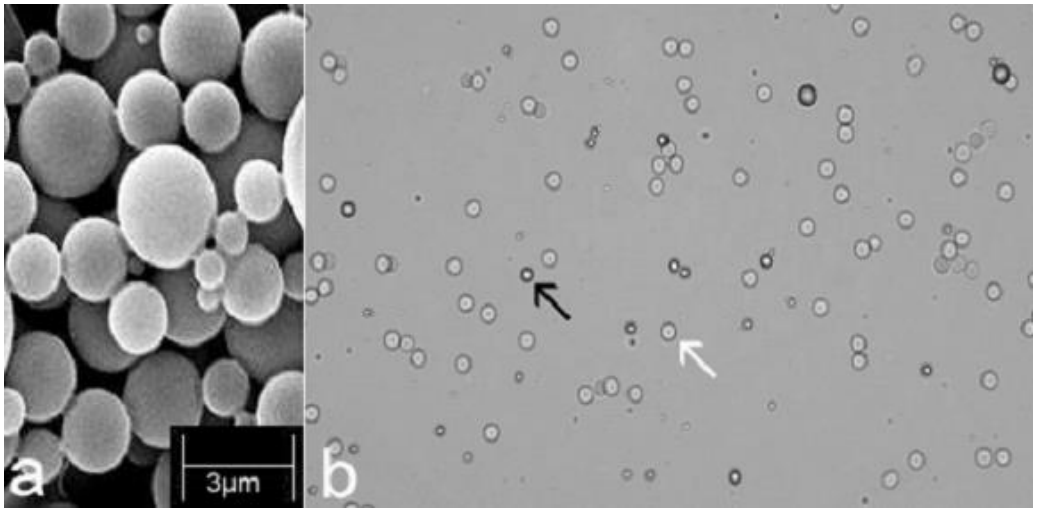
Détection des récidives
identifying recurrences
CEUS

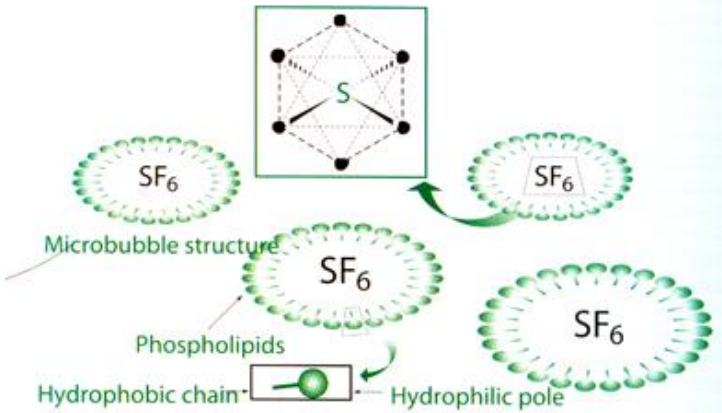
O Lucidarme, L Bridal
Pitié-Salpêtrière, Paris

UPMC
PARIS UNIVERSITAS

US contrast agents



- ✓Sulfur hexafluoride-filled microbubbles
  - ✓SonoVue®
- ✓3-7microns diameter
- ✓Blood pool agent



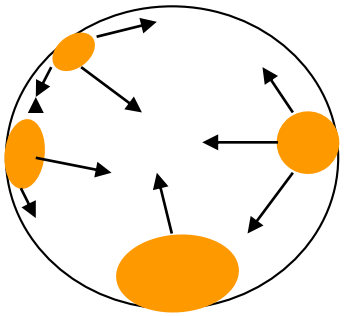
Interesting Feature #1 : TOLERANCE

- Extremely good tolerance in clinical practice
  - No nephrotoxicity,
  - No thyroid interaction
  - No need of Blood test before IV
- Rare anaphylactoïd reaction (≈ Gd chelates)
  - incidence < 0,002%
  - no cross allergy with Iodine contrast
- Do not use in case of pregnancy and Breast feeding (precaution)

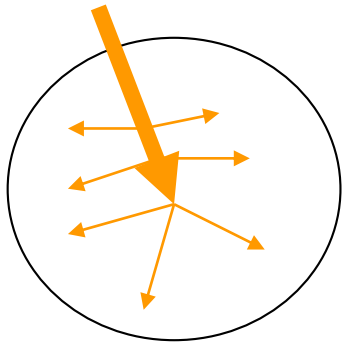
=> **Can be used when Iodine and Gadolinium cannot**

Interesting Feature #2

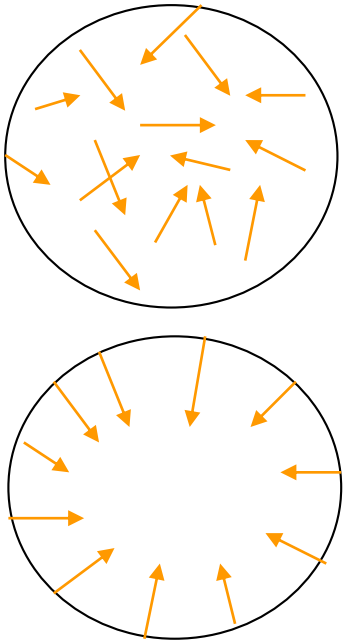
- **Early Phase**
  - Higher temporal resolution than CT or MRI



Hemangiomas



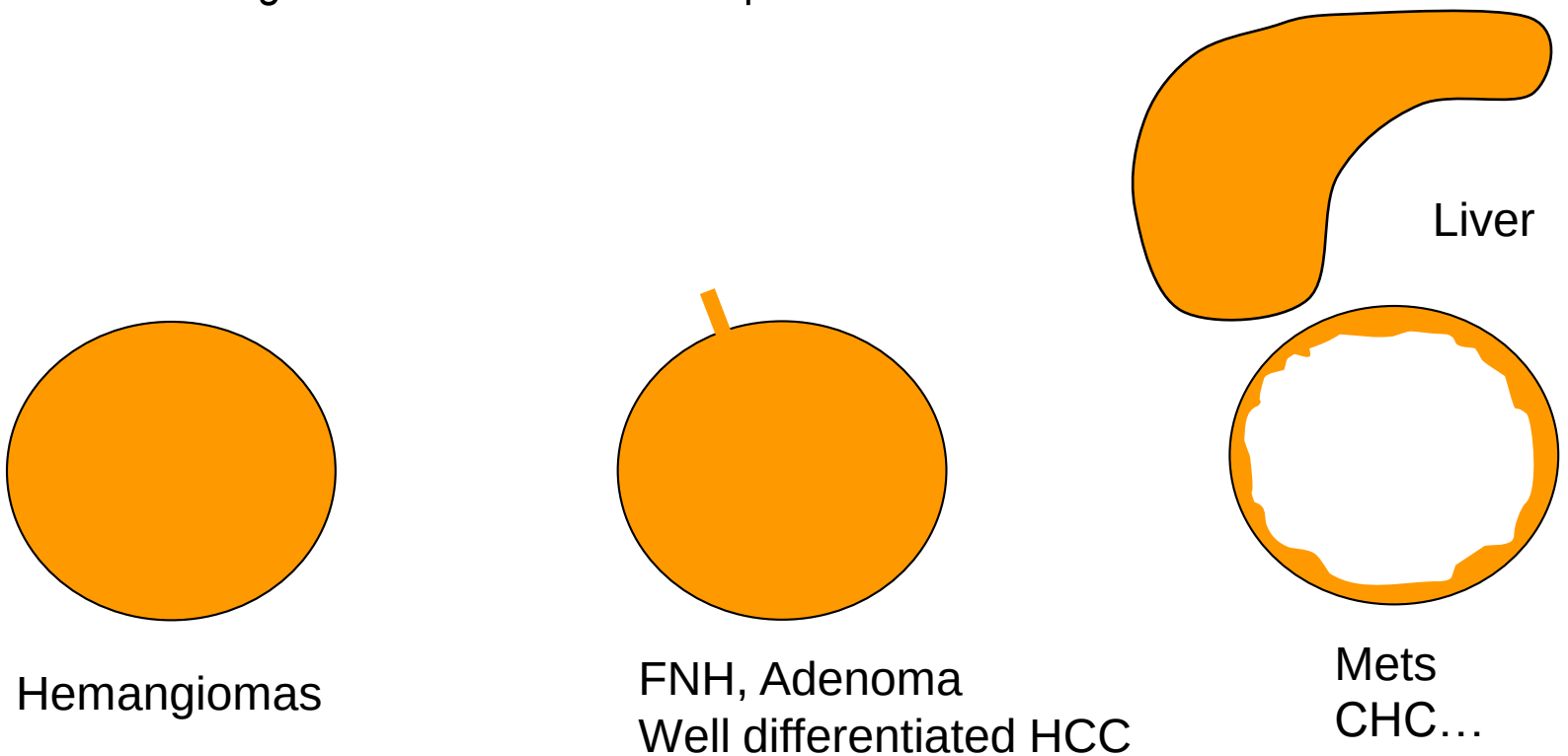
FNH



Adenoma
Mets
HCC…

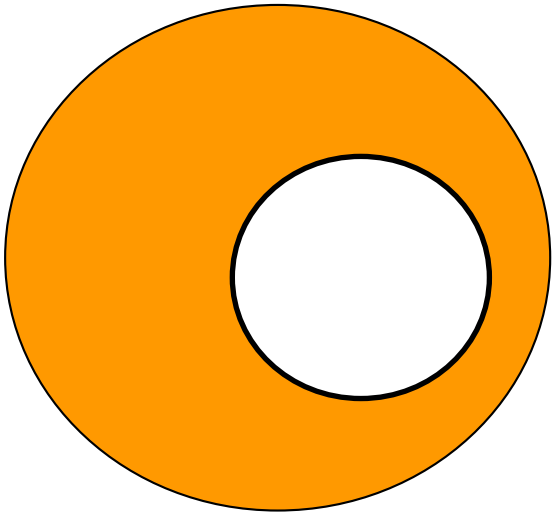
Interesting Feature #3

- **Late phase**
  - Iodine/gado : extravascular leaking ++ if tumoral vessels
  - Microbubbles :
    - Wash-out if tumoral vessels
    - Stagnation in the sinusoid capillaries or venous lakes



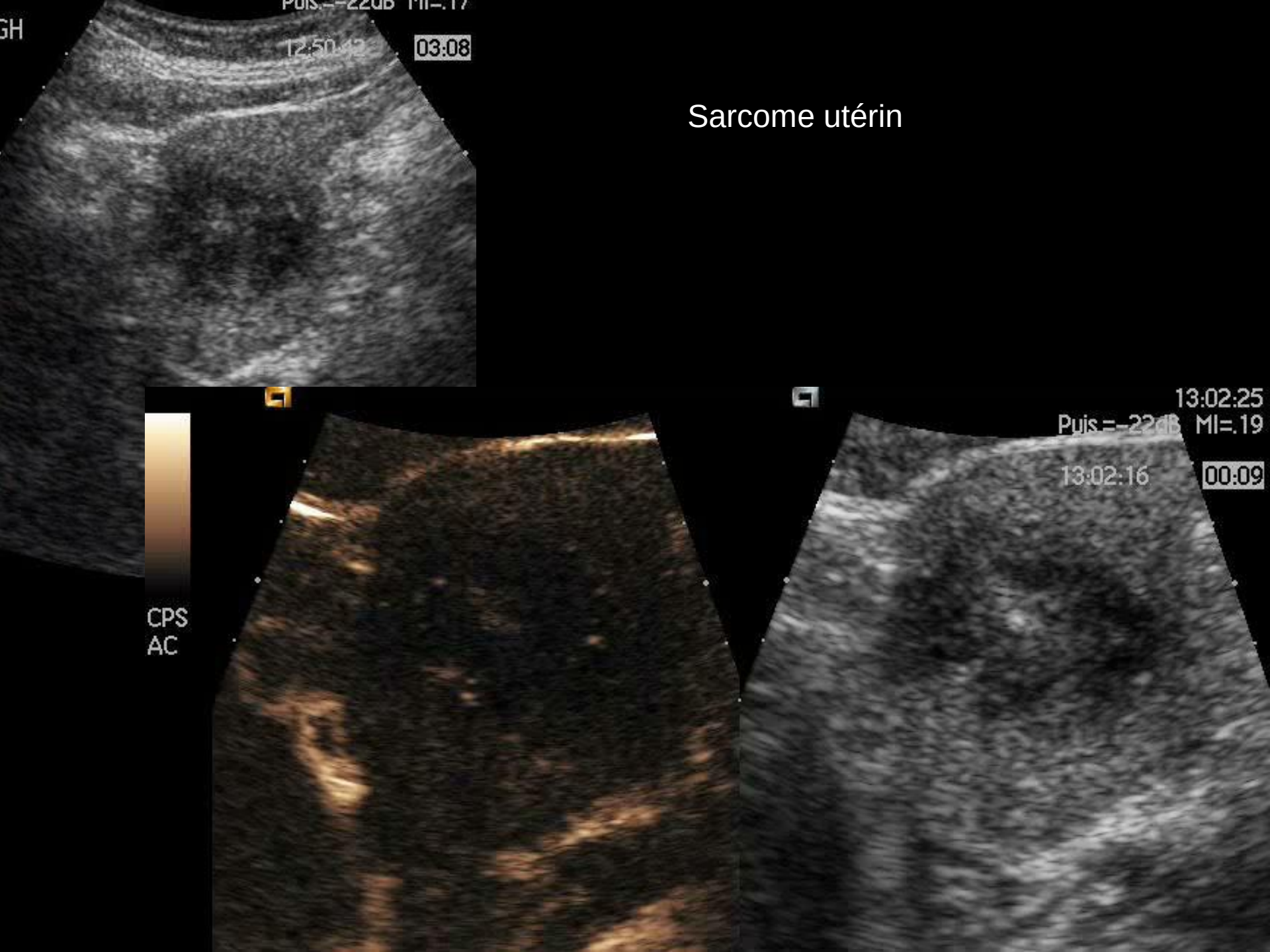
Interesting Feature #4

- **Early Phase**
  - Higher sensitivity to low amount of circulating contrast
  - No enhancement means no (or almost no) circulating vessels



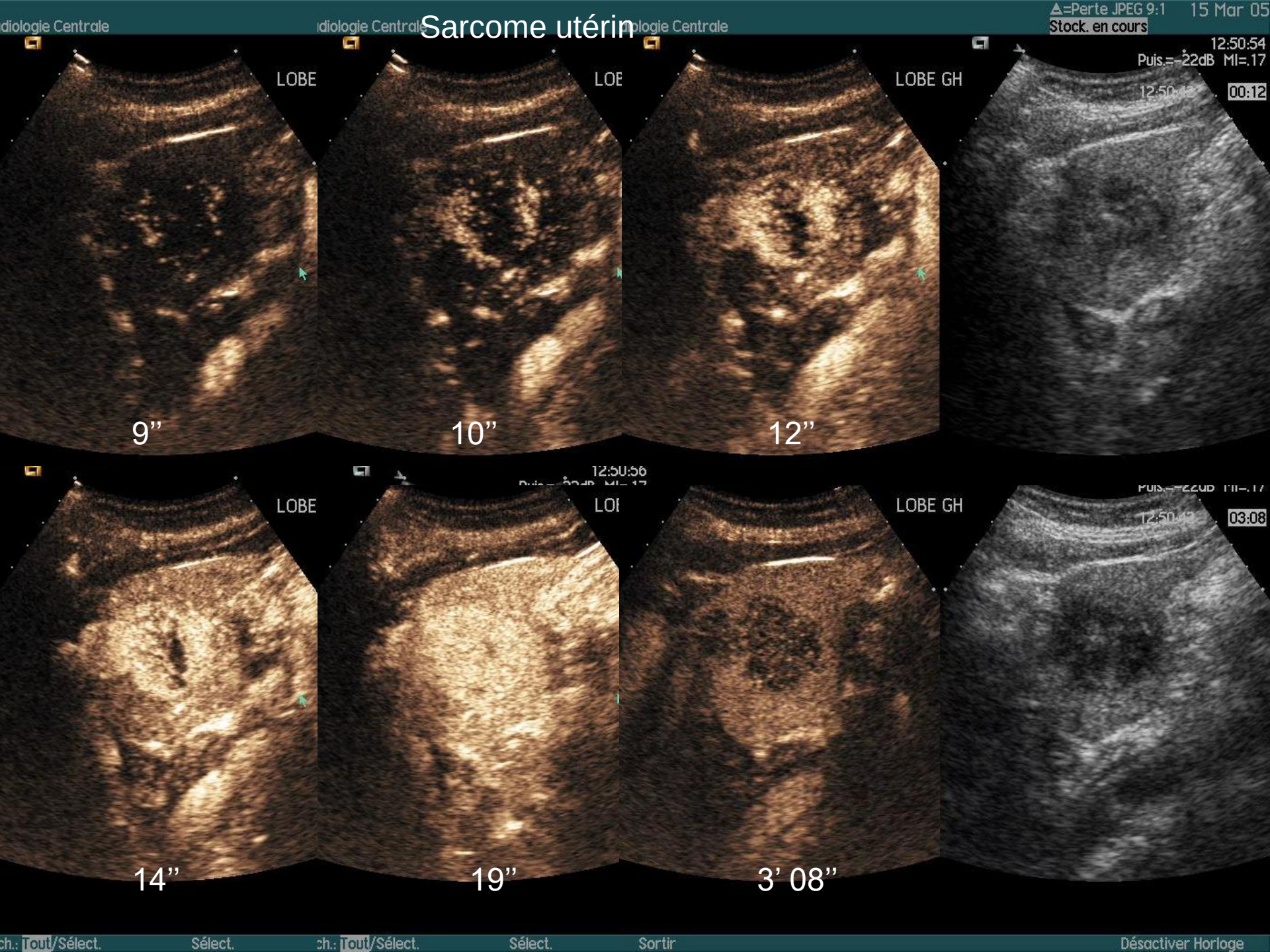
In oncology…

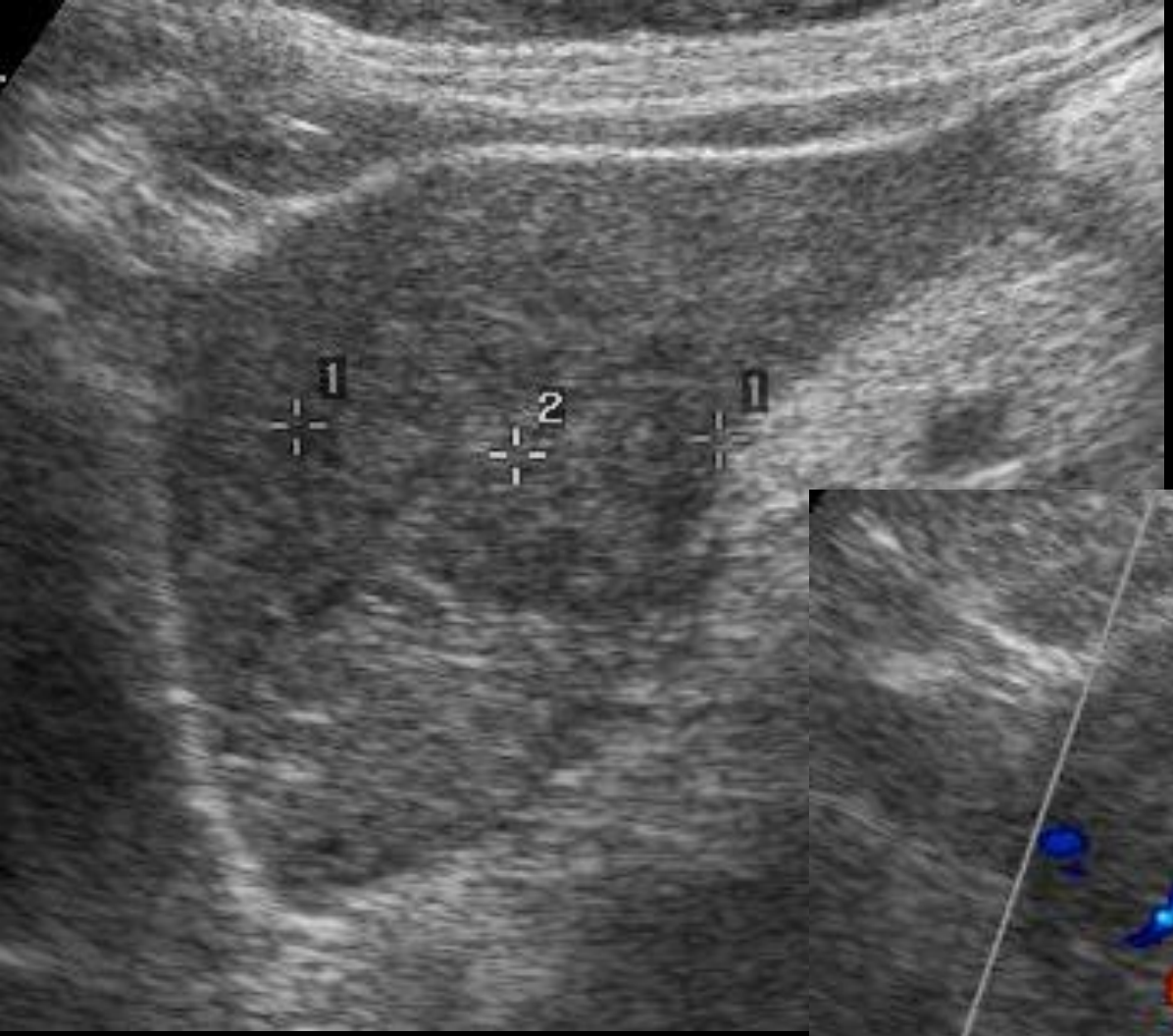
- CEUS is already very useful in every day practice:
  - to characterize FLL,
  - kidney and pancreas
  - to assess the effect of vascular destructive treatment like RFA or Chemoembolisation
  - CEUS can be also interesting in more advanced research imaging in oncology
  - To identify recurrences ? Way?

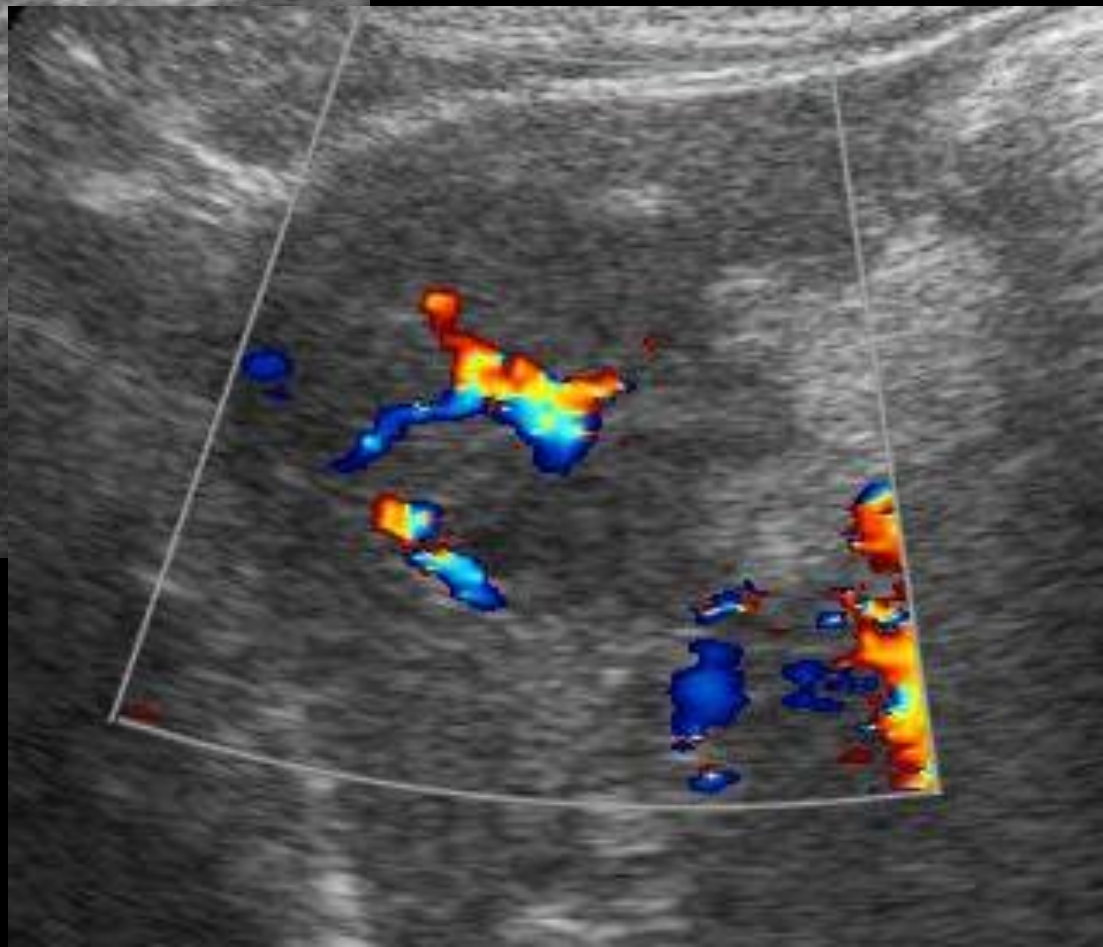


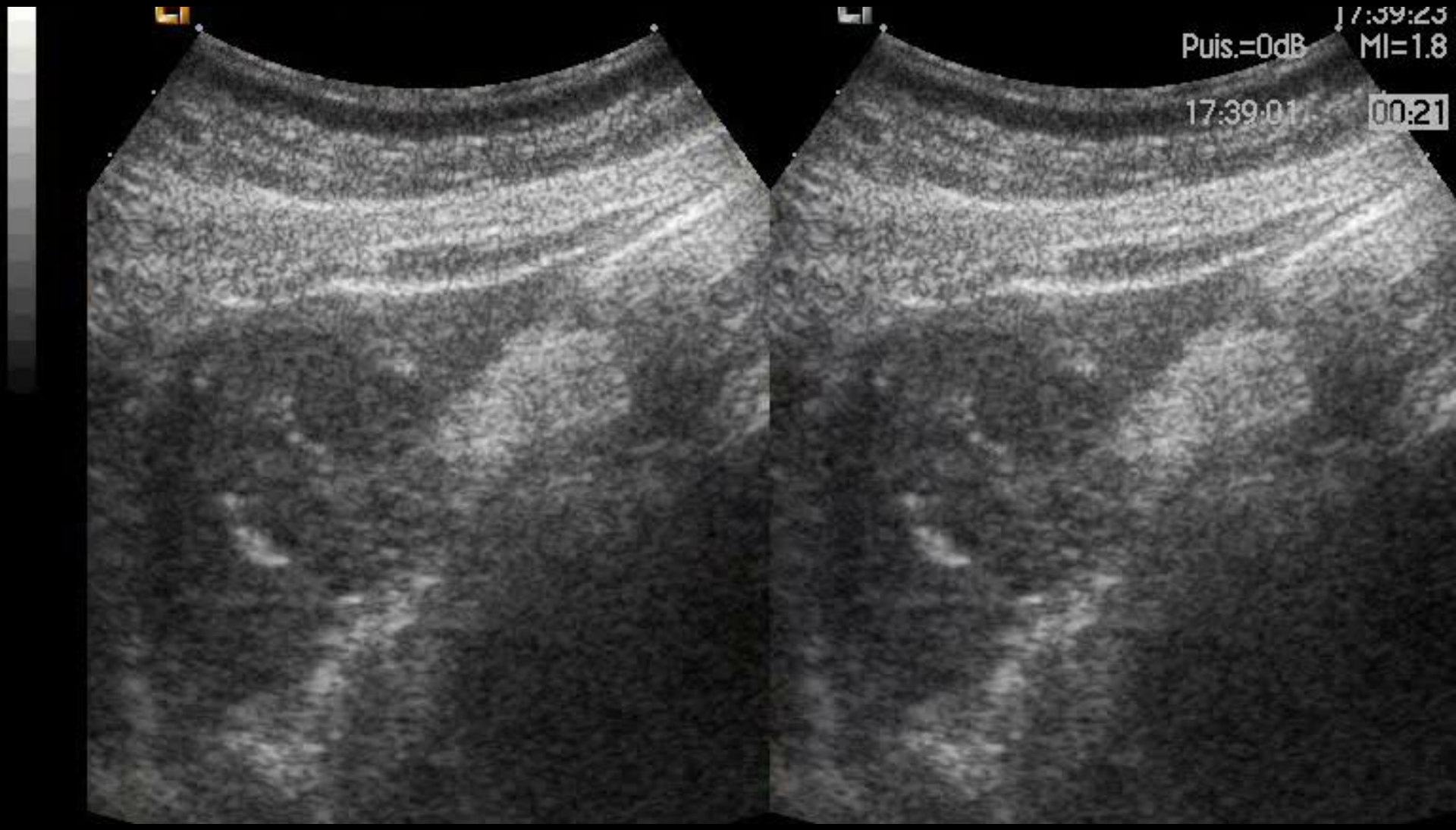
Sarcome utérin

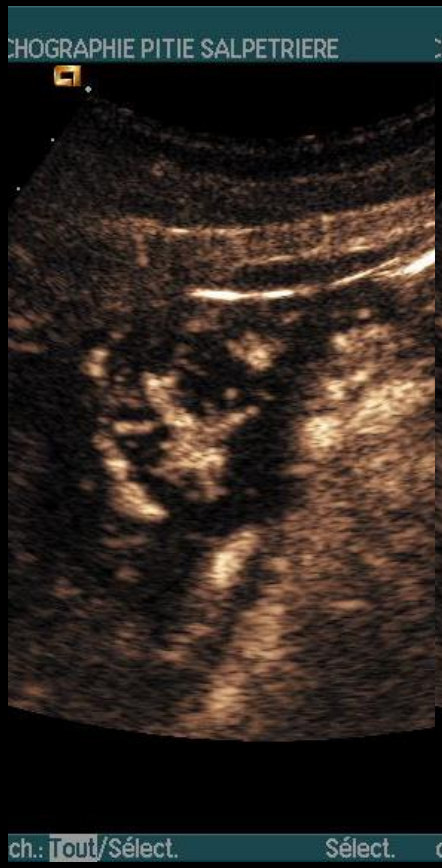
Sarcome utérin

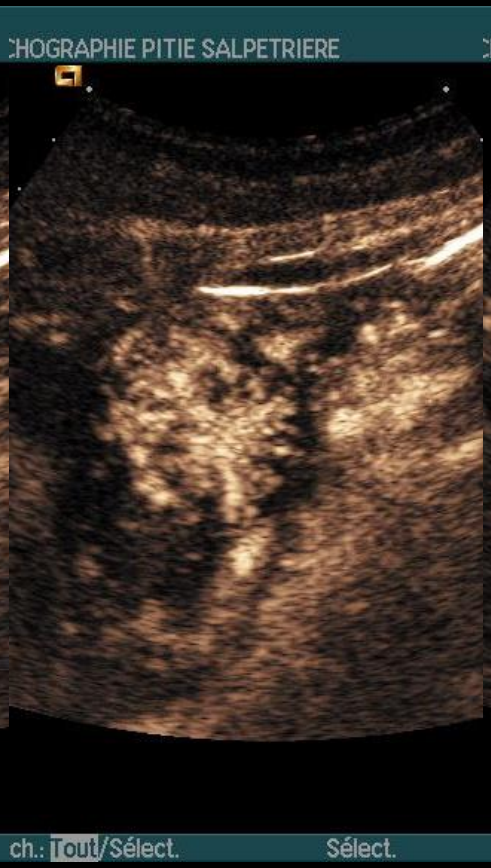


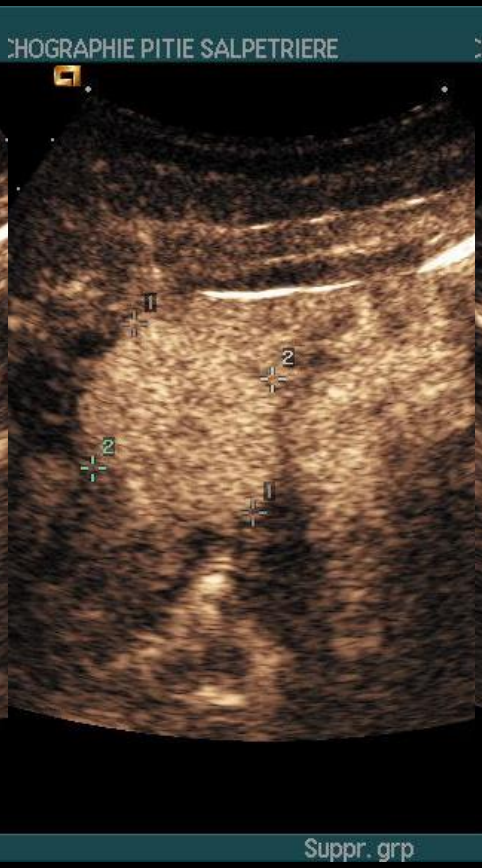

1
2
1

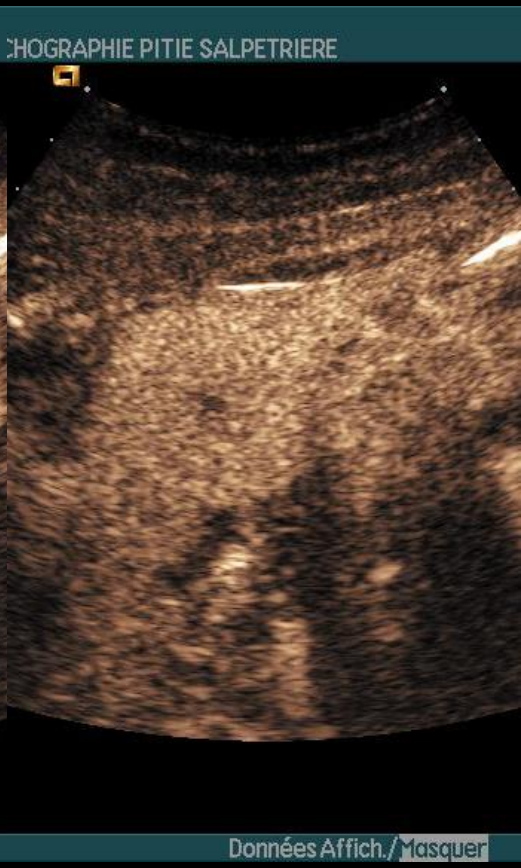



Puis.=0dB
MI=1.8
17:39:01
00:21


CHOGRAPHIE PITIE SALPETRIERE
ch.: Tout/Sélect.
Sélect.


CHOGRAPHIE PITIE SALPETRIERE
ch.: Tout/Sélect.
Sélect.


CHOGRAPHIE PITIE SALPETRIERE
1
2
2
1
Suppr. grp


CHOGRAPHIE PITIE SALPETRIERE
Données Affich./Masquer

characterization

- **Percentage of correct diagnosis**
  - US without contrast : **38[3]-65%[1]**
  - US with contrast : **81[3]-92%[1]**

1 Alrecht T. Eur Radiol. 2004 Oct;14 Suppl 8:P25-33

[2] Tranquart F. J Radiol 2009, 90: 123-138

[3] Trillaud H, World J Gastroenterol 2009; 15:3748-3756

Characterizing any malignancy in incidentally detected focal liver lesions

	Sensitivity for malignancy	Specificity for malignancy	FP	FN
CEUS	95%	94%	6%	5%
CECT	95%	93%	7%	5%

Pooled estimates from the meta-analysis of 4 studies: Seitz K Ultraschall Med 2009;30:383–9. Li R, J Clin Ultrasound 2007;35:109–17. Catala V, Eur Radiol 2007;17:1066–73. Solbiati L. Abstract D-55. European Congress of Radiology 2006

CEUS	90%	67%	13%	10%
CEMRI	82%	63%	17%	18%

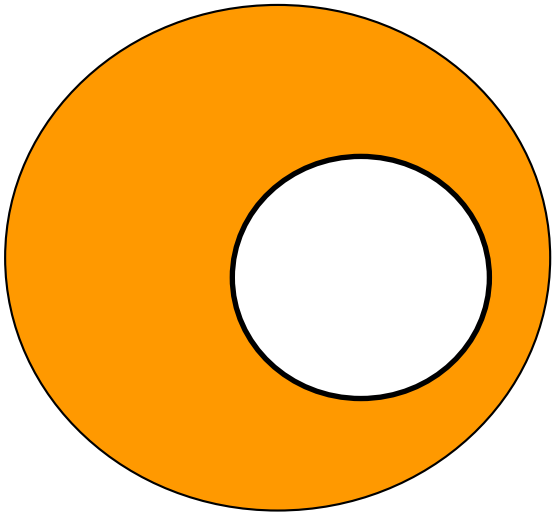
Seitz K Ultraschall Med 2009;30:383–9

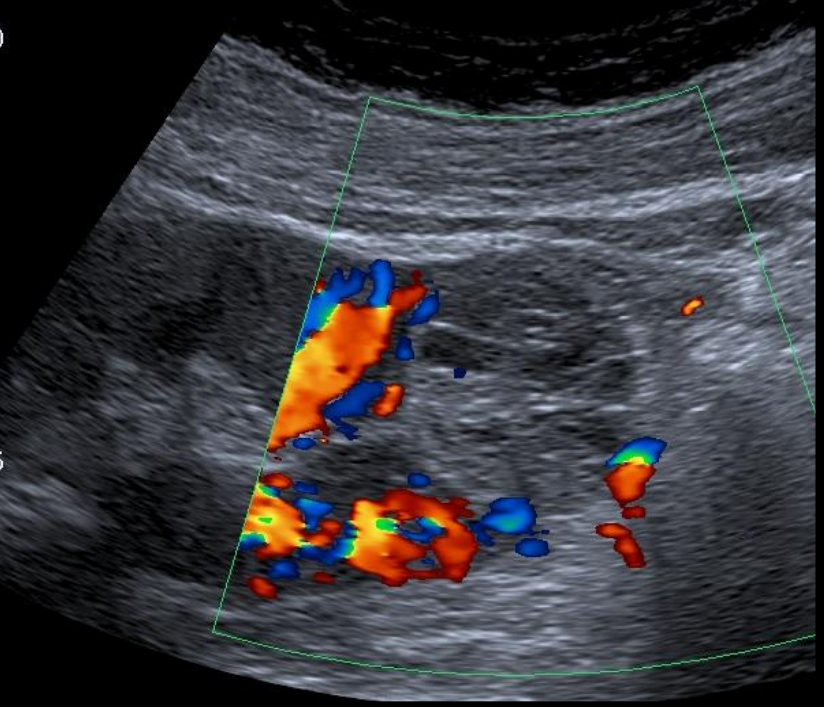
→ No significant difference in the accuracy of CEUS and CECT or CEMRI for the characterization (as malignant) of focal FLLs

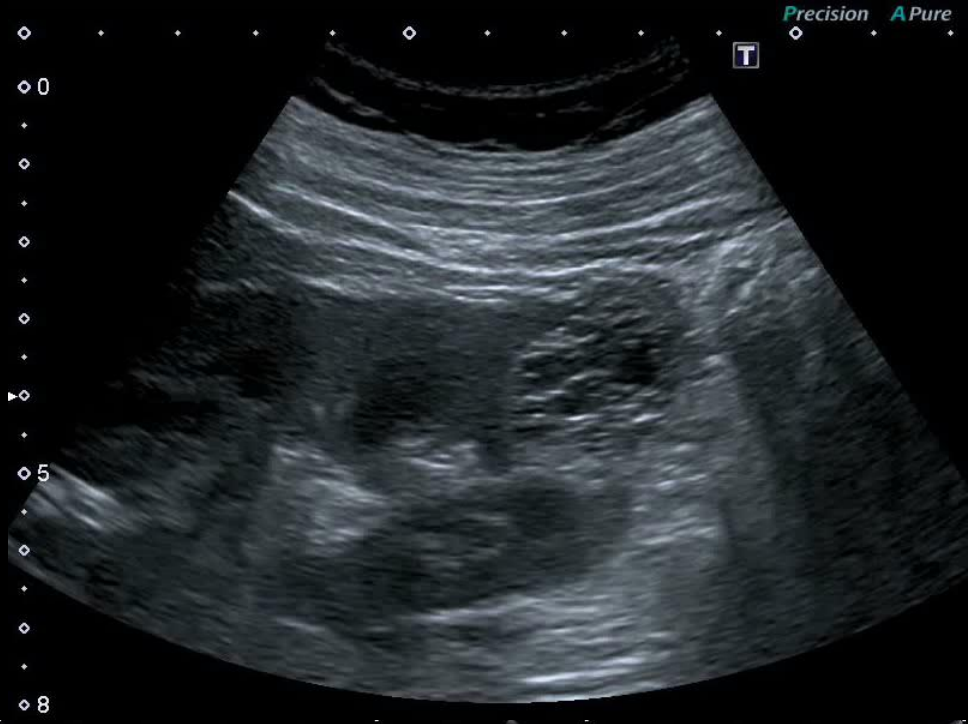
→CEUS alone may be adequate to rule out liver malignancy in people with incidentally detected FLL

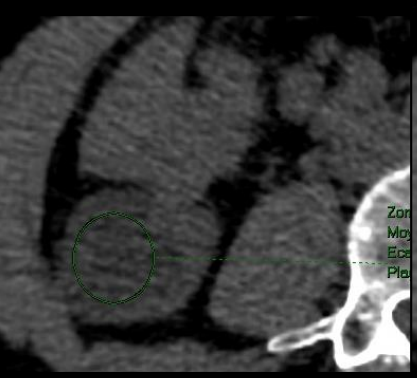
Interesting Feature #4

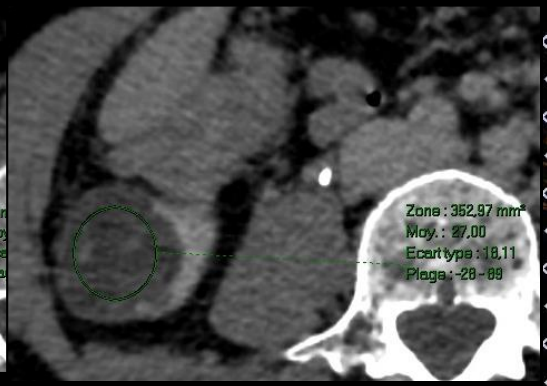
- **Early Phase**
  - Higher sensitivity to low amount of circulating contrast
  - No enhancement means no (or almost no) circulating vessels

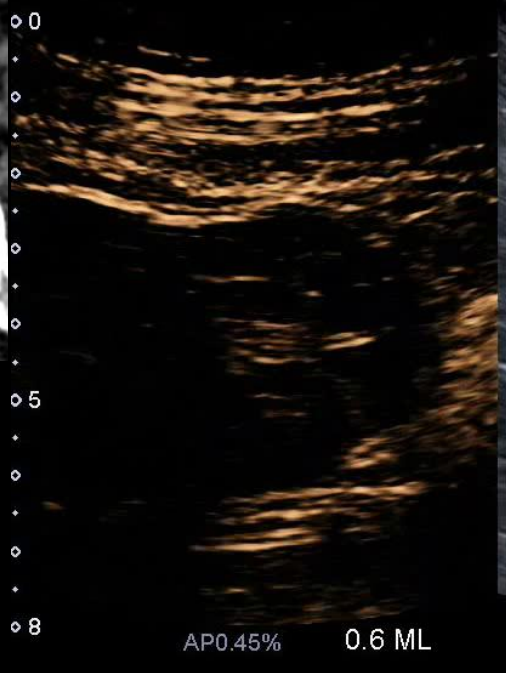


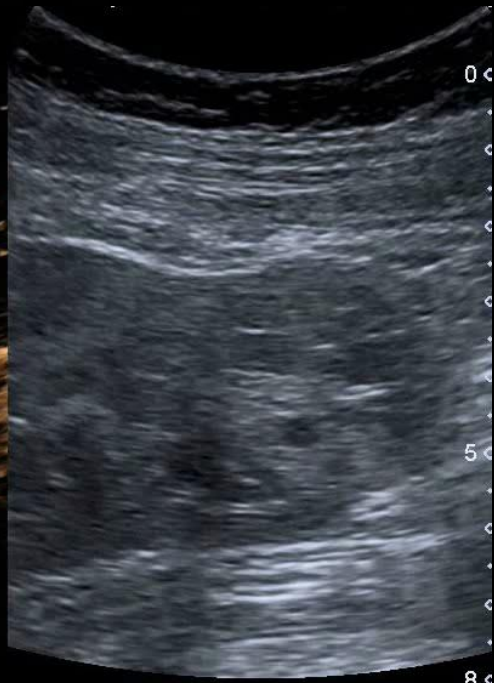




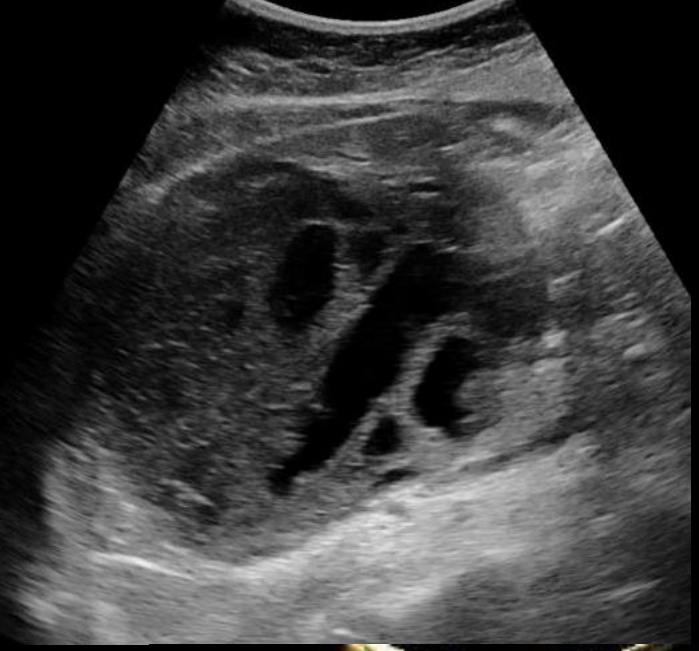
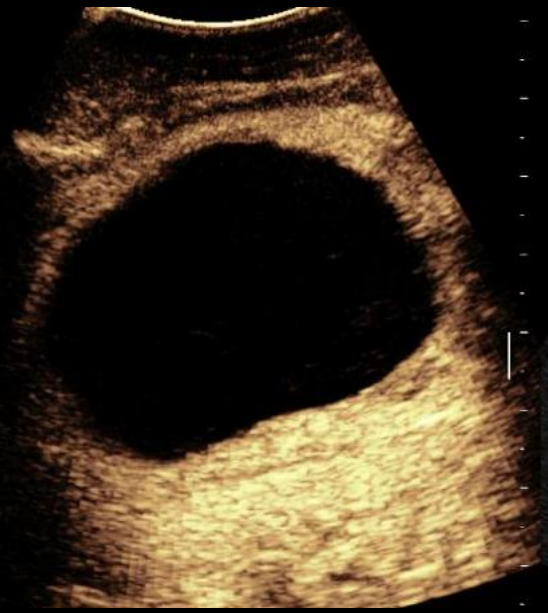
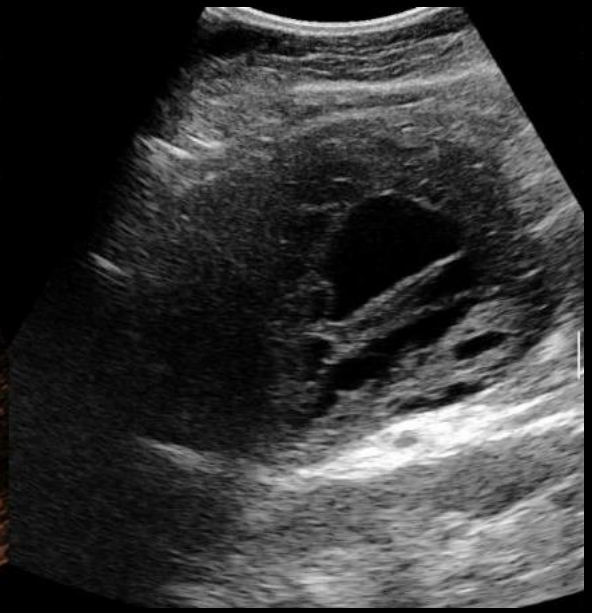
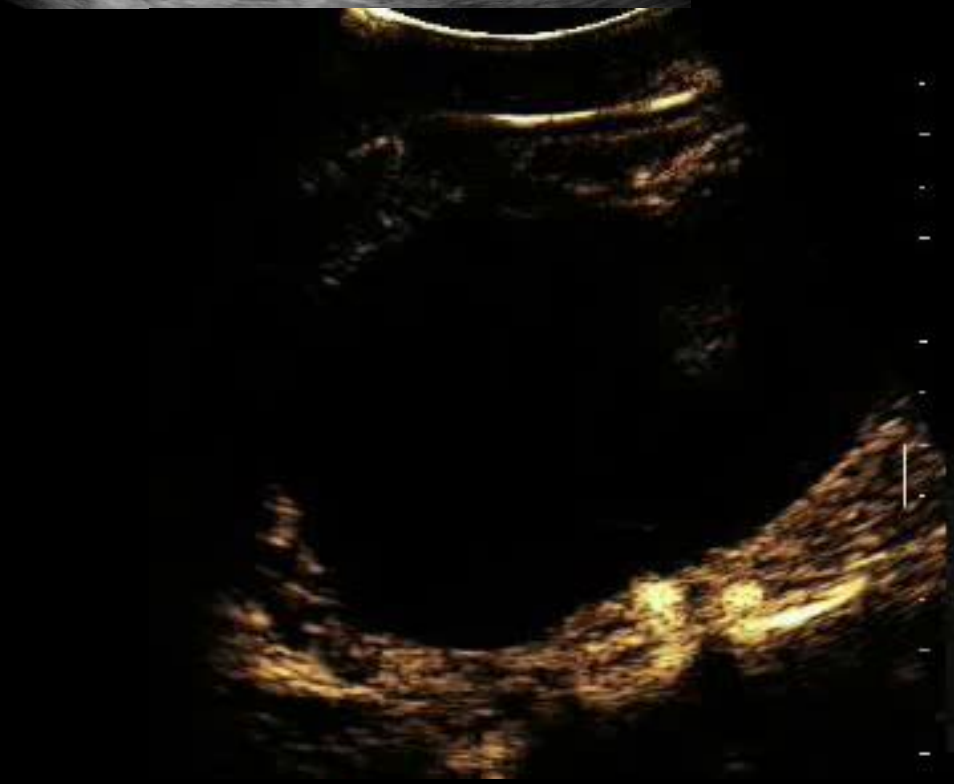
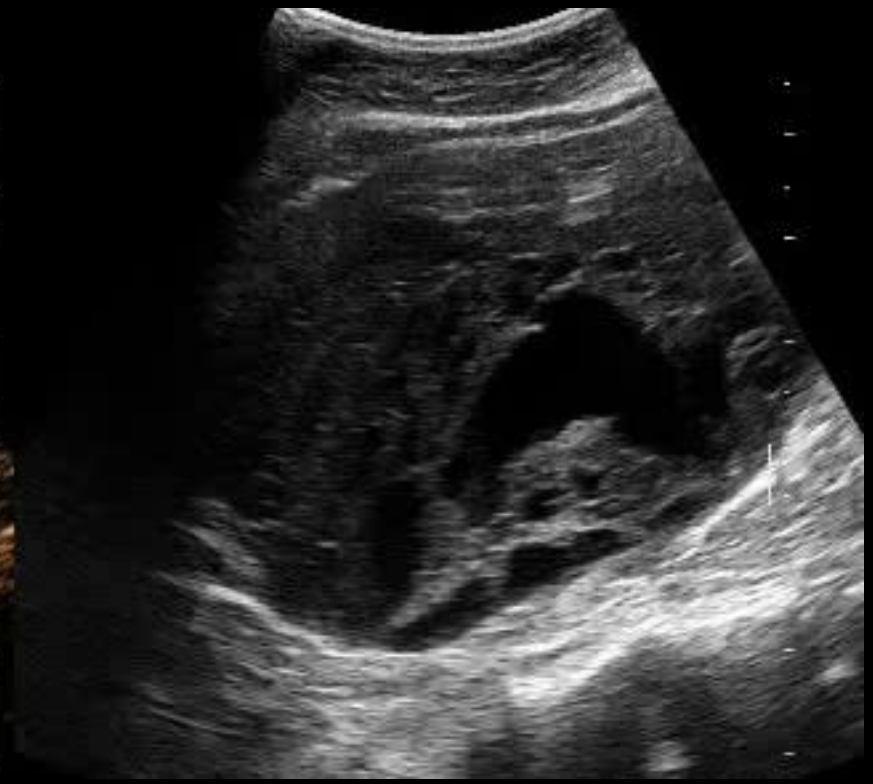








Courtesy Pr Correas,
Necker Hosp, Paris

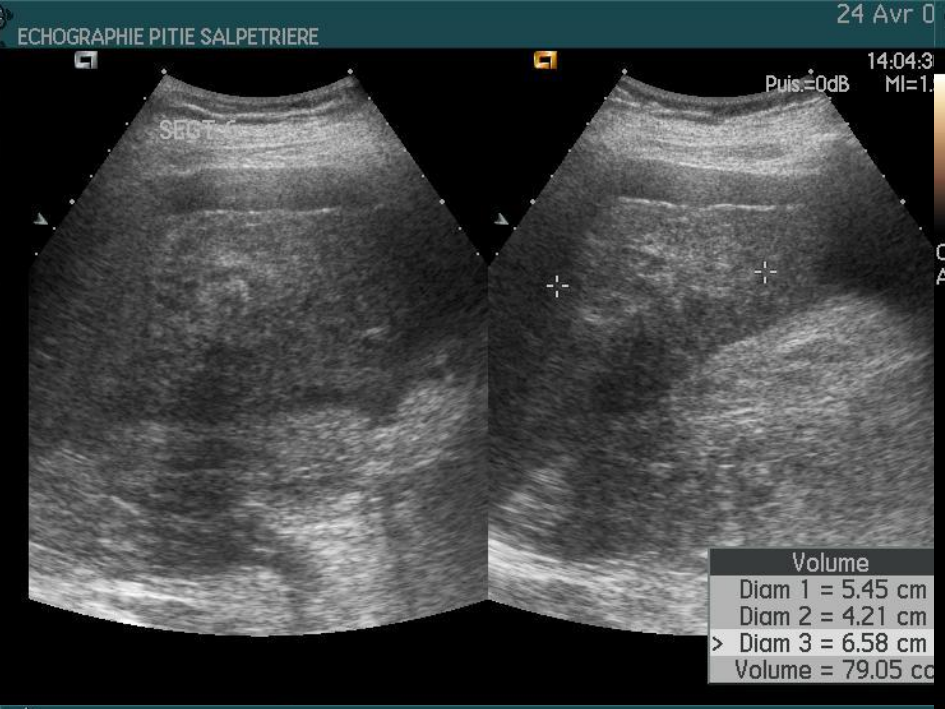






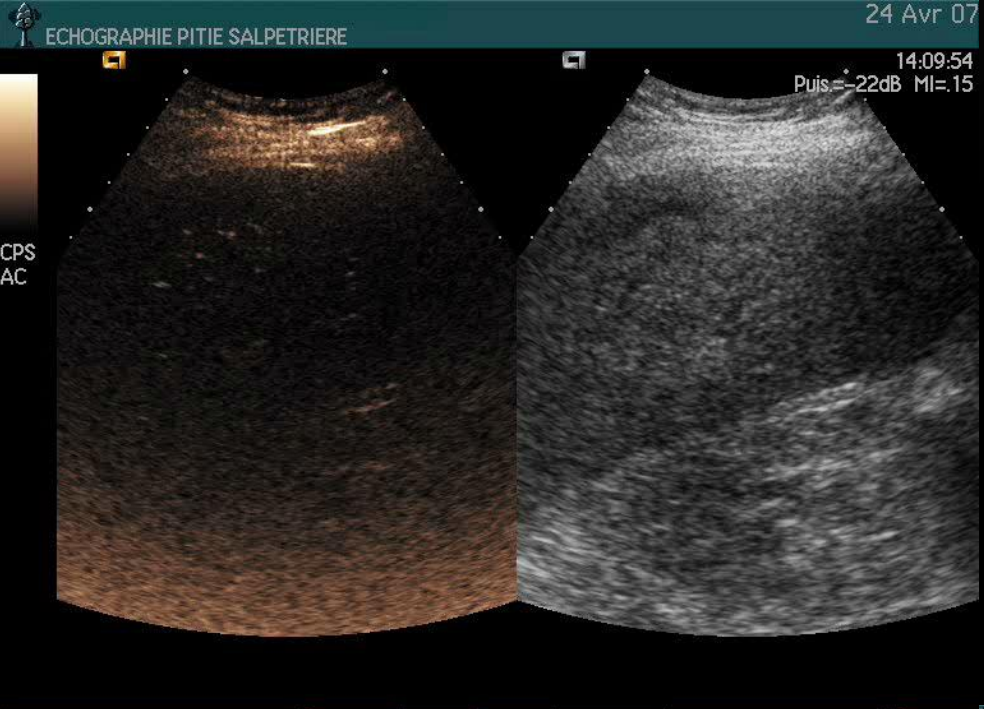
Renal complex cysts

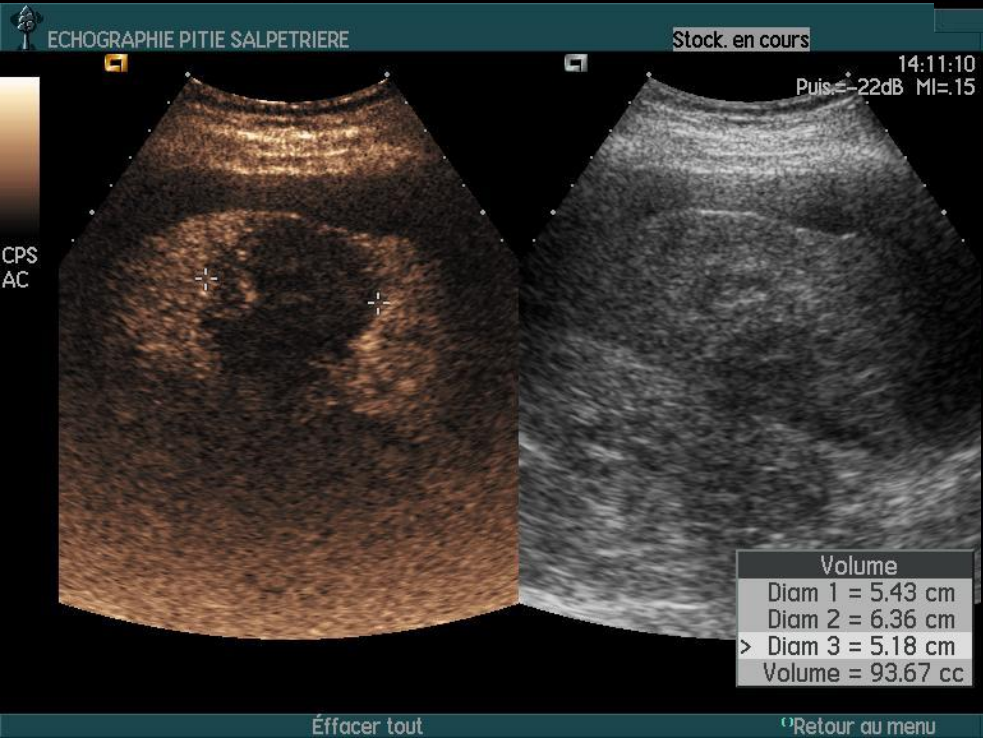
- Unlike Liver : not used to differentiate solid tumors (same pattern)
- But:
  - Characterization of complex cystic masses as benign, indeterminate or malignant (Recommendation level: A;1b)
  - To make the distinction between hypovascular solid lesions on CT and atypical cysts (Recommendation level: B;2b)

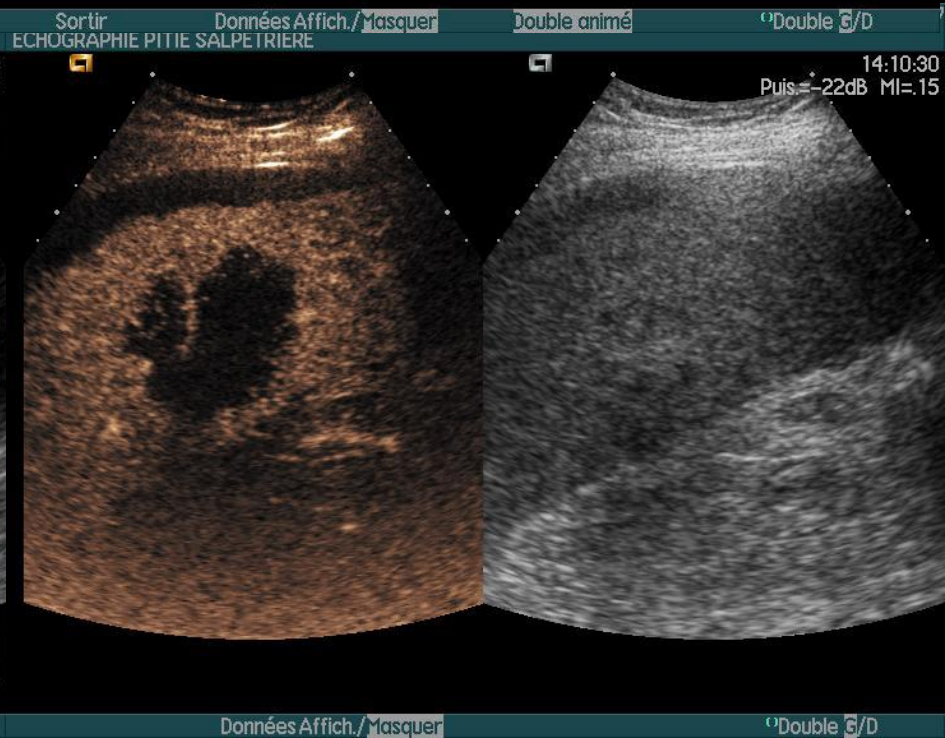
Qualitative assessment of treatment

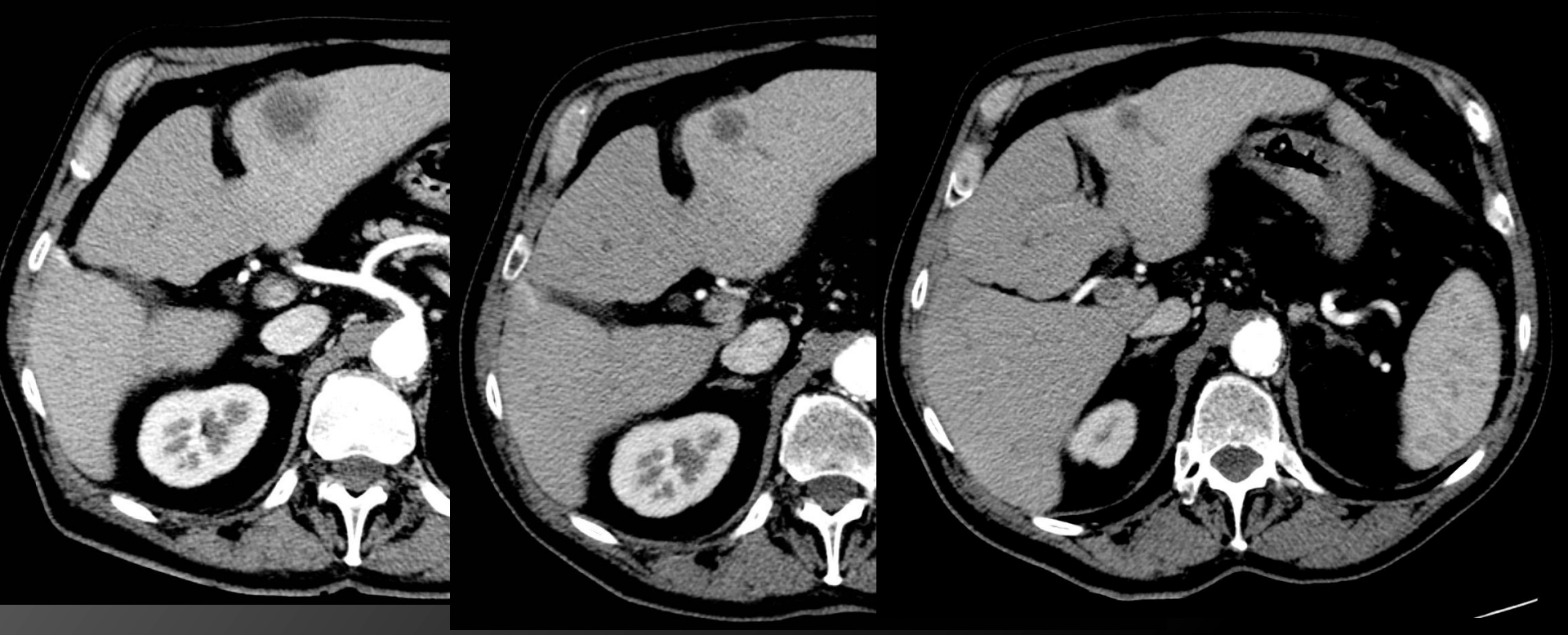
- Simple visual assessment
- To see if vessels are present or not
  - Usefull for liver lesion treated with Tace, RFA, Vascular disruptive agents

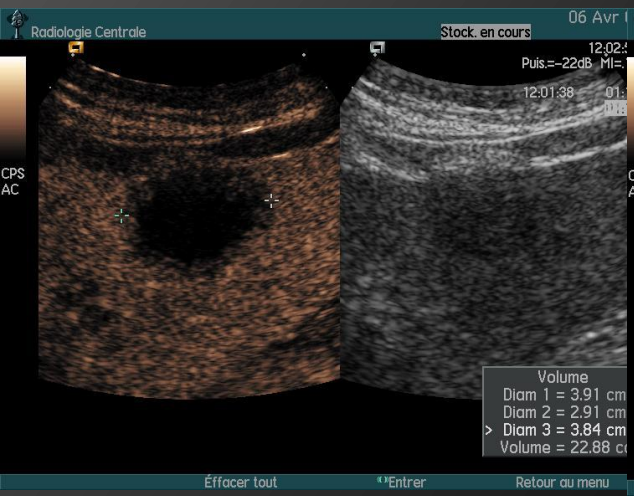

ECHOGRAPHIE PITIE SALPETRIERE
24 Avr 0
14:04:3
Puis.=0dB
MI=1.
CPS
AC
Volume
Diam 1 = 5.45 cm
Diam 2 = 4.21 cm
> Diam 3 = 6.58 cm
Volume = 79.05 cc


ECHOGRAPHIE PITIE SALPETRIERE
24 Avr 07
14:09:54
Puis.=-22dB MI=.15
Sortir
Données Affich./Masquer
Double animé
Double G/D

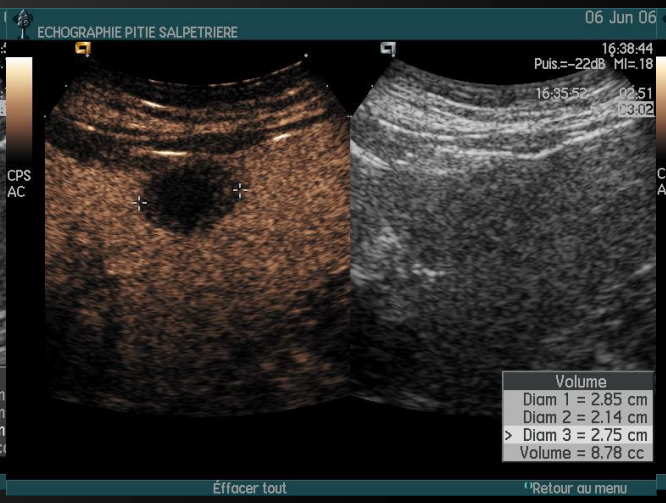

ECHOGRAPHIE PITIE SALPETRIERE
Stock. en cours
14:11:10
Puis.=-22dB MI=.15
CPS
AC
Volume
Diam 1 = 5.43 cm
Diam 2 = 6.36 cm
> Diam 3 = 5.18 cm
Volume = 93.67 cc
Effacer tout
Retour au menu


ECHOGRAPHIE PITIE SALPETRIERE
14:10:30
Puis.=-22dB MI=.15
Données Affich./Masquer
Double G/D

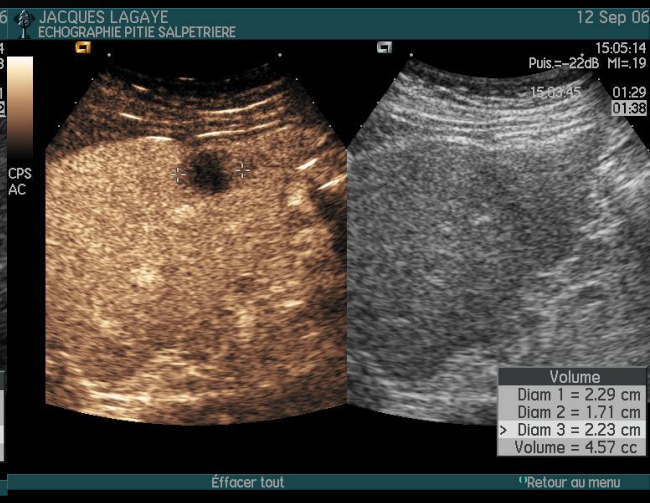




1 month

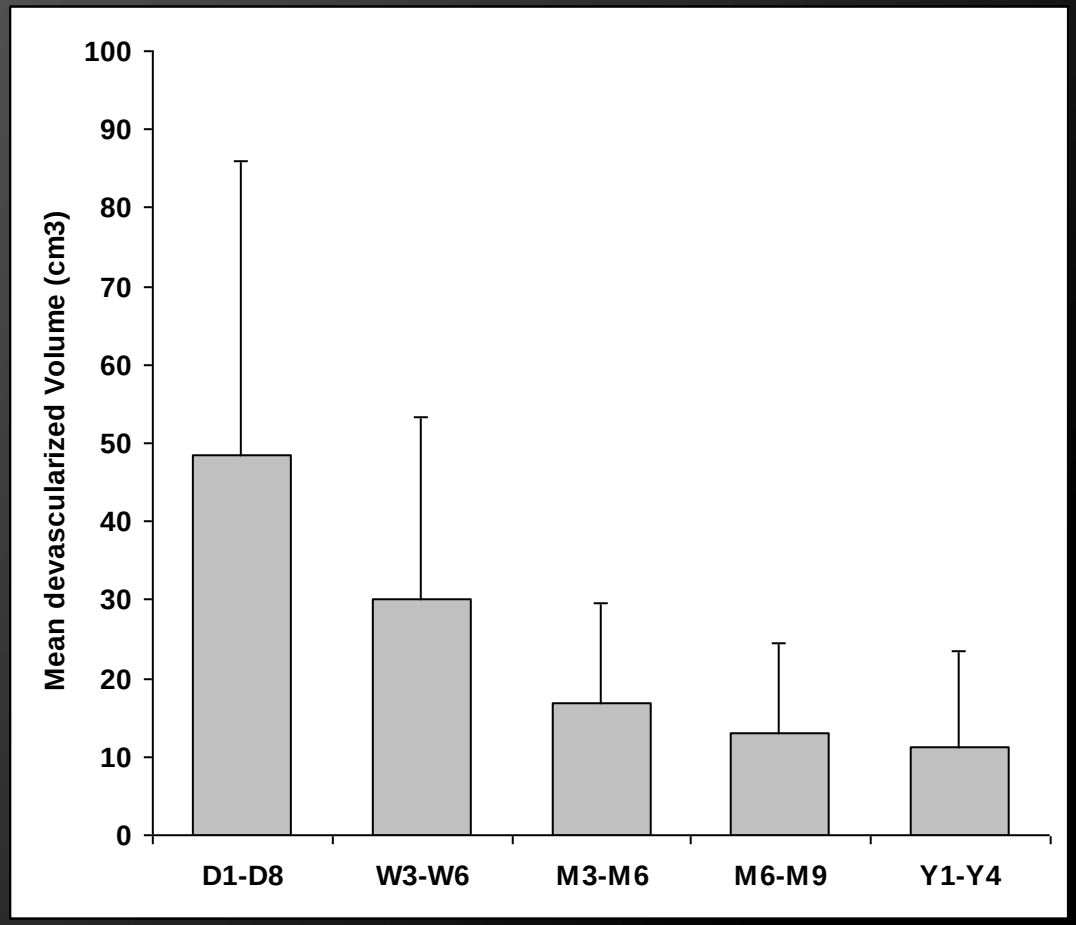


3 months



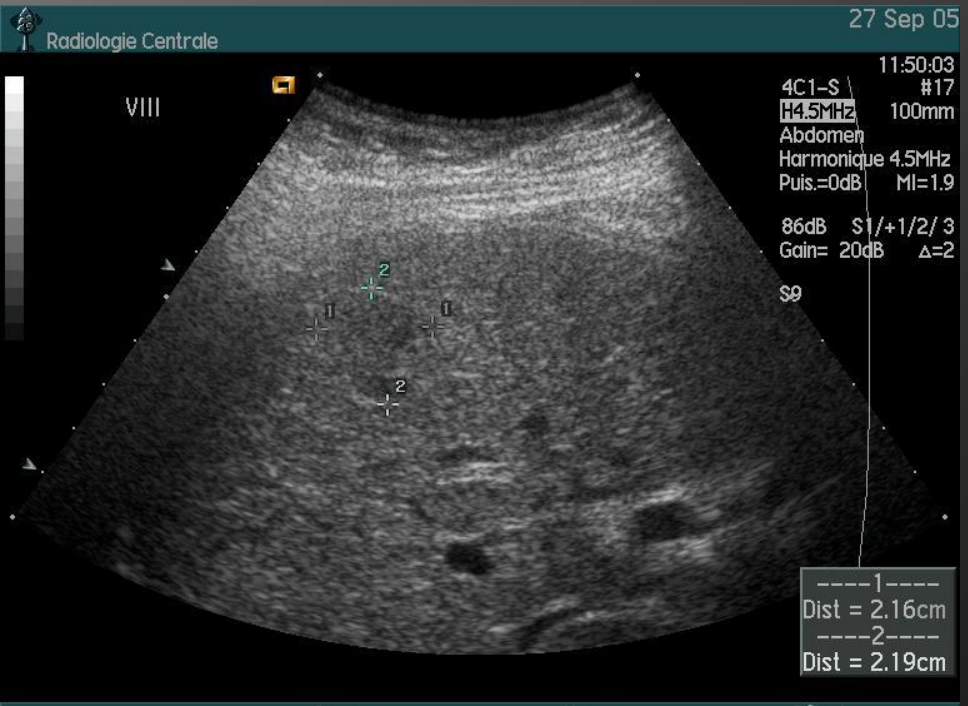
6months

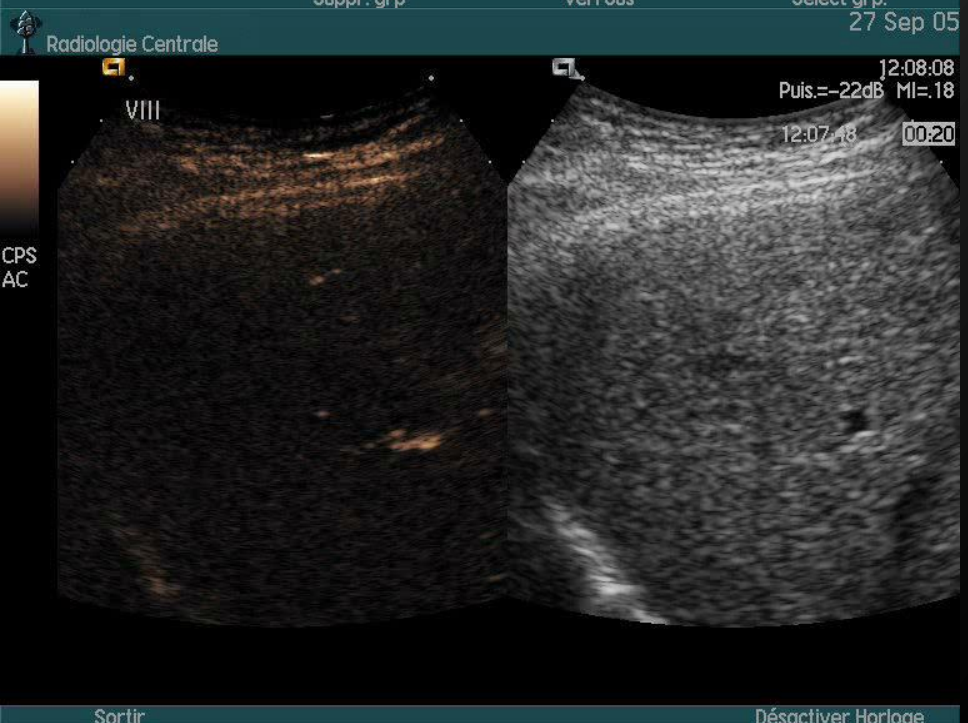
RFA scar: Volume

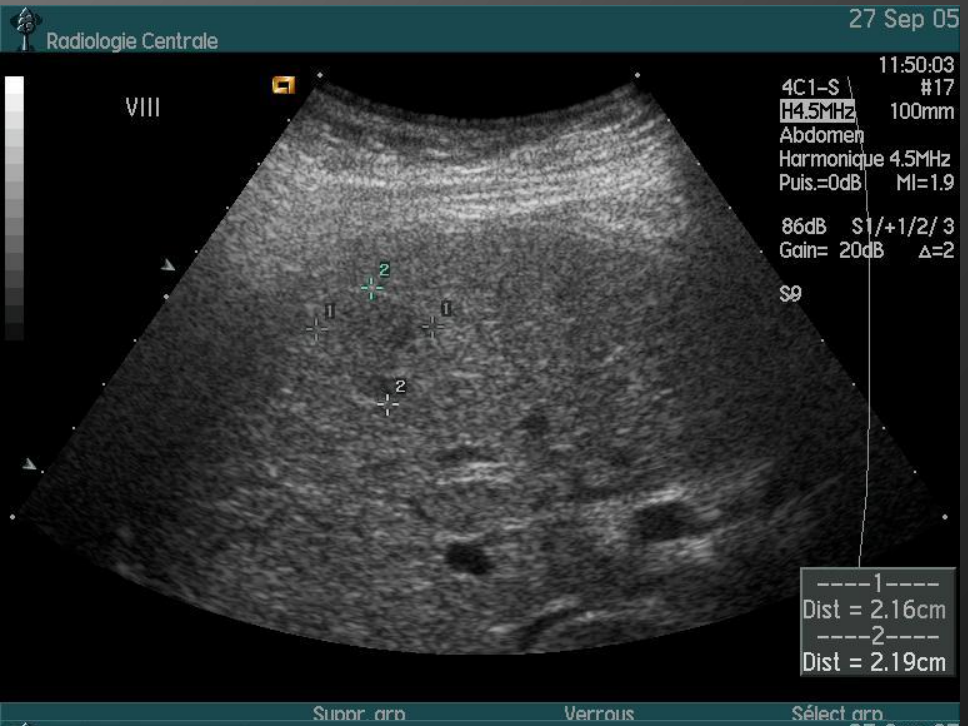


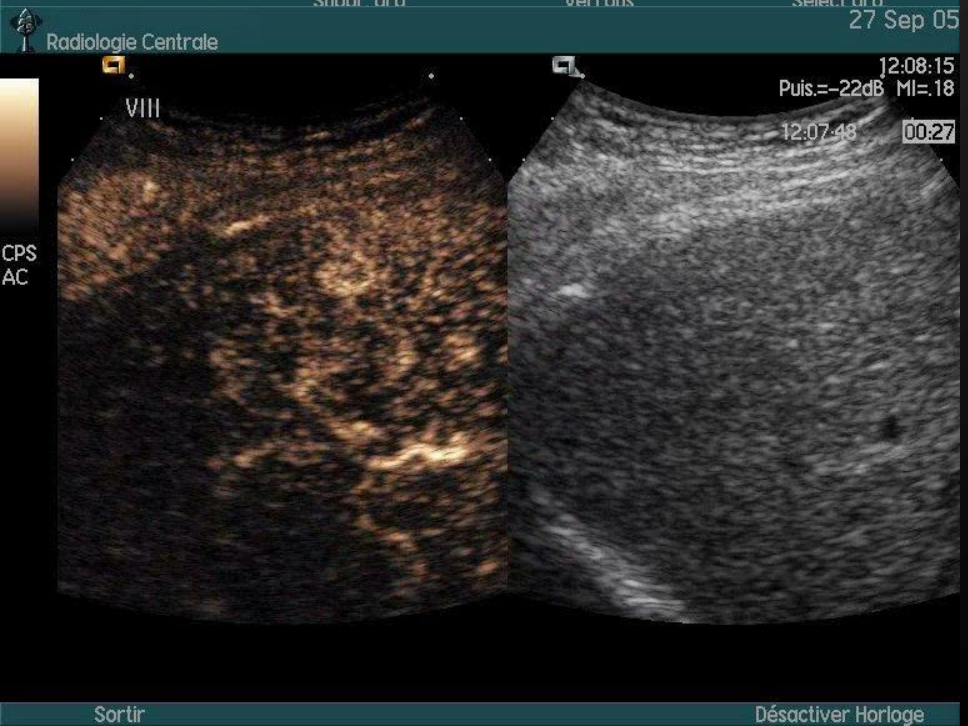
48.4 ± 37.4 cc

11.3 ± 12.1 cc

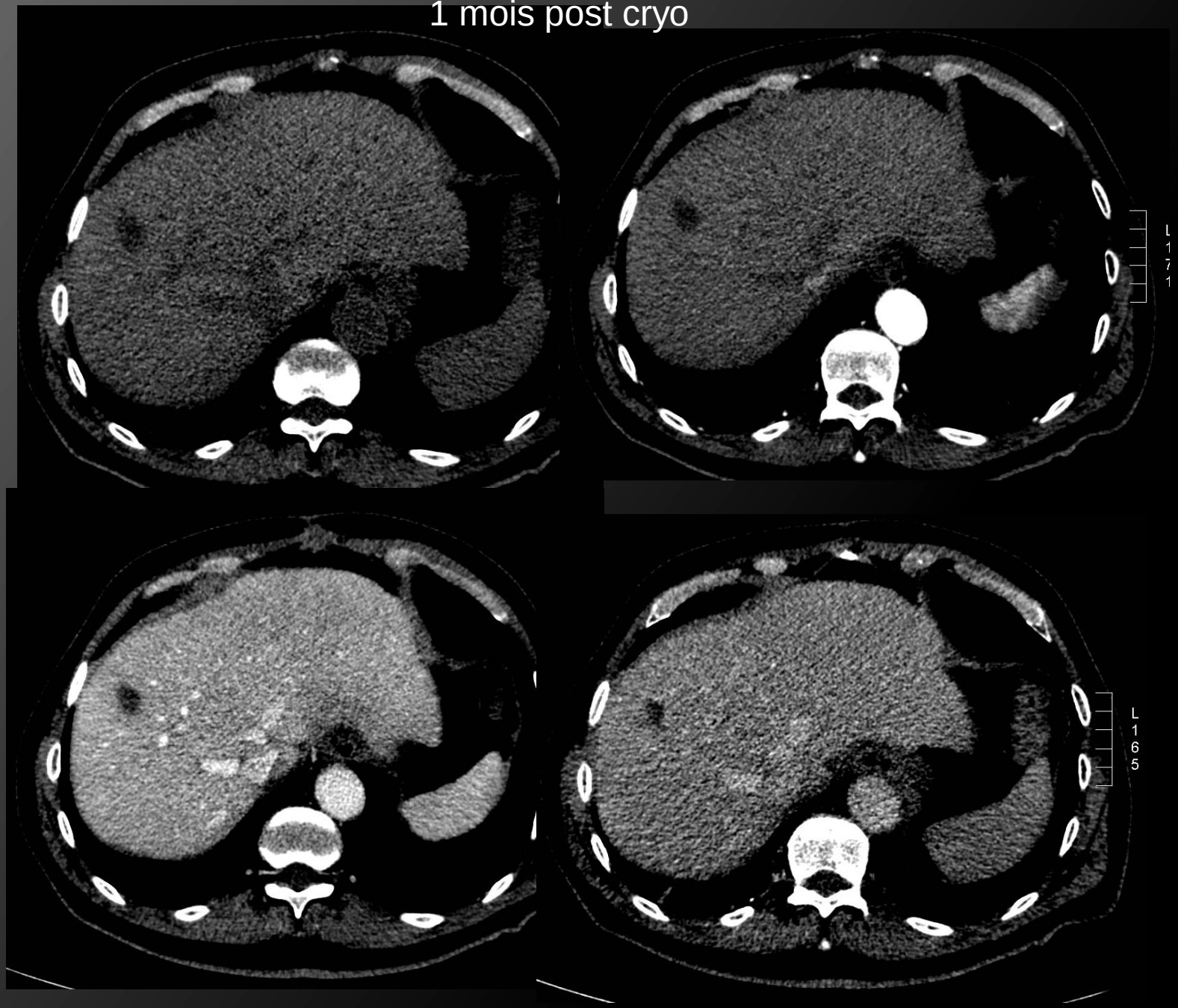

Radiologie Centrale
27 Sep 05
VIII
11:50:03
4C1-S #17
H4.5MHz 100mm
Abdomen
Harmonique 4.5MHz
Puis.=0dB MI=1.9
86dB S1/+1/2/3
Gain= 20dB Δ=2
S9
----1----
Dist = 2.16cm
----2----
Dist = 2.19cm
Suppr. grp
Verrous
Sélect grp.

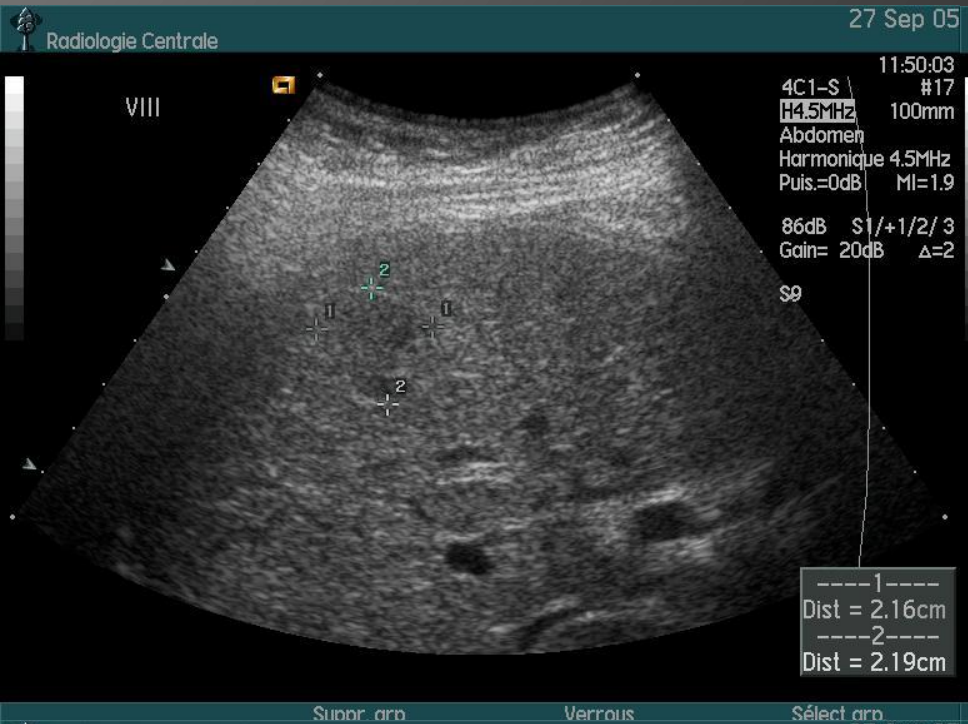

Radiologie Centrale
27 Sep 05
VIII
12:08:08
Puis.=-22dB MI=.18
12:07:18
00:20
CPS
AC
Sortir
Désactiver Horloge

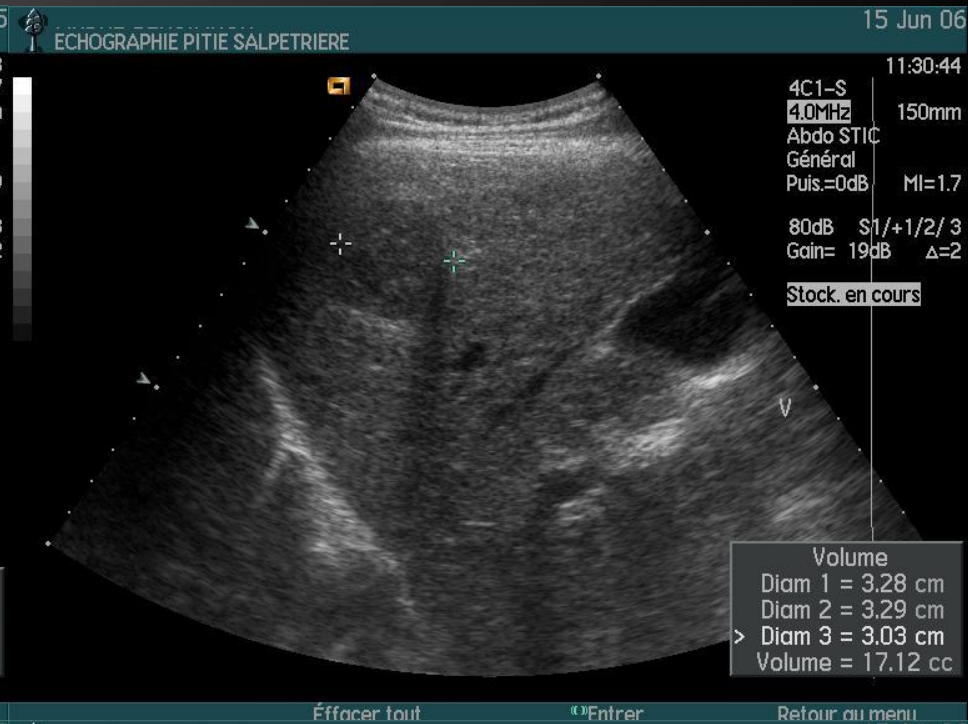

Radiologie Centrale
27 Sep 05
11:50:03
4C1-S #17
H4.5MHz 100mm
Abdomen
Harmonique 4.5MHz
Puis.=0dB MI=1.9
86dB S1/+1/2/3
Gain= 20dB Δ=2
S9
VIII
----1----
Dist = 2.16cm
----2----
Dist = 2.19cm
Suppr. grp
Verrous
Sélect grp

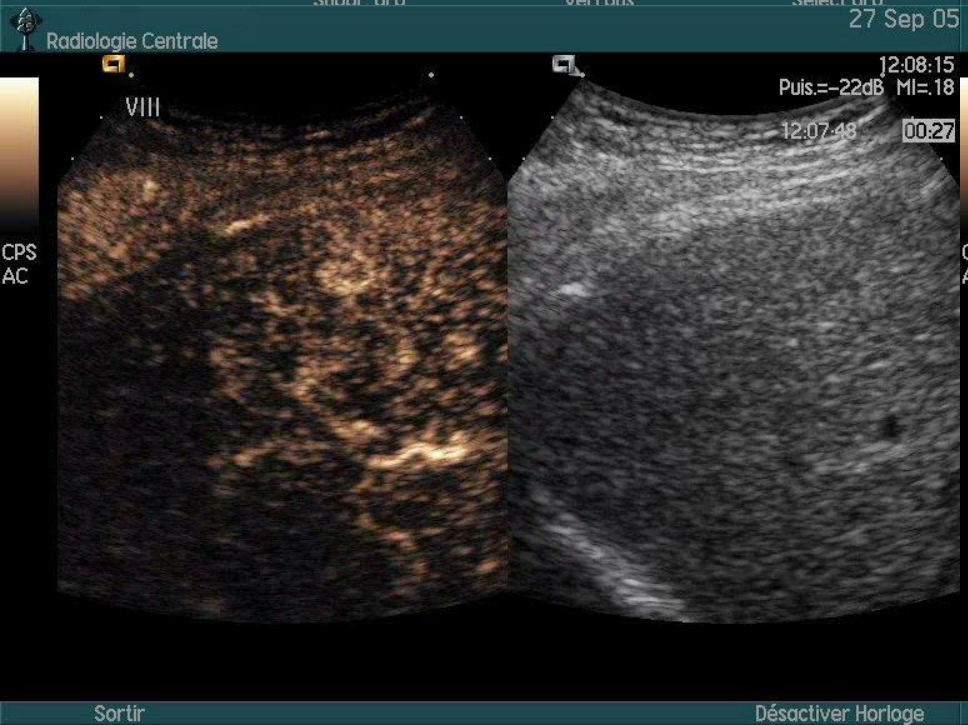

Radiologie Centrale
27 Sep 05
12:08:15
Puis.=-22dB MI=.18
VIII
12:07:48
00:27
CPS
AC
Sortir
Désactiver Horloge

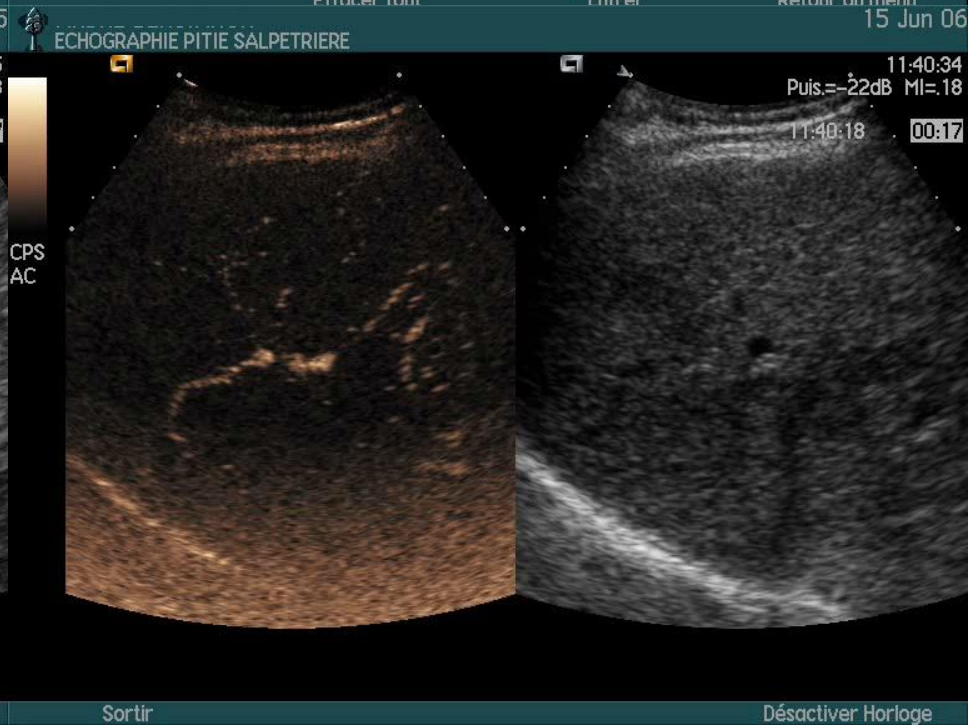
1 mois post cryo




Radiologie Centrale
27 Sep 05
11:50:03
4C1-S #17
H4.5MHz 100mm
Abdomen
Harmonique 4.5MHz
Puis.=0dB MI=1.9
86dB S1/+1/2/3
Gain= 20dB Δ=2
S9
VIII
----1----
Dist = 2.16cm
----2----
Dist = 2.19cm
Suppr. grp
Verrous
Sélect grp


ECHOGRAPHIE PITIE SALPETRIERE
15 Jun 06
11:30:44
4C1-S
4.0MHz 150mm
Abdo STIC
Général
Puis.=0dB MI=1.7
80dB S1/+1/2/3
Gain= 19dB Δ=2
Stock. en cours
V
Volume
Diam 1 = 3.28 cm
Diam 2 = 3.29 cm
> Diam 3 = 3.03 cm
Volume = 17.12 cc
Effacer tout
Entrer
Retour au menu


Radiologie Centrale
27 Sep 05
12:08:15
Puis.=-22dB MI=.18
12:07:48
00:27
VIII
CPS
AC
Sortir
Désactiver Horloge


ECHOGRAPHIE PITIE SALPETRIERE
15 Jun 06
11:40:34
Puis.=-22dB MI=.18
11:40:18
00:17
CPS
AC
Sortir
Désactiver Horloge

RFA: CEUS vs CT ?

Shiozawa et al, J Clin Ultrasound 2010;38:182-189

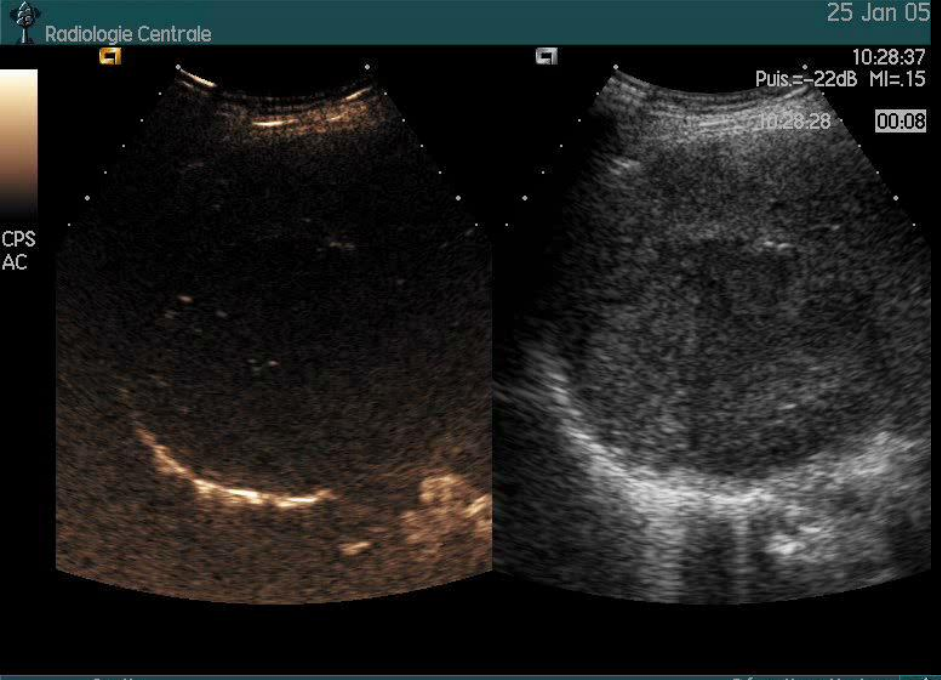
TABLE 1
Area Under the ROC Curve and *p* Value for CEUS Using Sonazoid and Dynamic CT in Detecting Local Recurrence of HCC

	Observer 1	Observer 2	Mean Az	*p* Value
CT	0.939	0.988	0.964	<0.05*
CEUS	0.985	0.986	0.986	NS
p	NS	NS	NS	

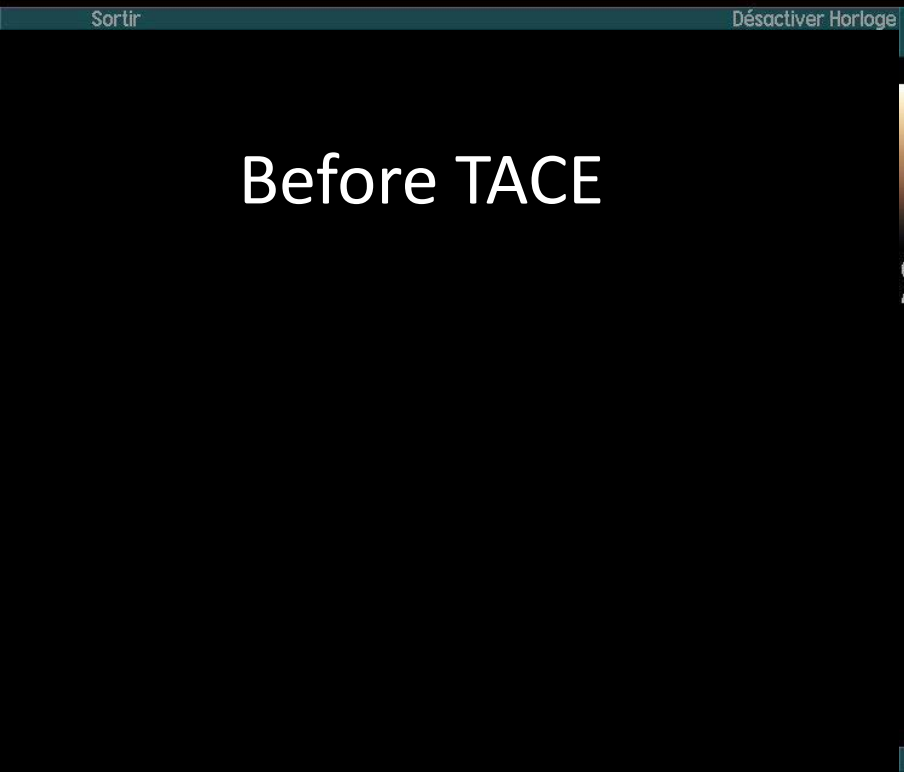
* Statistical significance.

Abbreviations: CEUS, contrast-enhanced ultrasonography; HCC, hepatocellular carcinoma; ROC, receiver operating characteristic.

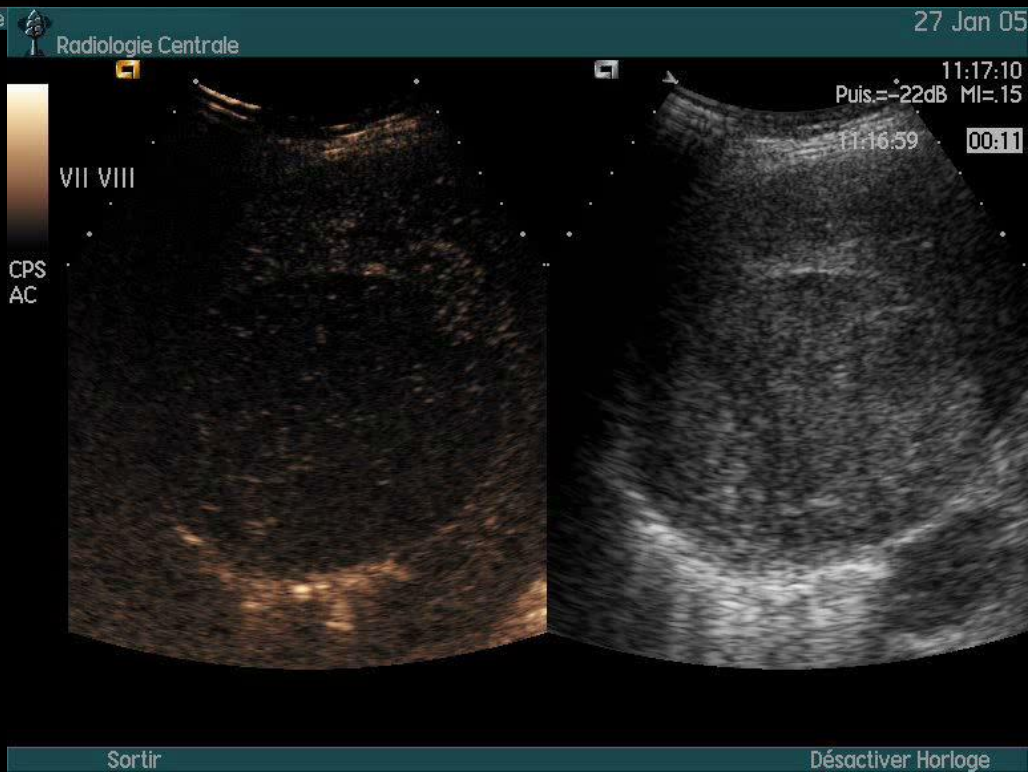
CEUS proposed alternately with CT or MRI to reduce irradiation or cost ?

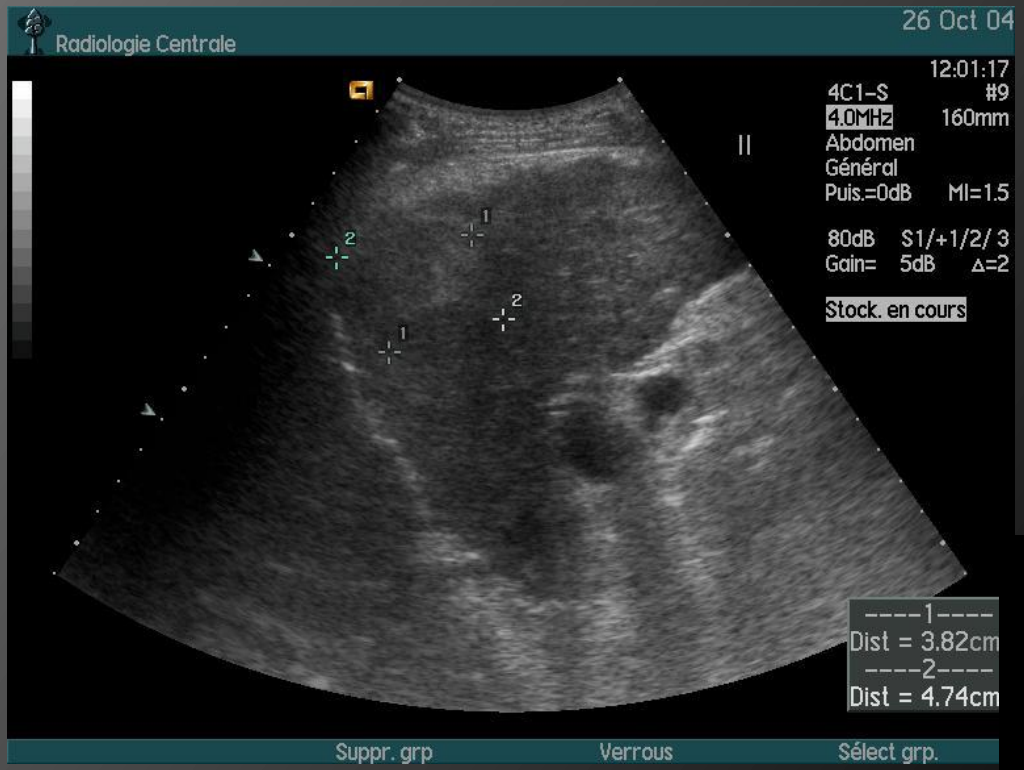


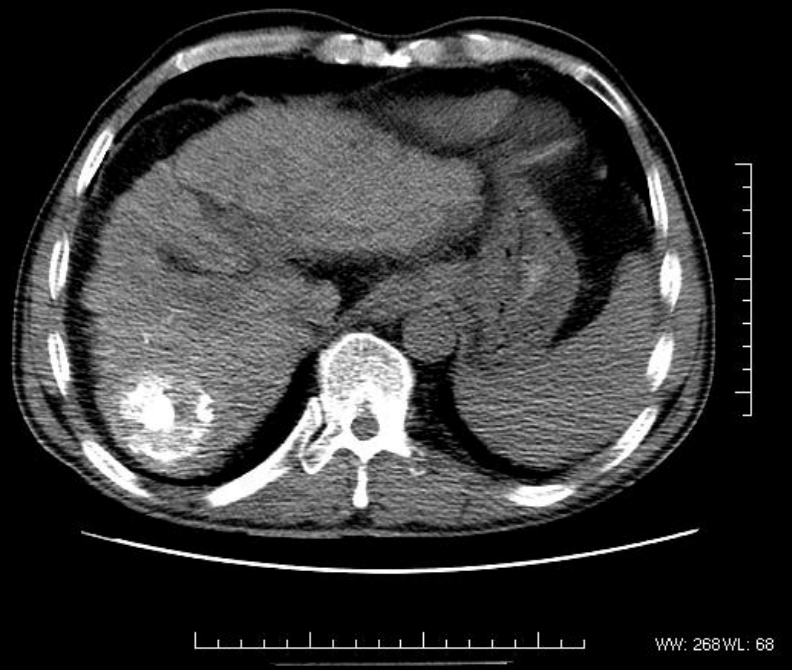
Before TACE

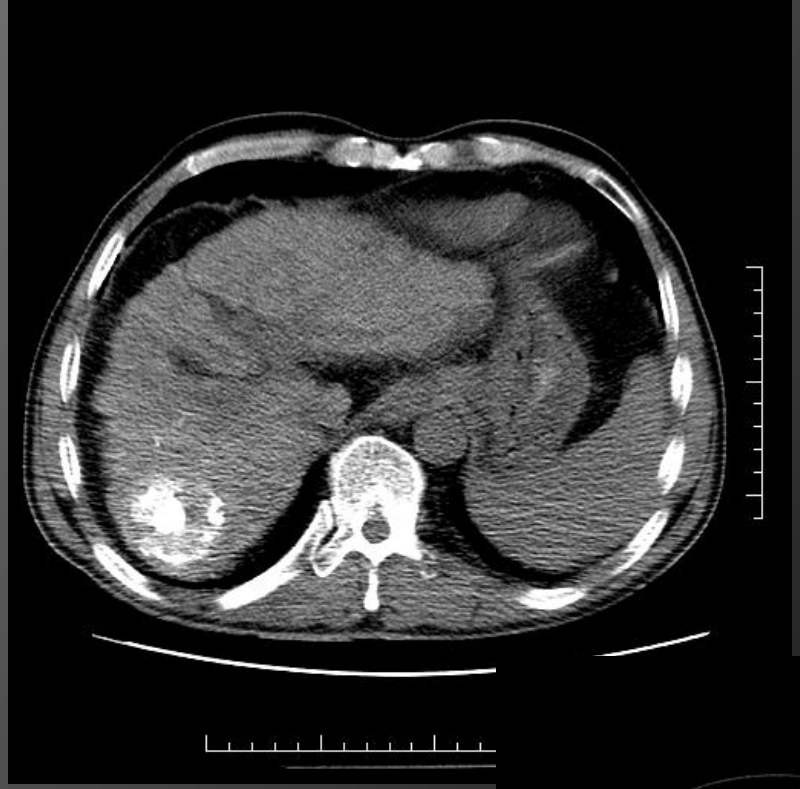


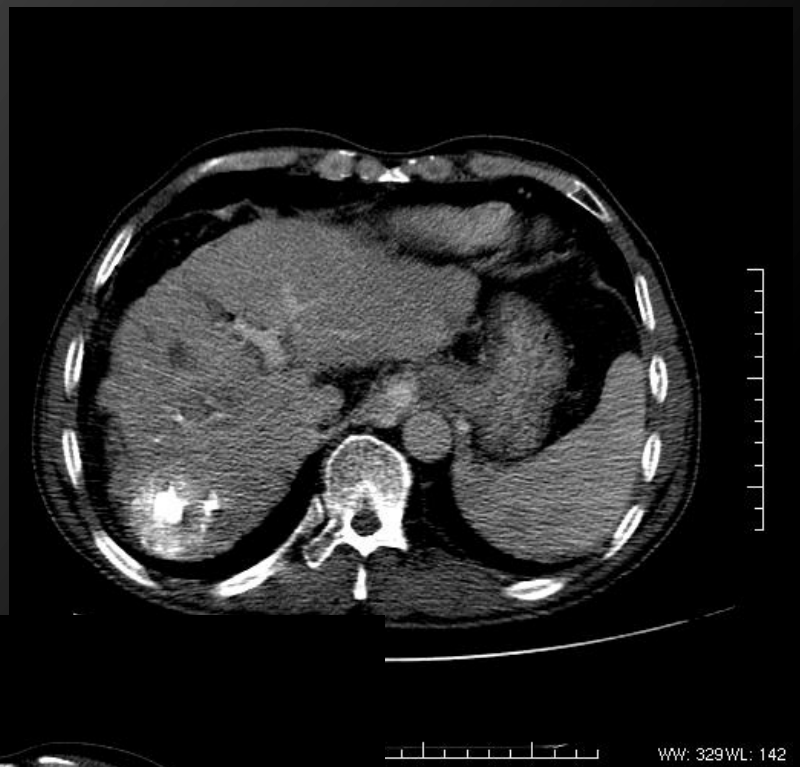
After TACE

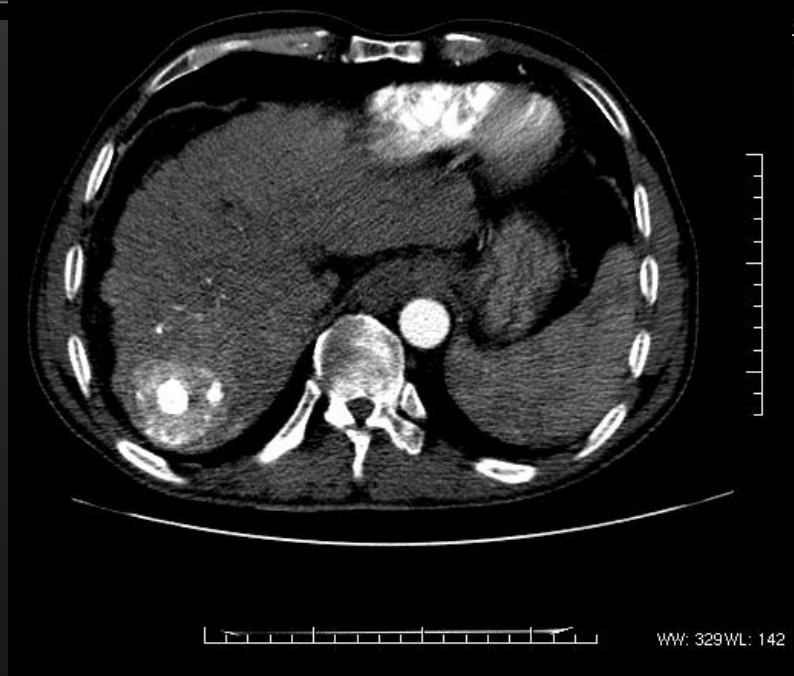


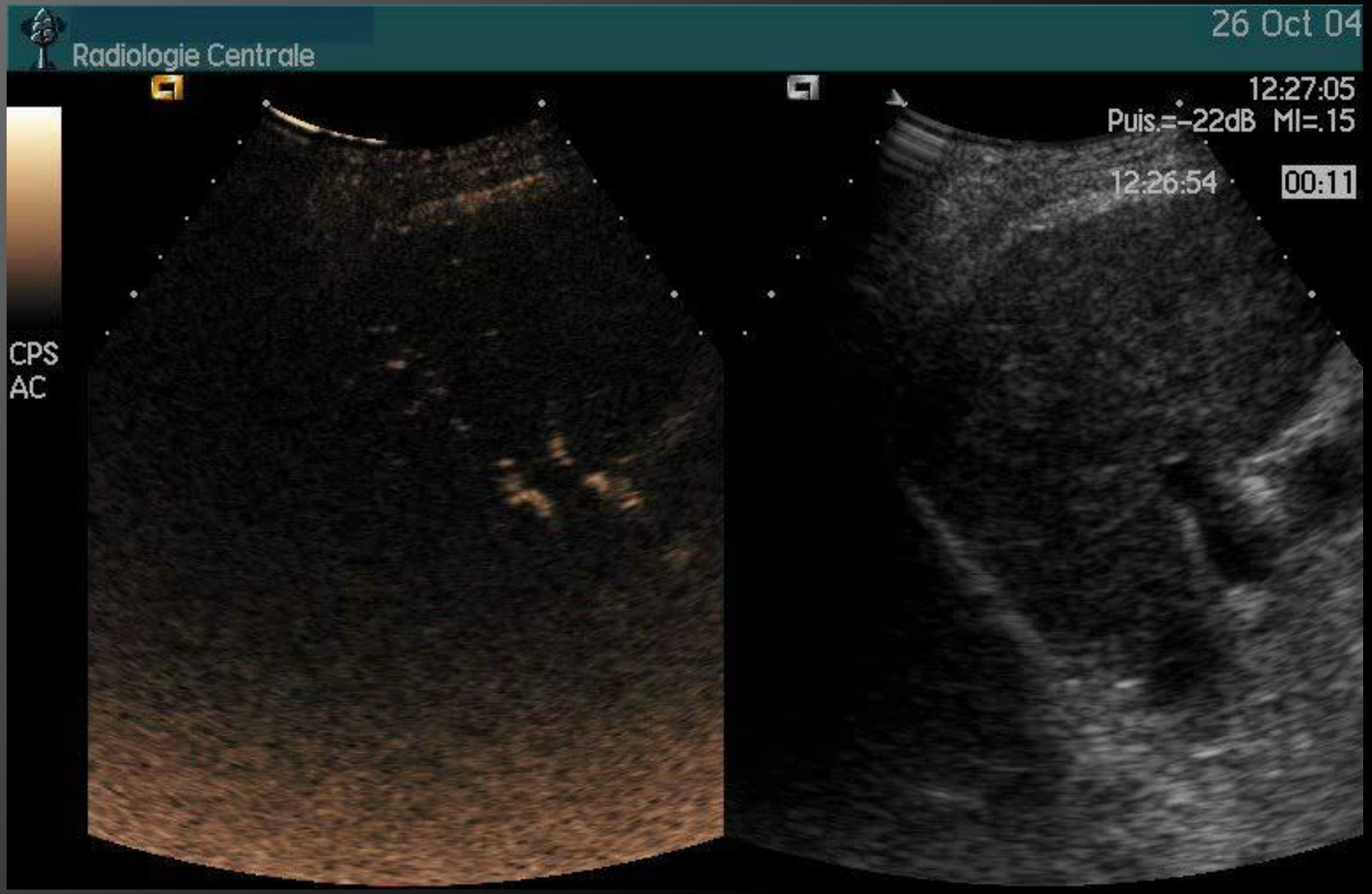

Radiologie Centrale
26 Oct 04
12:01:17
4C1-S
#9
4.0MHz
160mm
Abdomen
Général
Puis.=0dB
MI=1.5
80dB
S1/+1/2/ 3
Gain=
5dB
Δ=2
Stock. en cours
----1----
Dist = 3.82cm
----2----
Dist = 4.74cm
Suppr. grp
Verrous
Sélect grp.


WW: 268 WL: 68




WW: 329 WL: 142


WW: 329 WL: 142

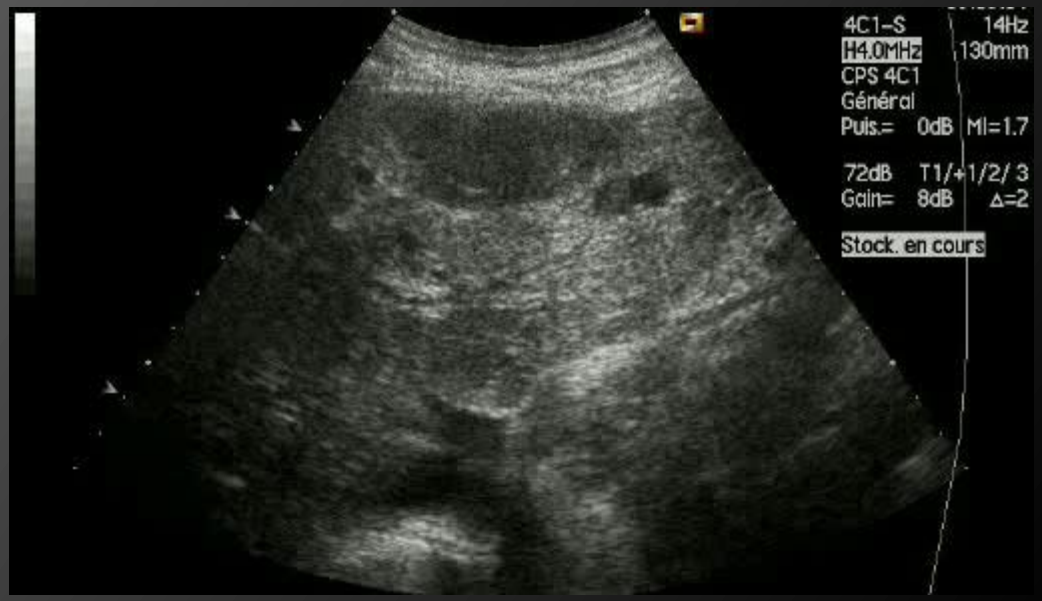

Radiologie Centrale
26 Oct 04
12:27:05
Puis.=-22dB MI=.15
12:26:54
00:11
CPS
AC

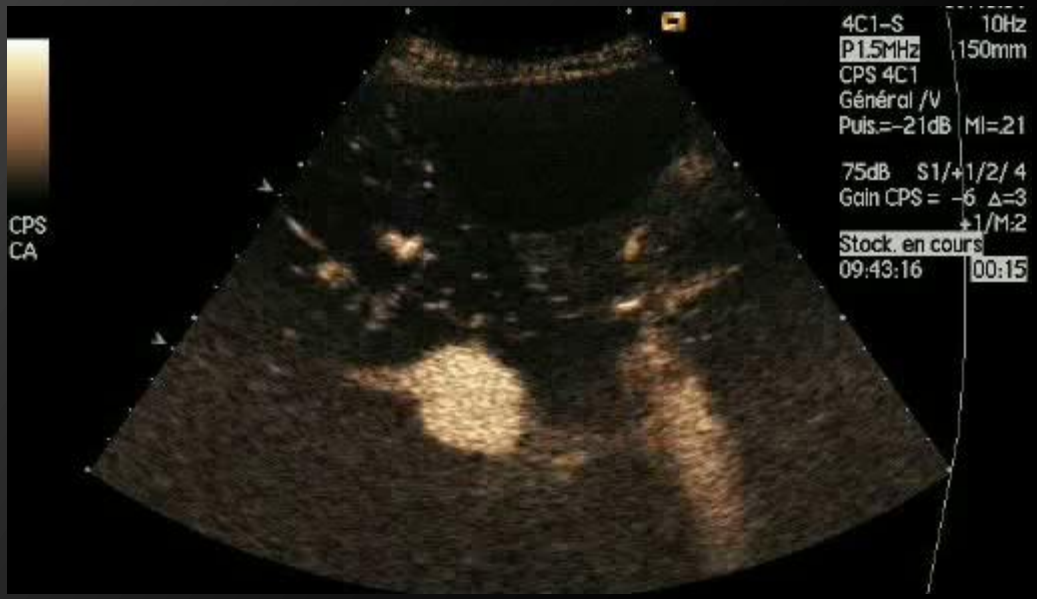
TACE: CEUS vs MRI or CT ?

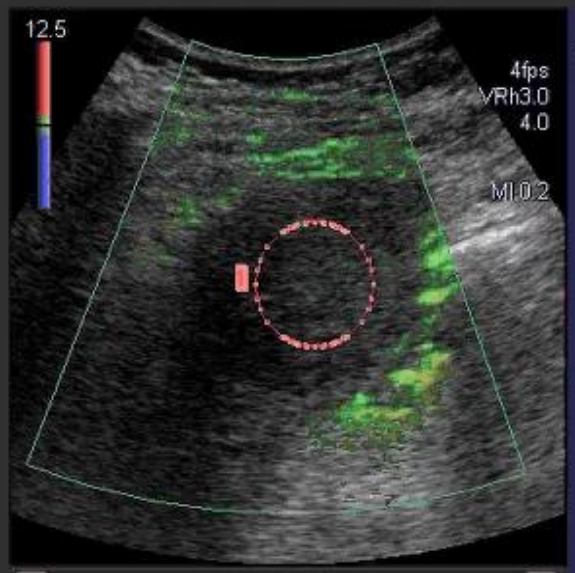
- During the procedure to immediately assess the success of the procedure[1]
- CEUS seems to be more sensitive than dynamic CT in depicting the residual tumor blood supply to HCCs one week after TACE[2-3]
- No comparison between CEUS and MRI seems to be

1- Moshouris et al, Cardiovasc Intervent Radiol 2010;16:Ahead of print
2- Xia et al, Oncology 2008;75:99-105
3- Kim et al, j Ultrasound Med 2006;25:477-86

GIST


4C1-S
14Hz
H4.0MHz
130mm
CPS 4C1
Général
Puis.= 0dB MI=1.7
72dB T1/+1/2/ 3
Gain= 8dB Δ=2
Stock. en cours

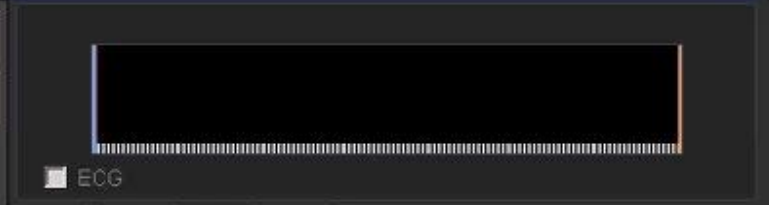

4C1-S
10Hz
P1.5MHz
150mm
CPS 4C1
Général /V
Puis.=-21dB MI=.21
75dB S1/+1/2/ 4
Gain CPS = -6 Δ=3
+1/M:2
Stock. en cours
09:43:16
00:15
CPS
CA


12.5
4fps
VRh3.0
4.0
MI:0.2


1053msec
Active


Power x 10^(-3)
Time:1053msec
6.39
5.99
5.59
5.19
4.80
4.40
4.00
3.60
3.20
2.80
2.41
2.01
1.61
1.21
0.81
0.42
0.02
[msec]


TCA
M-Graph
Fitting
Set ROI
Draw ROI
Del CH
Scale
Linear
Log
Del All CH
ROI Tracking
off
on

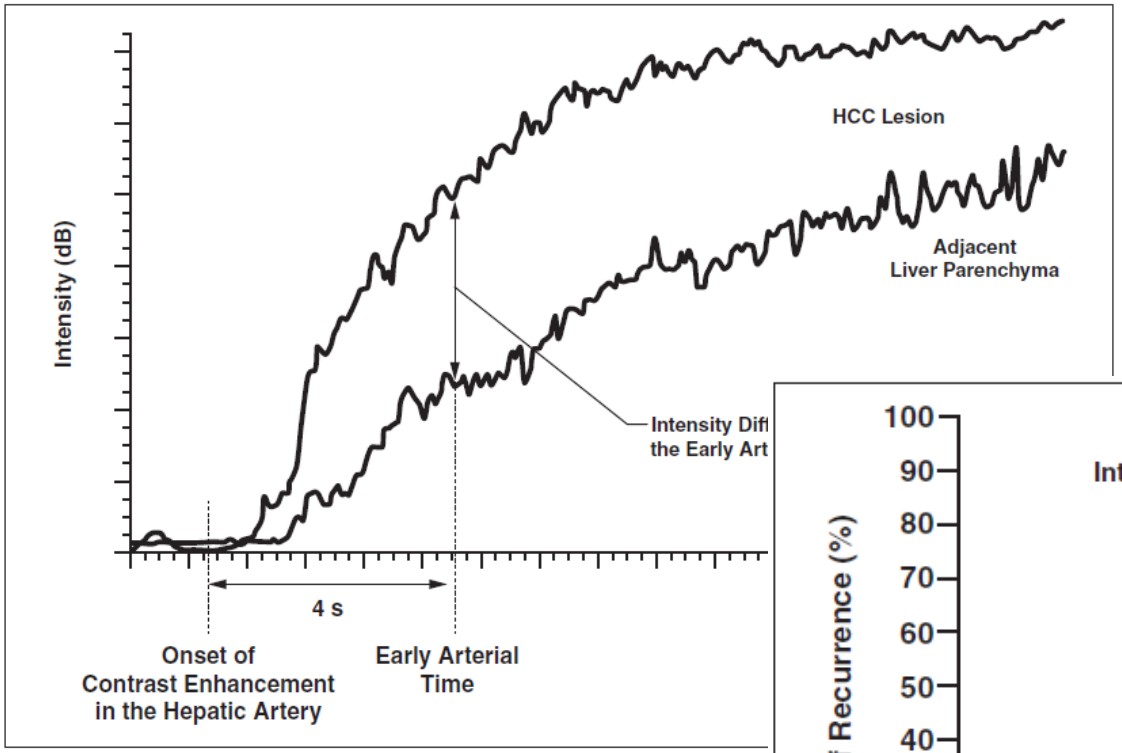

ECG

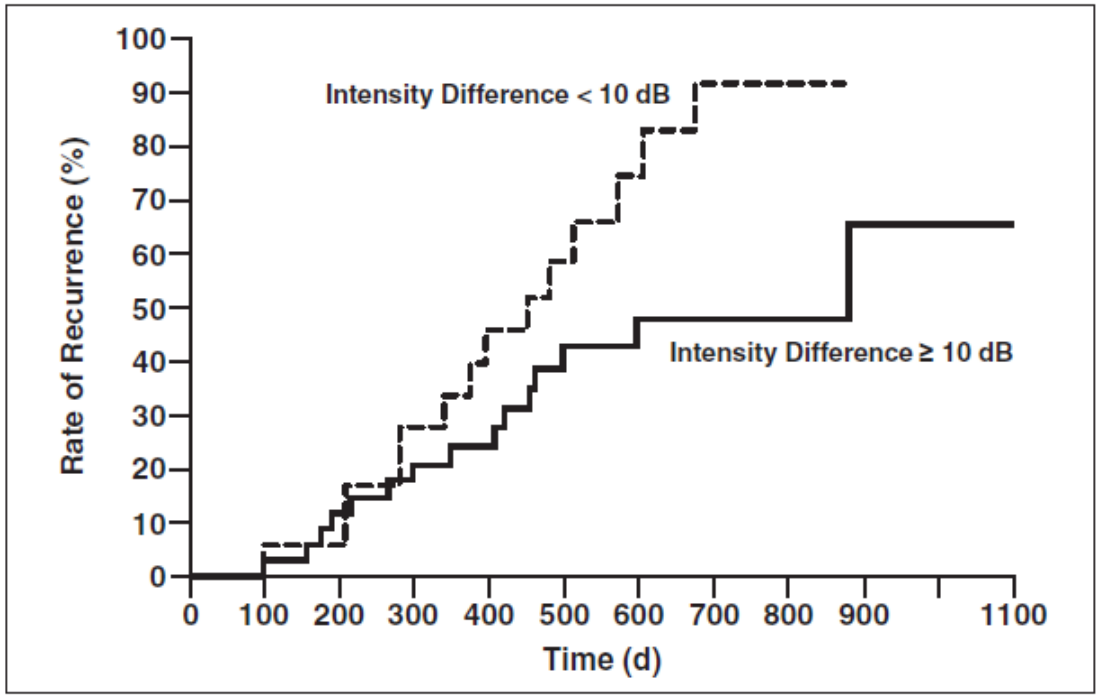

ROI
Cf
CV
Err
Type: Ellipse
Boundary Box: (23.3mm, 24.6mm)
Circumference: 77.0mm
Area: 448.3mm2

AJR 2013; 200:570–577

Hitoshi Maruyama[1]
Masanori Takahashi
Taro Shimada
Tadashi Sekimoto
Hidehiro Kamesaki
Fumihiko Kanai
Osamu Yokosuka

Pretreatment Microbubble-Induced Enhancement in Hepatocellular Carcinoma Predicts Intrahepatic Distant Recurrence After Radiofrequency Ablation



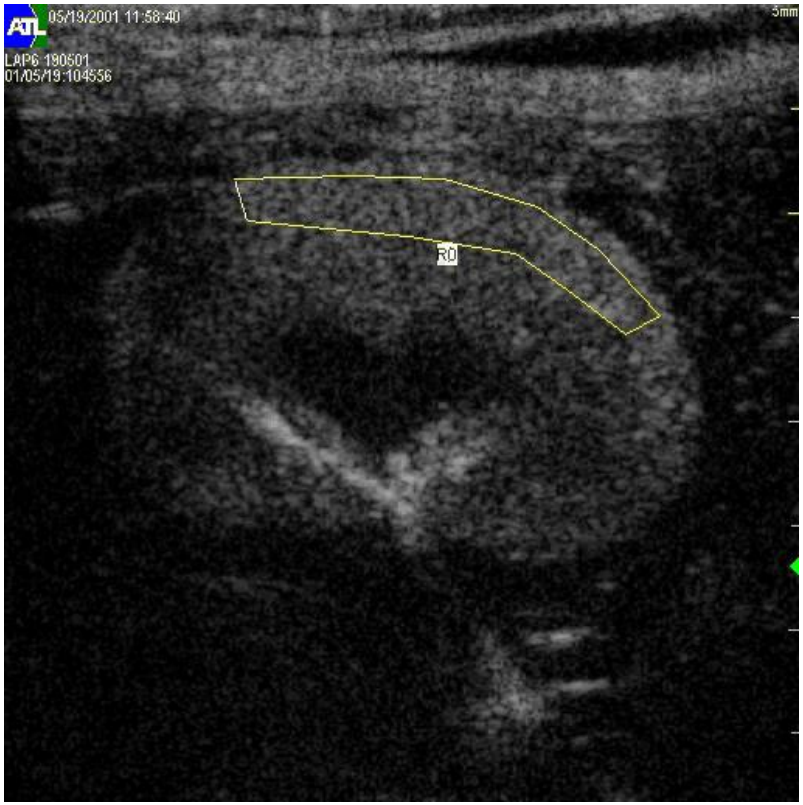


Functional Imaging: Quantitative assessment

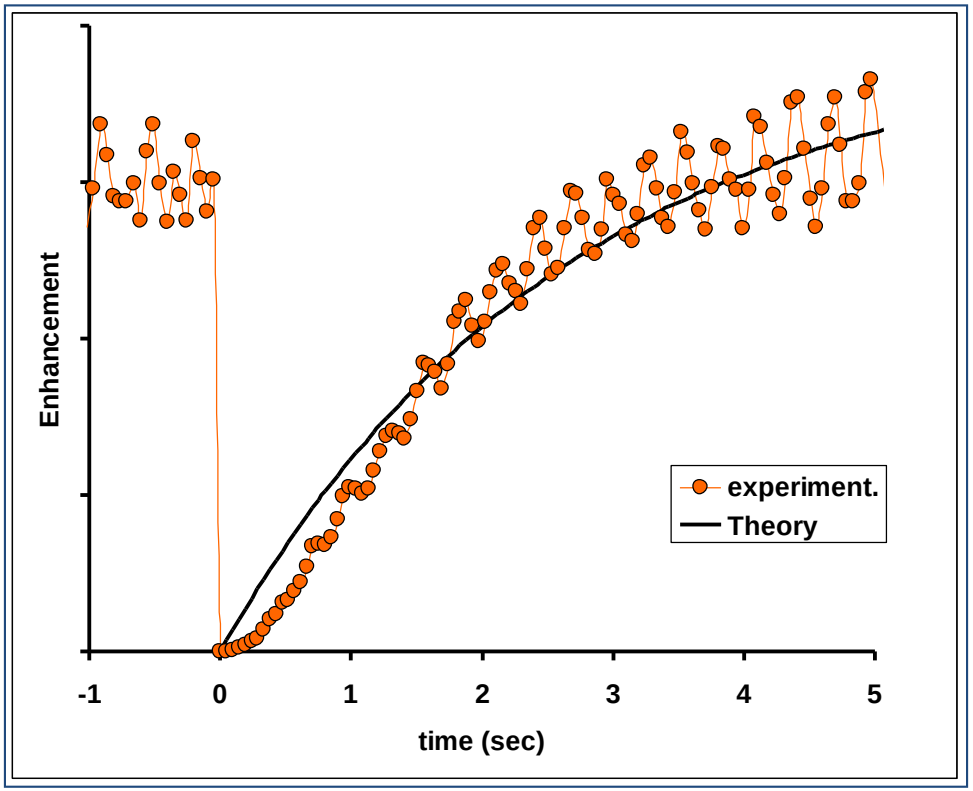
- quantitative assessment of the vascular bed of the lesion
  - Similar to DCE MRI or functional CT
  - Variation of the local concentration of microbubbles as a function of time
  - By measuring the effect on the images
- Pb or AIF

Functional Imaging: Quantitative assessment

Destruction replenishment



Rabbit kidney



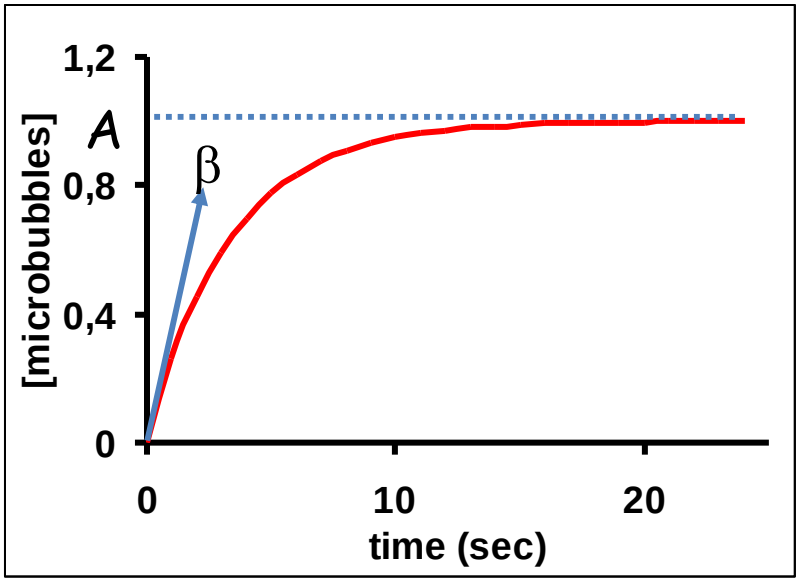
Continuous injection SonoVue

Destruction replenishment

$$C(t) = A\left(1 - e^{-\beta t}\right)$$

A ⇨ Fractional bld vol

β : Fraction of blood replaced per s



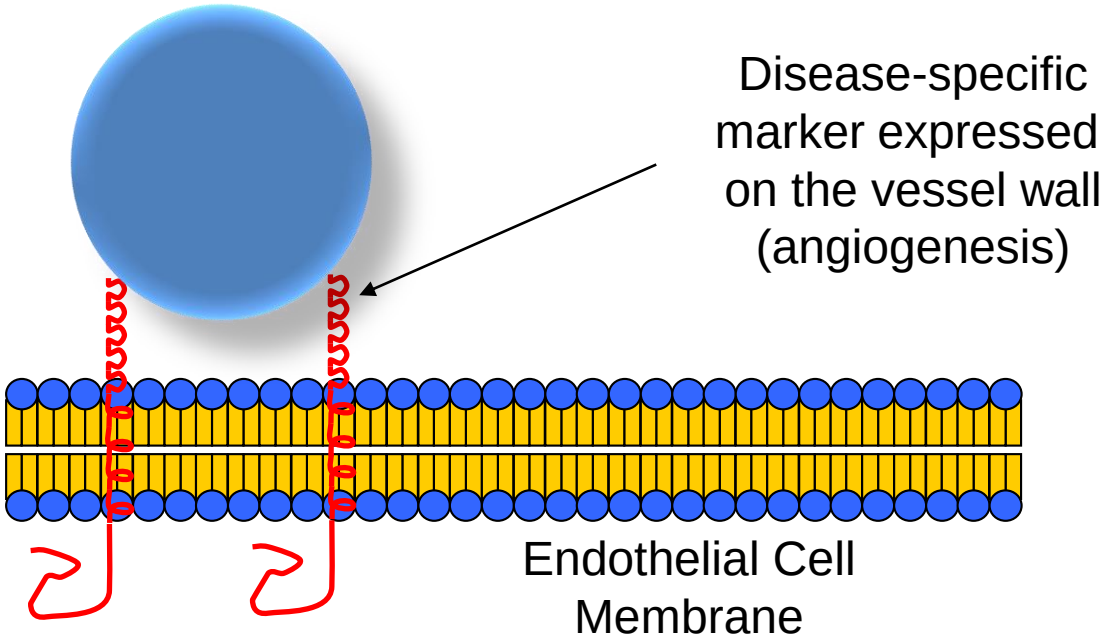
Aβ reflects the relative BF

DCE-US

- True blood pool agent
  - => BV, BF, MTT
  - ≠> PS, Ktrans, Kep, VE

Targeted imaging

Ligand specific for a selected marker



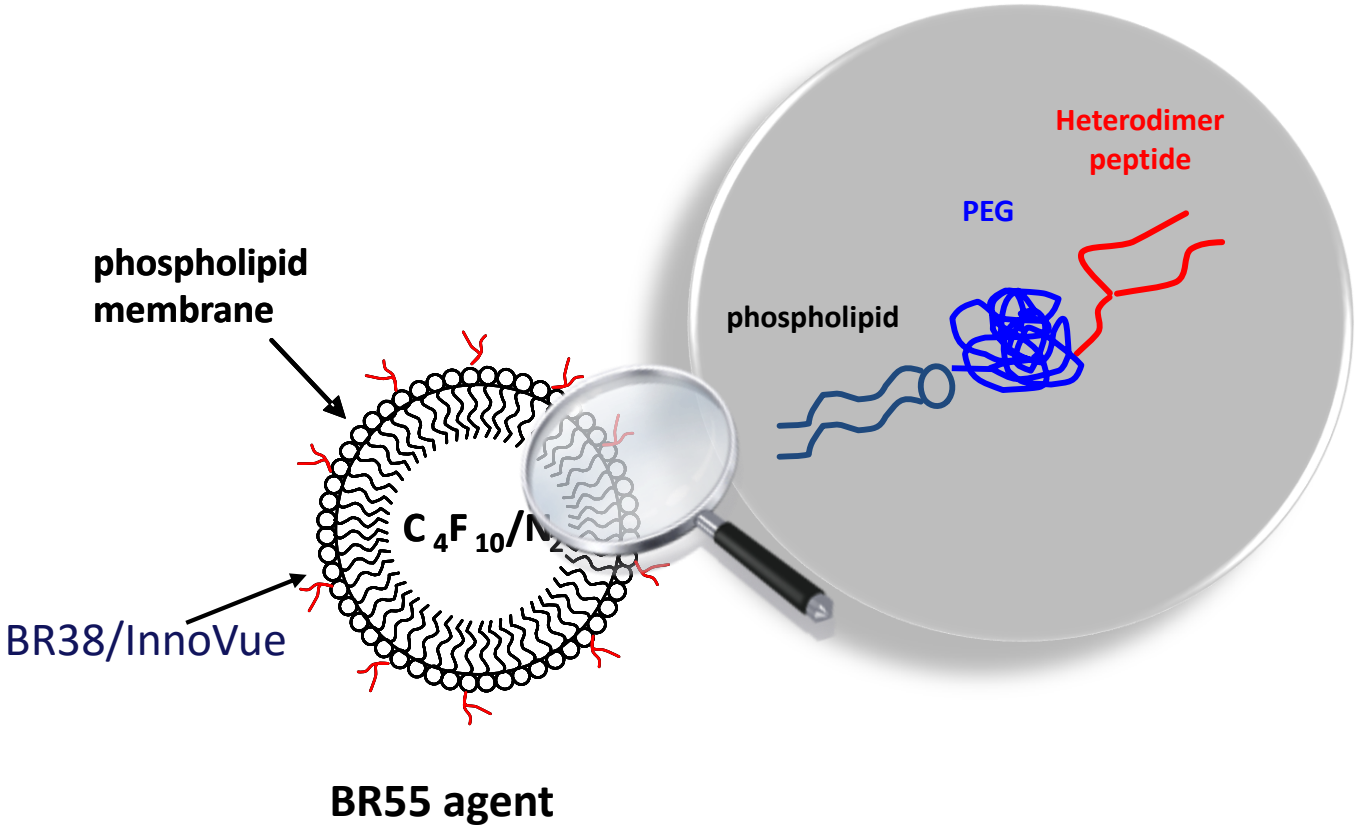
Sensitivity +

↓

Sensitivity -

PET
Microbubbles
MRI

BR55 targeted agent



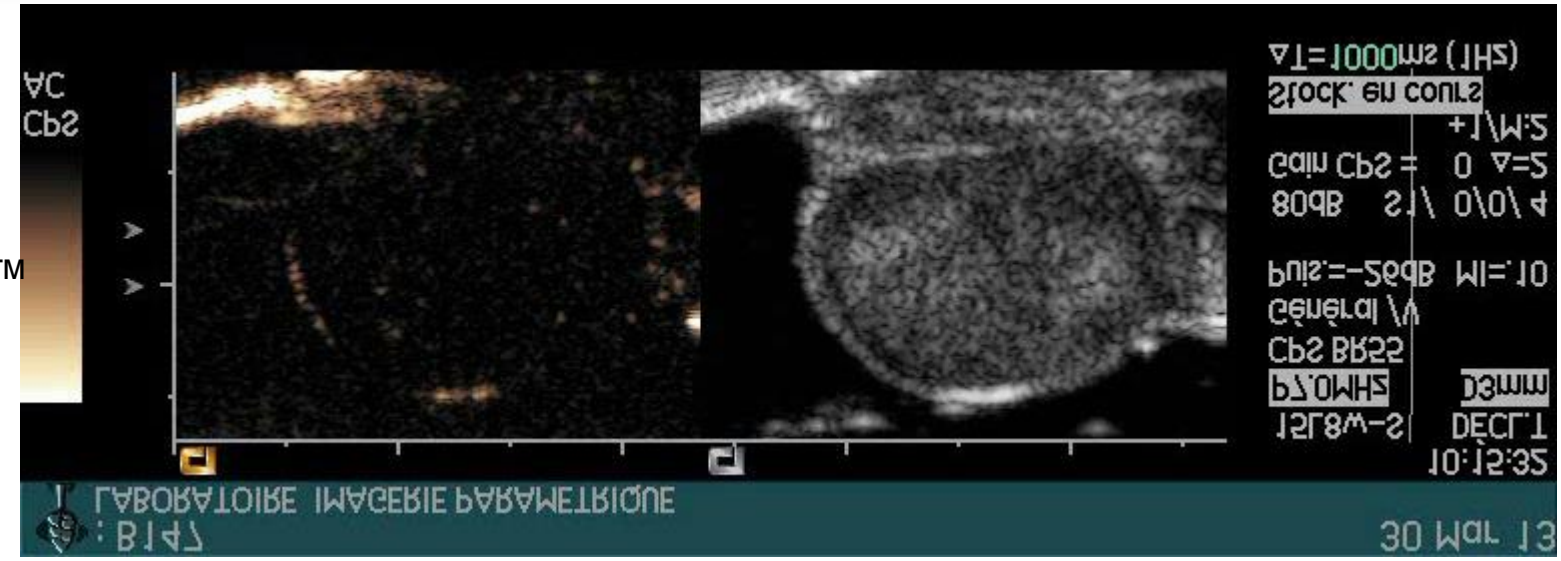
BRACCO
LIFE FROM INSIDE

VEGFR2

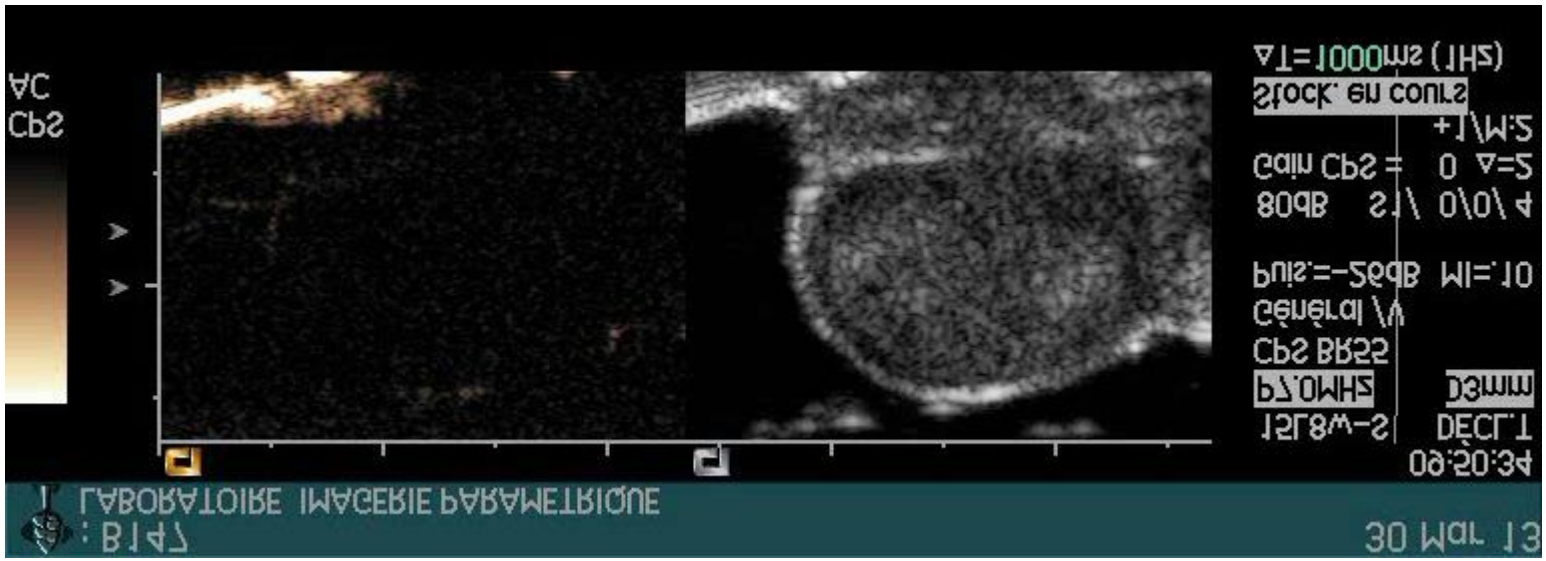
Over expressed in tumoral vessels

Targeted imaging

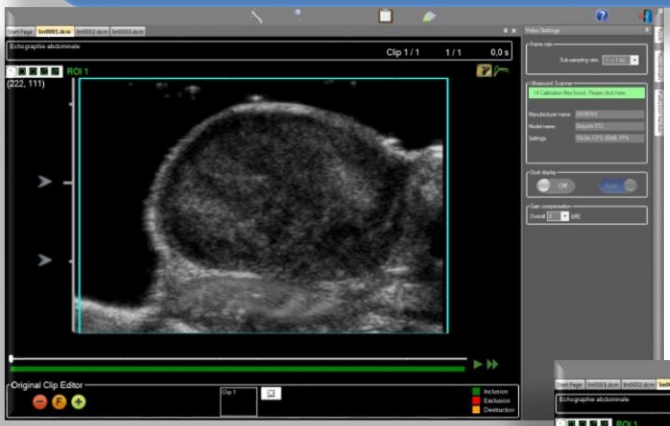
SonoVue™



BR55



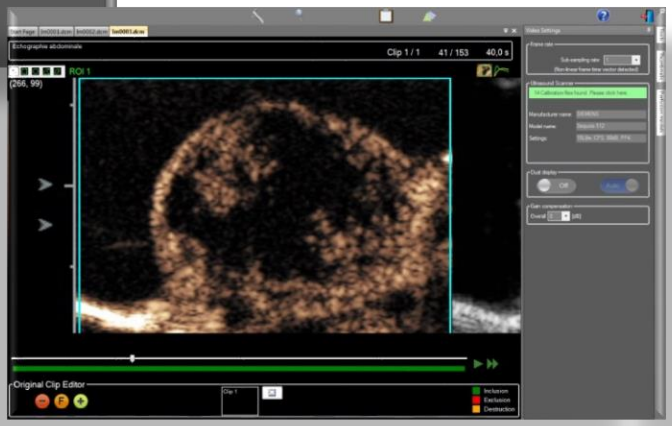
Targeted imaging

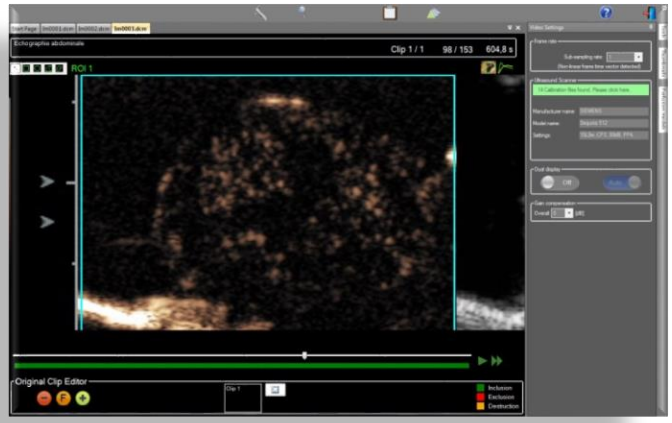


40 sec

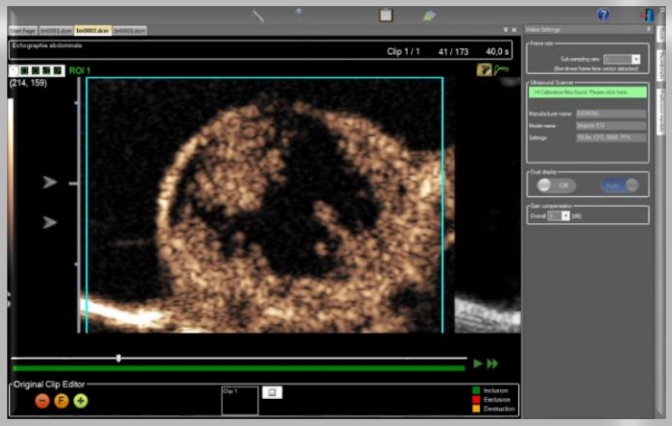
10 min

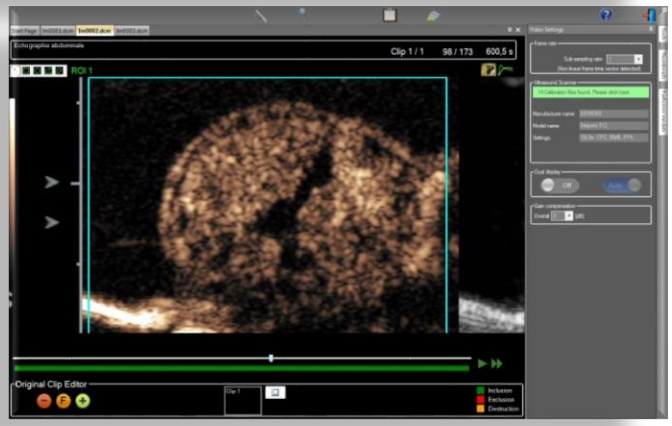
SonoVue™

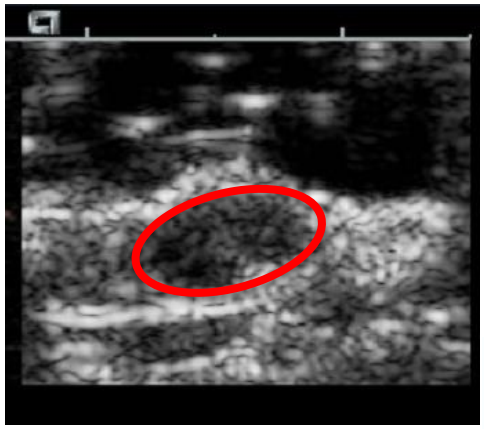




BR55



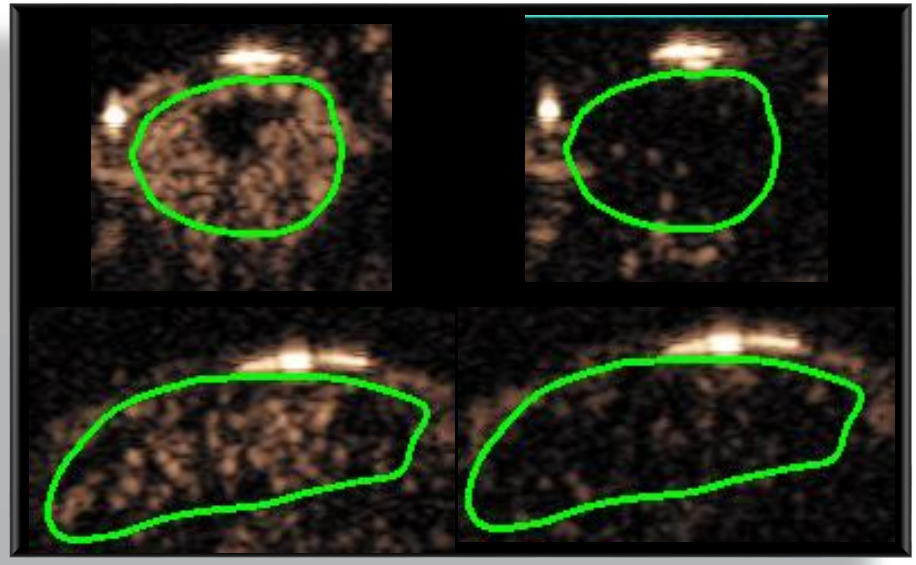


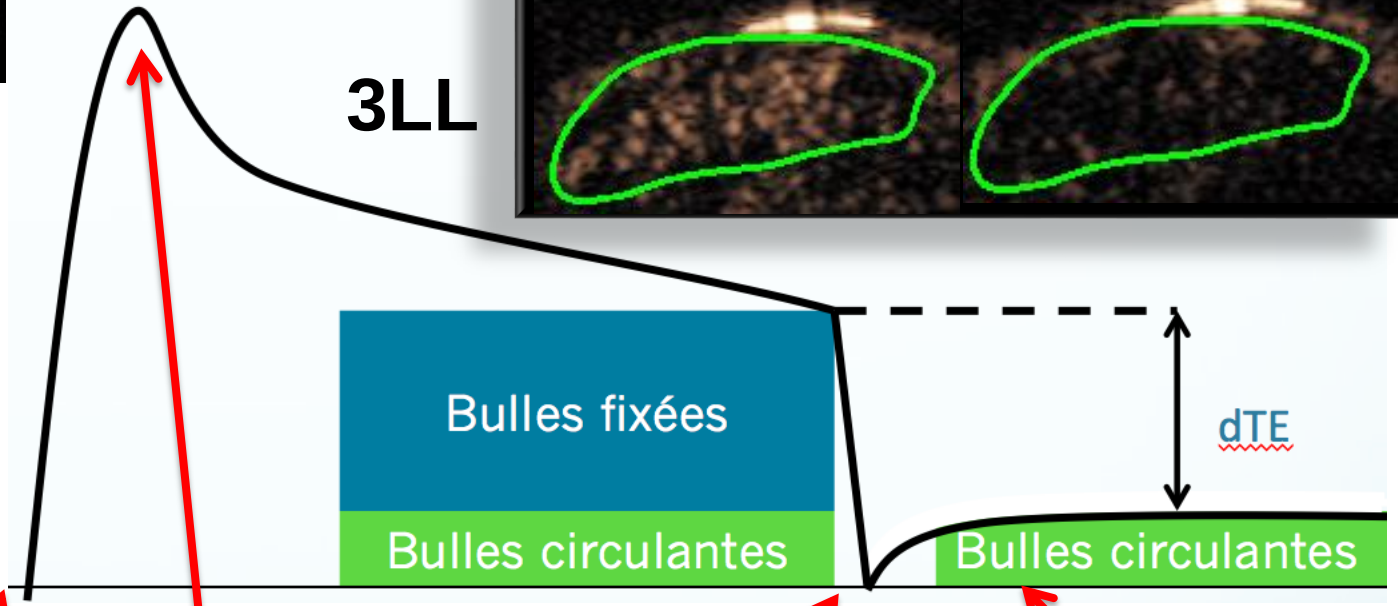


Bmode
14MHz

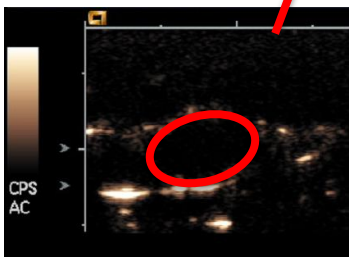
CT26

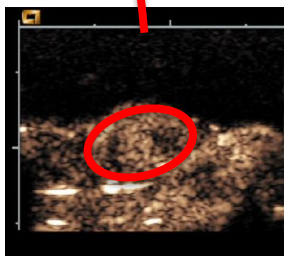
3LL

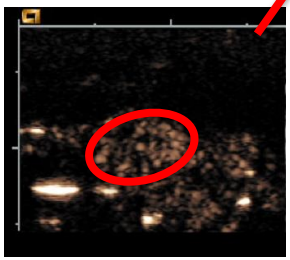


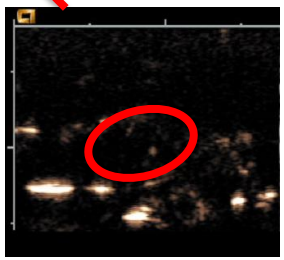


7 MHz
IM = 0,1









00:00
baseline

00:22
bolus

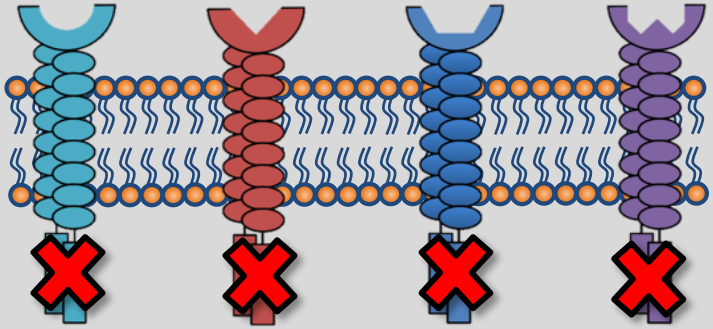
10:10
pre–destruction

10:23
post–destruction

Targeted imaging

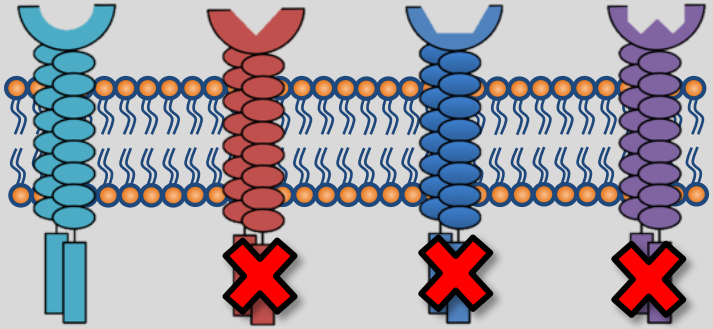
Sunitinib

- *(40mg/kg per day)*



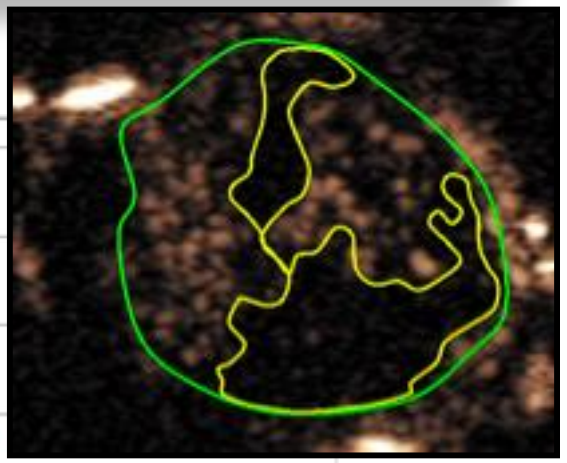
Imatinib

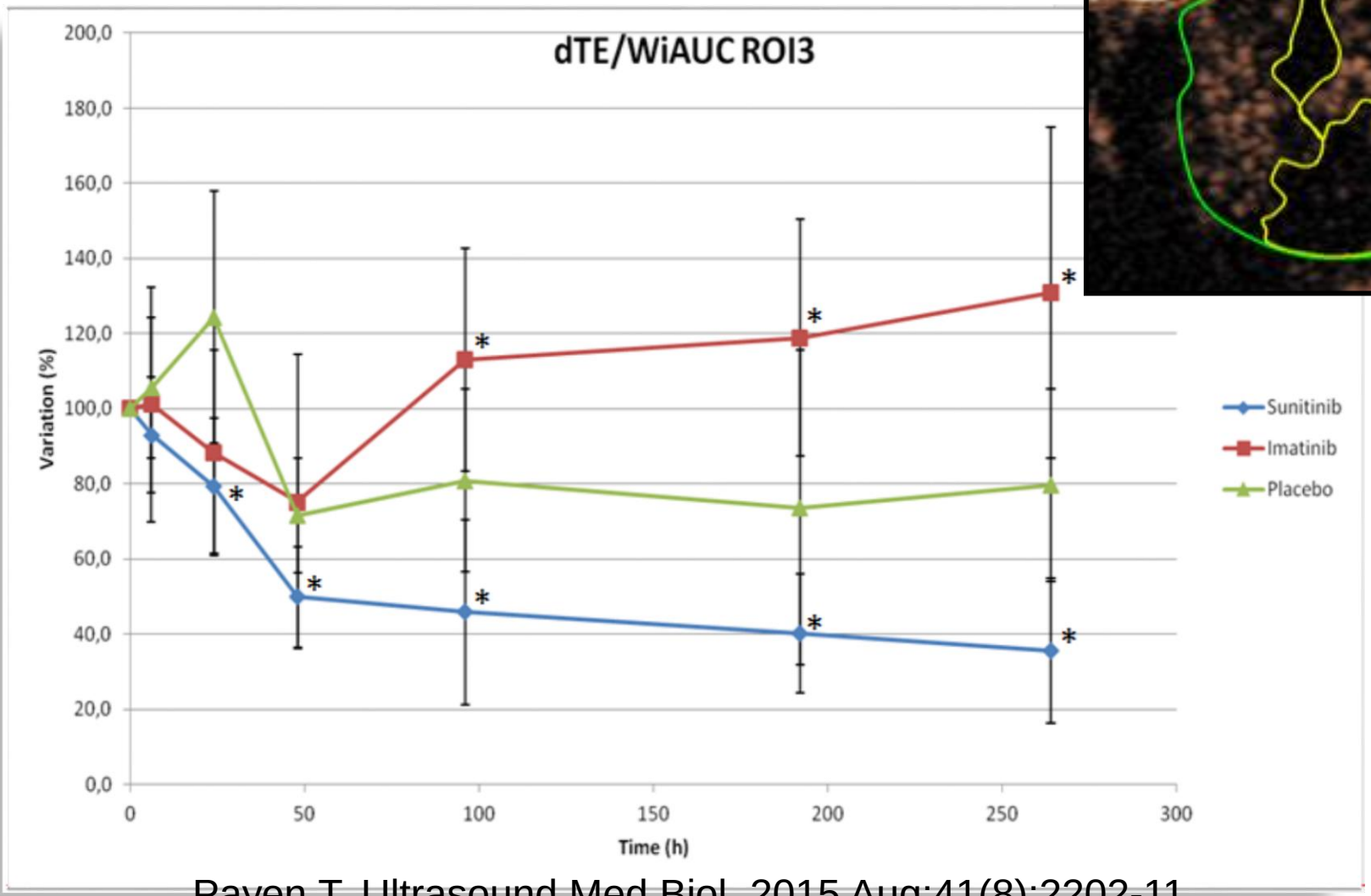
- *(30mg/kg per day)*



45 CT26

LIP : Targeted imaging

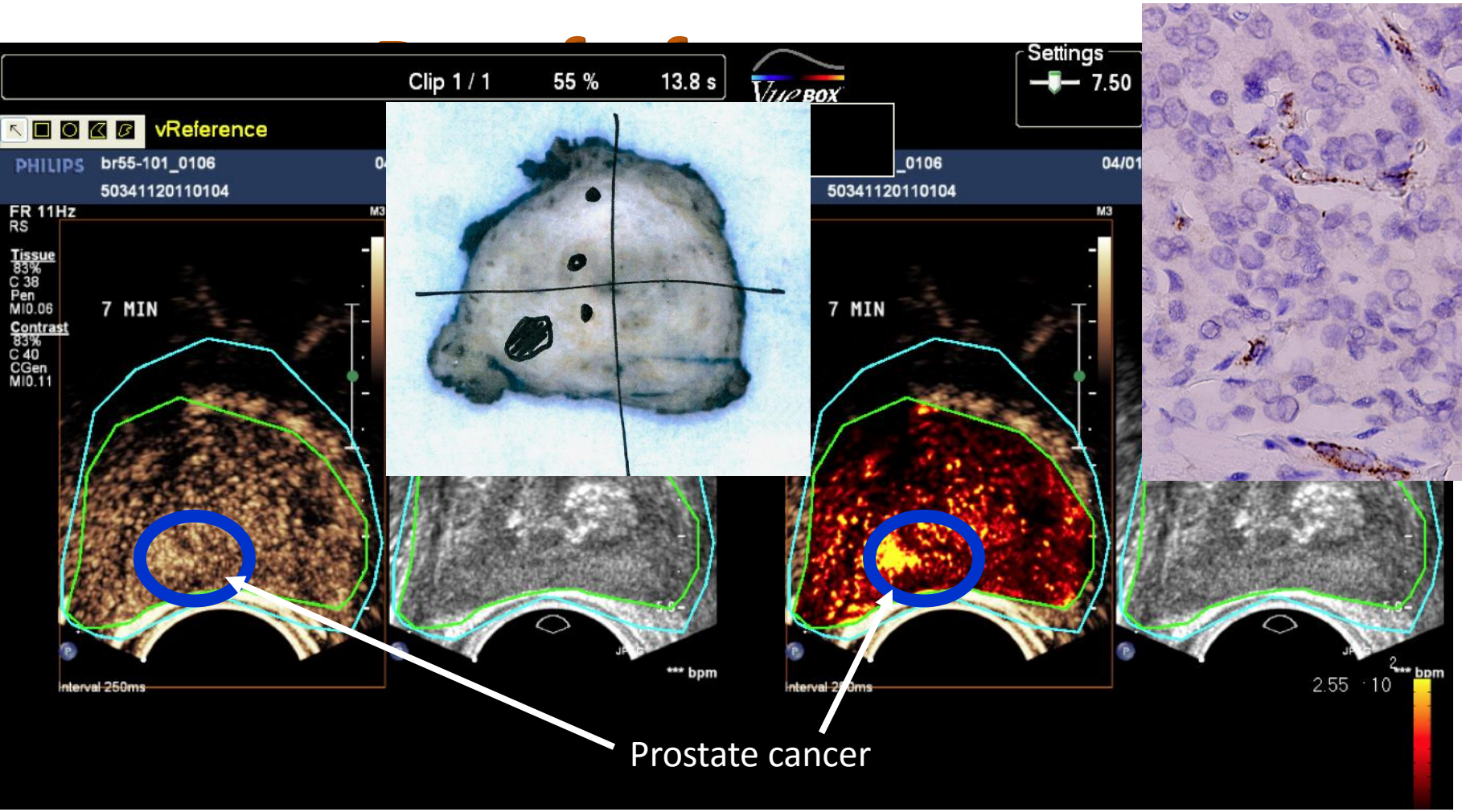




Payen T, Ultrasound Med Biol. 2015 Aug;41(8):2202-11

LIP : Targeted imaging: Main results

- Mice treated with Sunitinib => ↘expression of VEGFR2 (significant after 24h to reach 40% of the initial level
- VEGFR2 expression of mice treated with Imatinib ↘ initialy and ↗ afterward but without significance
- VEGFR2 expression of mice treated with Placebo ↘ significantly ($p<0.02$) after 48h to reach 80% of the initial level
- VEGFR2 expression is significantly lower in the group Sunitinib compared to placebo after 24h ($p<0.04$)
- VEGFR2 expression is significantly lower in the group Sunitinib compared to Imatinib after 96h ($p<0.003$)
- VEGFR2 expression is significantly higher in the group Imatinib compared to Sunitinib after 96h($p<0.05$)



Immunostaining demonstrates moderate VEGFR2 expression in that PCa lesion

BRACCO
LIFE FROM INSIDE

BR55 Is able to bind to VEGFR2 in humans (prolonged enhancement >10 min) and is safe and well-tolerated

Conclusion

- Very powerful technique to visualize the microcirculation
  - Blood pool agent
  - Very sensitive technique
- Recommended
  - To characterize liver lesion, complex renal or pancreatic cysts
  - To assess vascular bed destruction after RFA, Tace …
- Great potential to quantify the microcirculation
  - Preclinical research
  - More and more in human
- New: targeted microbubbles


Thank you
Merci
Olivier.lucidarme@psl.aphp.fr