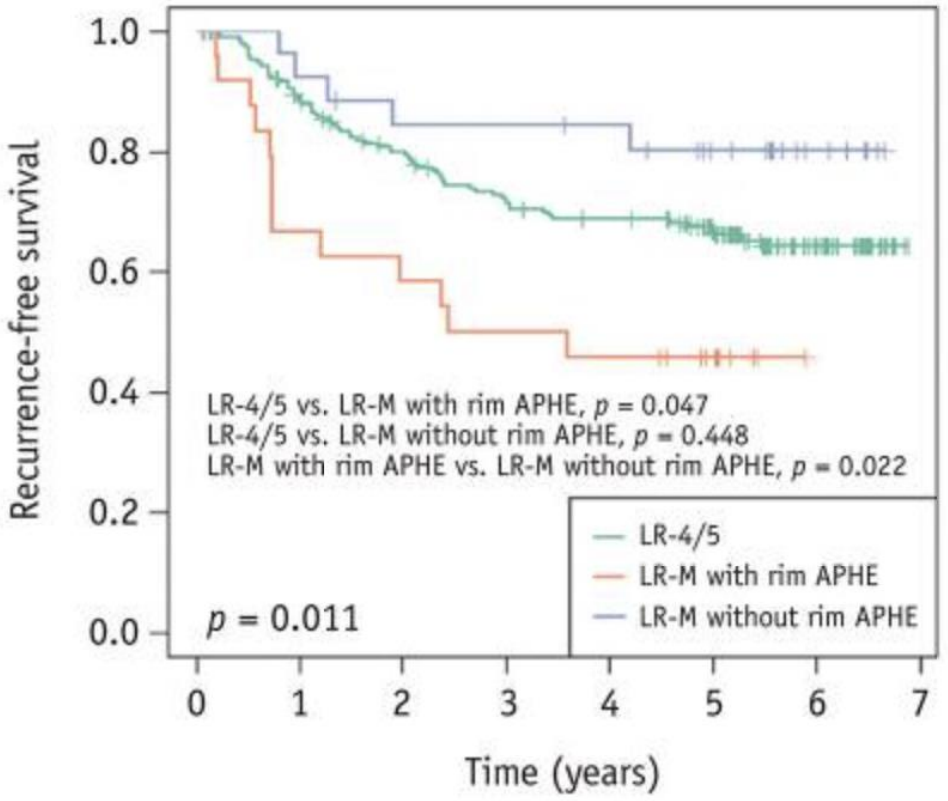
HBP



Targetoid appearance



No. at risk								
LR-4/5	190	185	176	173	164	134	58	0
LR-M with rim APHE	25	23	22	19	17	11	2	0
LR-M without rim APHE	27	26	22	21	19	15	6	0



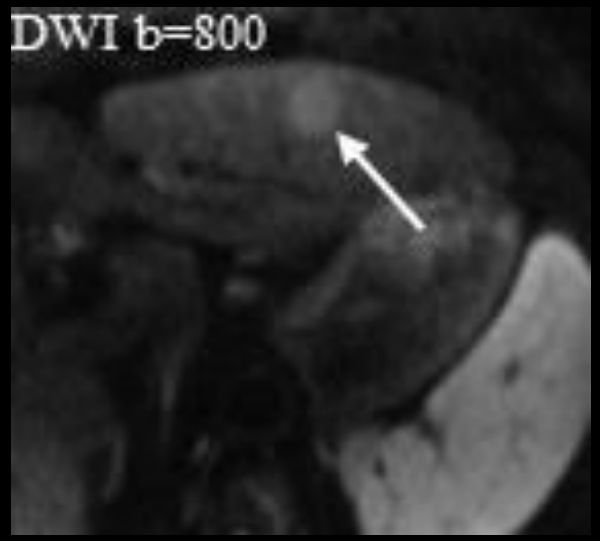
No. at risk								
LR-4/5	190	163	143	127	119	93	40	0
LR-M with rim APHE	25	16	14	12	11	7	0	0
LR-M without rim APHE	27	24	21	21	20	15	6	0

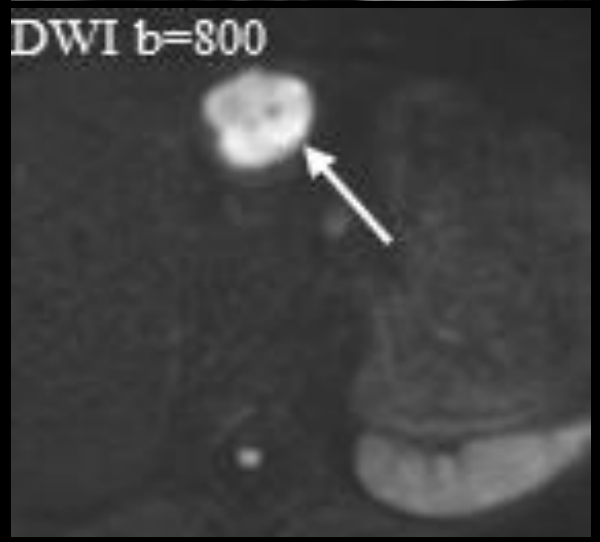
Moon KJR 2021

Prognosis

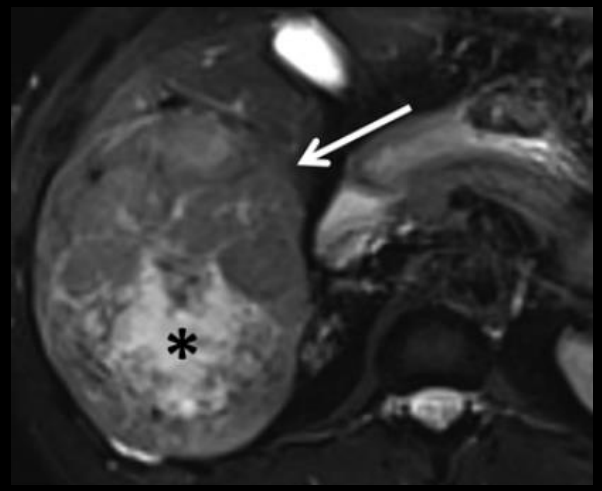
Other features

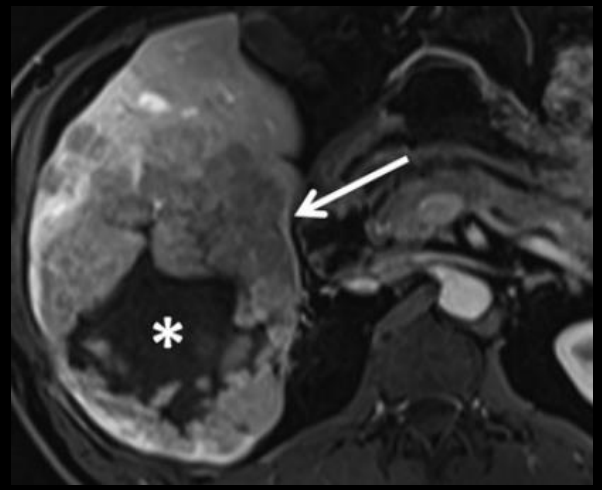
Marked Diffusion Restriction



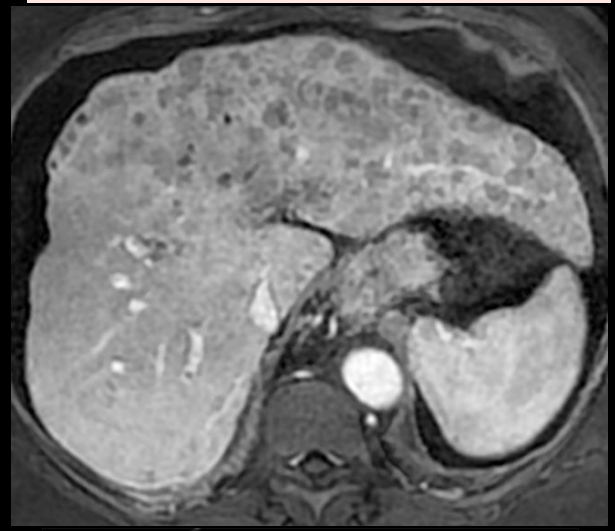


Necrosis





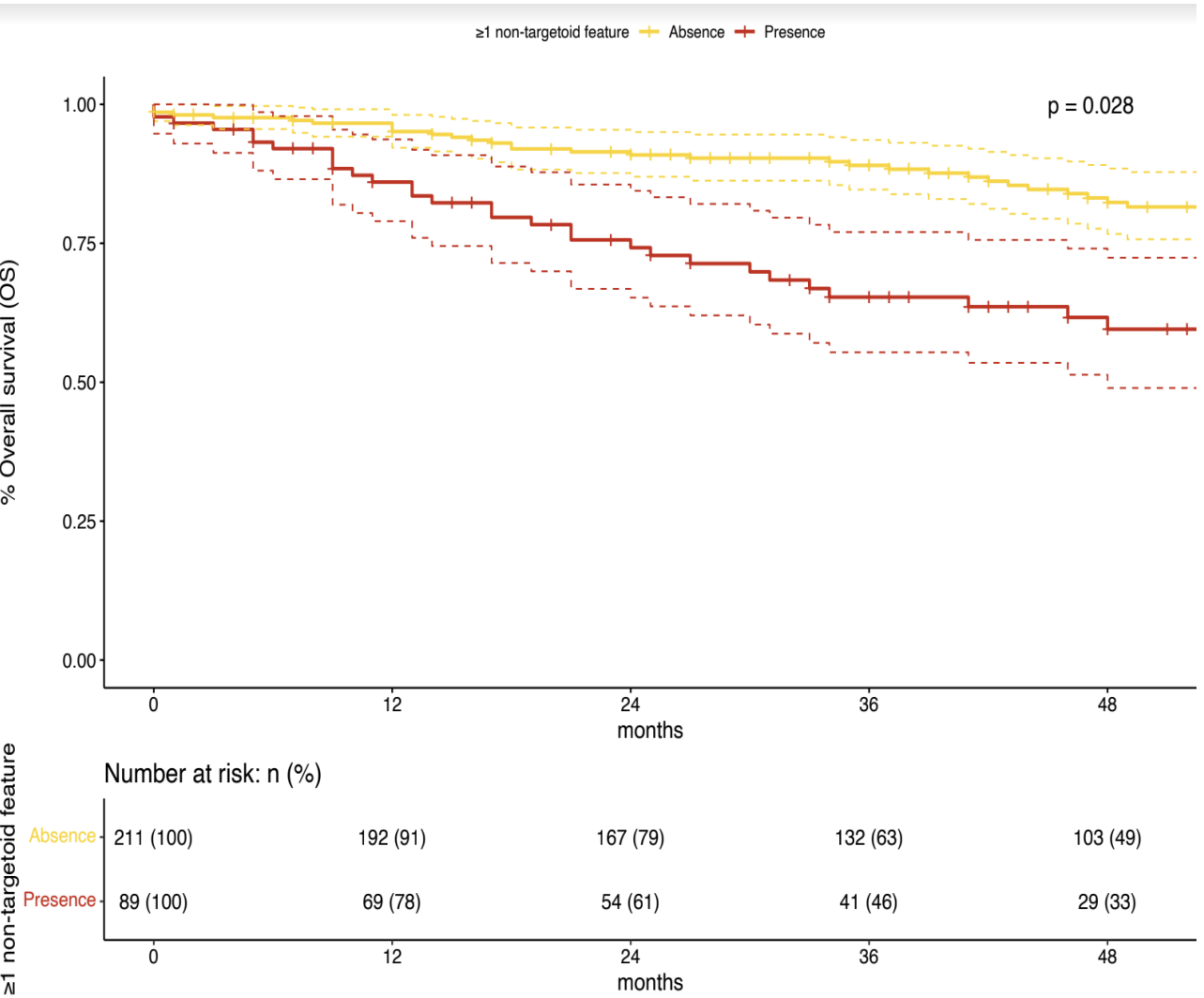
Infiltrating Forms

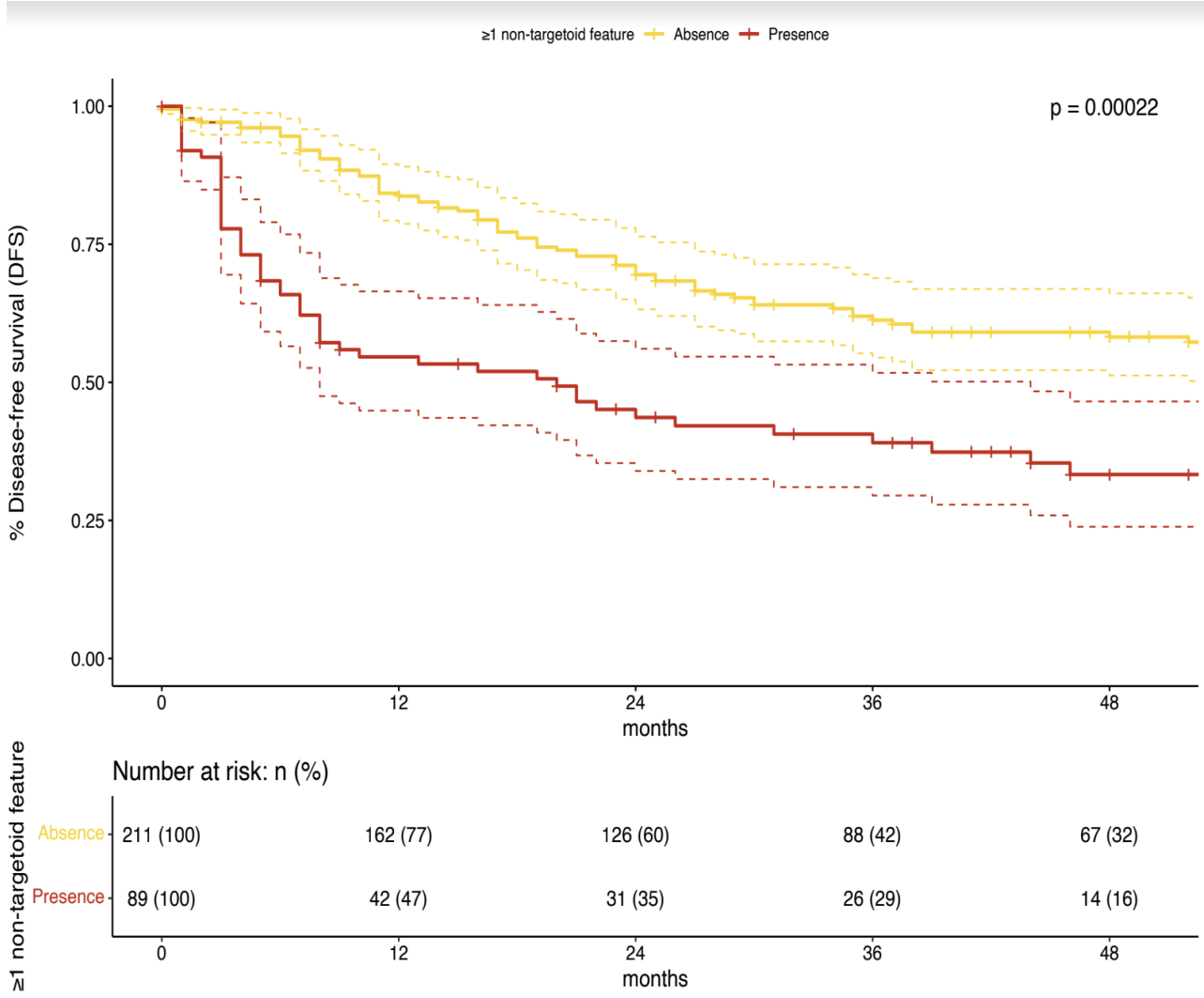


Mulé Radiology2015 ; Raynolds Radiographics 2021

Prognosis

Other features





Cannella Radiology revision

Subtypes

Macrotrabecular Massive HCC

Central necrosis

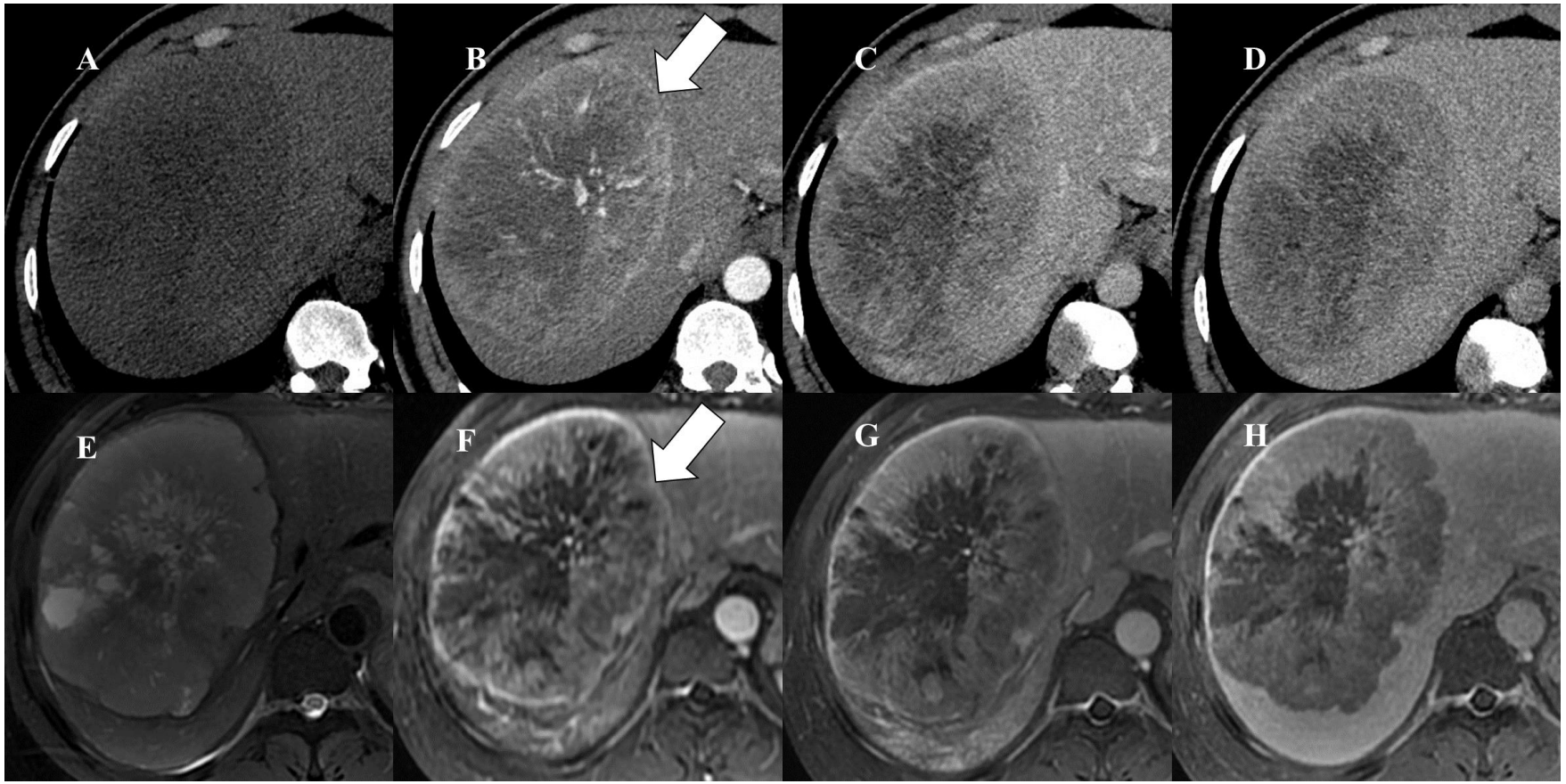
Rim enhancement

Vascular invasion

Contours

Advanced stage
Elevated aFP

HBV



LR-5 but often **LR-M** features

***56-69%** CT*
***60-70%** MRI*

Mulé Radilogy 2020, Cannella JHEP Reports 2021

Subtypes

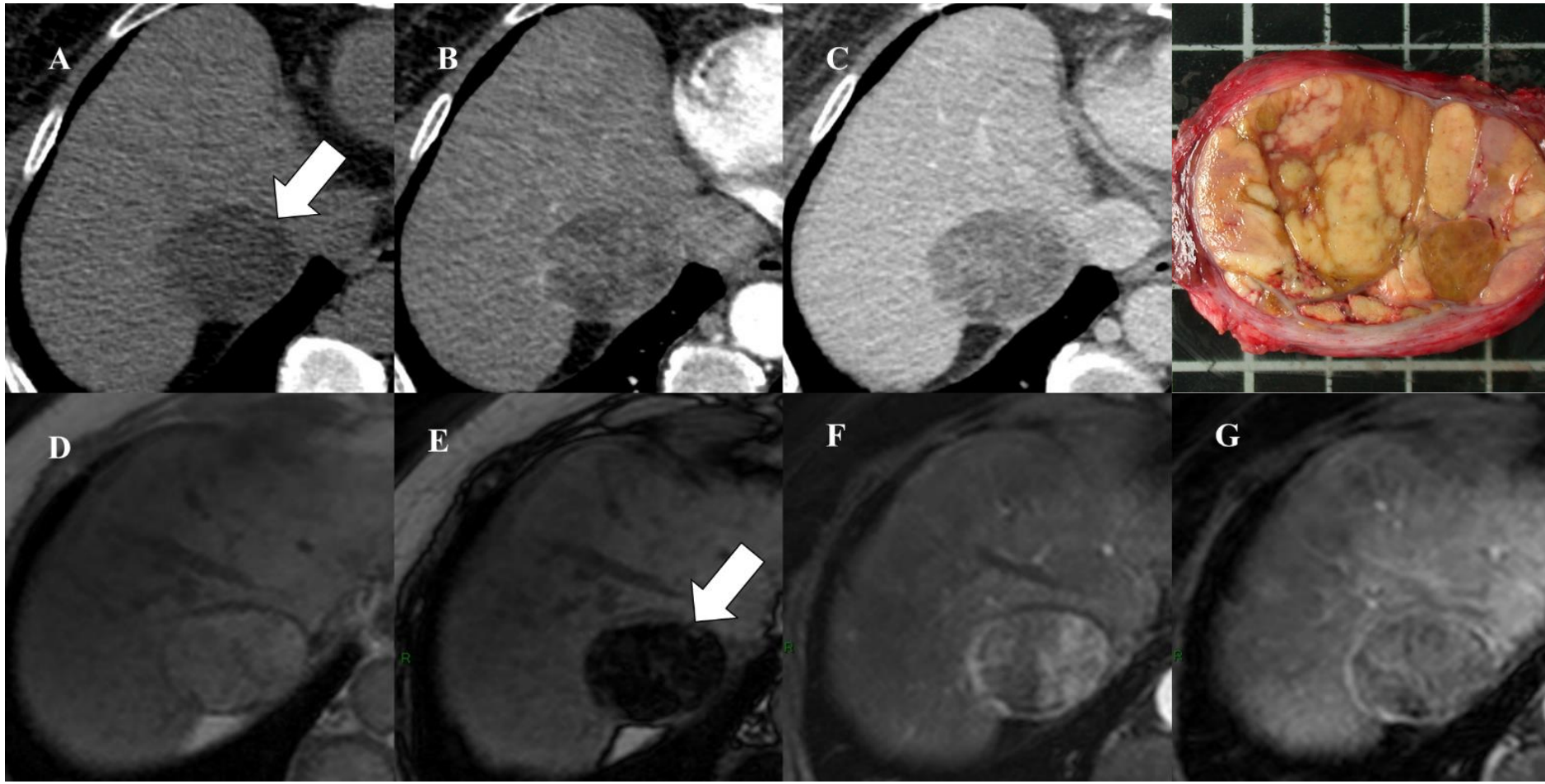
Steatohepatitic

Smallsize

Capsule

Fat
Metabolic Sd

MASH

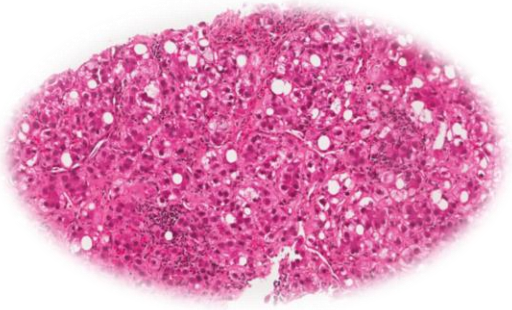


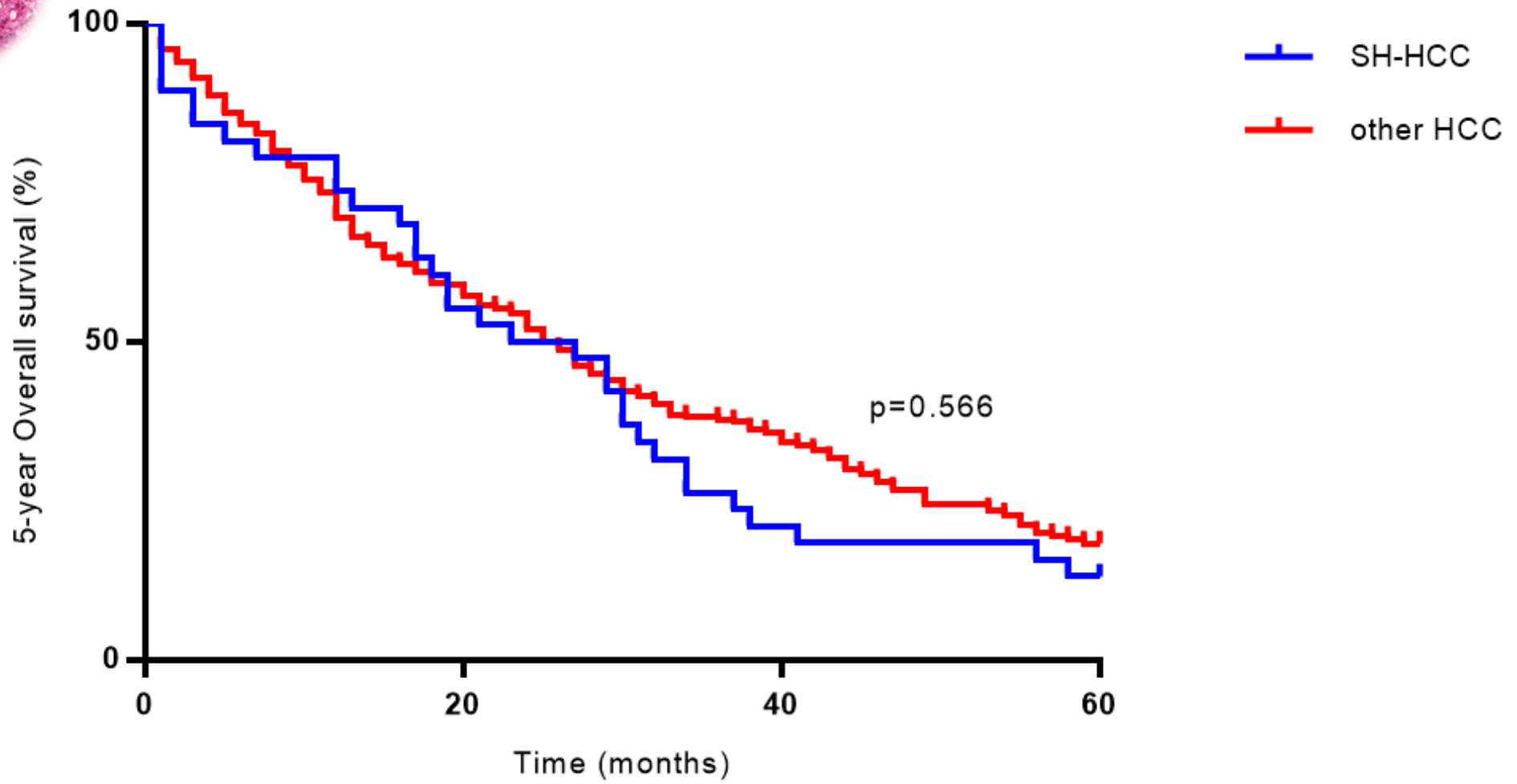
LR-5 **70-80%** CT; **72-88%** MRI

LR-M **0-3%** CT; **4%** MRI

Cannella JHEP Reports 2021

Prognostic implication?

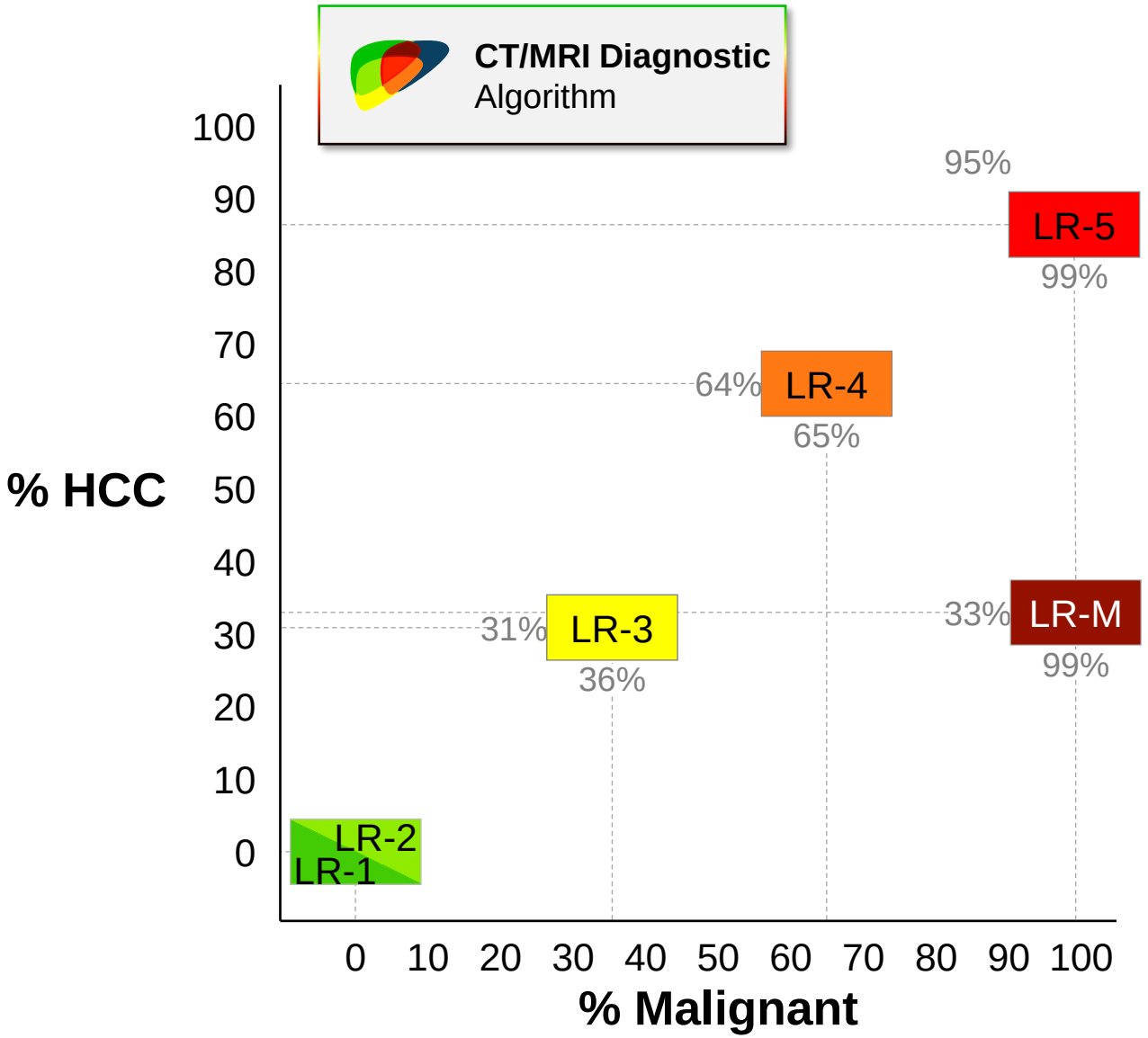




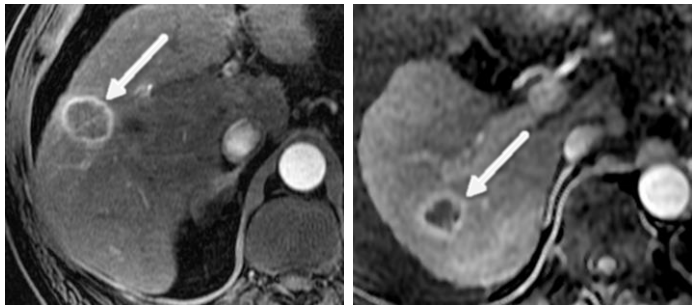
Trapani et al. Steatohepatitic hepatocellular carcinoma: morphological diagnostic criteria and clinicopathological characteristics. Histopathology 2023

LI-RADS

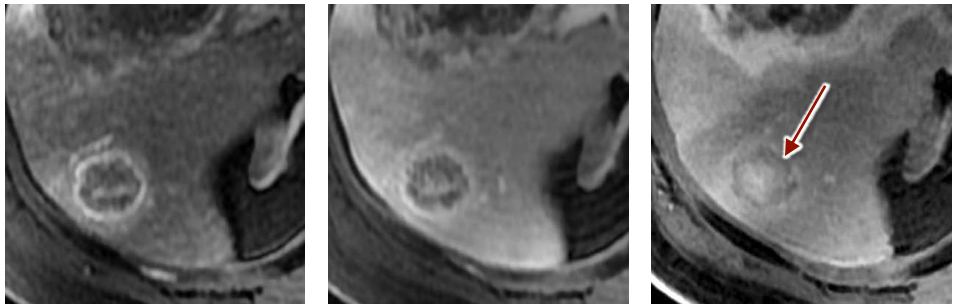
LR-M



Arterial



Venous

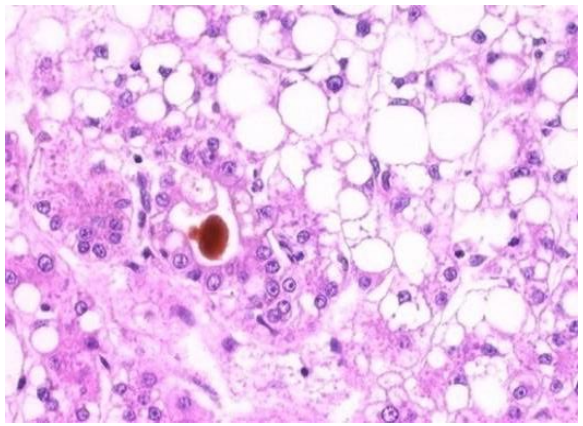


Lee et al *JACR* 2020 PMID 32640250

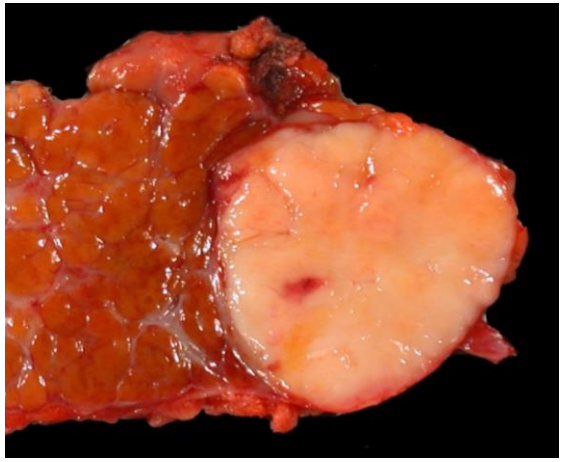
Biopsy

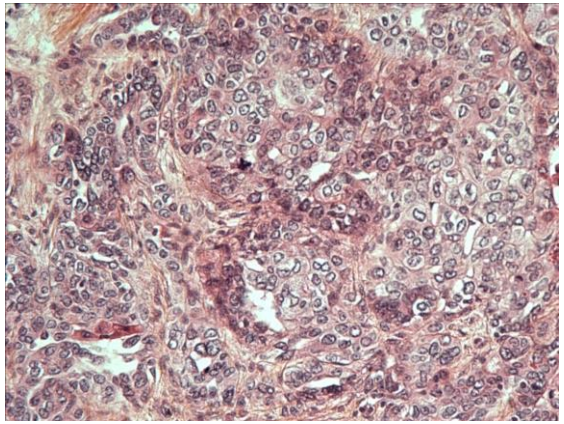
Primary Liver Cancers

Hepatocellular carcinoma

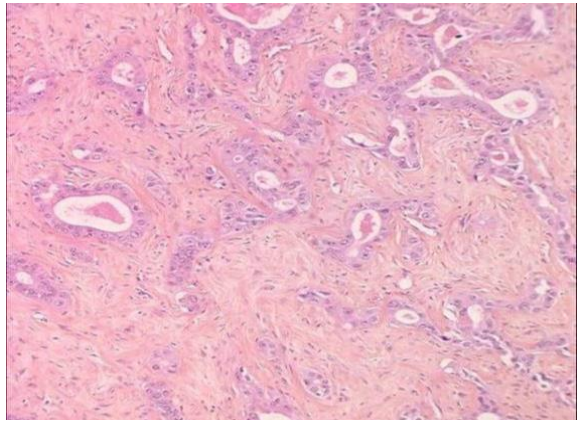


Mixed tumor
Hepatocholangiocarcinoma





Intrahepatic
Cholangiocarcinoma

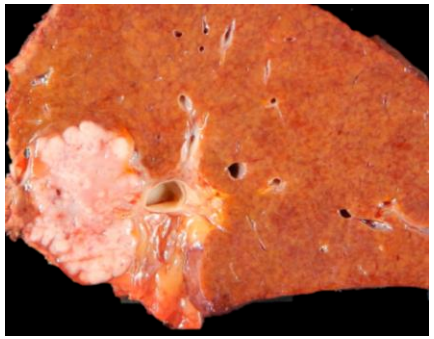


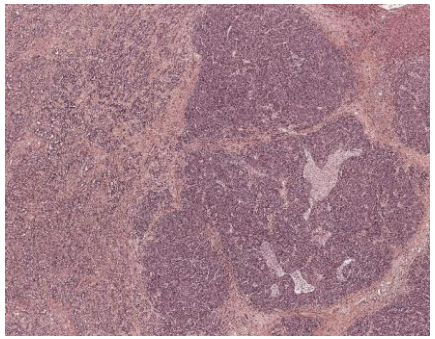
Cirrhosis

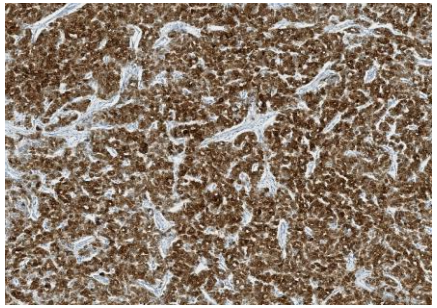
HCC-CCA

A diagnostic challenge

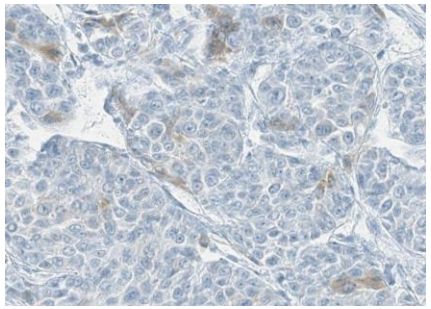
70-year old man, metabolic syndrome
Liver nodule 3.8 cm







CK7

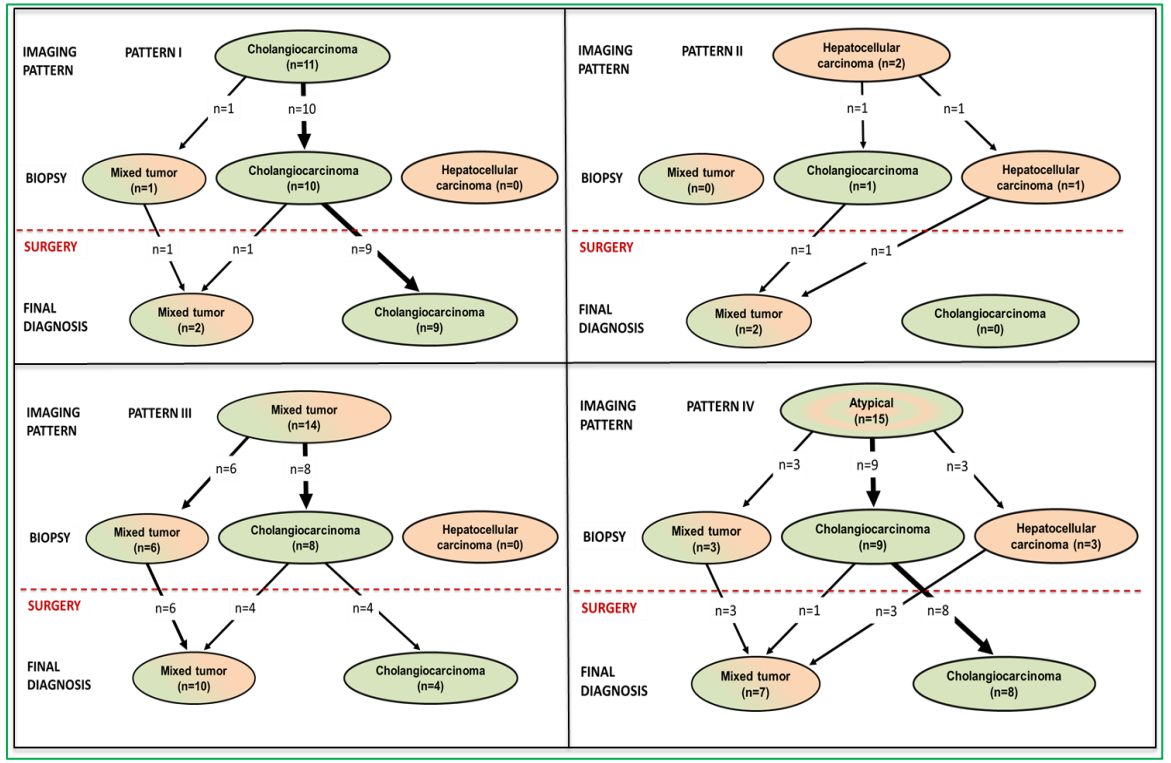


Glypican-3

Rare tumor (< 5%, **probably underdiagnosed**)

Presence of 2 components (HCC & CCA) identified on H&E staining (confirmed by immunos)

Combining imaging and tumour biopsy improves the diagnosis of combined hepatocellular-cholangiocarcinoma

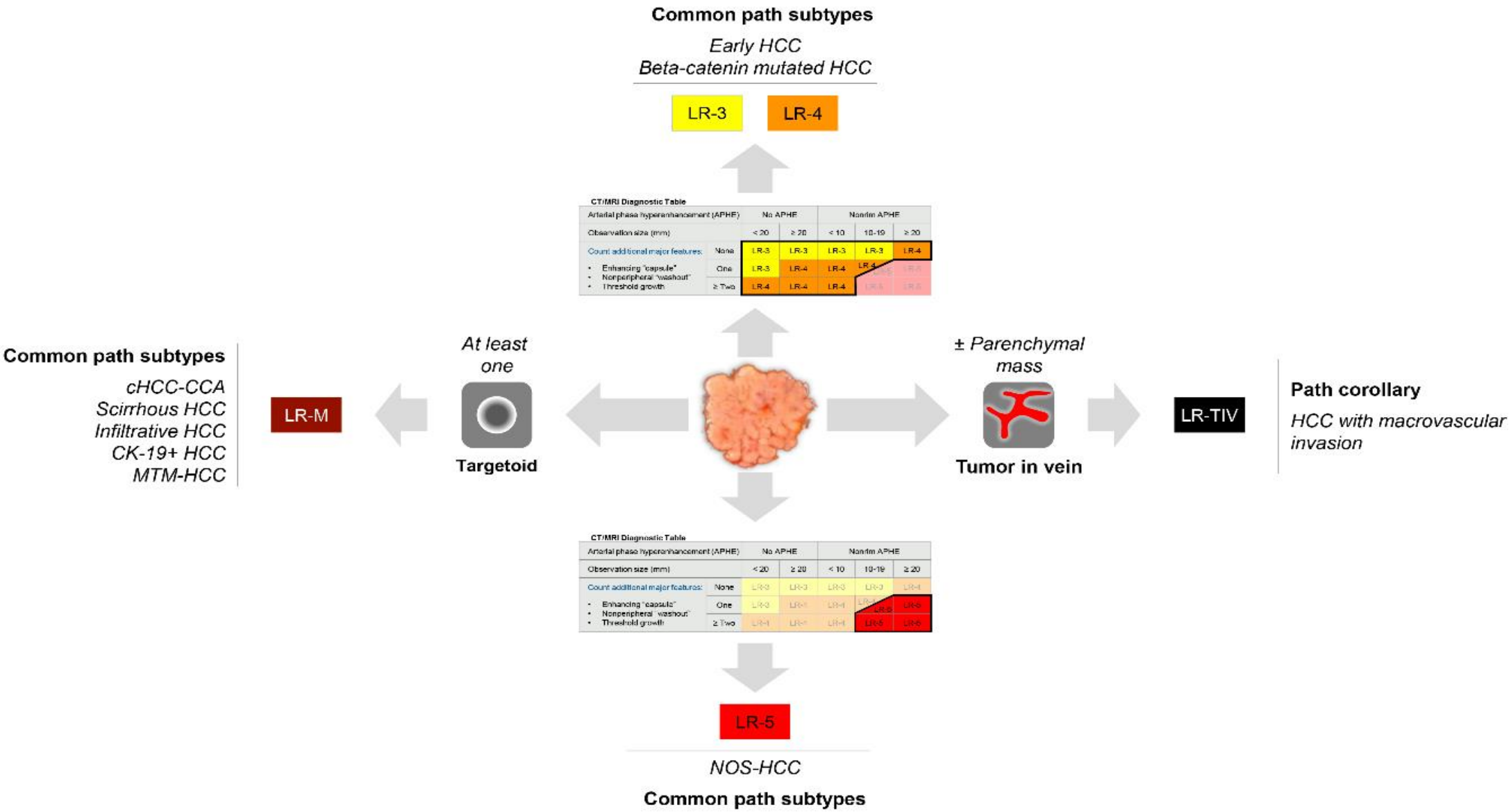


A 2-step strategy
imaging & biopsy agreement → correct diagnosis in 90%

Gigante E Liver int 2019

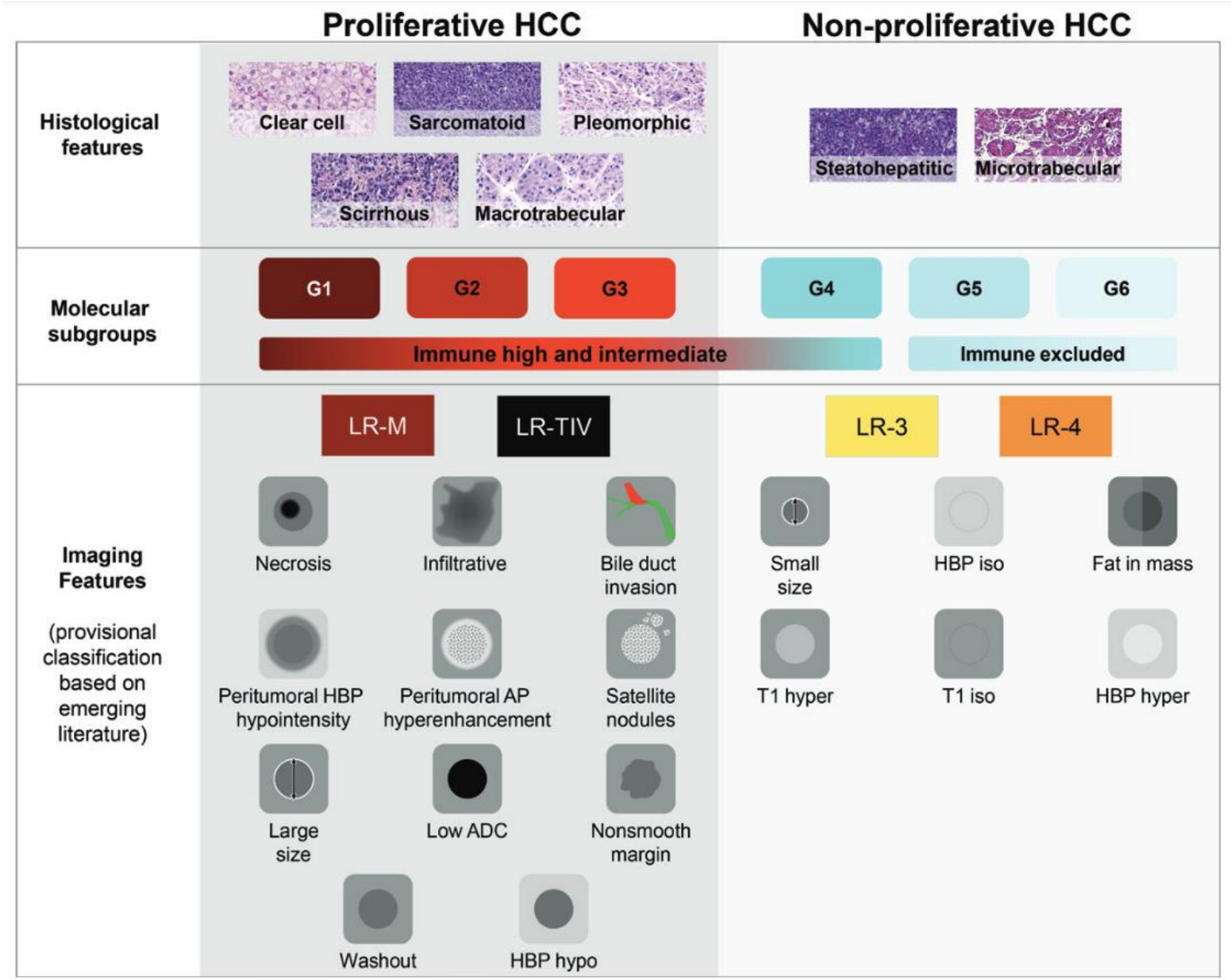
Imaging

From diagnosis to prognosis



Fowler Radiographics 2023 – Ronot Radiolofgy 2023

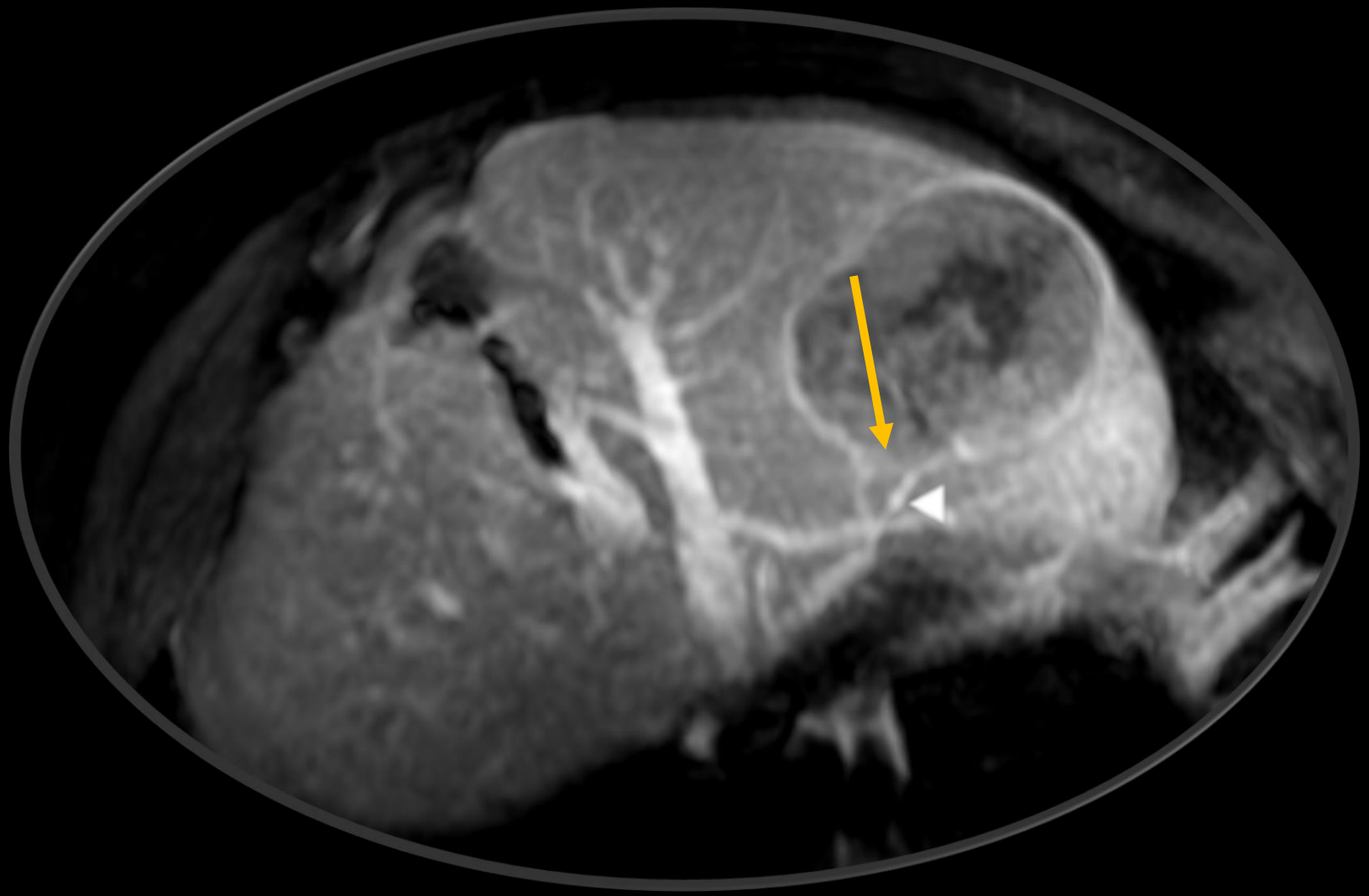
From diagnosis to prognosis



Fowler Radiographics 2021

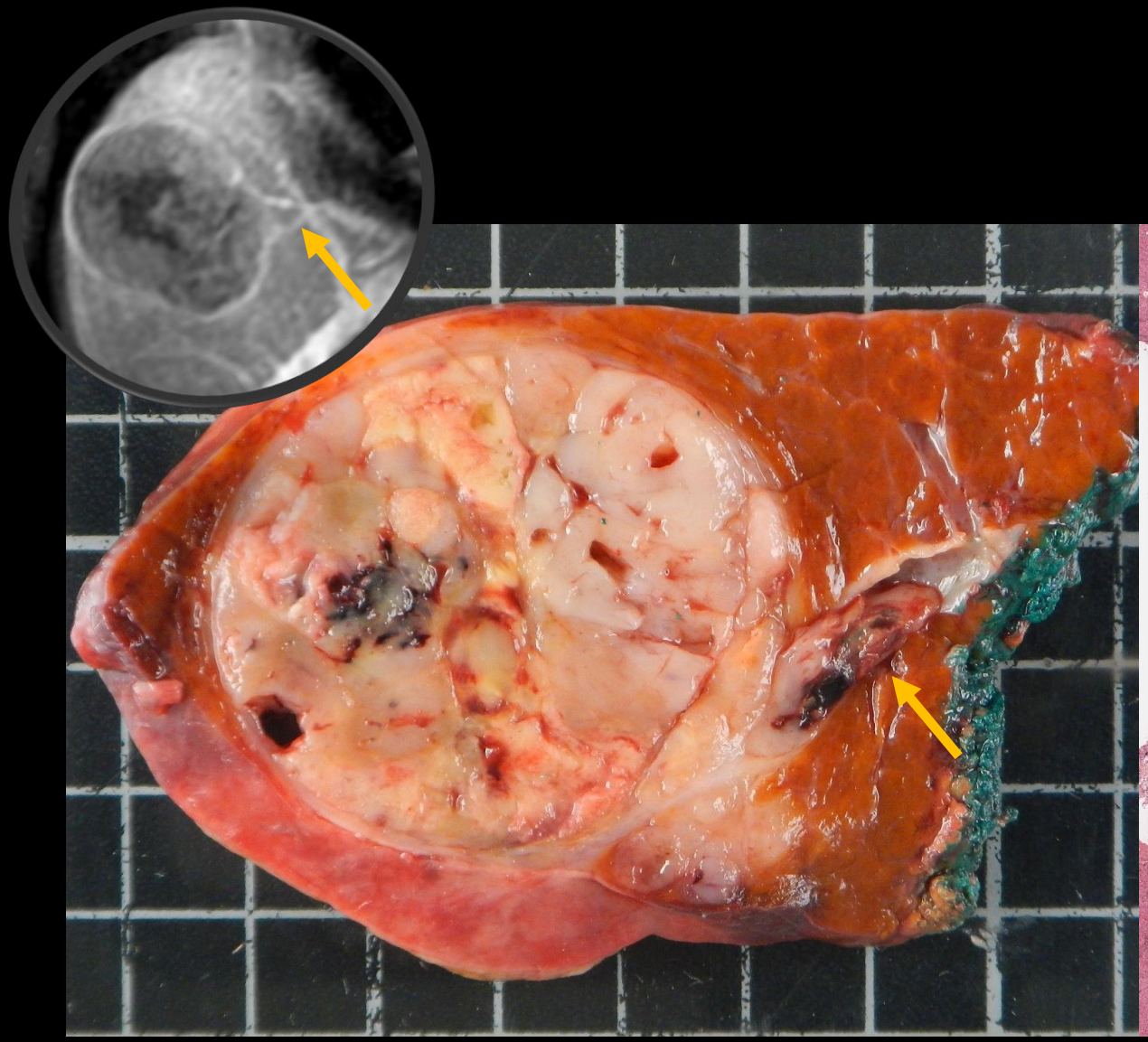
Imaging

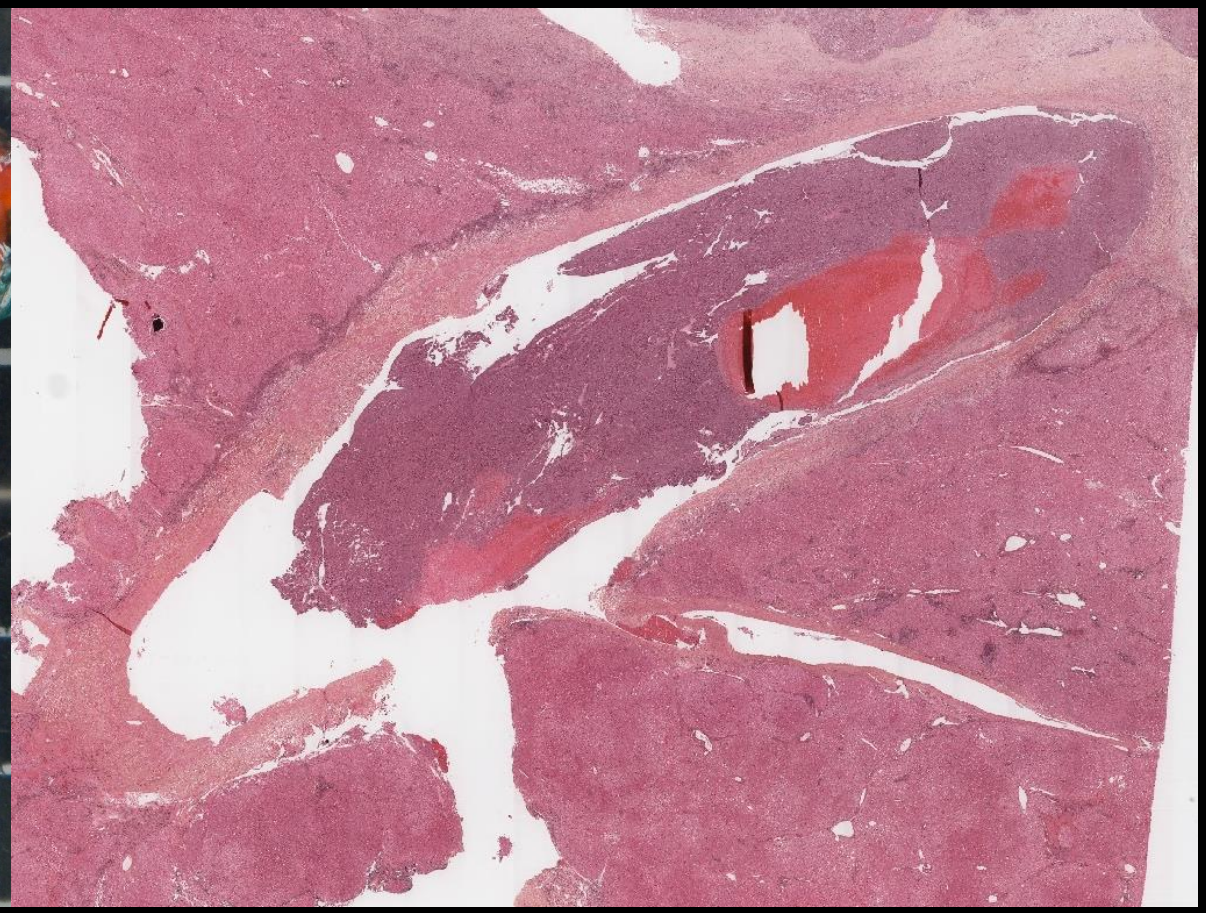
We can analyze the environment!



Imaging

Macrovascular invasion





Macrovascular invasion

1322 patients with (n=101) or without (n=1221) macrovascular invasion
Reference = pathology

Feature	Sensitivity			Specificity		
	CT	HBA MRI	*P* Value*	CT	HBA MRI	*P* Value*
Enhancing soft tissue in vein itself	64.4 (65/101) [54.2, 73.6]	62.4 (63/101) [52.2, 71.8]	.79	99.8 (1218/1221) [94.2, 100.0]	99.8 (1218/1221) [94.2, 100.0]	>.99
Enhancing soft tissue in vein with consideration of features suggestive of TIV (ie, LR-TIV category)	67.3 (68/101) [57.3, 76.3]	67.3 (68/101) [57.3, 76.3]	>.99	99.7 (1217/1221) [94.2, 100.0]	99.7 (1217/1221) [94.2, 100.0]	>.99
Occluded vein with ill-defined walls	68.3 (69/101) [58.3, 77.2]	64.4 (65/101) [54.2, 73.6]	.50	99.1 (1210/1221) [93.6, 100.0]	99.3 (1212/1221) [93.8, 100.0]	>.99
Occluded vein with restricted diffusion	NA	63.4 (64/101) [53.2, 72.7]		NA	99.6 (1216/1221) [94.1, 100.0]	
Occluded or obscured vein in contiguity with malignant parenchymal mass	69.3 (70/101) [59.3, 78.1]	68.3 (69/101) [58.3, 77.2]	>.99	99.1 (1210/1221) [93.6, 100.0]	98.8 (1206/1221) [93.3, 100.0]	.29
Heterogeneous vein enhancement not attributable to artifacts	60.4 (61/101) [50.2, 70.0]	48.5 (49/101) [38.4, 58.7]	.02	99.7 (1217/1221) [94.2, 100.0]	99.8 (1218/1221) [94.2, 100.0]	.50
LR-TIV category and/or any features suggestive of TIV	70.3 (71/101) [60.4, 79.0]	70.3 (71/101) [60.4, 79.0]	>.99	98.7 (1205/1221) [93.2, 100.0]	98.6 (1204/1221) [93.1, 100.0]	>.99

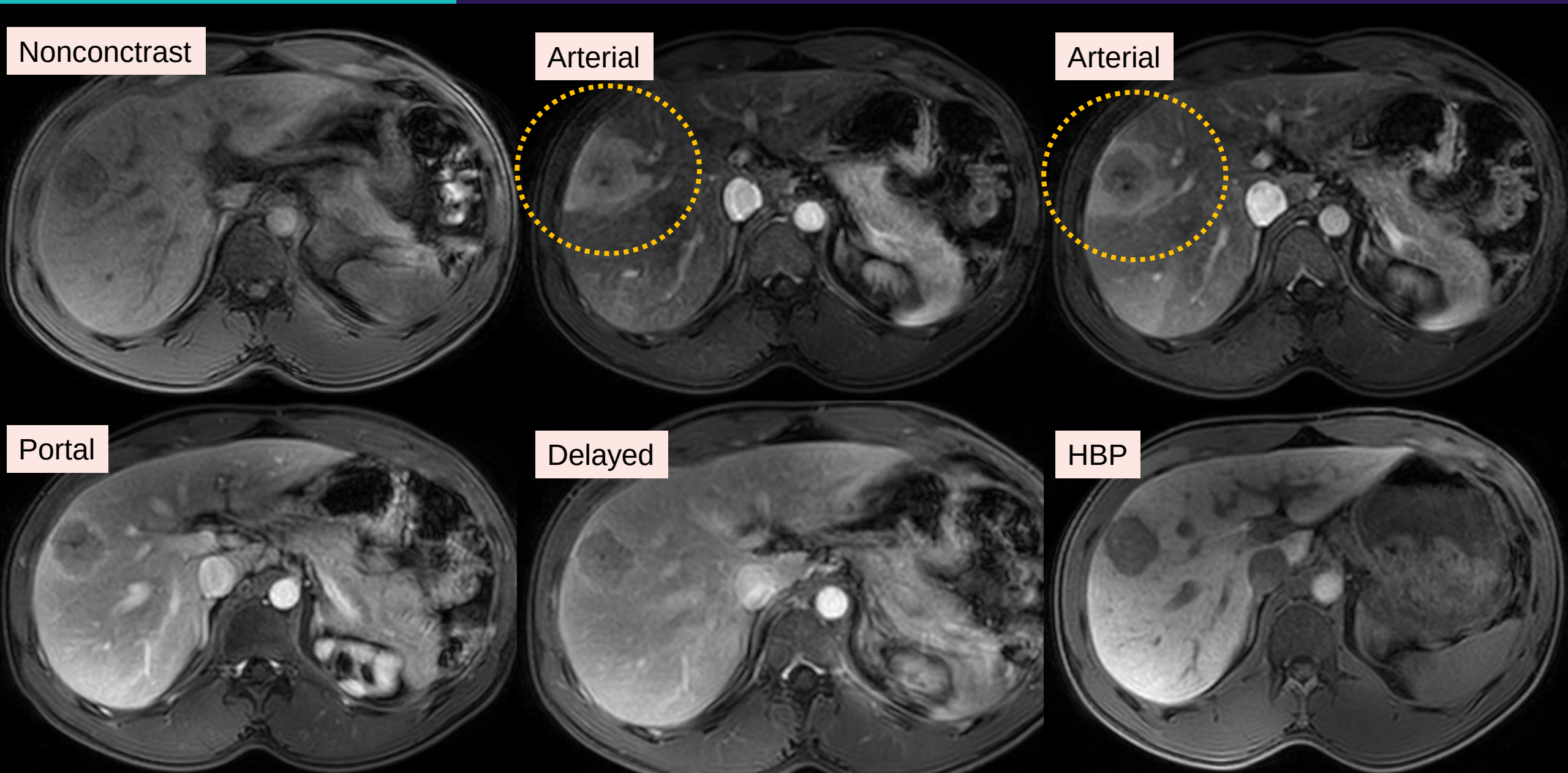
Low sensitivity

High Specificity

Bar Radiology 2021

Imaging

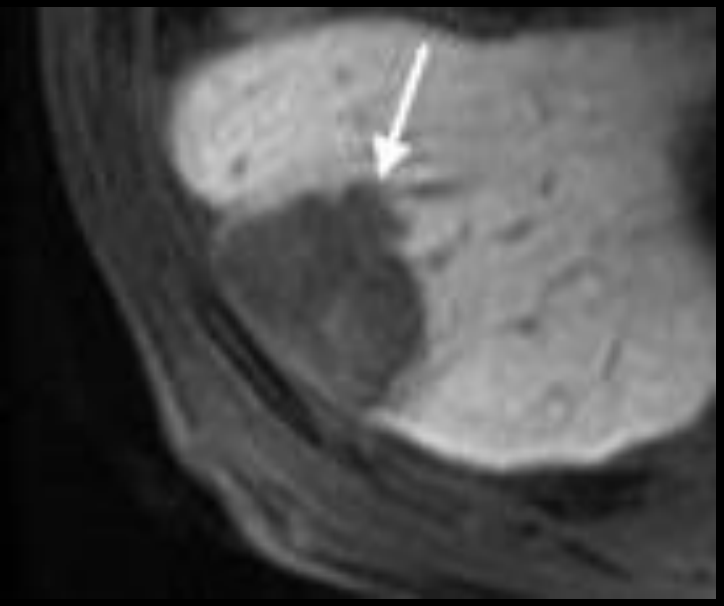
Microvascular invasion



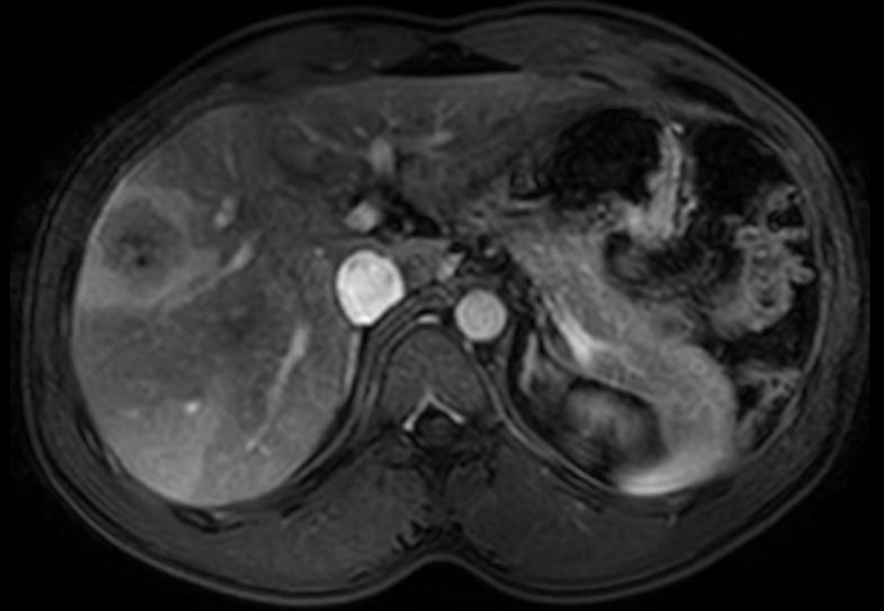
Imaging

Microvascular invasion

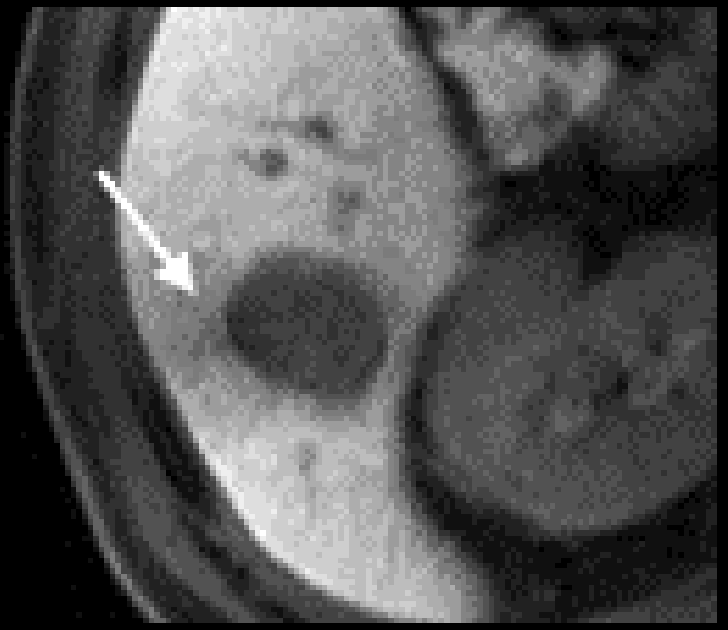
Ruptured Capsule

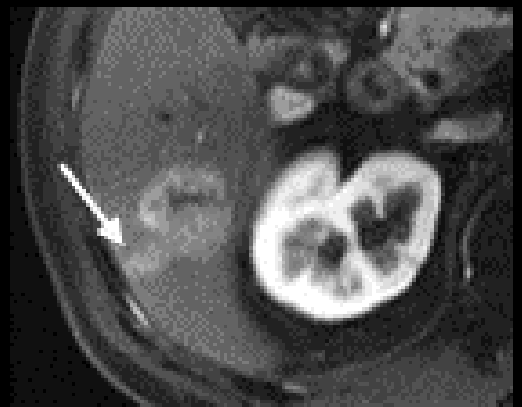


Peritumoral enhancement



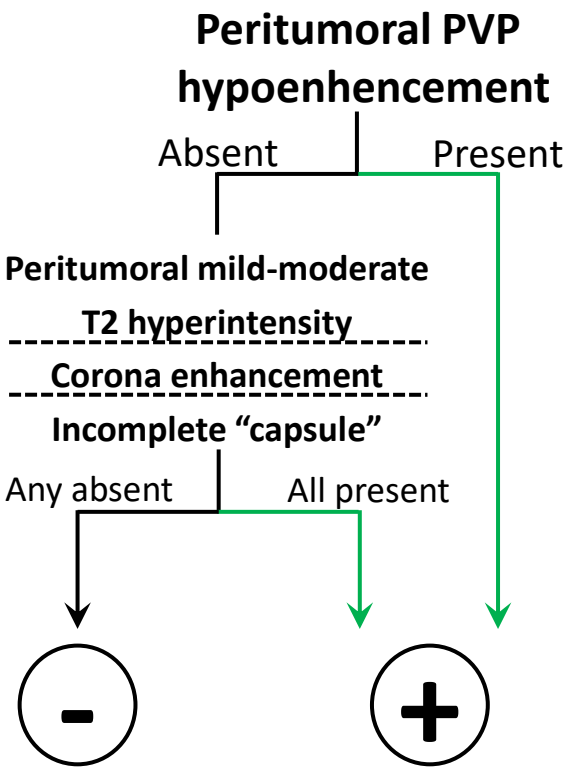
HBP hypointensity

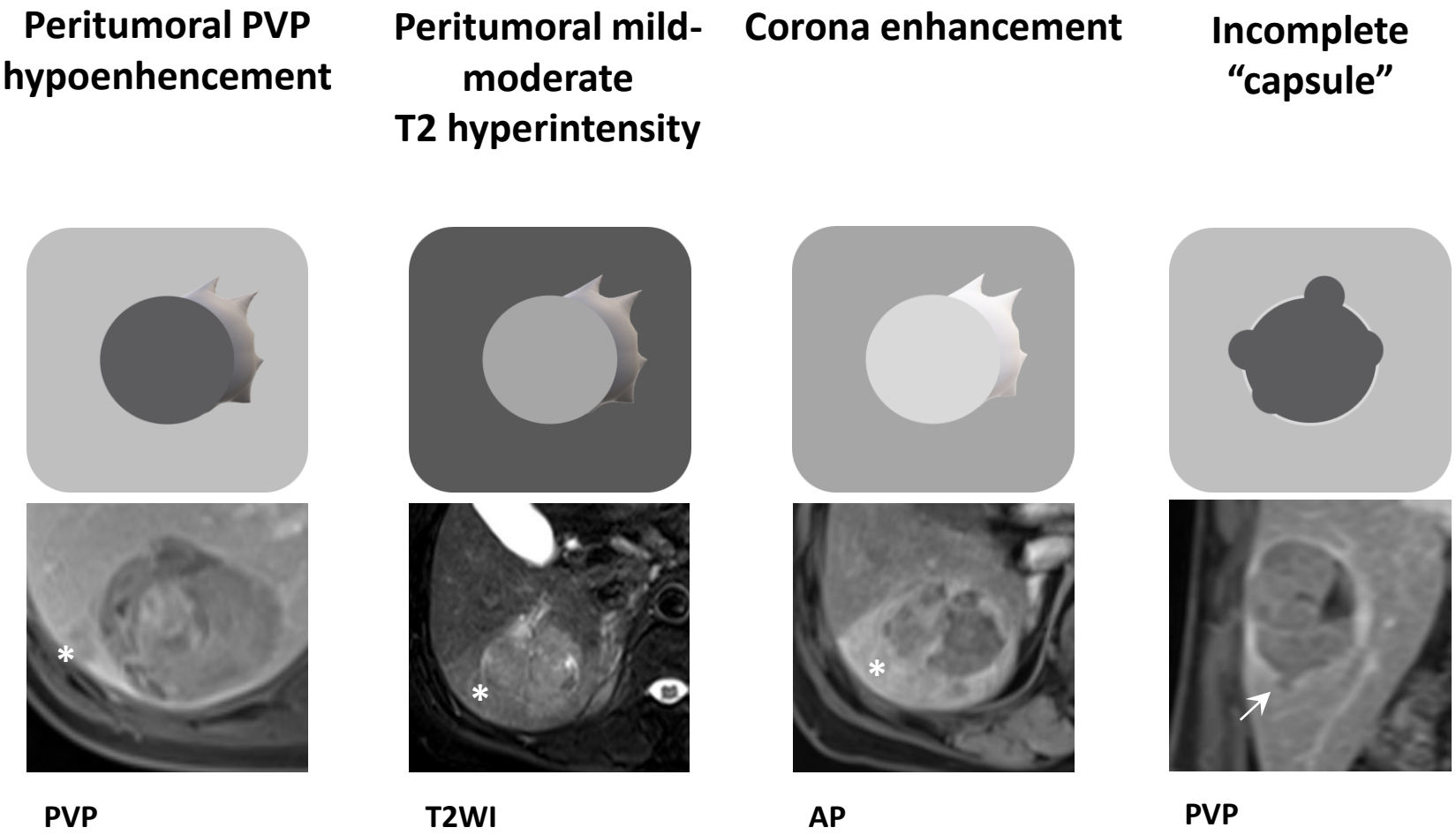




Microvascular invasion

A non-hepatobiliary-specific prognostic marker equivalent to peritumoral HBP hypointensity





Jiang Radiology 2022

Suboptimal performance

Inter- and intra-observer variability

Table 3: Diagnostic Performance of the Prediction of Microvascular Invasion in HCC

Reviewer	AUC*	Sensitivity (%)	Specificity (%)	Accuracy (%)†	PPV (%)	NPV (%)
More experienced reviewers						
Reviewer 1	0.72 (0.62, 0.81)	69 (52, 83)	57 (44, 70)	62 (52, 72)	51 (37, 65)	74 (60, 86)
Reviewer 2	0.66 (0.55, 0.76)	62 (45, 77)	57 (44, 70)	59 (49, 69)	48 (34, 63)	70 (55, 82)
Reviewer 3	0.66 (0.55, 0.77)	59 (42, 74)	57 (44, 70)	58 (48, 68)	47 (33, 62)	69 (54, 81)
Reviewer 4	0.68 (0.58, 0.78)	41 (26, 58)	80 (68, 89)	65 (55, 74)	57 (37, 76)	68 (56, 79)
Less experienced reviewers						
Reviewer 5	0.74 (0.64, 0.84)	59 (42, 74)	84 (72, 92)	74 (64, 82)	70 (51, 84)	76 (64, 86)
Reviewer 6	0.60 (0.49, 0.71)	26 (13, 42)	85 (74, 93)	62 (52, 72)	53 (29, 76)	64 (53, 75)
Reviewer 7	0.67 (0.57, 0.78)	51 (35, 68)	72 (59, 83)	64 (54, 73)	54 (37, 71)	70 (57, 81)
Reviewer 8	0.64 (0.53, 0.74)	15 (06, 31)	92 (82, 97)	62 (52, 72)	55 (23, 83)	63 (52, 73)

Low sensitivity and specificity 😥

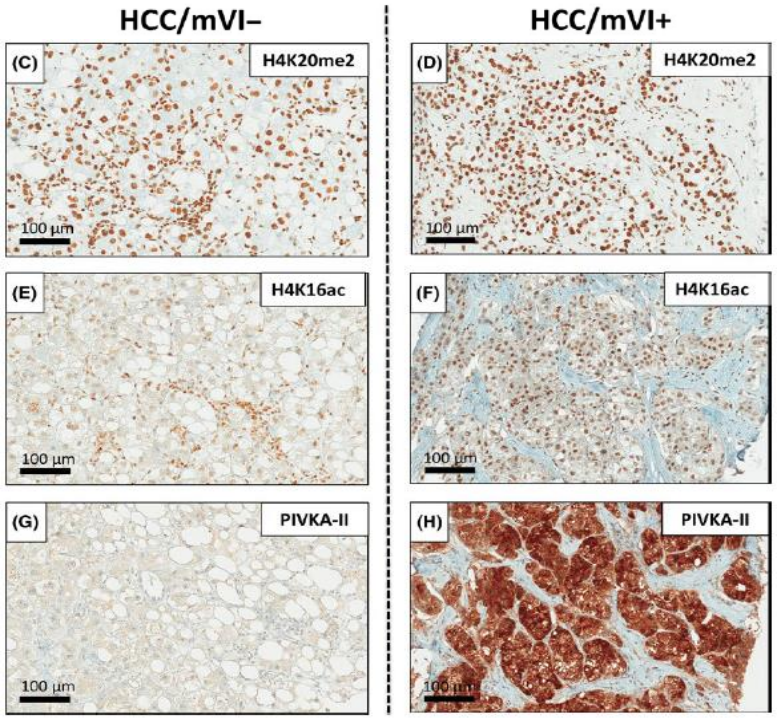
Min Radiology 2020

Biopsy

Surrogate markers of Microvascular invasion

Microscopic vascular invasion

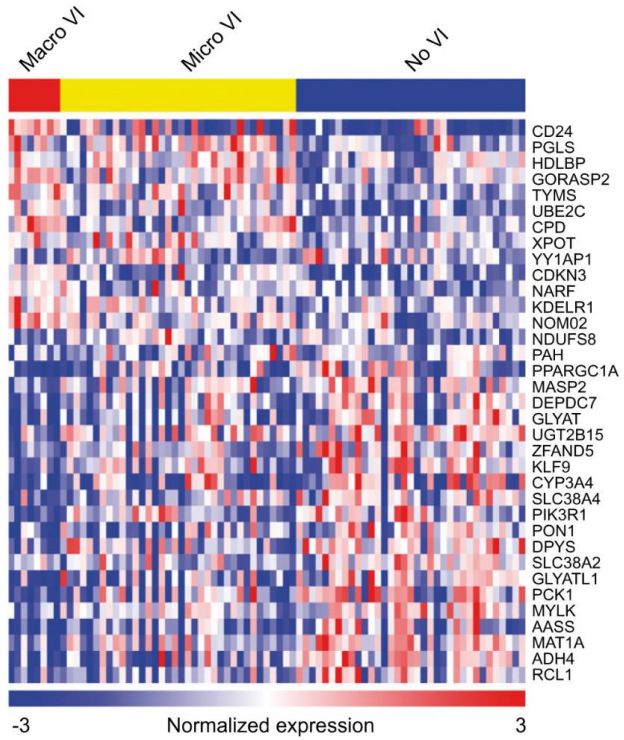
Contribution of virtual biopsy to the screening of microvascular invasion in hepatocellular carcinoma: A pilot study



2 +ve markers: sst 72 %, spe 64%
3 +ve markers: sst 36%, spe 90%

Poté N et al Hepatology 2013, J Hepatol 2015 & Liver Int 2017

Gene-expression signature of vascular invasion in hepatocellular carcinoma



35-gene signature predicting microvascular invasion (accuracy of 69%)

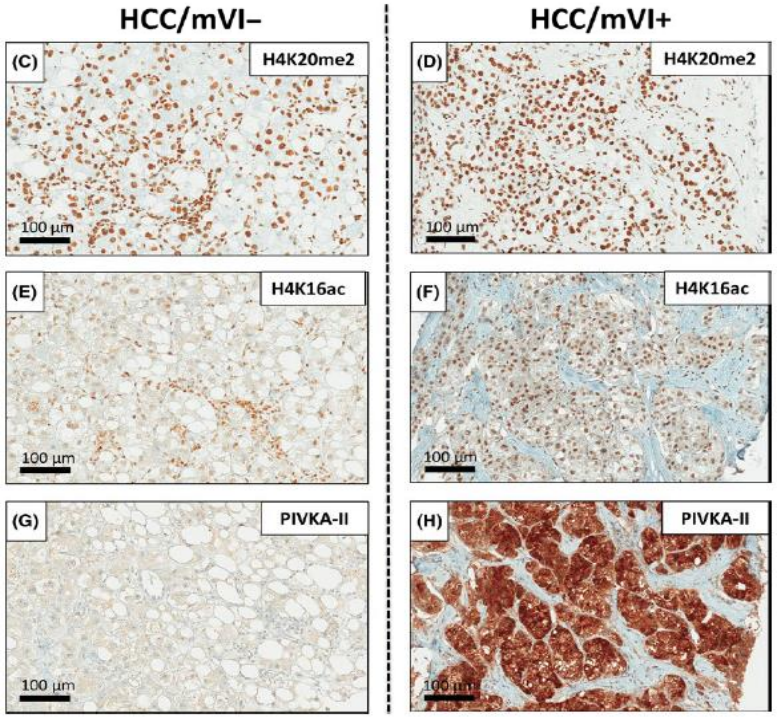
Minguez B J Hepatol 2011

Biopsy

Surrogate markers of Microvascular invasion

Microscopic vascular invasion

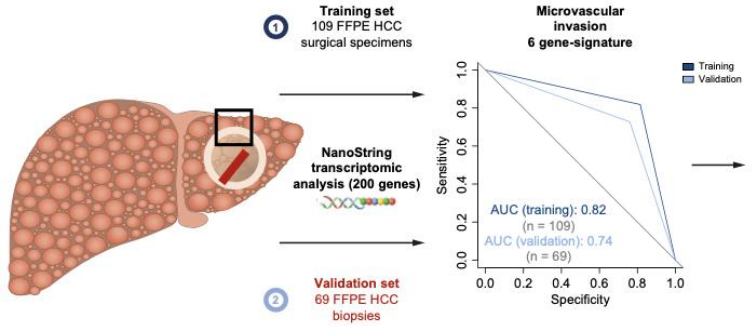
Contribution of virtual biopsy to the screening of microvascular invasion in hepatocellular carcinoma: A pilot study



2 +ve markers: sst 72 %, spe 64%
3 +ve markers: sst 36%, Spe 90%

Poté N et al Hepatology 2013, J Hepatol 2015 & Liver Int 2017

Gene expression signature as a surrogate marker of microvascular invasion on routine hepatocellular carcinoma biopsies

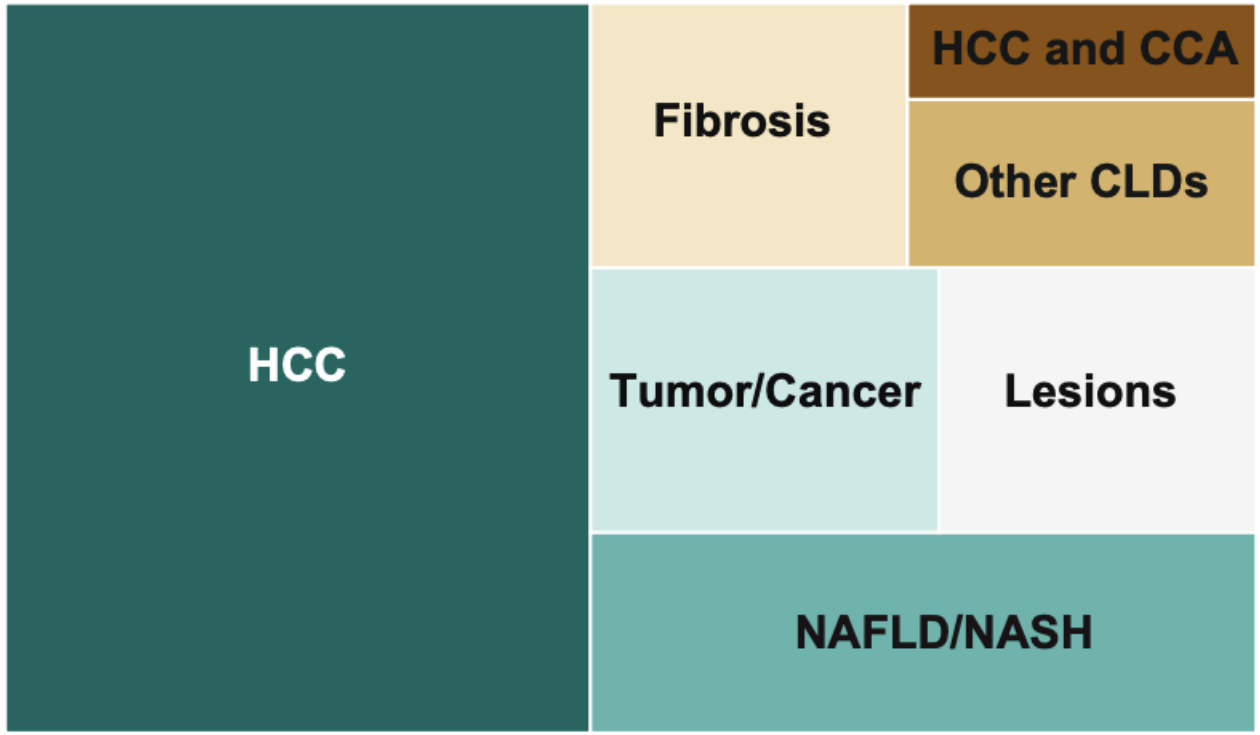


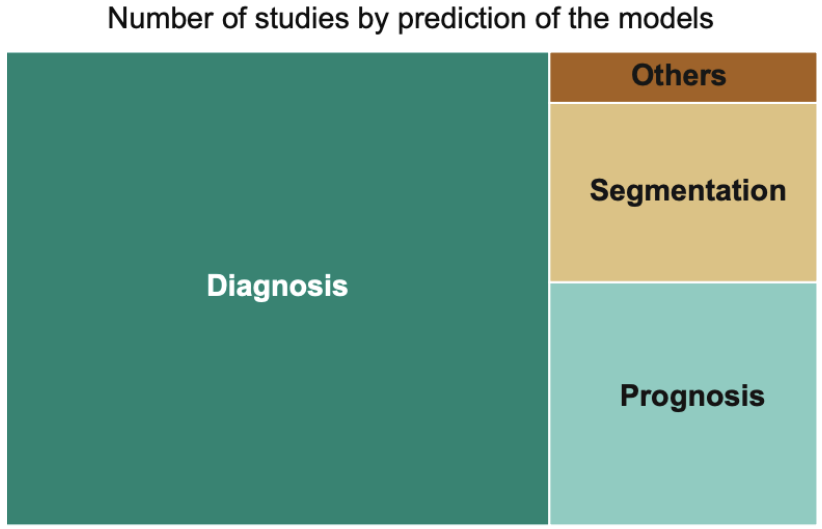
6-gene signature
(*ROS1*, *UGT2B7*, *FAS*, *ANGPTL7*, *GMNN*, *MKI67*)

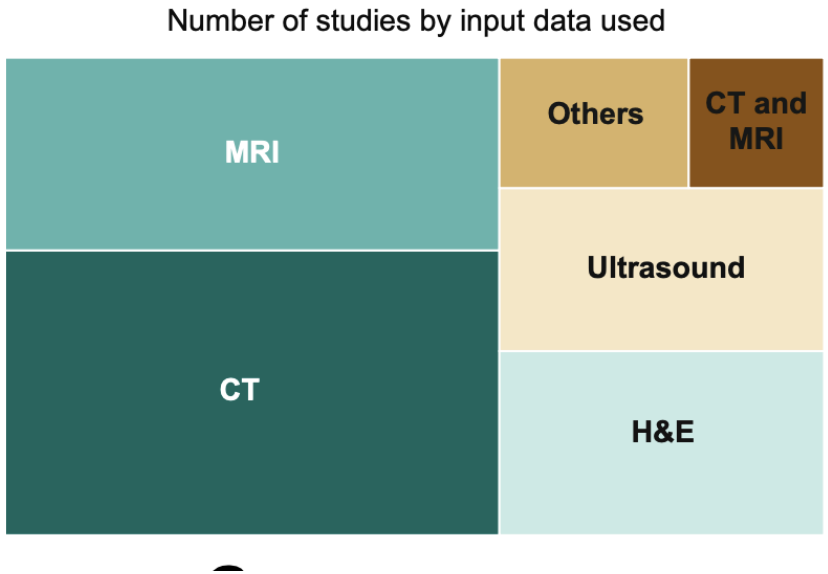
predicting microvascular invasion
(accuracy of 74-82%)

Beaufrère A J Hepatol 2022

AI-based imaging



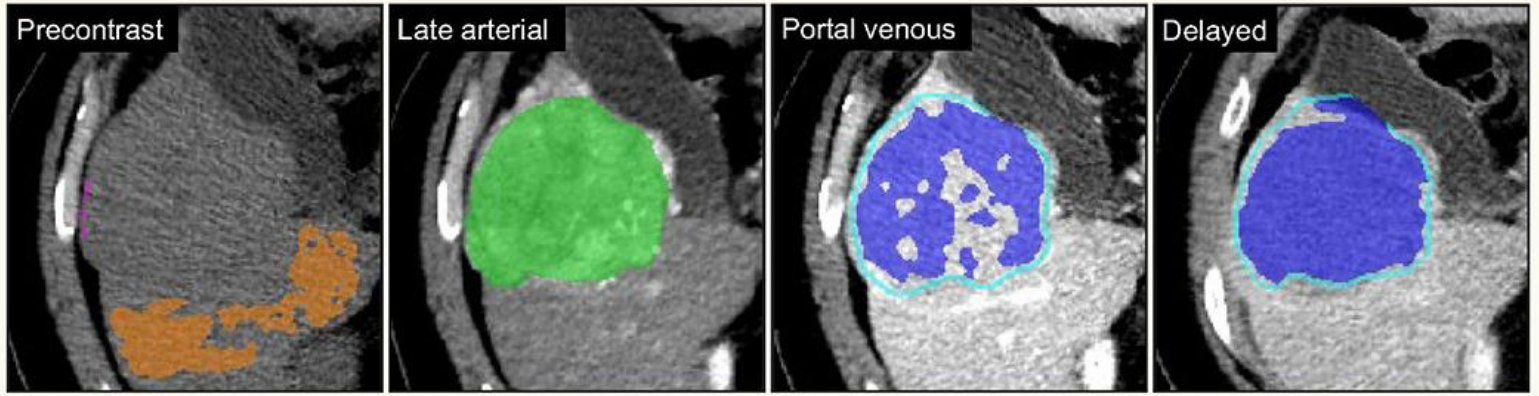


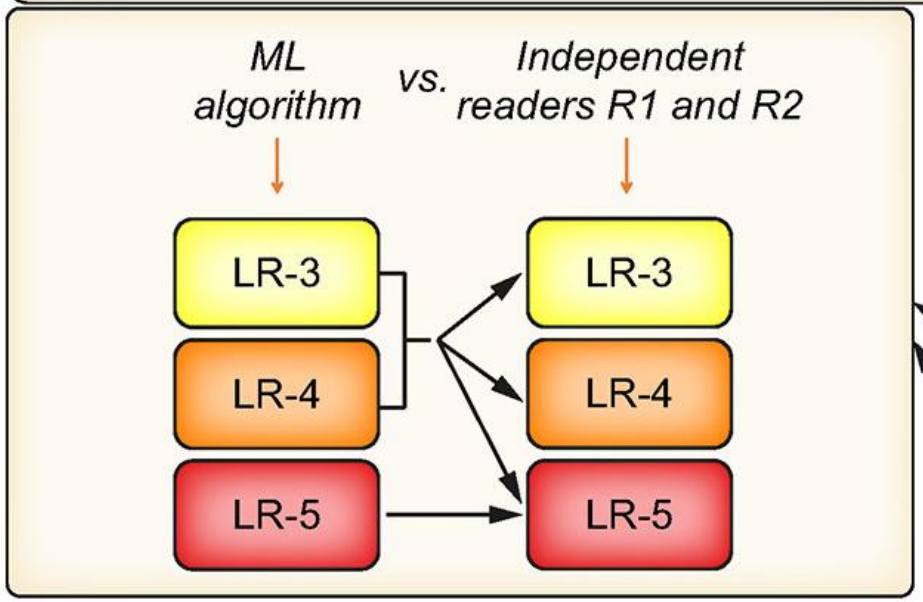


Nam JHEP Reports 2021

AI-based imaging

318 patients with 429 liver observations





	Sensitivity for LR-5	***Specificity for LR-5***	***LI-RADS accuracy***
ML algorithm alone	*0.67*	*0.91*	*70.1%*
Reader 1 alone	*0.78*	*0.88*	*66.7%*
ML algorithm + R1	*0.86*	*0.82*	*78.0%*
Reader 2 alone	*0.90*	*0.82*	*77.7%*
ML algorithm + R2	*0.93*	*0.76*	*82.3%*

Mulé S. J HEP Reports 2023

Biopsy

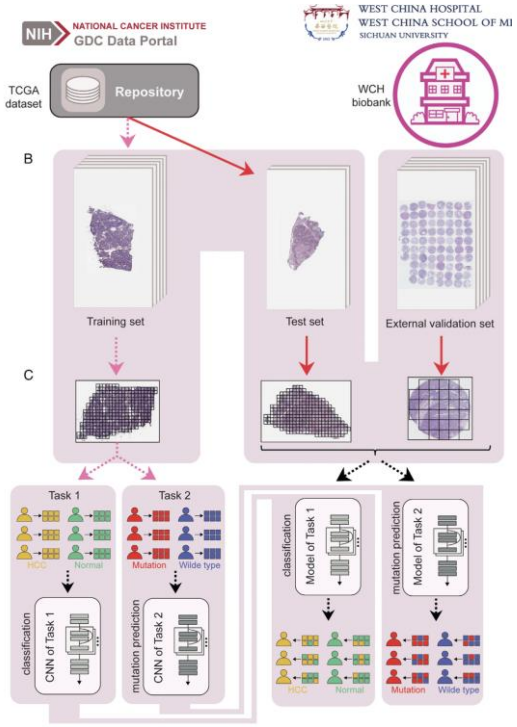
AI-based pathology

Deep learning-based classification and mutation prediction from histopathological images of hepatocellular carcinoma

Task : Distinguish HCC from adjacent normal liver

< 10% of tiles misclassified (test set)

< 20% of tiles misclassified (validation set)



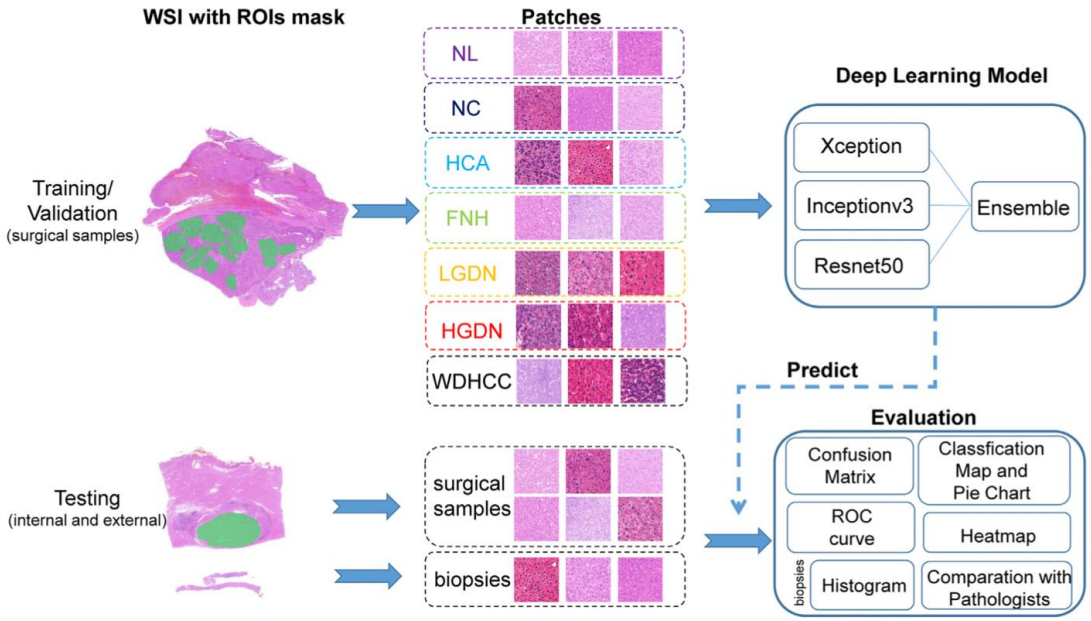
Liao TH Clin Med Transl 2020

Deep Learning-Based Classification of Hepatocellular Nodular Lesions on Whole-Slide Histopathologic Images

Task : Differentiate hepatocellular nodular lesions

AUC values (092-0.99)

Rate of agreement with 3 subspecialists > for HnAIM (*vs* 9 pathologists)

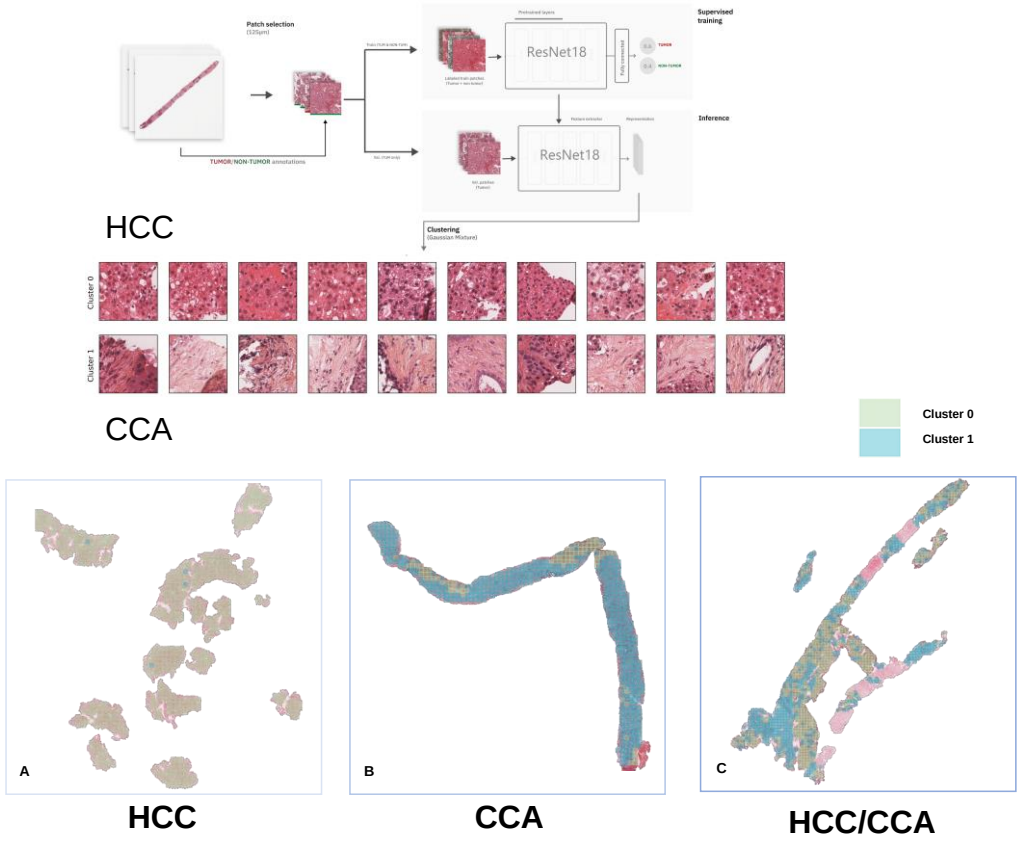


Cheng N Gastro 2022

Biopsy

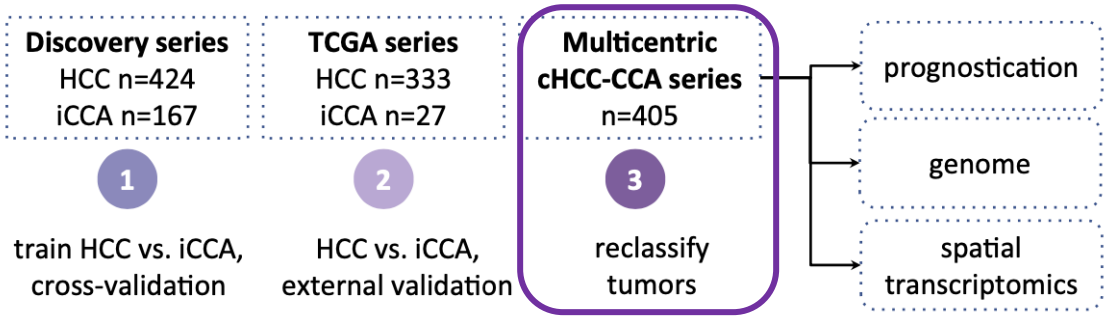
AI-based pathology

Weakly supervised primary liver cancer classification from routine tumour biopsy: a proof of concept

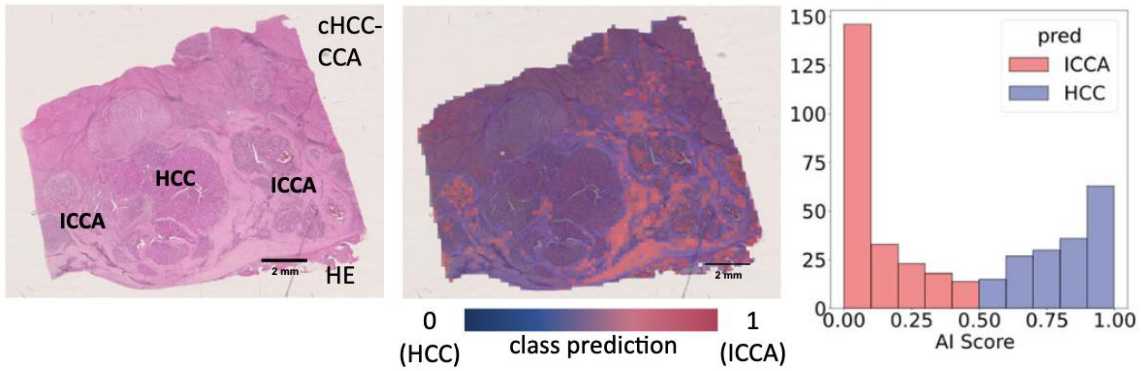


Beaufrère A JHep Rep 2024

Deep learning-based phenotyping reclassifies combined hepatocellular-cholangiocarcinoma



Patient level prediction scores



Calderaro J Nat Com 2023

Biopsy

AI-based pathology

Predicting Survival After Hepatocellular Carcinoma Resection Using Deep Learning on Histological Slides

Saillard C Hepatol 2020

Deep learning predicts postsurgical recurrence of hepatocellular carcinoma from digital histopathologic images

Yamashita Y Sci Rep2021

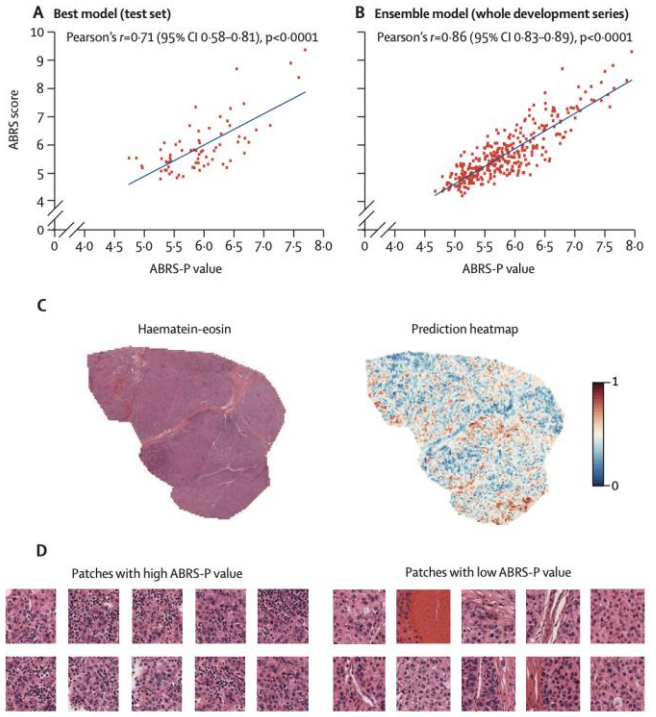
Exploring prognostic indicators in the pathological images of hepatocellular carcinoma based on deep learning

Shi JY Gut 2021

Artificial intelligence predicts immune and inflammatory gene signatures directly from hepatocellular carcinoma histology

Zheng Q J Hepatol 2022

Artificial intelligence-based pathology as a biomarker of sensitivity to atezolizumab–bevacizumab in patients with hepatocellular carcinoma: a multicentre retrospective study



Zheng Q Lancet Oncol 2023

Messages

Complementarity and Integration

HCC is a heterogeneous group of tumors

Morphology (≠ subtypes)

Molecular (≠ groups)

Differentiation

Non invasive diagnosis is possible

- Target population
- « poor » information

Radio-pathological complementarity +++

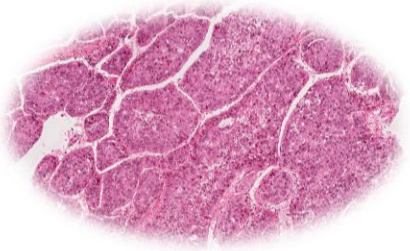
- Prognostic
- Therapeutic Implications

Biopsy as often as possible!

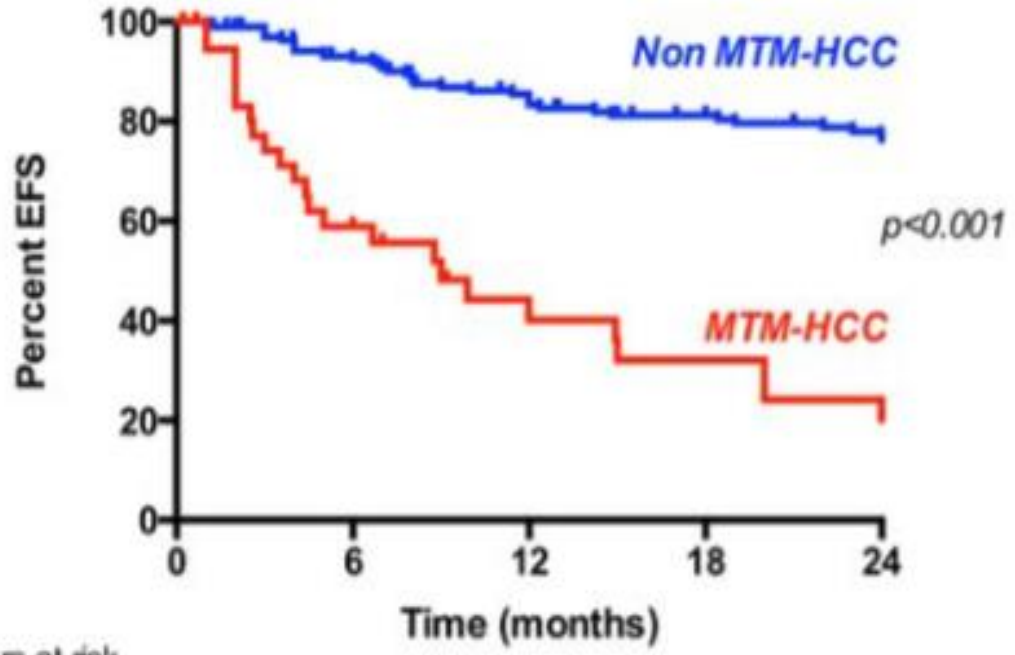
maxime.ronot@aphp.fr
valerie.paradis@aphp.fr
@maximeronot
@valerie_paradis

Always biopsy!

Different prognosis



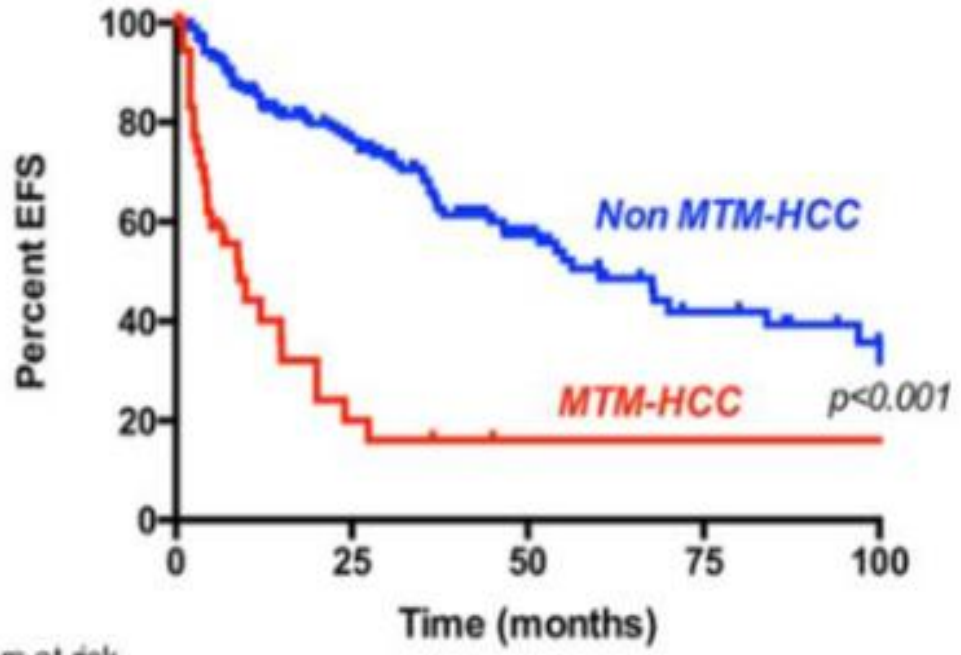
Early recurrence



Numbers at risk

Non MTM-HCC	199	161	123	107	98
MTM-HCC	38	19	11	8	6

Overall recurrence



Numbers at risk

Non MTM-HCC	199	85	38	17	9
MTM-HCC	38	5	2	2	2

Ziol M Hepatology 2018, Mulé Radiology 2020