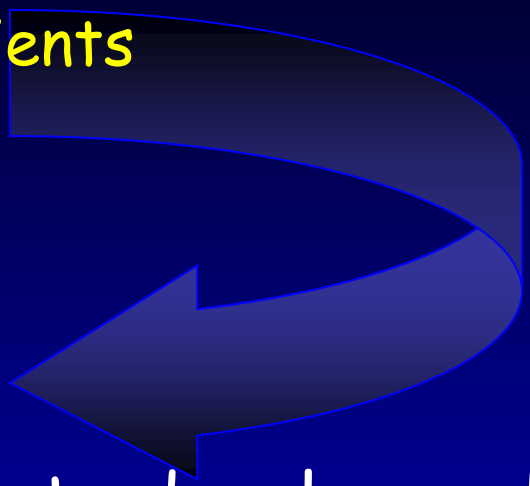
HCC e CEUS

Prof. A. Giorgio

Direttore IX UOC di Malattie Infettive
ad Indirizzo Ecointerventistico

The natural history of compensated cirrhosis due to hepatitis C virus:
a 17 – year cohort study of 214 patients



HCC was the first complication to develop and the dominant cause for increased mortality

Sangiovanni A et al. Hepatology June (43) 2006

Hepatocellular carcinoma (HCC) is the 7th most common cancer worldwide.

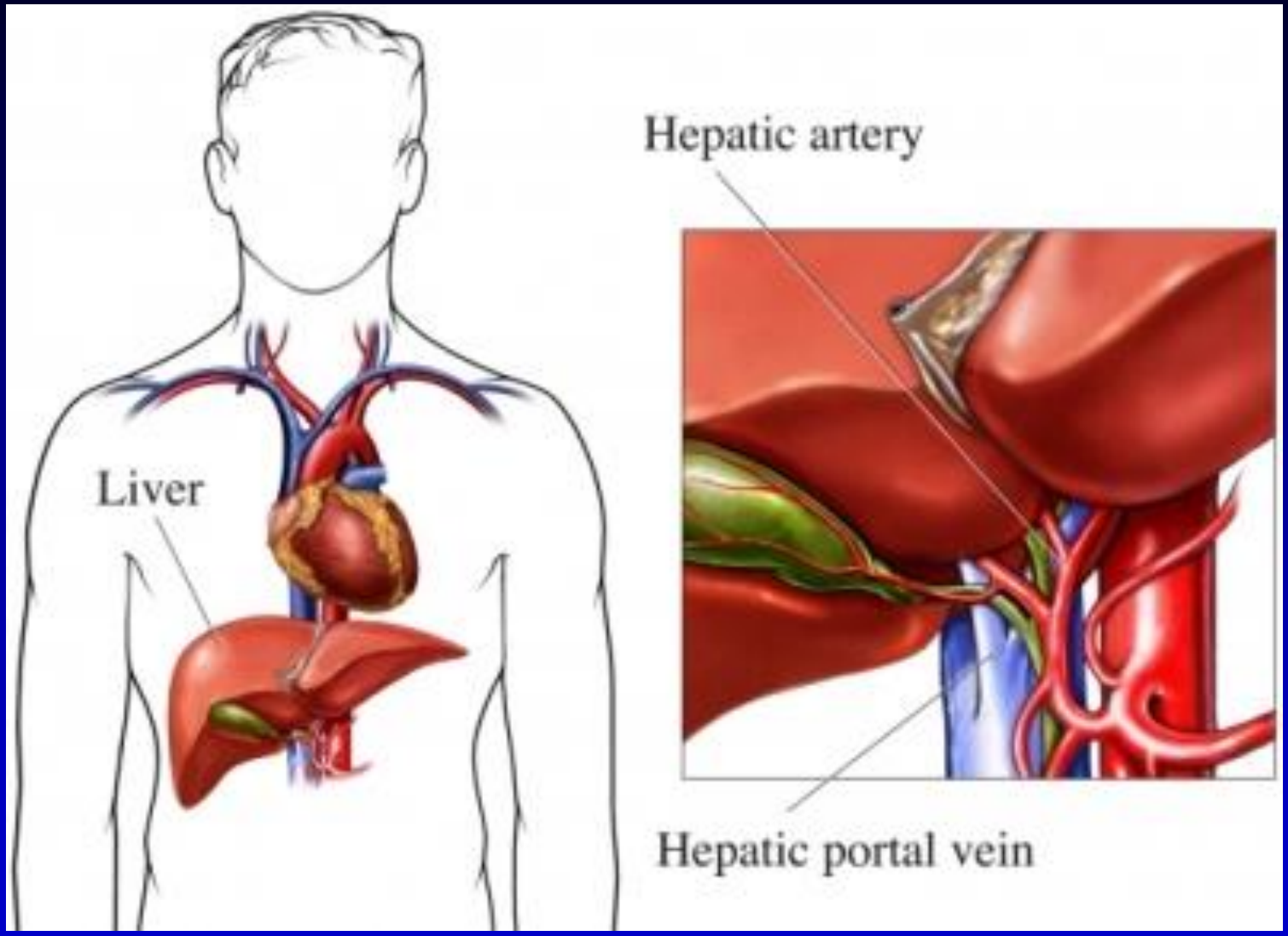
In 2008:
748,000 new cases
696,000 deaths

Ferlay J et al. GLOBOCAN 2008. Int Journal Cancer 2010

Vascular changes in hepatocellular carcinoma ZF. Yang et al Anat Rec 2008

- ✓ HCC is one of the most vascular solid tumors, in which angiogenesis plays an important role

- ✓ the status of angiogenesis in HCC correlates with the disease progression and prognosis and thus provides a potential therapeutic target

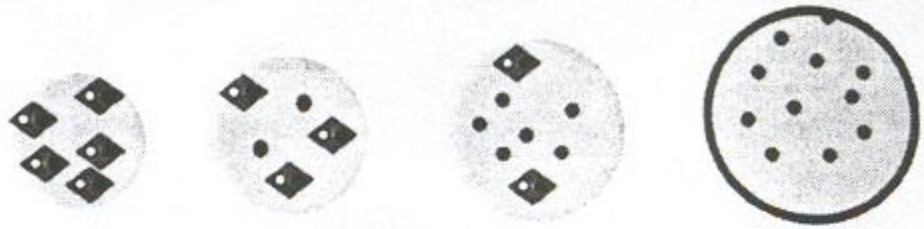

Liver
Hepatic artery
Hepatic portal vein

hepatocarcinogenesis

Neoangiogenesis and capillarization leads to gradual change in blood supply

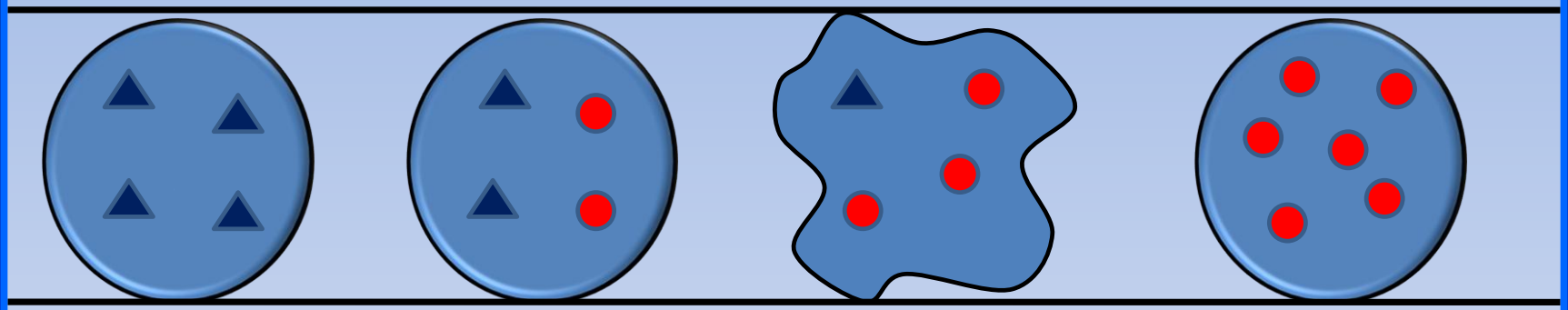
RN → DN → HCC

International Consensus on Small Nodular Lesions in cirrhotic liver



IWP classification	L-DN	H-DN	WD-HCC	MD-HCC
Pathological features				
gross appearance			vaguely-nodular	distinctly-nodular
stromal invasion	(−)	(−)	+ / −	+ / −
Clinical (imaging)				
arterial supply	iso / hypo	iso / hypo	iso / hypo rarely hyper	hyper
portal vein supply	+	+	+	−
Clinico-pathological	Premalignant		Early HCC	Progressed HCC

Hepatology, february 2009



L-DN | H-DN | WD-HCC | MD-HCC

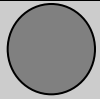
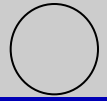
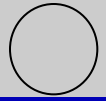
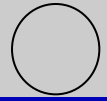
Partially modified by Hepatology
Feb. 2009

AJR November 2004

Contrast-Enhanced Sonographic Appearance of Hepatocellular Carcinoma in Patients with Cirrhosis: Comparison with Contrast-Enhanced Helical CT Appearance

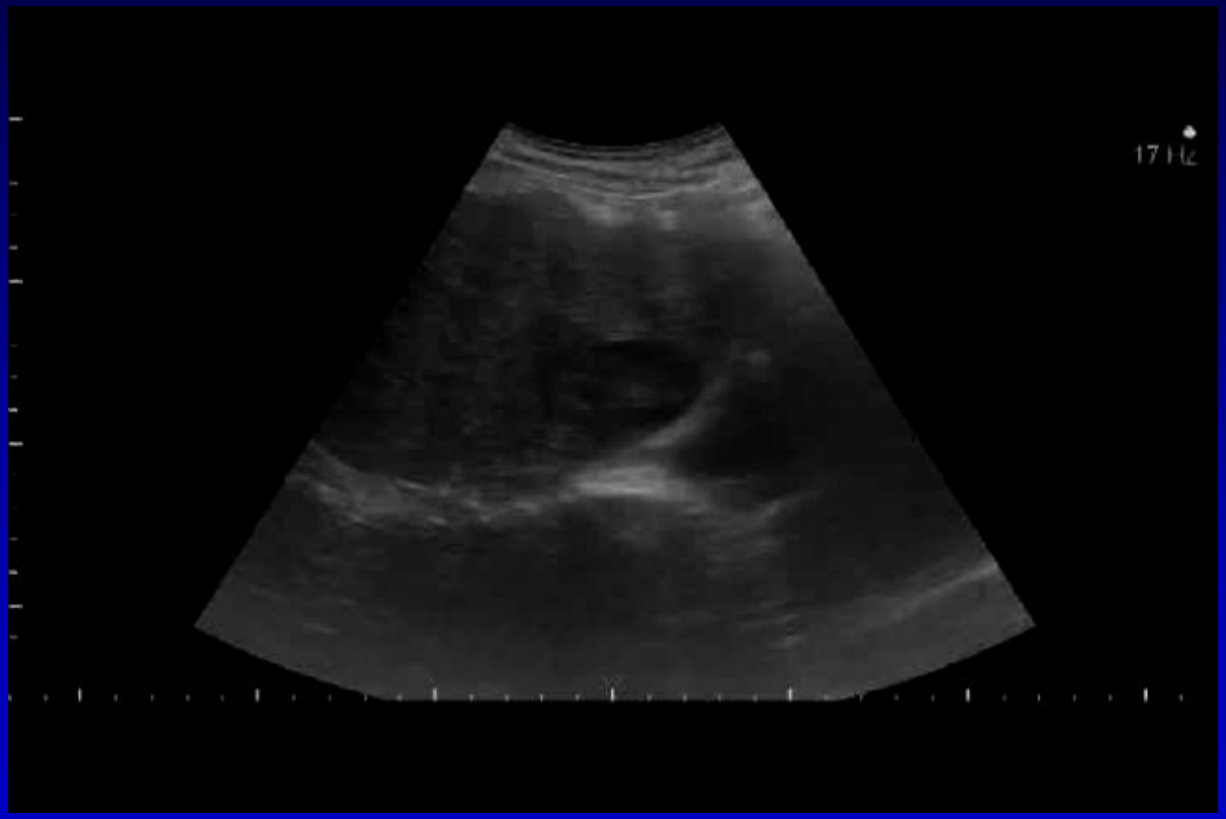
Antonio Giorgio et al

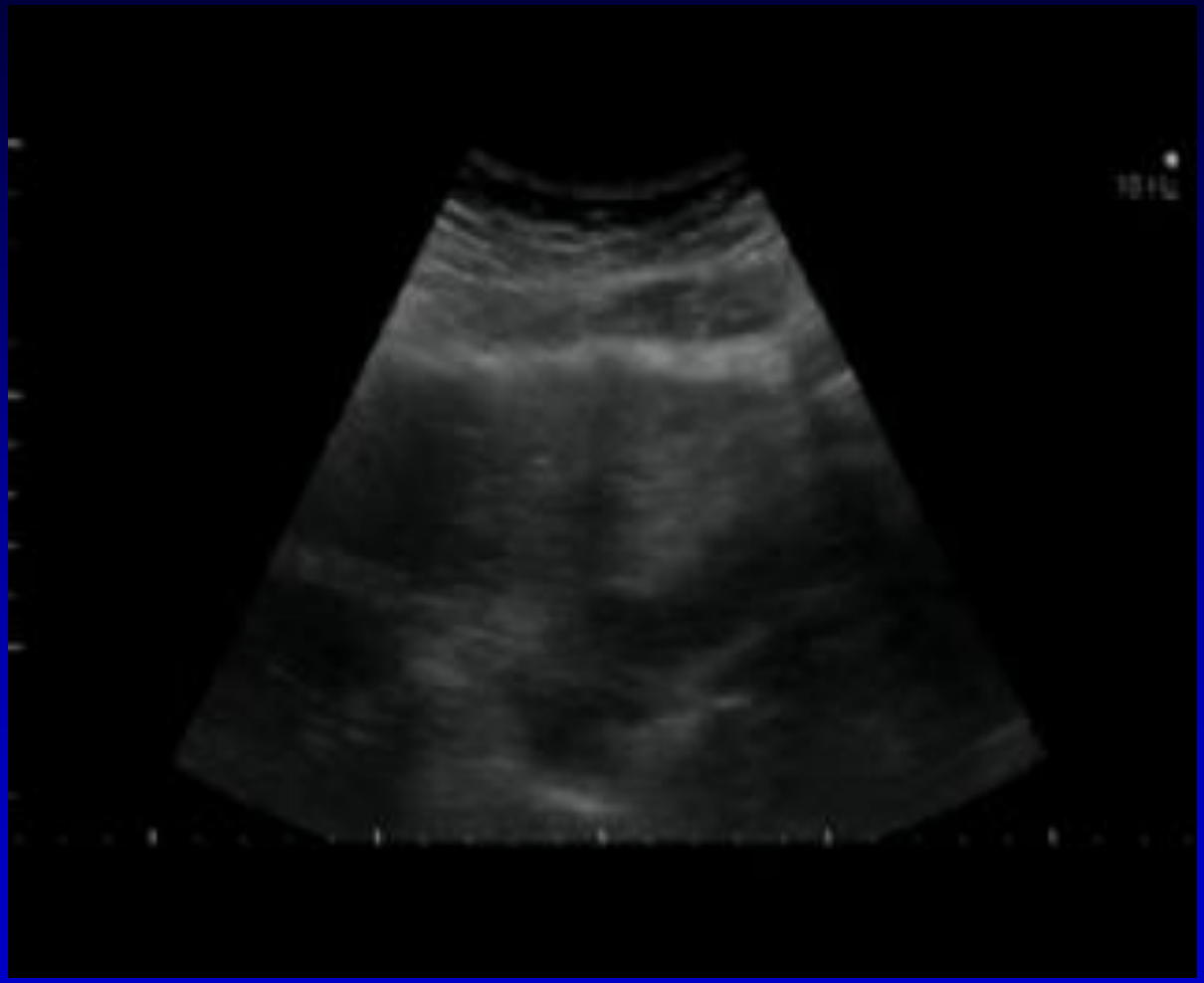
CEUS: Patterns HCC

Comportamento	Fase arteriosa 15-30 sec.	Fase portale 30-60 sec	Fase sinusoidale 60-240 sec
Ipervascolare			
Ipervascolare			
Avascolare			
Non visibile			

A. Giorgio AJR 2004


ALOKA Interventional US
Cotugno Hosp -Naples
Y
20-03-'09
12:47:16
MI(Mon)=0.17
A:**.*s **f
MI =0.56 TIS< 0.4 70%
3.7SM
27Hz1
R13.0
G70
C11
5.00M
27Hz2
R13.0
G52
C11
14:Addome CHE 30% Probe:9130



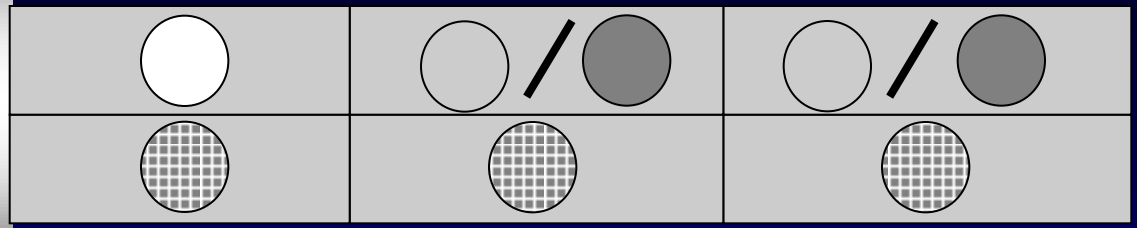


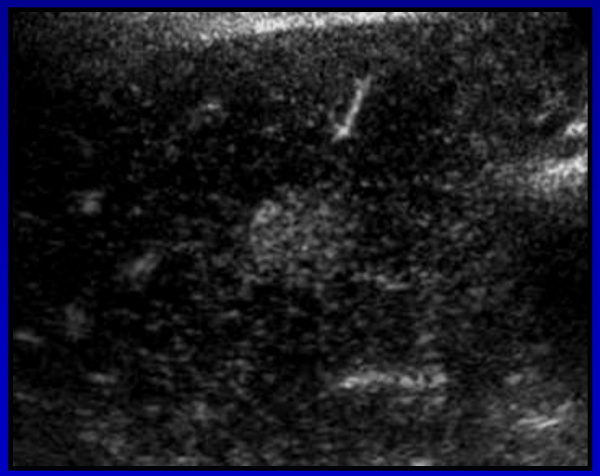

ALOKA Interventional US
Cotugno Hosp -Naples
Y
20-03-'09
13:26:30
MI(Mon)=0.07
A:**.*s ***f
MI =0.13 TIS< 0.4 30%
3.75M
13Hz1
R17.0
G74
C11
1.50MB
13Hz2
R17.0
G56
C12
A1
13:Addome CHE 30% Probe:9130

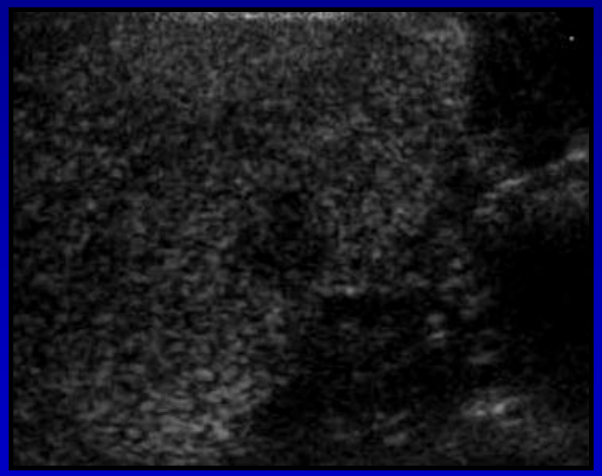
Comportamento

Ipervascolare

Ipervascolare



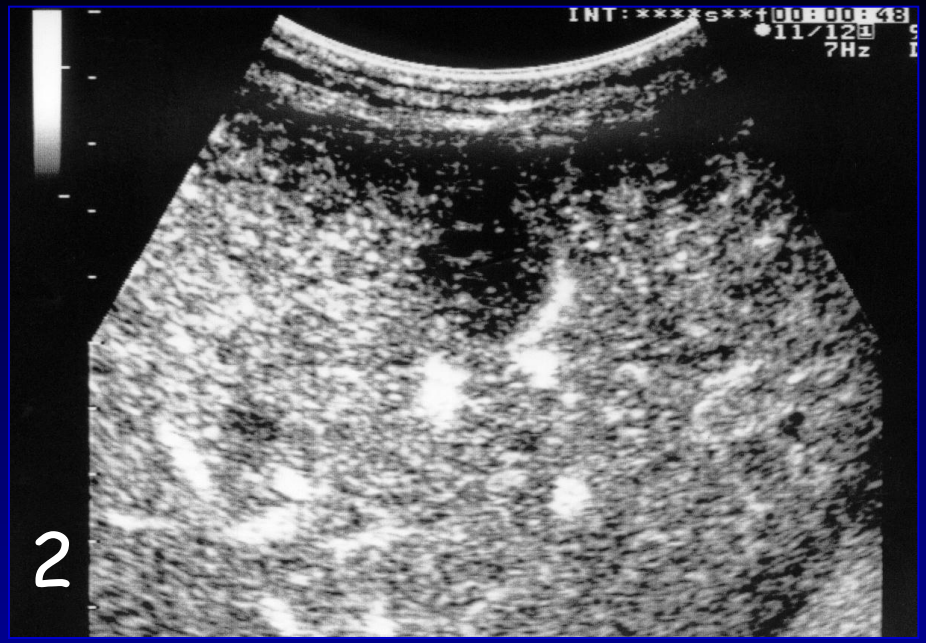


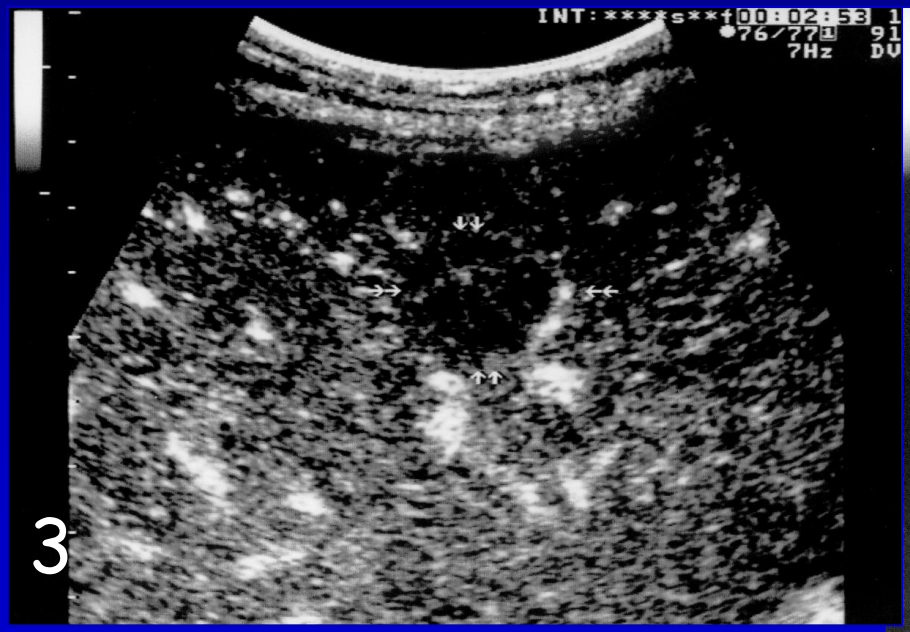


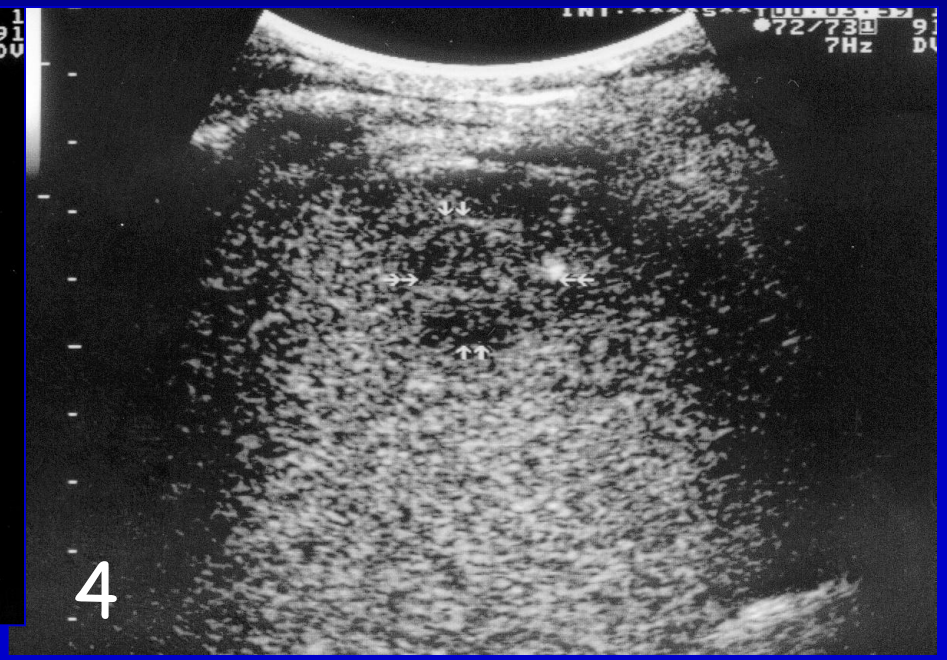
CEUS: Patterns HCC

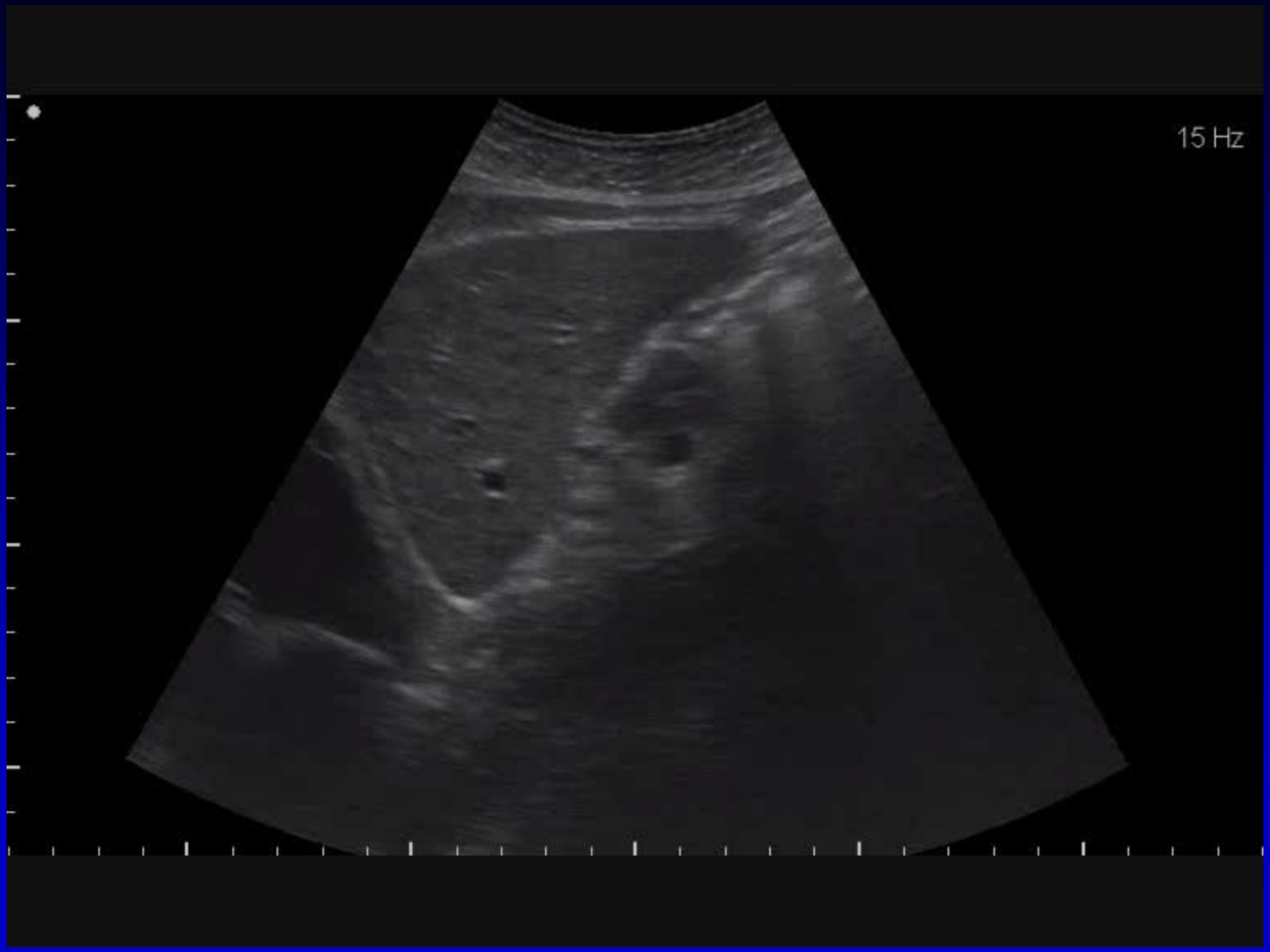
Comportamento	Fase arteriosa 15-30 sec.	Fase portale 30-60 sec	Fase sinusoidale 60-240 sec
Ipervascolare omogeneo			
Ipervascolare reticolare			


12/13
8Hz
49
F12
1


INT:
11/12
7Hz
2


INT:
00:02:53
76/77
7Hz
3


72/73
7Hz
4


15 Hz

Small nodular lesions in cirrhotic livers: characterization with contrast enhanced ultrasound

A. Giorgio et al, Anticancer Research, June 2011

to investigate the usefulness of
CEUS in the characterization of dysplastic nodules (DN), early hepatocellular carcinoma (HCC) and overt HCC ≤ 2 cm during US surveillance in cirrhosis

✓ 36 consecutive pts with a single nodule ≤ 2 cm (9-20 mm) underwent CEUS, all 36 underwent biopsy

histology

6 pts had low grade dysplastic nodule (LGDN)
5 had high grade dysplastic nodule (HGDN), 14 and 11 patients had early and overt HCC, respectively

Small nodular lesions in cirrhotic livers: characterization with contrast enhanced ultrasound

A. Giorgio et al, Anticancer Research, June 2011

CEUS

On CEUS, 3 LGDN were missed and 8 HGDN were avascular;
1 early HCC was missed
and 1 was avascular, 12 early HCC showed
the so called "reticular pattern"

10 overt HCC presented the typical rapid, intense and homogeneous enhancement on arterial phase and washout in the portal phase and 1 showed the "reticular pattern"

Small nodular lesions in cirrhotic livers: characterization with contrast enhanced ultrasound

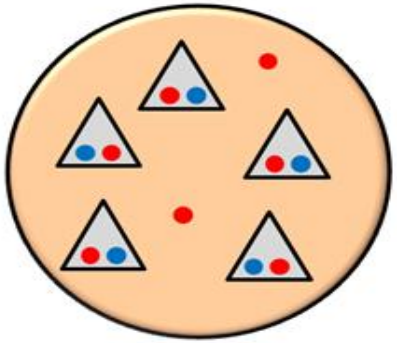
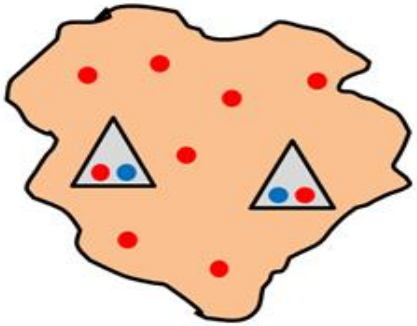
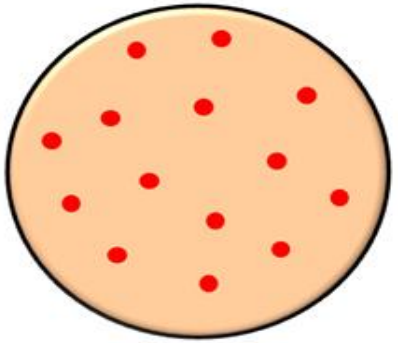
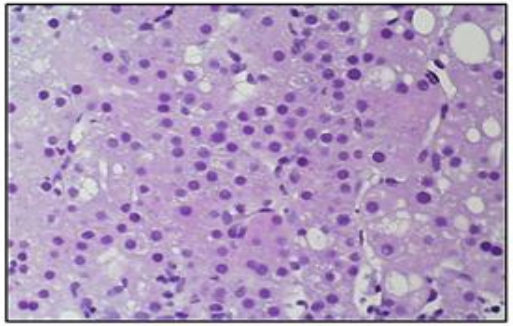
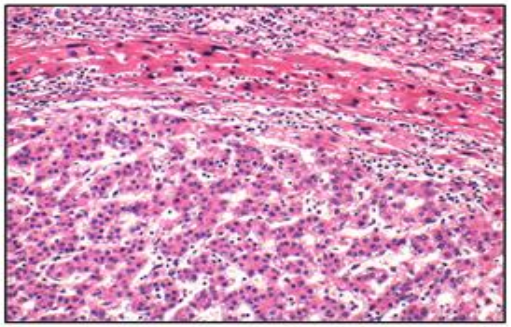
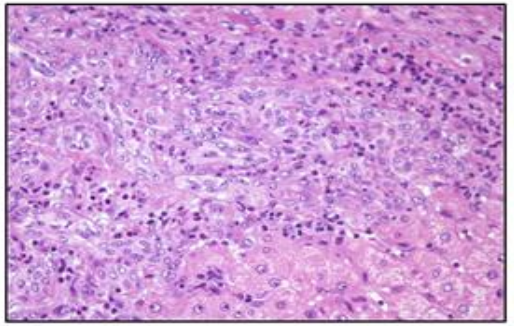
A. Giorgio et al, Anticancer Research, June 2011

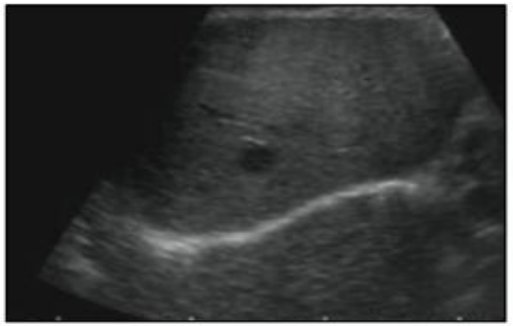
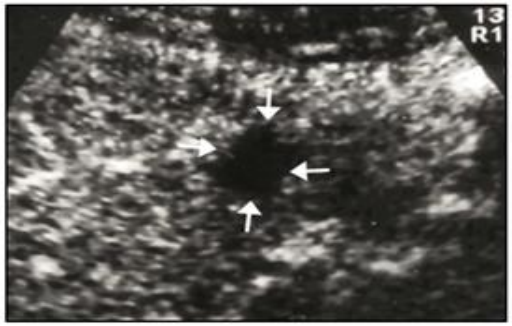
conclusion

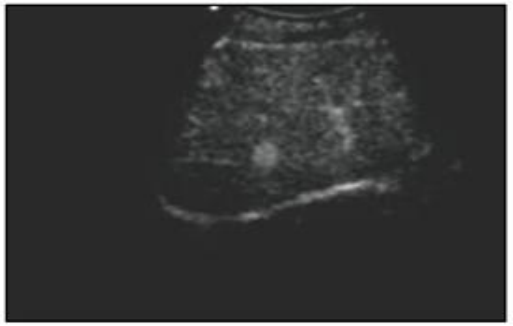
✓ CEUS is a useful technique in the characterization of small nodular lesions emerging during US surveillance of cirrhosis, with high sensitivity and high specificity

✓ CEUS is able to identify the unpaired arteries substituting portal tracts of early HCC which lead to well differentiated overt HCC

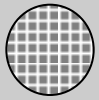
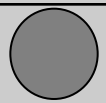
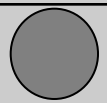
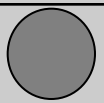
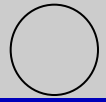
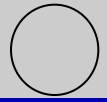
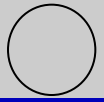
✓ On the basis of arterial hypervascularity, sensitivity of CEUS for early HCC was 87% and specificity 100%; for overt HCC sensitivity was 91% and specificity 98%

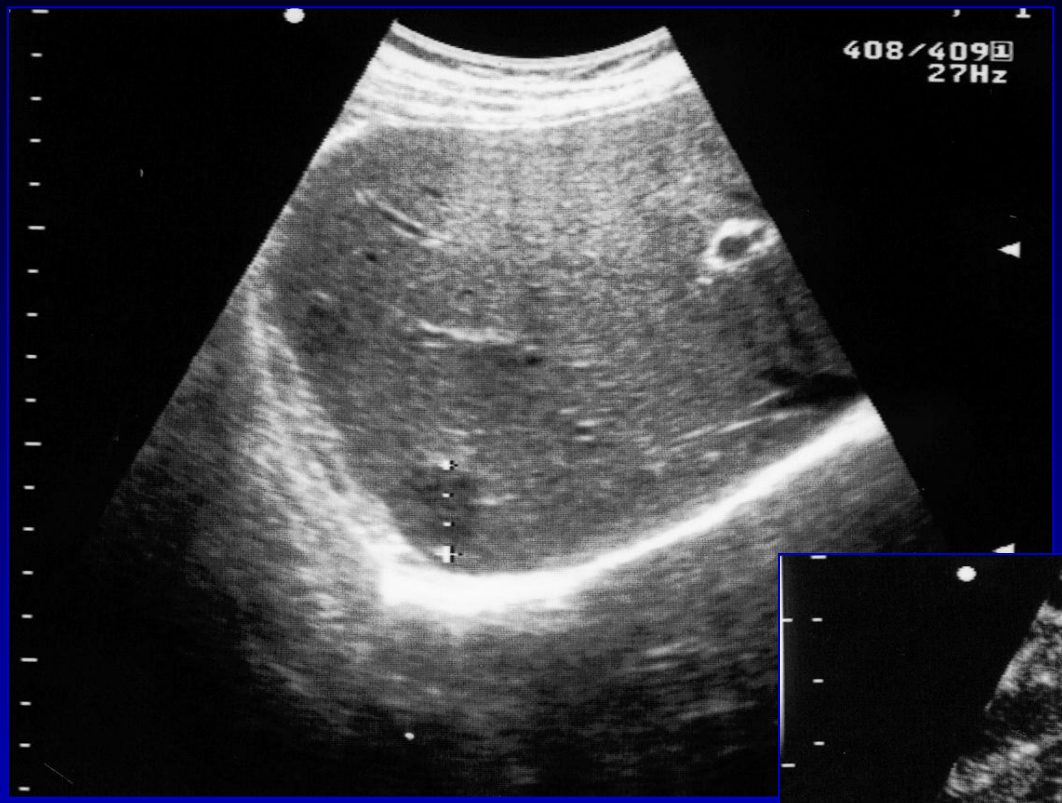



13
R1



CEUS: Patterns HCC

Comportamento	Fase arteriosa 15-30 sec.	Fase portale 30-60 sec	Fase sinusoidale 60-240 sec
Ipervascolare			
Ipovascolare			
Avascolare			
Non visibile			

A. Giorgio et al AJR 2004


408/409
27Hz


51/52
10Hz

Cotrast-enhanced ultrasound of hepatocellular carcinoma: Correlation of washout time and angiogenesis

Xia Y et al, Clin Hem Microcirc, 2011

The wash-out time was longer in well differentiated HCC pts compared to those with moderately poorly to differentiated HCC

Evaluation of HCC by contrast enhanced sonography: correlation with pathologic differentiation

Xu JF et al, J Ultrasound Med, 2011

The time to peak, contrast enhanced time, and wash-out time of the well differentiated HCC were longer than those of the moderately to poorly differentiated HCC

Cost-effectiveness analysis on the surveillance for HCC in liver cirrhosis pts using contrast enhanced ultrsonography

Tanaka H et al, Hepatol Res, Jan 2012

CONCLUSION

"CEUS survellance for HCC is a cost effective strategy for cirrhotic and gains longest additional life years,with similar degree for Incremental Cost-Effectiveness Ratio in the US surveillance group.

CEUS surveillance using Sonazoid is expected to be used not only in Japan, but also world-wide"

CEUS and contrast enhanced CT

Giorgio et al. AJR;2004

Gaiani et al. J Hepatol; 2004

Day et al. Hepatol Res; 2008

Pompili et al. Dig Liver Dis; 2009

Similar sensitivity and specificity

Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: prospective validation of the noninvasive diagnostic criteria for HCC. Forner A Llovet JM, Bruix J et al, Hepatology, 47 (1) 2008

AIM

to evaluates the accuracy of CEUS and MRI for the diagnosis of nodules 20 mm or smaller detected US surveillance

89 cirrhotic pts without prior HCC in whom US detected a small solitary nodule (mean 14 mm)

Methods

✓ MRI, CEUS and FNB were performed at baseline

✓ intense arterial contrast uptake followed by washout in the delayed/venous phase was registered as conclusive for HCC

Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: prospective validation of the noninvasive diagnostic criteria for HCC. Forner A, Llovet JM, Bruix J et al, Hepatology, 47 (1) 2008

results

- ✓ diagnosis of HCC 20 mm or smaller can be established without a positive biopsy if both CEUS and MRI are conclusive
- ✓ however, sensitivity of these noninvasive criteria is 33% and as occurs with biopsy, absence of a conclusive pattern does not rule out malignancy
- ✓ these results validate the American Association for the study of Liver Disease (AASLD) guidelines

Contrast-enhanced sonography in the characterization of small hepatocellular carcinomas in cirrhotic patients comparison with contrast-enhanced ultrafast magnetic resonance imaging

A. Giorgio et al, AntiCancer Research (27); December 2007

Results

Concordance between CEUS and MRI

Overall: 75.0%

HCCs 11-30 mm: 89.2%

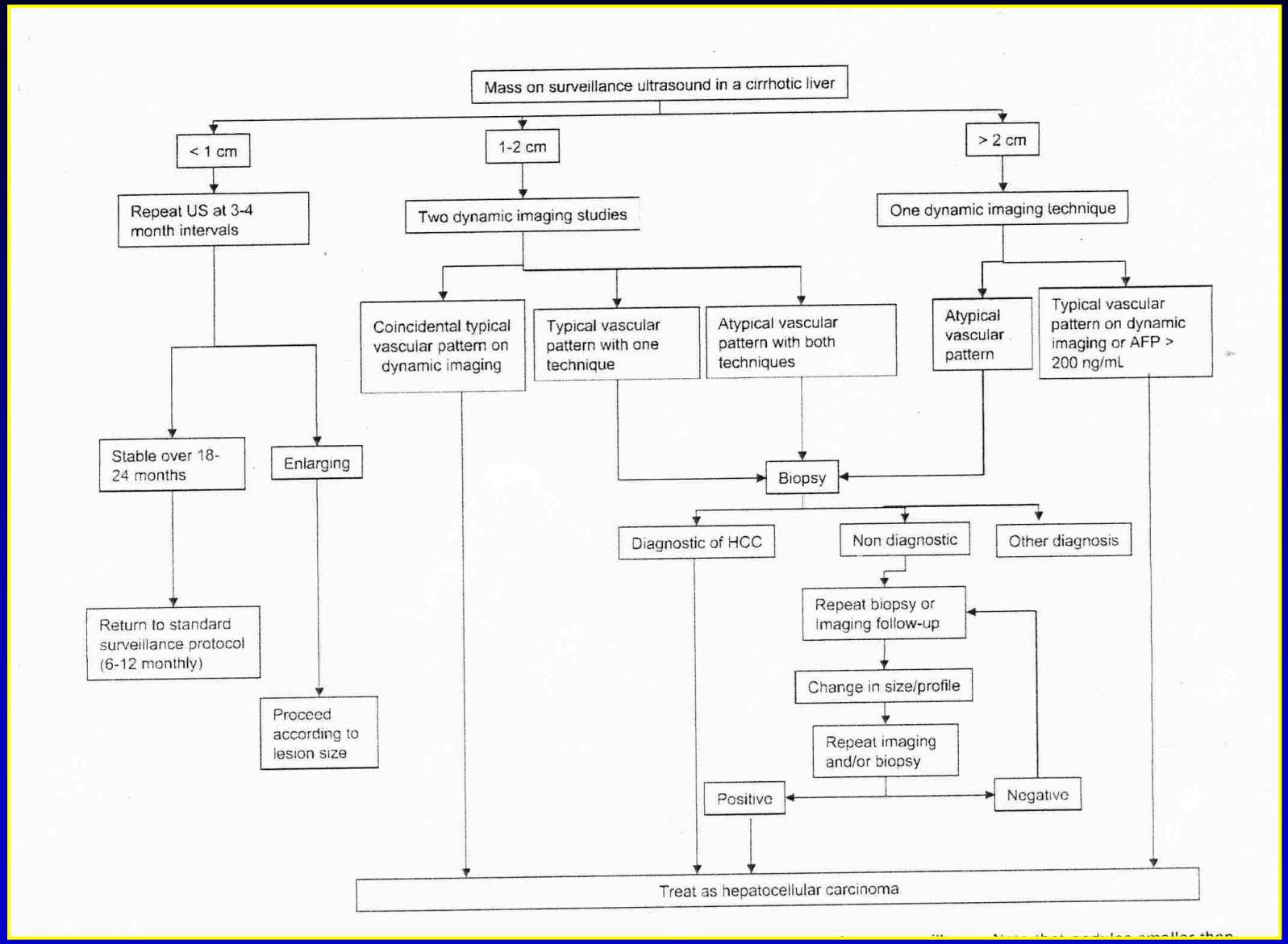
HCCs ≤ 10 mm: 27.3%

AASLD practice guideline

Management of Hepatocellular Carcinoma

Jord Bruix and Morris Sherman

Hepatology, November 2005


Mass on surveillance ultrasound in a cirrhotic liver
< 1 cm
1-2 cm
> 2 cm
Repeat US at 3-4 month intervals
Two dynamic imaging studies
One dynamic imaging technique
Coincidental typical vascular pattern on dynamic imaging
Typical vascular pattern with one technique
Atypical vascular pattern with both techniques
Atypical vascular pattern
Typical vascular pattern on dynamic imaging or AFP > 200 ng/mL
Stable over 18-24 months
Enlarging
Biopsy
Diagnostic of HCC
Non diagnostic
Other diagnosis
Repeat biopsy or imaging follow-up
Return to standard surveillance protocol (6-12 monthly)
Change in size/profile
Proceed according to lesion size
Repeat imaging and/or biopsy
Positive
Negative
Treat as hepatocellular carcinoma

Guidelines and Good Clinical Practice Recommendations for Contrast Enhanced Ultrasound (CEUS) – Update 2008

EFSUMB study group

M. Claudon[1], D. Cosgrove[2], T. Albrecht[3], L. Bolondi[4], M. Bosio[5], F. Calliada[6], J.-M. Correas[7], K. Darge[8], C. Dietrich[9], M. D'Onofrio[10], D. H. Evans[11], C. Filice[12], L. Greiner[13], K. Jäger[14], N. de. Jong[15], E. Leen[16], R. Lencioni[17], D. Lindsell[18], A. Martegani[19], S. Meairs[20], C. Nolsøe[21], F. Piscaglia[22], P. Ricci[23], G. Seidel[24], B. Skjoldbye[25], L. Solbiati[26], L. Thorelius[27], F. Tranquart[28], H. P. Weskott[29], T. Whittingham[30]

EFSUMB Study Group et al. Guidelines and Good... Ultraschall in Med 2008; 29: 28–44

Guidelines and Good Clinical Practice Recommendations for Contrast Enhanced Ultrasound (CEUS) – Update 2008

✓ the diagnostic of HCC for lesions >2 cm, newly emerged during surveillance in cirrhosis, can be established on CEUS alone

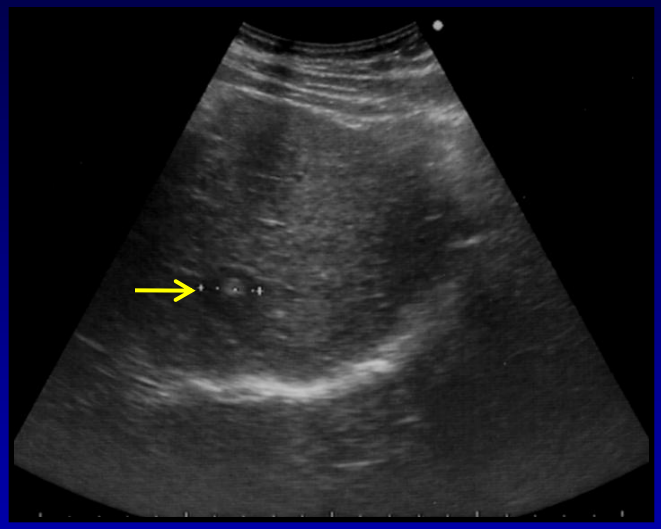
✓ in addition to CEUS, a confirmation of arterial hypervascularisation and subsequent wash out by CT/MR is requested to established the diagnostic of HCC in FLL 1-2 cm detected during surveillance, programs

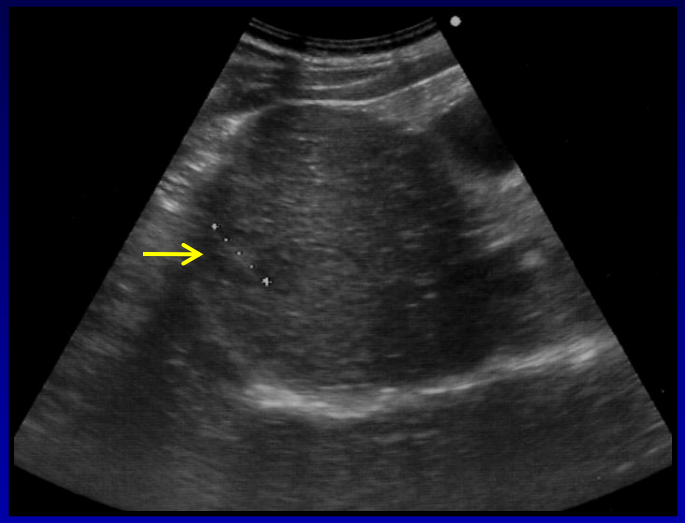
M. Claudon et al, European Journal of Ultrasound (29),2008

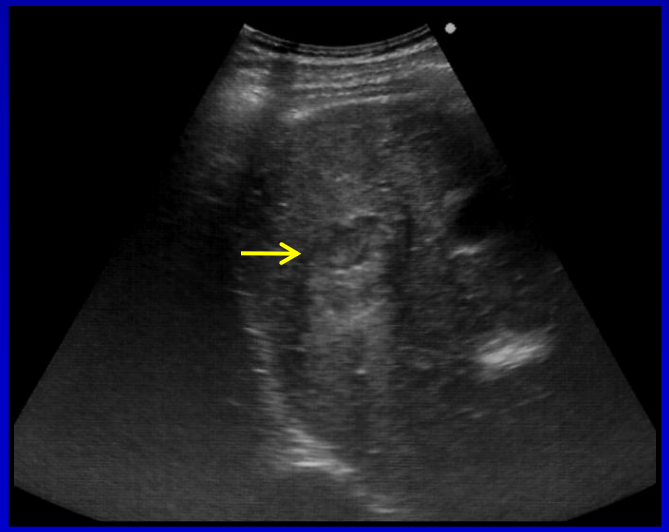
INTRAHEPATIC CHOLANGIOCARCINOMA

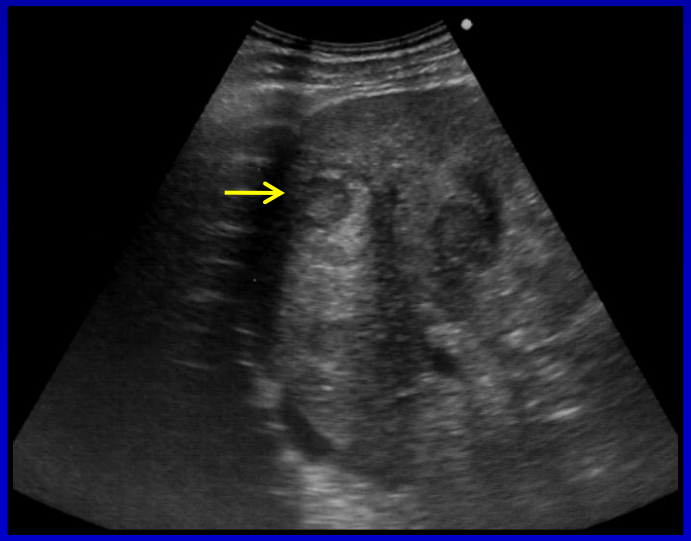
Intrahepatic Cholangiocarcinoma (ICC)

US appearance



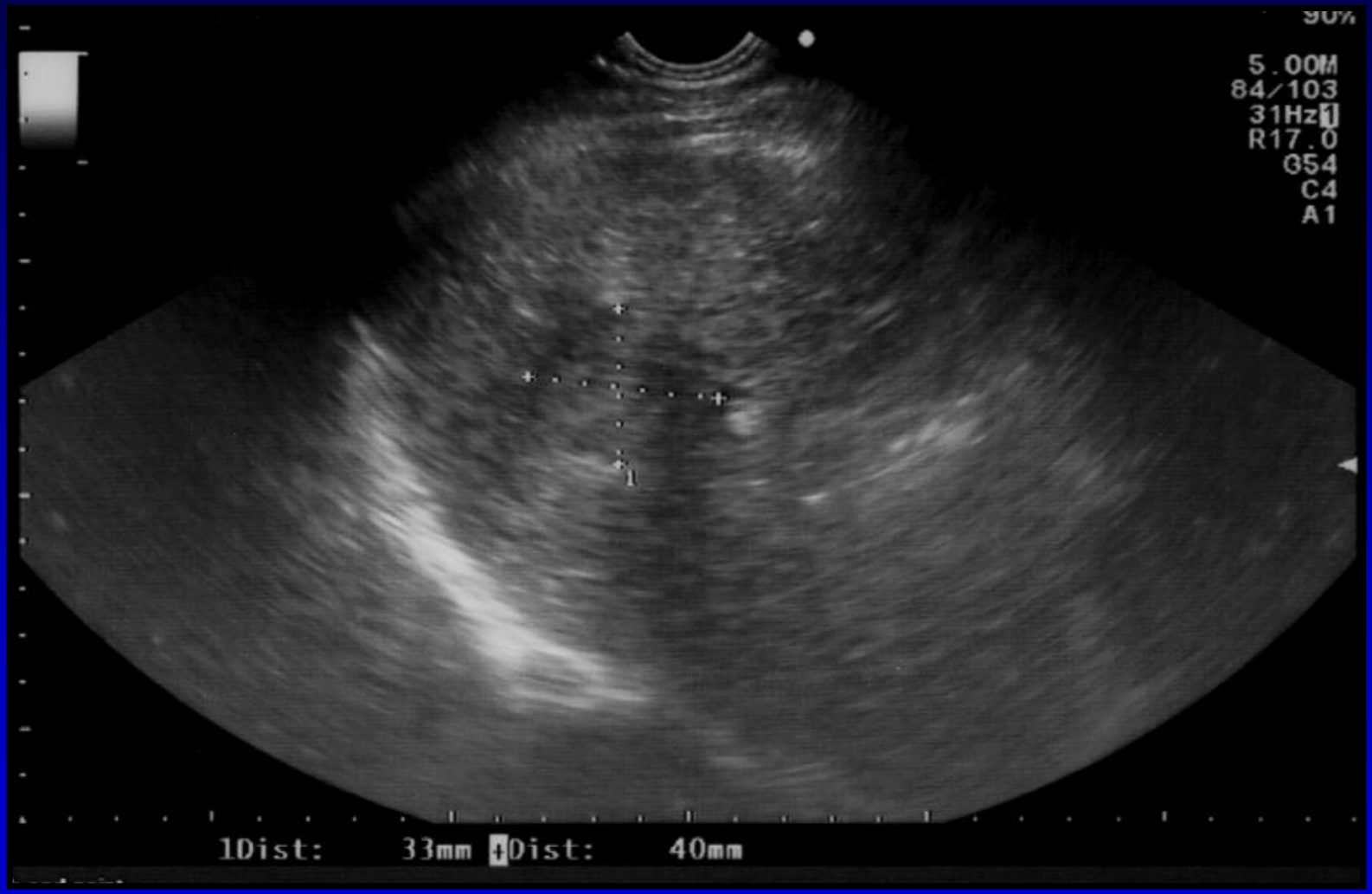






Intrahepatic Cholangiocarcinoma (ICC)

US appearance



Enhancement patterns of intrahepatic cholangiocarcinoma: comparison between contrast-enhanced ultrasound and contrast-enhanced CT

Chen LD et al. BJR 2008

ARTERIAL PHASE ENHANCEMENT PATTERNS OF ICC ON CEUS AND CECT

Type 1 - Peripheral irregular rim-like hyperenhancement
Irregular rim-like hyperenhancement at the peripheral portion of the lesion and inhomogeneous hypoenhancement at the central portion, with strip-like enhancement extending to the central portion of the lesion .

Type 2 – Diffuse heterogeneous hyperenhancement
Heterogeneous hyperenhancementat at both the periphery and the central portion of the lesion

Type 3 – Diffuse homogeneous hyperenhancement
Homogeneous hyperenhancementat at both the periphery and the central portion of the lesion

Type 4 – Diffuse heterogeneous hypoenhancement
Heterogeneous hypoenhancement at both the periphery and the central portion of the lesion

Enhancement patterns of intrahepatic cholangiocarcinoma: comparison between contrast-enhanced ultrasound and contrast-enhanced CT

Chen LD et al. BJR 2008

PORTAL PHASE (CEUS 31-120 sec; CECT 50-60 sec)

- **97,5% of the lesions were hypoenhancing on CEUS**
- 62,5% of the lesions were hypoenhancing on CECT

LATE PHASE (CEUS 121-360 sec)

100% of the lesions were hypoenhancing on CEUS

Intratumoral blood vessels were exhibited in

- **50% of the lesions on CEUS**
- 22,5% of the lesions on CECT

Enhancement patterns of intrahepatic cholangiocarcinoma: comparison between contrast-enhanced ultrasound and contrast-enhanced CT

Chen LD et al. BJR 2008

The different enhancement patterns during arterial phase may relate to different pathological components in the tumour:

- **Rim-like hyperenhancement** may be due to the presence of a rich tumour cellularity in the peripheral portion and fibrosis in the central portion

- **Diffuse hyperenhancement** may be the result of a rich cellularity in all the portions of the tumour

- **Diffuse hypoenhancement** may be due to the presence of abundant fibrous stroma in the tumour

Smaller lesions tend to show homogeneous hyperenhancement

Enhancement patterns of intrahepatic cholangiocarcinoma: comparison between contrast-enhanced ultrasound and contrast-enhanced CT

Chen LD et al. BJR 2008

CONCLUSIONS

The enhancement patterns of ICC on CEUS were consistent with those on CECT in the arterial phase, whereas in the portal phase ICC faded out more obviously on CEUS than on CECT.

CEUS had the same accuracy as CECT for diagnosing of ICC, and thus could be used as a new modality for the characterization of ICC


24Hz
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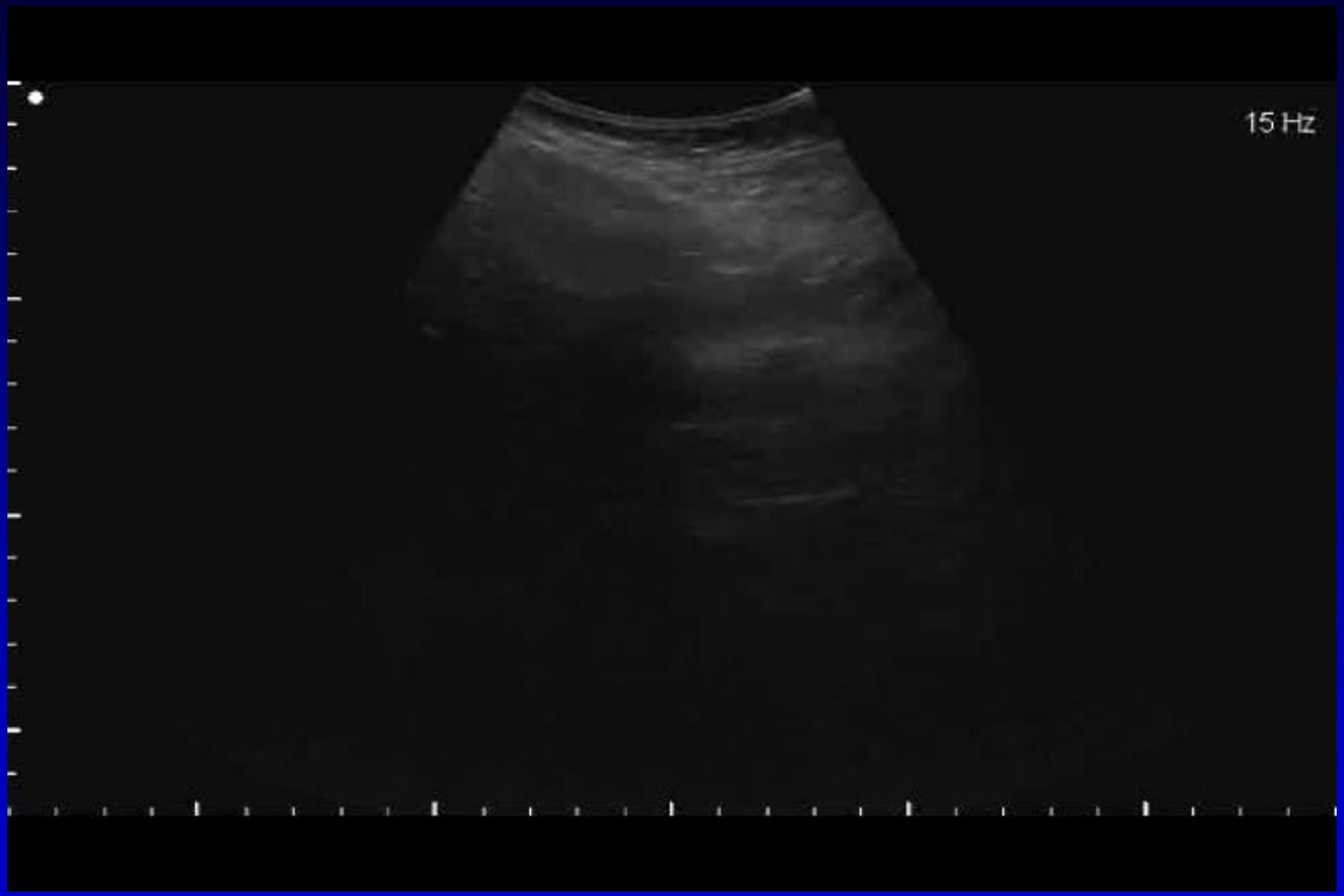
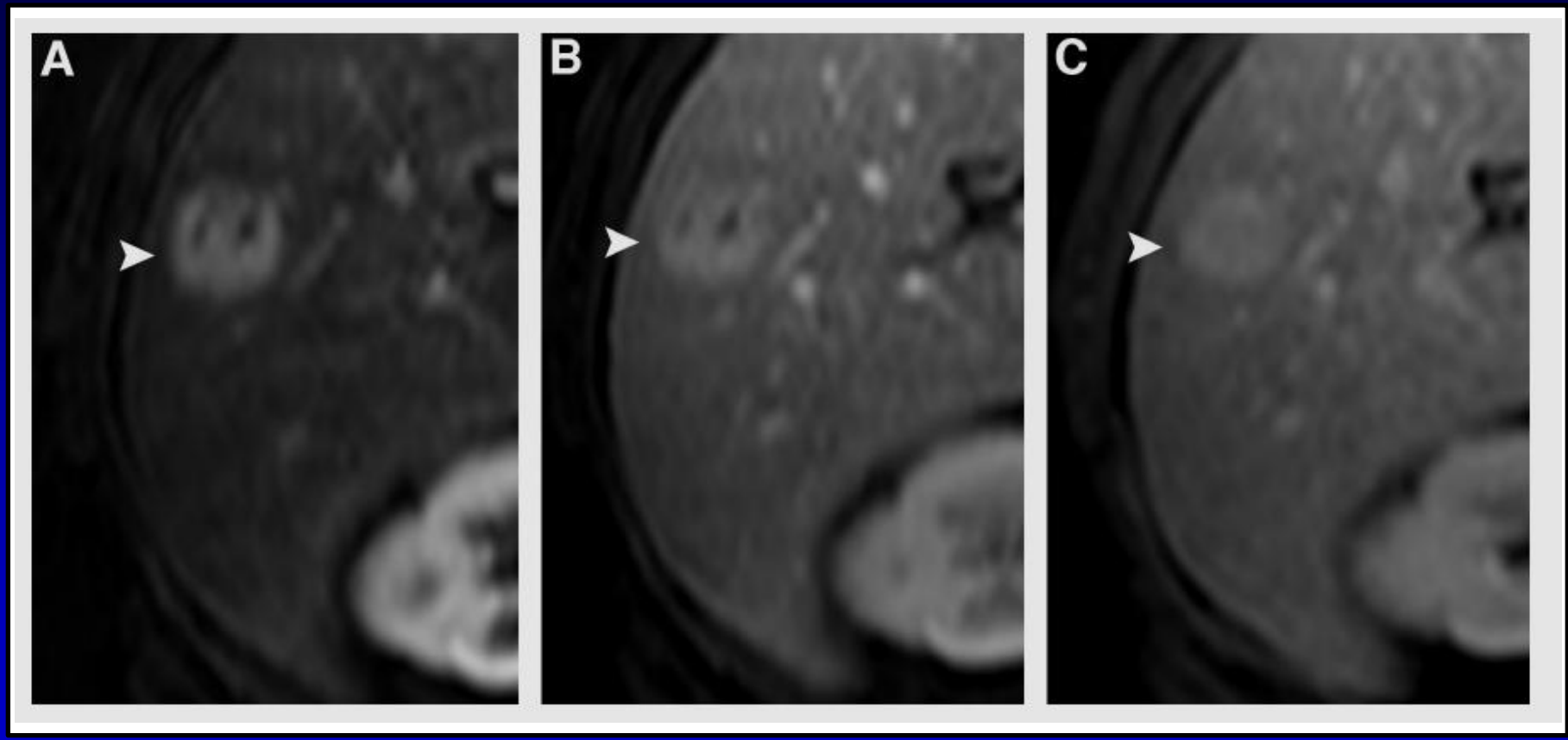

15 Hz

Cholangiocarcinoma in cirrhosis:absence of contrast washout in delayed phases by MRI avoids misdiagnosis of HCC

Rimola J et al. Hepatology 2009



Arterial phase | Portal phase | Delayed phase

A 57 year old woman with ICC in the right lobe of the liver

Intrahepatic Peripheral Cholangiocarcinoma in Cirrhosis Patients May Display a Vascular Pattern Similar to Hepatocellular Carcinoma on Contrast-Enhanced Ultrasound

Vilana et al. Hepatology 2010

CEUS findings

"in our study 5 ICC displayed a homogeneous arterial contrast uptake followed by a rapid contrast washout in the portal phase (<60 sec), thus being fully indistiguishable from HCC"

"Strict applications of the AASL guidelines would have led to a false HCC diagnosis in those 3 nodules larger than 2 cm if CEUS had been the only dynamic imaging technique applied"

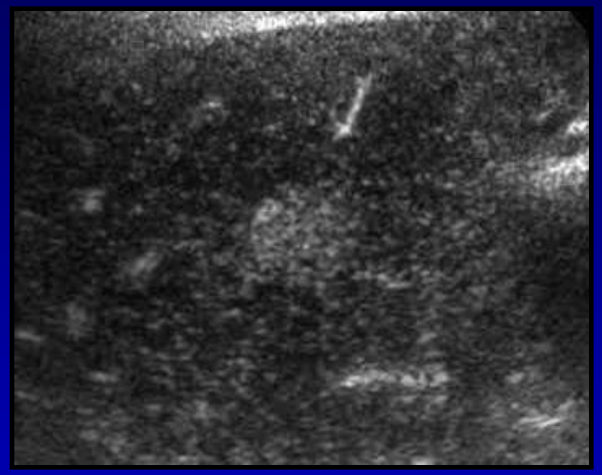
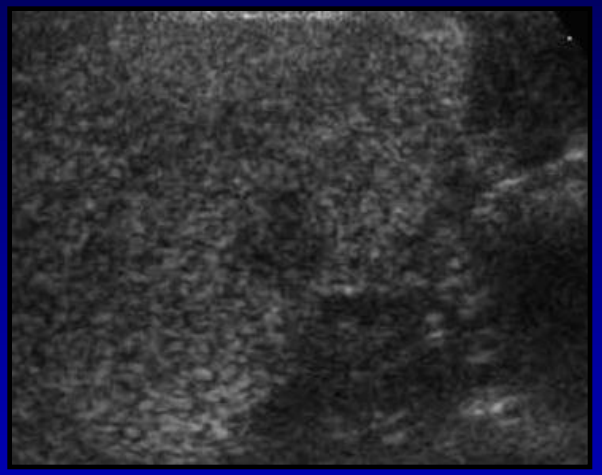
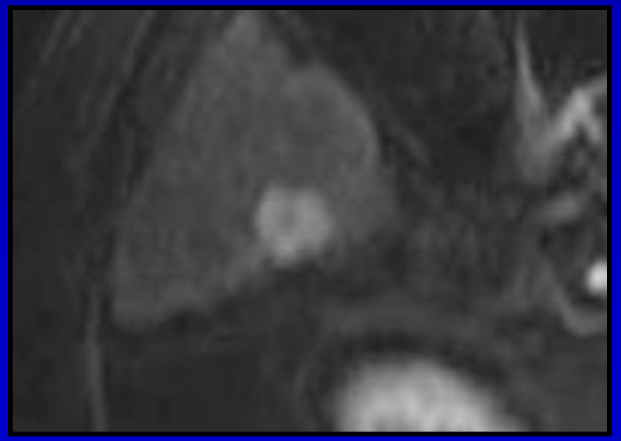
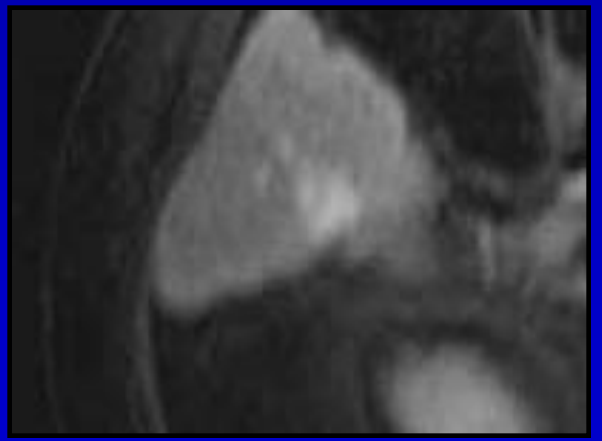
MRI findings

"in all our patients an MRI scan was done for diagnosis and staging purposes. The most frequent finding was progressive contrast uptake through the different phases, and in no cases was a wash-out detected, allowing a clear differentiation with HCC"

Intrahepatic Peripheral Cholangiocarcinoma in Cirrhosis Patients May Display a Vascular Pattern Similar to Hepatocellular Carcinoma on Contrast-Enhanced Ultrasound

Vilana et al. Hepatology 2010

Homogeneous hyperenhancement

	Arterial phase	Delayed phase
CEUS		
MRI		

Intrahepatic Peripheral Cholangiocarcinoma in Cirrhosis Patients May Display a Vascular Pattern Similar to Hepatocellular Carcinoma on Contrast-Enhanced Ultrasound

Vilana et al. Hepatology 2010

About EFSUMB guidelines for CEUS:

"They suggested that the typical enhanced pattern for cholangiocarcinoma is a rim-like enhancement (or non-enhancement) during the portal and delayed phases"

"However, these reccomendations are based on case-series of limited number of patients, most of them non-cirrhosis, with large tumors"

Intrahepatic Peripheral Cholangiocarcinoma in Cirrhosis Patients May Display a Vascular Pattern Similar to Hepatocellular Carcinoma on Contrast-Enhanced Ultrasound

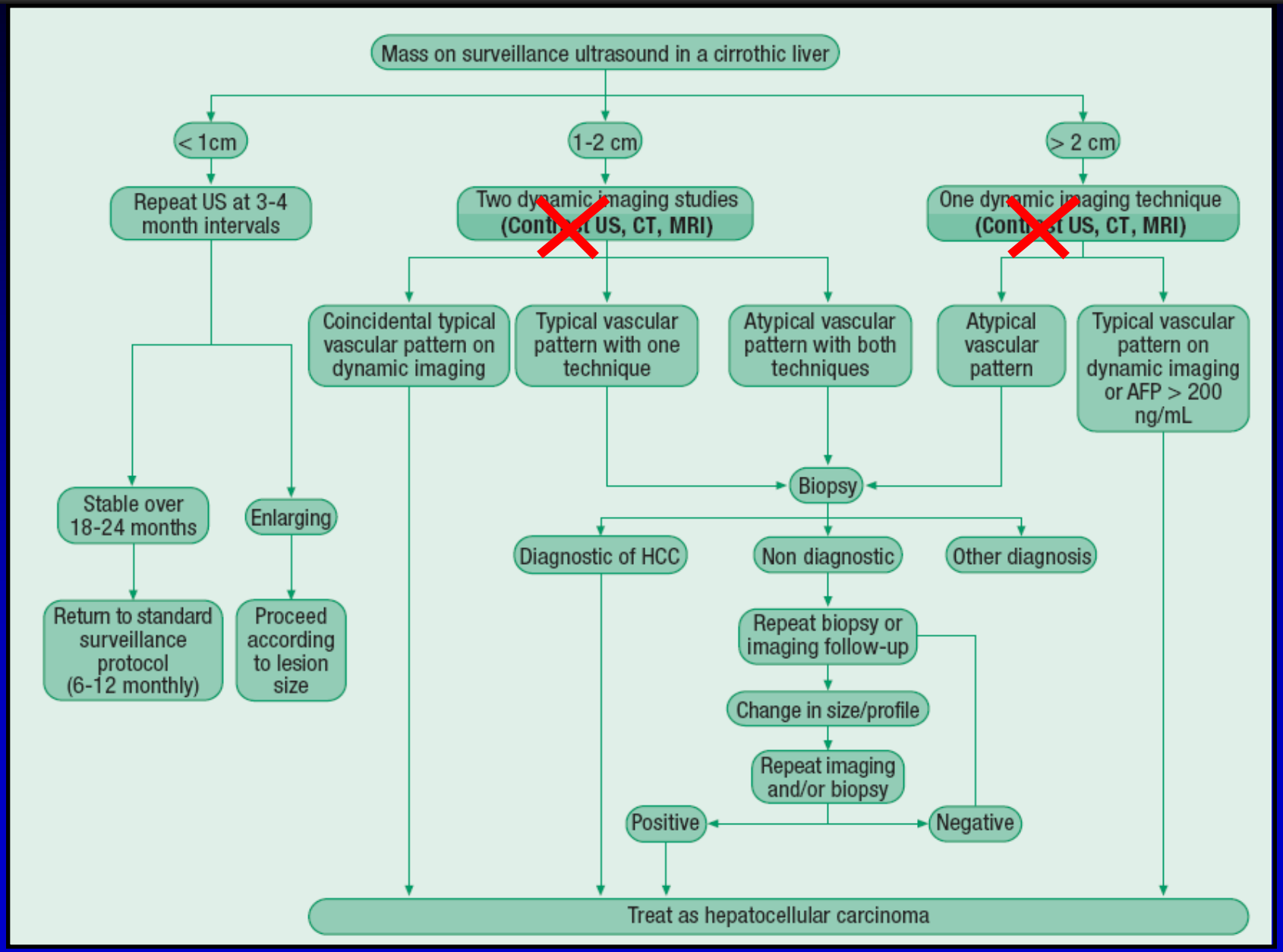
Vilana et al. Hepatology 2010

CONCLUSIONS:

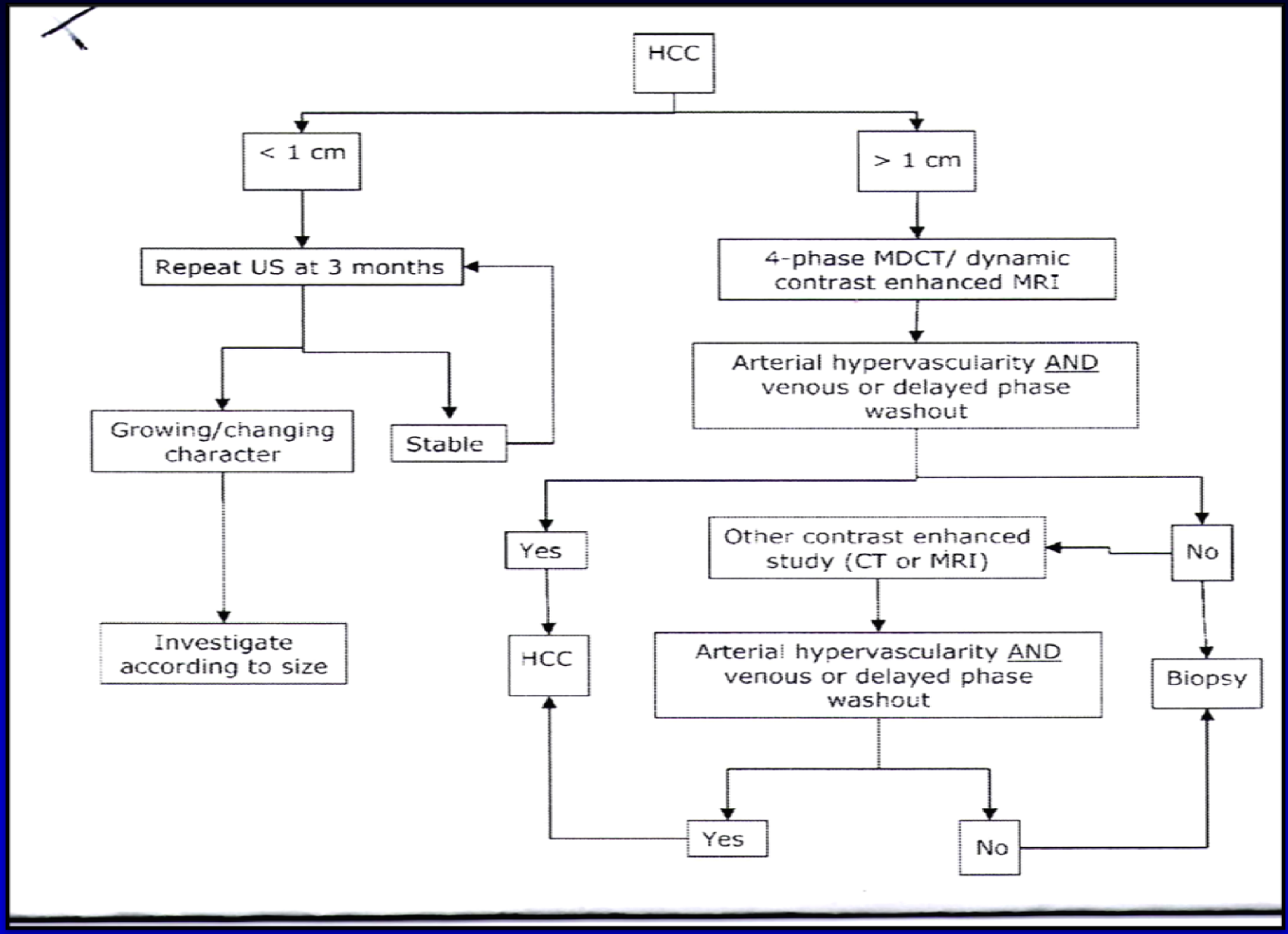
"The use of CEUS as the only imaging tool for noninvasive HCC diagnosis may be inappropriate and could not replace a dynamic MRI scan"

CEUS may establish the malignant nature of a hepatic nodule in a cirrhotic liver, ***but should not pretend to establish its final diagnosis"***

AASLD Practice Guidelines for HCC management 2005



AASLD Practice Guidelines for HCC management – Update 2010



Giorgio A, CEUS and HCC. Are the 2008 EFSUMB guidelines still valid or has their wash-out already started? Ultraschall June 2011

But, there is one more thing:

while it is well known that CEUS has become a complementary exam to the conventional US both in European and Asian countries as the first radiological tool in the characterization of focal liver lesions, it is also known that

CEUS cannot assess the staging of intra or extra hepatic HCC -i.e. presence of a single or multiple hepatic nodules or presence of spread in other abdominal organs- because, **using CEUS, it is possible to study a single nodule each time** (for the short duration of the arterial phase -10-30 seconds), and, therefore, **an enhanced CT or MRI is necessary in the clinical practice to stage the disease**, either for treatment strategies (especially surgical therapies-resection or transplantation-) and even for medical-legal reasons

Giorgio A, CEUS and HCC. Are the 2008 EFSUMB guidelines still valid or has their wash-out already started? Ultraschall June 2011

So, why eliminating such a valid and accurate technique in the evaluation of nodules > 1 cm arising in a cirrhotic liver?

If enhanced MRI or CT examinations, anyway to be performed after CEUS, will confirm the CEUS wash out in the portal and delayed phases -and this will be the largest majority of cases-, the diagnosis of the HCC nodules will be established without biopsy; on the other hand, in cases with discordant findings between CEUS and enhanced MRI (or enhanced multislice CT), a biopsy with cutting needle will be necessary.

Giorgio A, CEUS and HCC. Are the 2008 EFSUMB guidelines still valid or has their wash-out already started? Ultraschall June 2011

As a result, the EFSUMB 2008 guidelines, in my opinion, could still remain valid:

"In addition to CEUS, a confirmation of arterial hypervascularization and subsequent wash out by CT/MRI is requested to establish the diagnosis of HCC in focal liver lesions from 1-2 cm large detecting during surveillance programs "

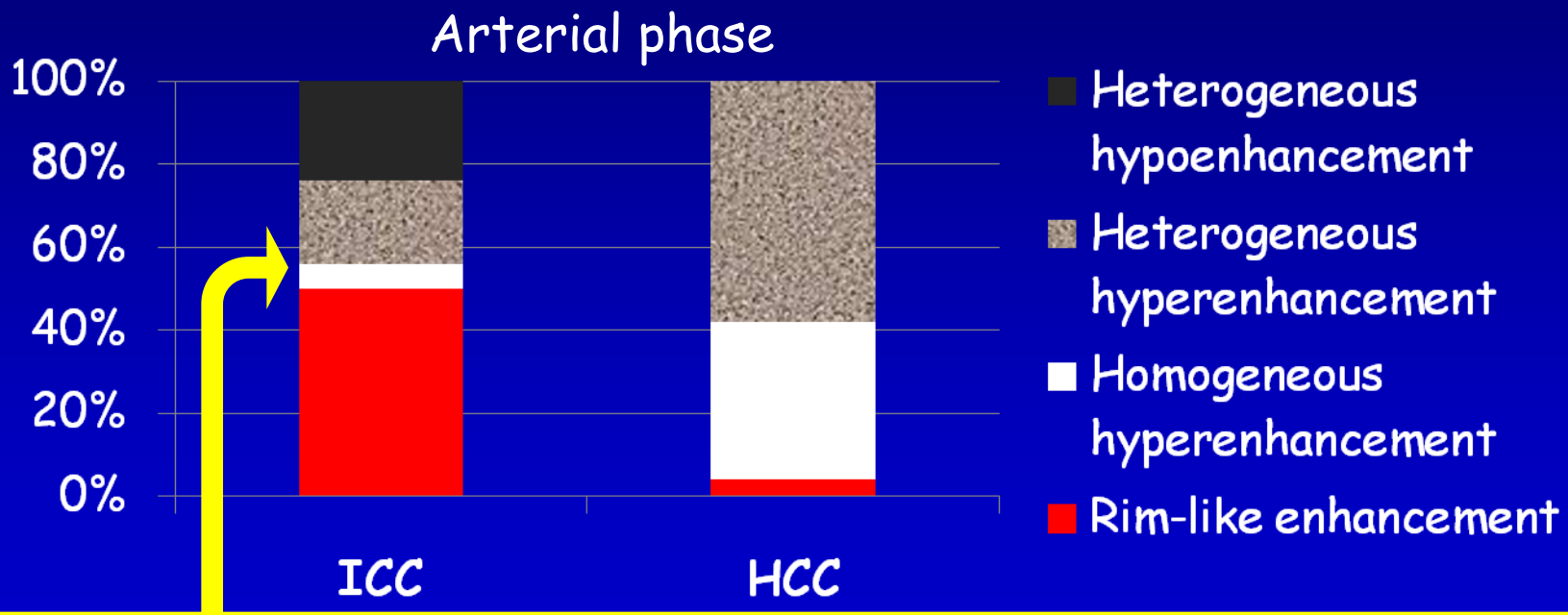
And, obviously, I would add also:

"in nodules >2 cm"

Intrahepatic Cholangiocarcinoma and Hepatocellular Carcinoma: Differential diagnosis with Contrast-Enhanced Ultrasound

Chen LD et al. Eur Radiol 2010

The CEUS enhancement patterns of 50 ICC were retrospectively analyzed and compared with 50 HCC



Only 3% of ICC showed homogeneous hyperenhancement

Enhancement patterns of intrahepatic cholangiocarcinoma: comparison between contrast-enhanced ultrasound and contrast-enhanced CT

Chen LD et al. BJR 2008

PORTAL PHASE (CEUS 31-120 sec)

- 97,5% of the lesions were hypoenhancing on CEUS

LATE PHASE (CEUS 121-360 sec)

100% of the lesions were hypoenhancing on CEUS

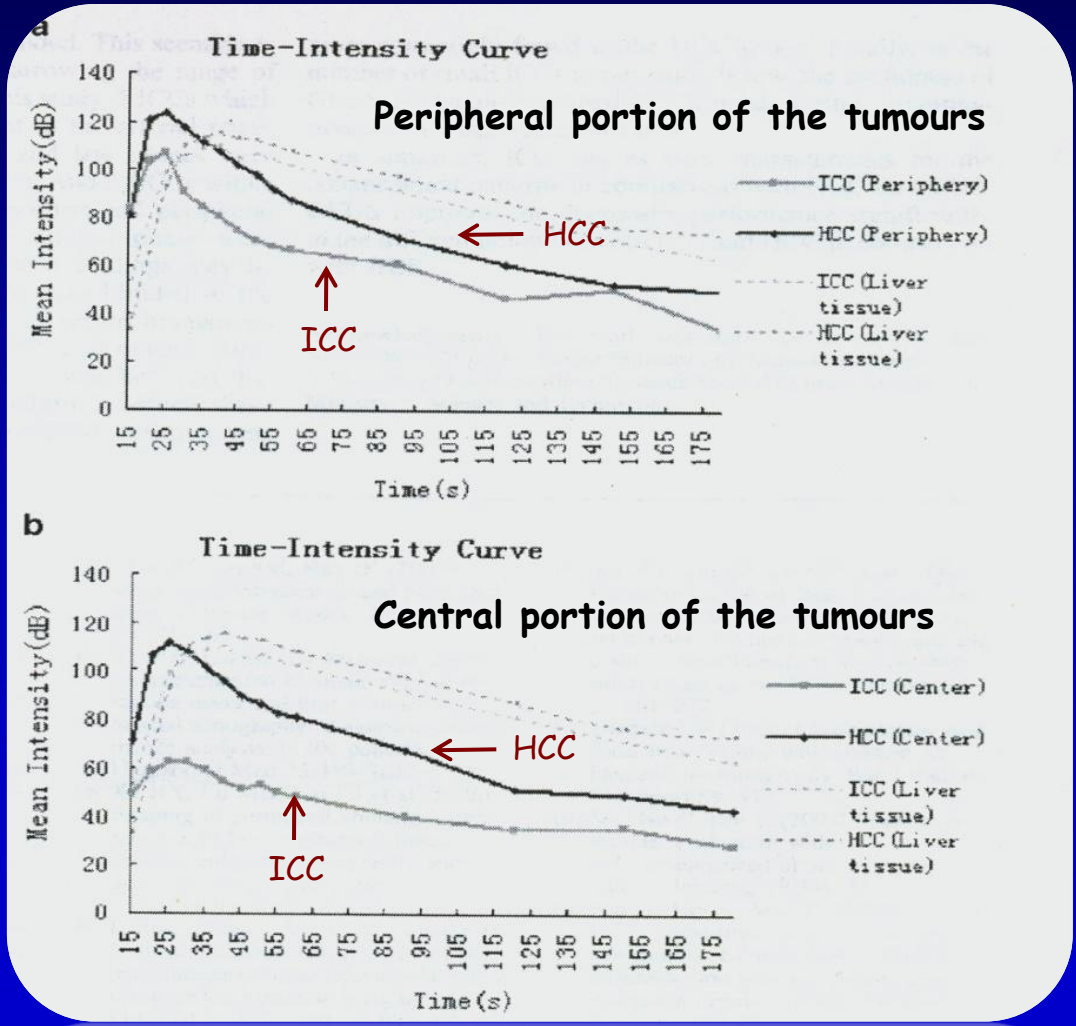
Intratumoral blood vessels were exhibited in

- 50% of the lesions on CEUS

Intrahepatic Cholangiocarcioma and Hepatocellular Carcinoma: Differential diagnosis with Contrast-Enhanced Ultrasound

Chen LD et al. Eur Radiol 2010

Time-intensity curves of both the central and the peripheral portion revealed marked enhancement after contrast agent injection in HCC and a weak enhancement in ICC throughout the phases.



Intrahepatic Cholangiocarcioma and Hepatocellular Carcinoma: Differential diagnosis with Contrast-Enhanced Ultrasound

Chen LD et al. Eur Radiol 2010

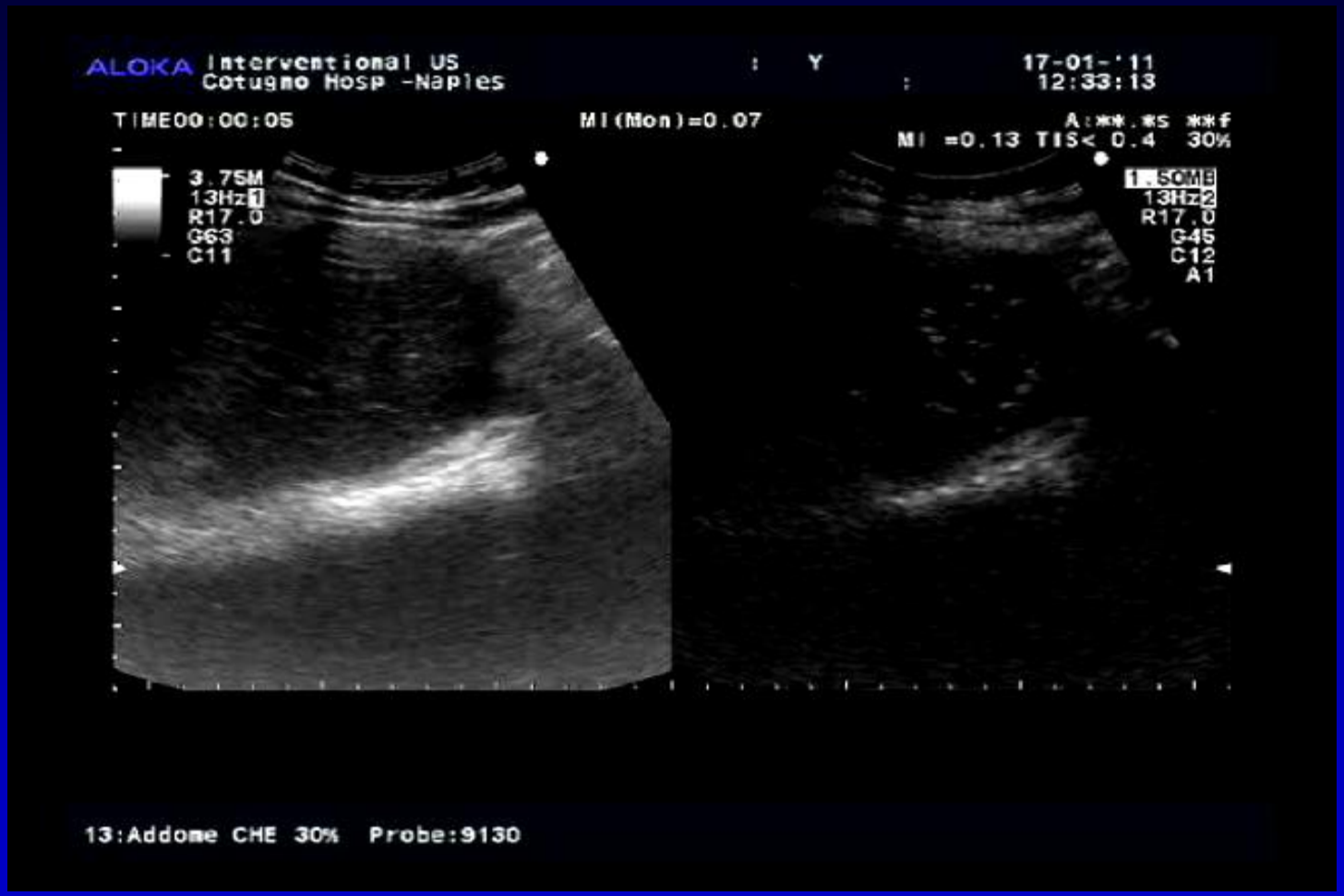
"The ICC washed out more thoroughly during the portal or late phase in comparison with HCC, both at the periphery and centre of the tumours, so that the intensity of ICC was lower than that of HCC. This phenomenon may indicate that more vessels that trapped microbulbbles were present in the HCC"

Intrahepatic Cholangiocarcioma and Hepatocellular Carcinoma: Differential diagnosis with Contrast-Enhanced Ultrasound

Chen LD et al. Eur Radiol 2010

"In comparison with ICC, the abnormal artery supply of HCC was richer, and microvascularisation increased owing to tumour angiogenesis, as well as the presence of abnormal arterovenous shunts, so the intensity of HCC was higher than ICC in the arterial phase"

IN CONCLUSION:
CEUS improves the diagnostic performance significantly in the differentiation between ICC and HCC"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C11
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R17.0
G45
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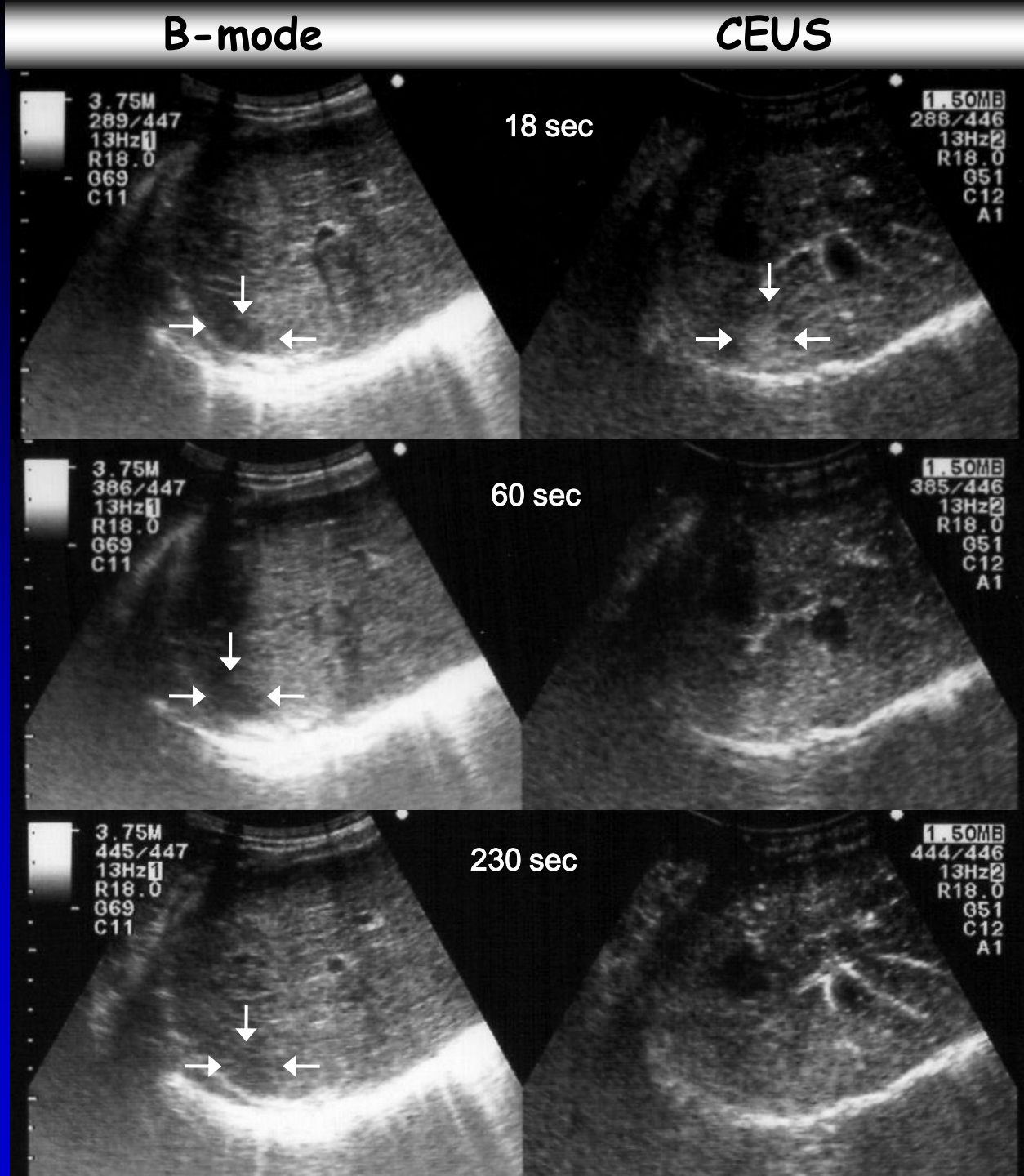
HCC

Arterial phase 15-30 sec

Portal phase 30-60 sec

Sinusoidal phase 60-120 sec

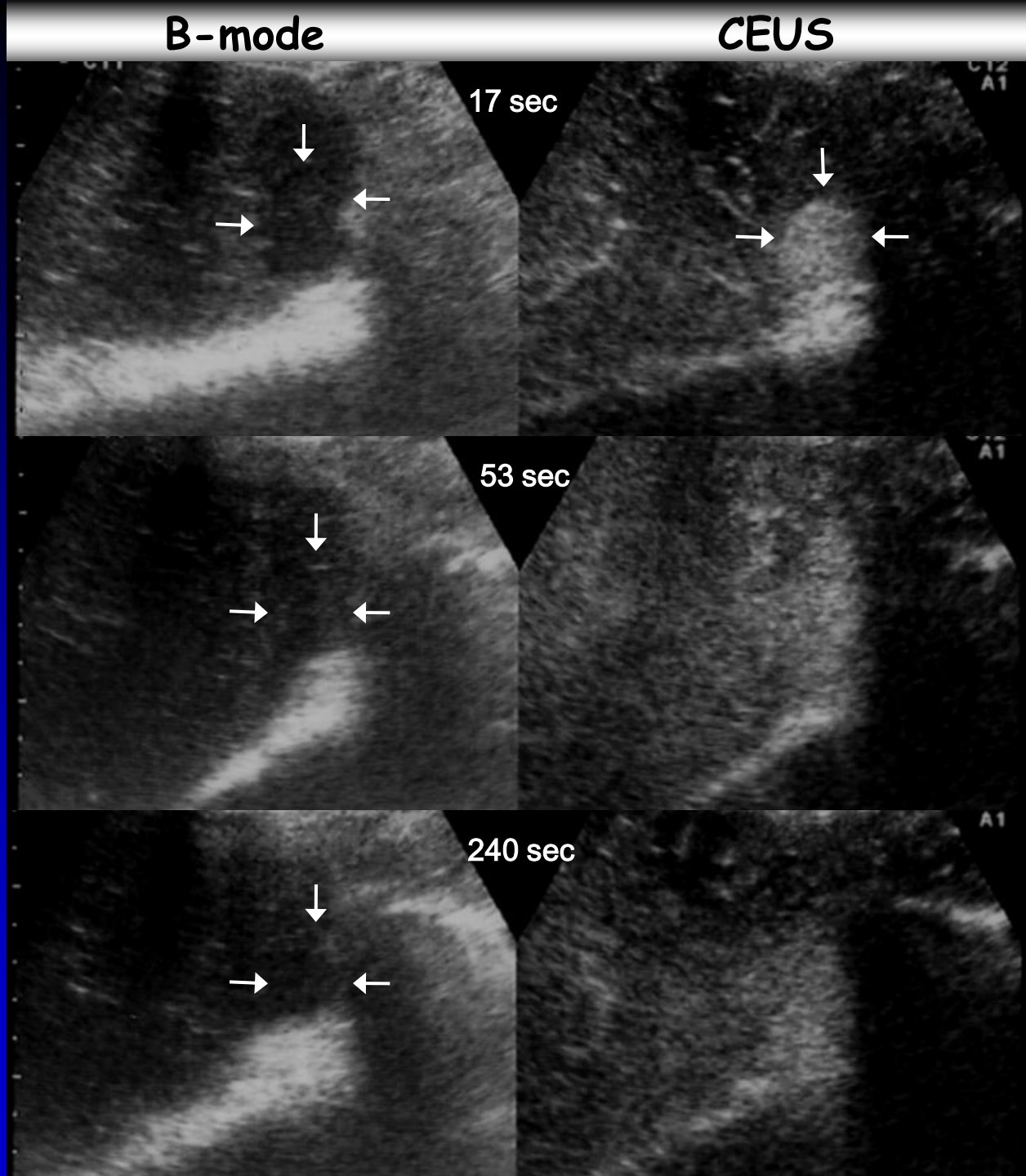


HCC

Arterial phase 15-30 sec

Portal phase 30-60 sec

Sinusoidal phase 60-120 sec



Guidelines and good clinical Pratice Recommendation for CEUS in the liver – Update 2012

M. Claudon et Al. Ultraschall 2012

"... Hyperhenancement in the arterial phase, followed by wash - out in the late phase corresponds to HCC in more than 97% of cases..."

"... CCC and hepatic lymphoma comprice the remining 1-3% of cases."

EFSUMB guidelines 2012

FLL in cirrhotic liver

Hyper-E in the arterial phase

yes

Hypo-E in late phase (=wash-out)

Malignant
Consider as HCC

Iso-E in the portal and late phases

Very suspicious for malignancy
(positive predictive value >85% for HCC, usually well differentiated