Contrast Enhanced US

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Disclosures

- None

Thank You

- Dr Stephanie Wilson
- Dr Richard Barr
- Dr Michelle Robbin

Objectives

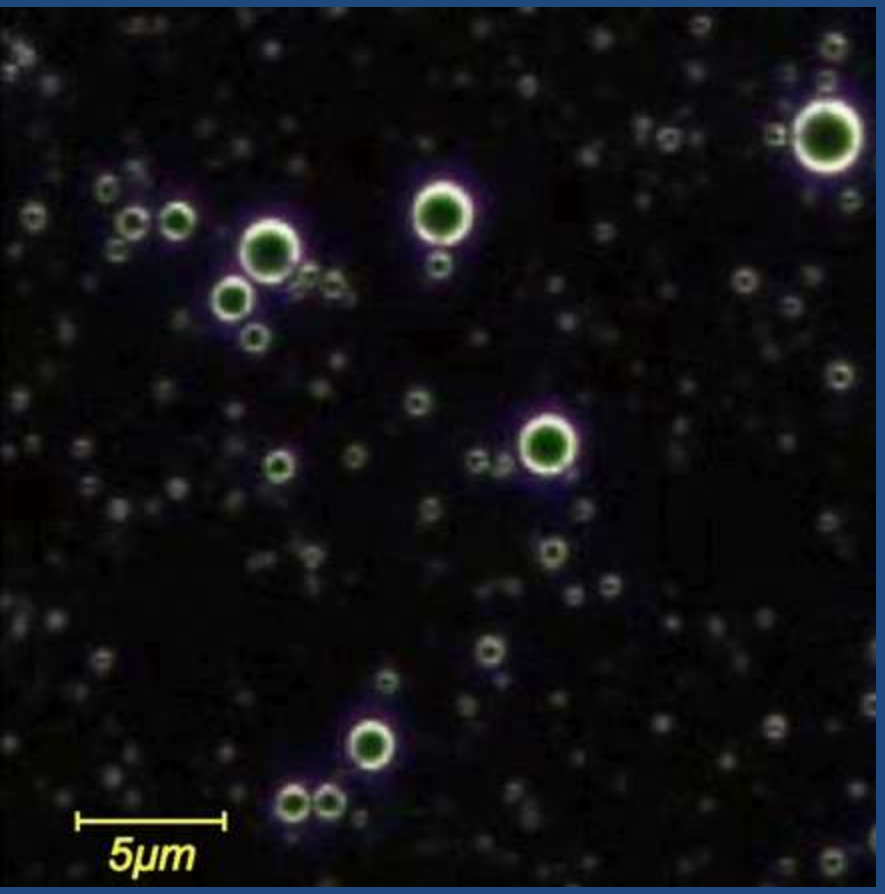
- Describe US contrast agents
  - How they differ from MR/CT agents
- Review safety/administration
- Highlight major applications
- Describe some future applications

Ultrasound Contrast Agents

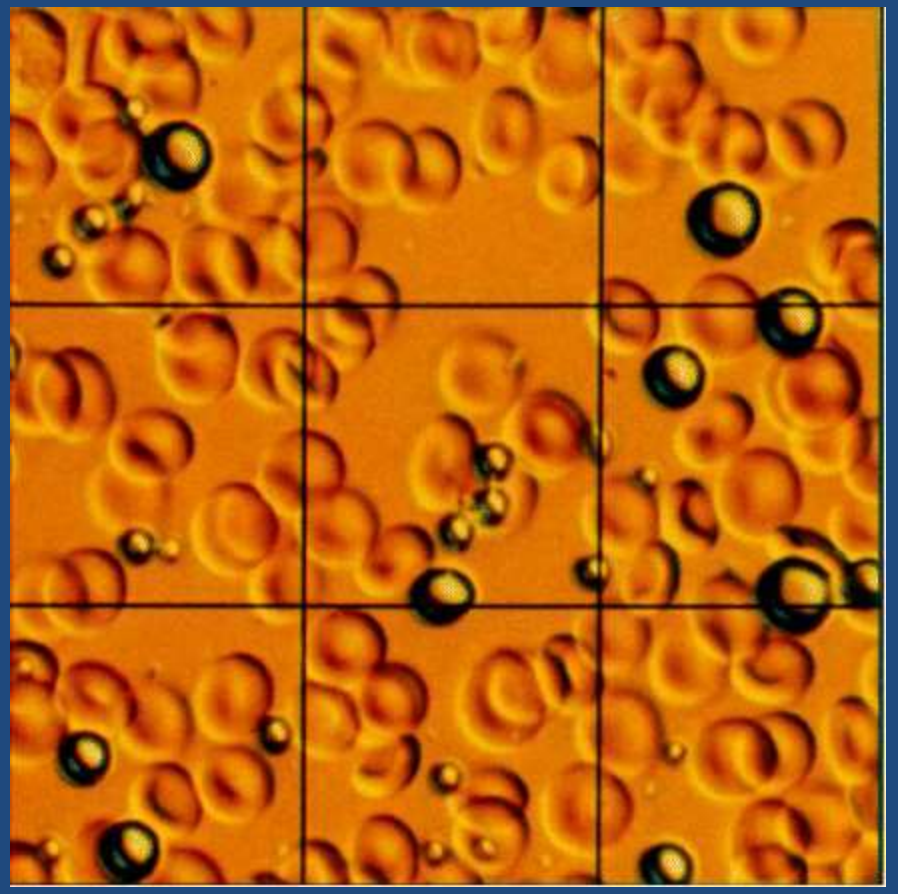
- Earliest agitated saline (Gramiak, 1968)
- Short half-life, trapped by pulmonary capillaries
- Manufactured microbubbles from 2 – 7 microns
- Smaller than RBC, so can pass through pulmonary circulation

Gramiak R, Shah PM. Echocardiography of the aortic root.
Invest Radiol 1968;3:356–66
Quaia, E. Eur Radiol 2007; 17:1995-2008.

Microbubbles ex vivo



Definity (lipid shells)



Optison (protein shell) against RBCs

Wilson SR , Burns PN ***Microbubble-enhanced US in Body Imaging: What Role?*** *Radiology 2010, 257, 24-39.*

Chemical Content

- Microbubbles of gas in an encapsulating shell
  - Air in a polysaccharide (Levovist)
  - perflurocarbon or sulfur hexachloride stabilized by a thin shell (Definity, Lumason, Imagent-lipid) (Optison-protein)
- Most only intravascular
- Some drugs have hepatic (Levovist, Sonazoid) or splenic (Lumason) phase

Stewart and Sidhu; The British Journal of Radiology, 79 (2006), 188–194

Mode of Administration

- .5-2cc IV- bolus (preferred) or infusion
- Enhances blood signal 500-1000x
- Lasts 5 min (avg.) with bolus- longer with infusion.
- Bubbles rupture, gas exhaled via lungs, shell metabolized by the body
- Major risk is anaphylaxis- at rate of 1/7000 (U.S.) to 1/10,000 (Europe) less than that of CT, comparable to most antibiotics.

Wilson SR , Burns PN ***Microbubble-enhanced US in Body Imaging: What Role?*** *Radiology 2010, 257, 24-39.*

Is it Safe?

- U of R has administered >10,000 doses without a serious adverse event
- Definity does cause mild back pain-self limited- in 1/200 patients.
- October 2007 FDA issued “black box” warning due to a few serious events (possible anaphylaxis) worldwide (4 deaths in the US) in patients having cardiac events- No cause and effect established
- Black Box modified 9 months later

Retrospective Results

- Kusnetsky reviews 18,671 hospitalized patients undergoing echocardiography
- No effect of contrast on mortality
- Patients receiveing CEUS exams did better than those who did not get agent

Kusnetzky LL , Khalid A , Khumri TM , Moe TG , Jones PG , Main ML . Acute mortality in hospitalized patients undergoing echocardiography with and without an ultrasound contrast agent: results in 18,671 consecutive studies . J Am Coll Cardiol 2008 ; 51 (17): 1704 – 1706 .

Current FDA recommendations

- Assess all patients for the presence of any condition precluding contrast administration (allergy)
- In patients with pulmonary hypertension or unstable cardiopulmonary conditions, monitor VS, ECG and O2sat for 30 minutes after Optison or Definity or Lumason
- Have resuscitation equipment available

US Contrast in Radiology

- Approved for Liver in UK, Canada, Europe and Japan since early 2000's
- 2016- Lumason approved for liver imaging in the US for lesion characterization.

April 4, 2016 -- The long wait is over. The U.S. Food and Drug Administration (FDA) for the first time has approved the use of an ultrasound contrast agent for radiology applications, giving the nod to Lumason from Bracco Diagnostics to be used for focal liver lesions. Lumason was known previously in the U.S. as SonoVue, and it received initial FDA approval in October 2014 for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border. The agent is still offered by Bracco under the SonoVue brand outside of the U.S.

Current Contraindications

- Known allergy to US contrast
- Patients with right to left or bidirectional cardiac shunts
  - Recent MI
  - Severe Heart Failure
  - Consider Cardiology Consult
- Not for intra-arterial injection

How do they work?

- Unlike blood cells (same size) which we do not see, we see US contrast because
  - Bubbles contain gas which reflects the sound
  - Bubbles oscillate in the 3-5MHz range (same as we use for abdominal US) creating echoes of their own, independent of those transmitted by the machine.
  - These independent echoes are a multiple of the inciting frequency, and are known as harmonics
  - We can selectively receive the harmonic frequency and see only the bubbles signal, suppressing background.

Liver Imaging with Contrast

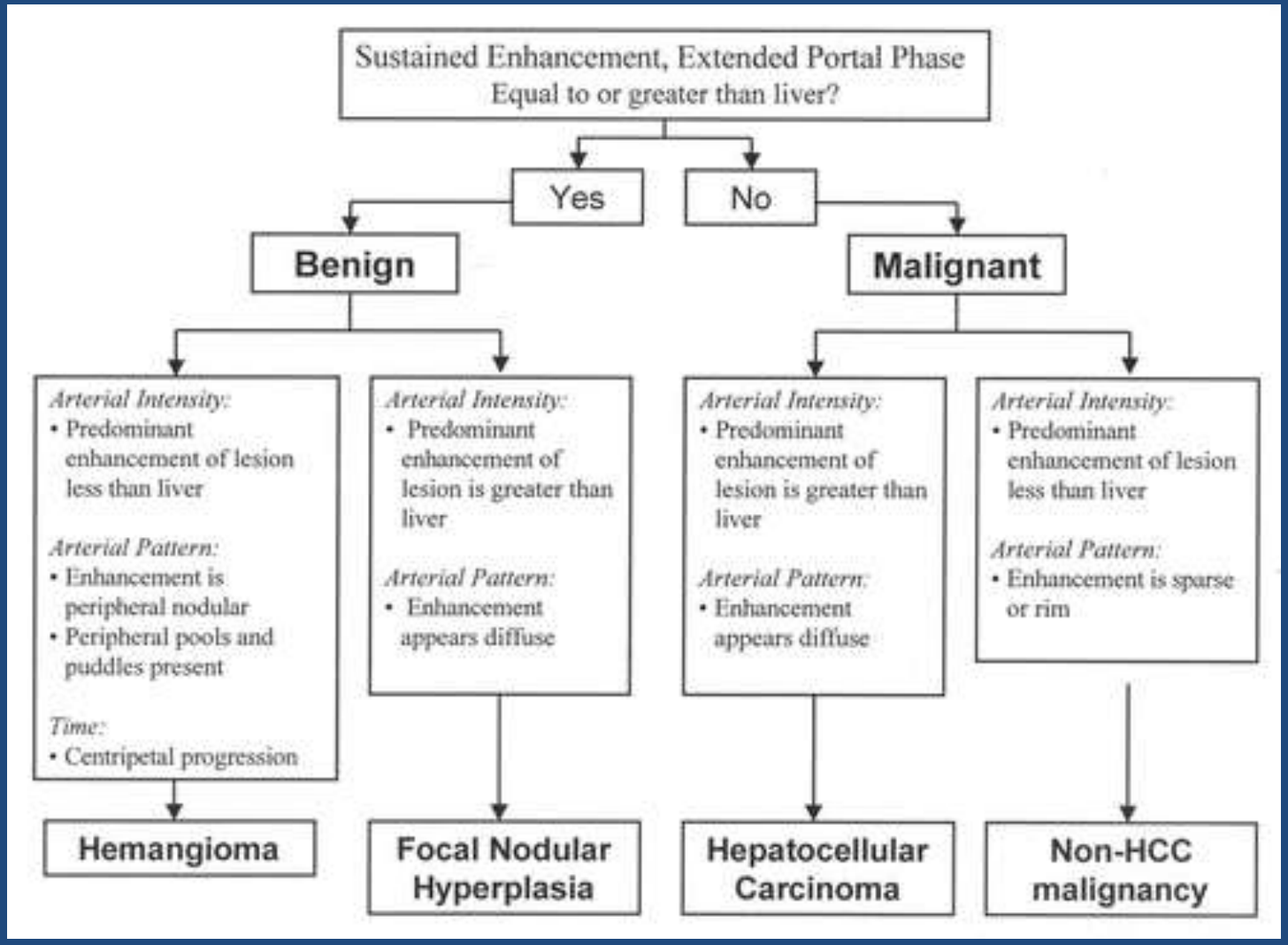
- Liver image (MIP) 11 sec after injection.
- Note the number and small size of the vessels (down to 5th order branches) seen only with contrast.
- Deficit area is a hemangioma

Wilson SR , Burns PN ***Microbubble-enhanced US in Body Imaging: What Role?*** *Radiology 2010, 257, 24-39.*

Liver Mass Characterization

- Benign lesions: Hemangioma, FNH, equivalent to CT or MR- prolonged delayed enhancement
- Adenoma has some overlap with HCC- soft washout
- Metastases and HCC equivalent to CT/MR
  - Better for early wash-in and washout due to high frame rate and long observation times (up to 20 minutes)
  - Difficulty with deep lesions, blind spots under diaphragm and behind ribs

Wilson et AJR 2006



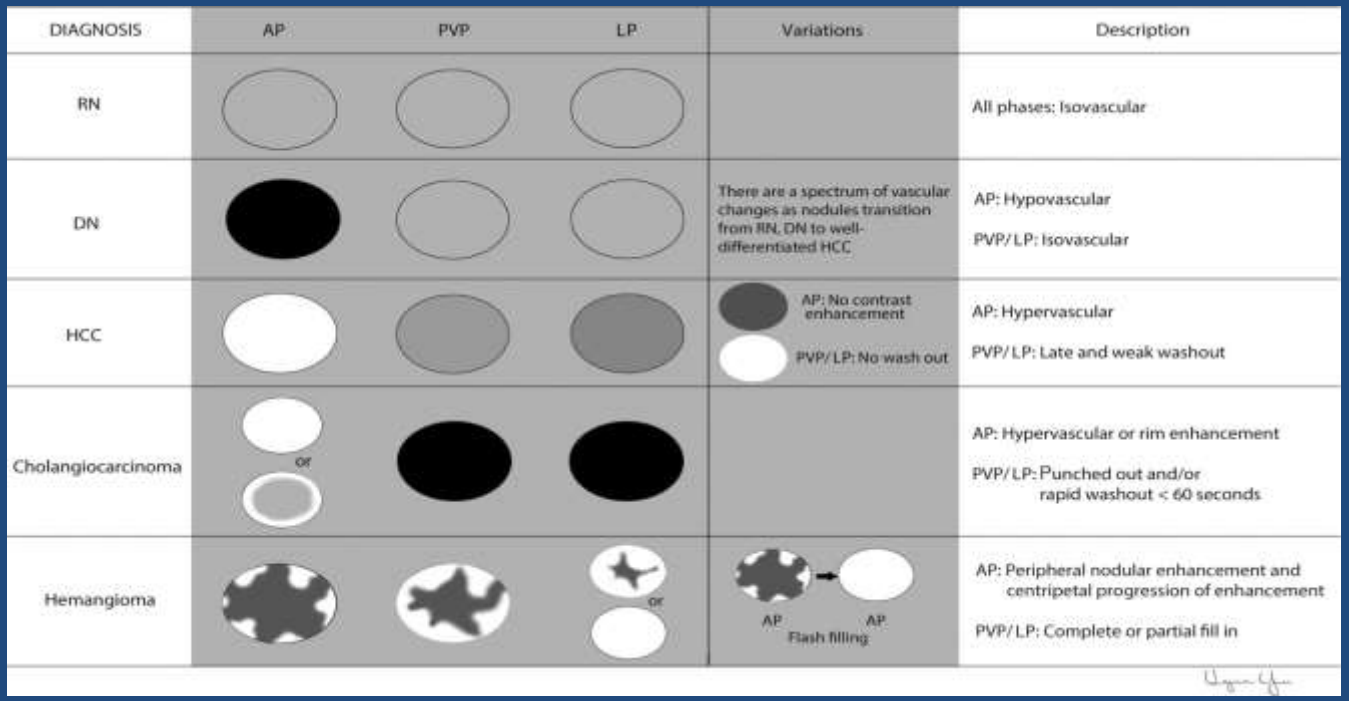
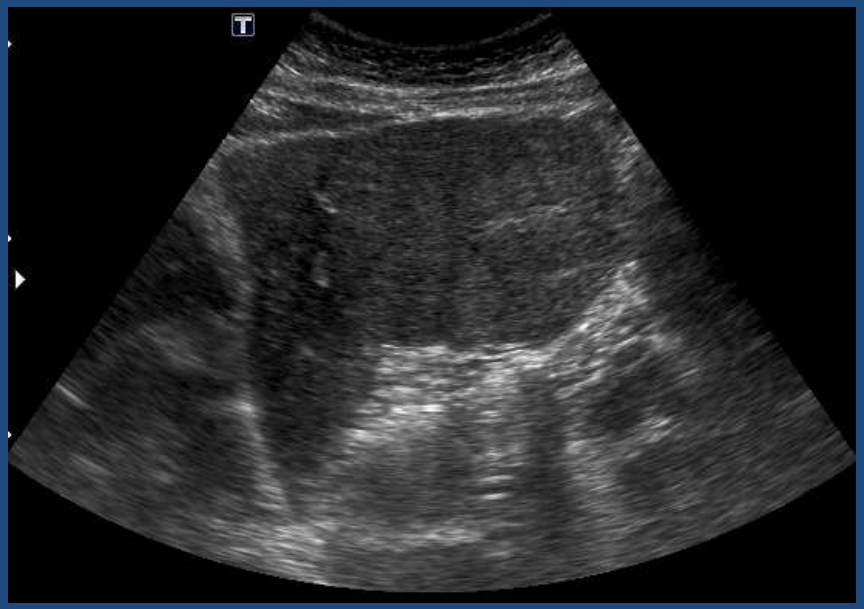


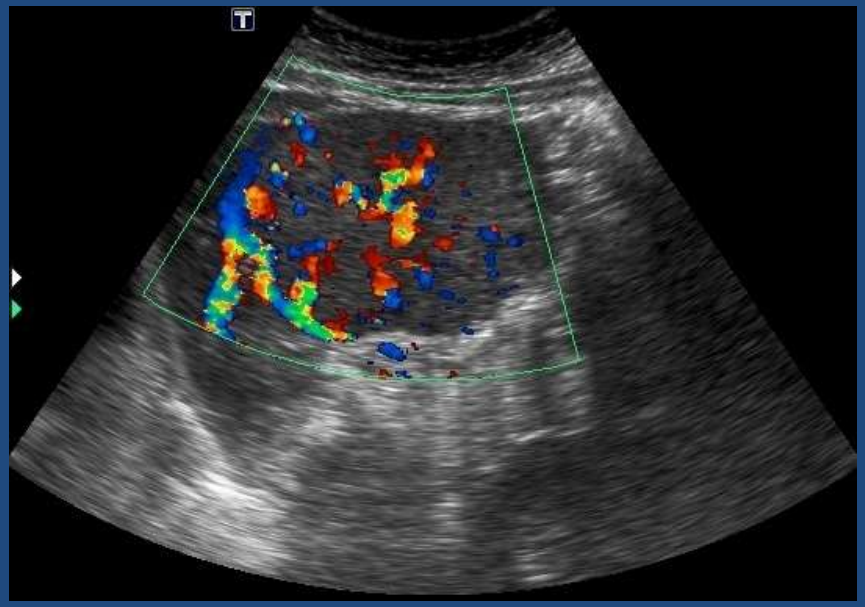
Figure 1: Schematic shows the typical enhancement patterns of common benign and malignant lesions in the cirrhotic liver. *RN* = regenerative nodule, *DN* = dysplastic nodule, *AP* = arterial phase, *PVP* = portal venous phase, *LP* = late phase.

Radiology,
http://pubs.rsna.org/doi/abs/10.1148/radiol.2016151732

Published in: Patricia C. Jo; Hyun-Jung Jang; Peter N. Burns; Kelly W. Burak; Tae Kyoung Kim; Stephanie R. Wilson; *Radiology* **2017,** 282, 317-331.
DOI: 10.1148/radiol.2016151732

Baseline/CDI





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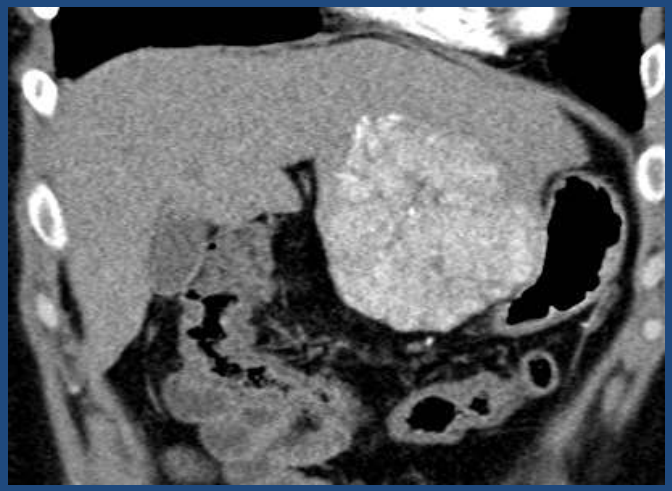
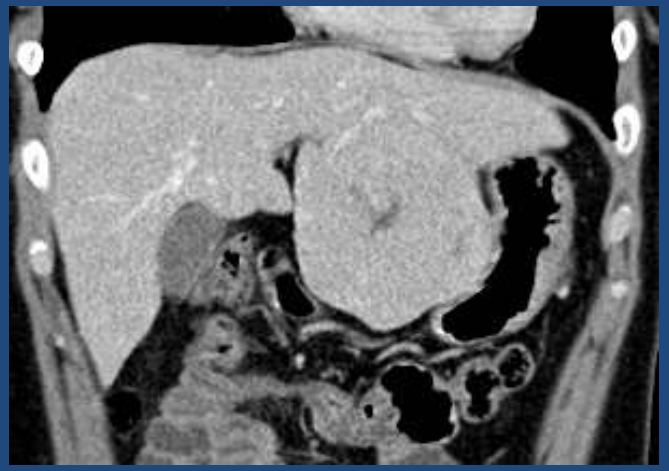
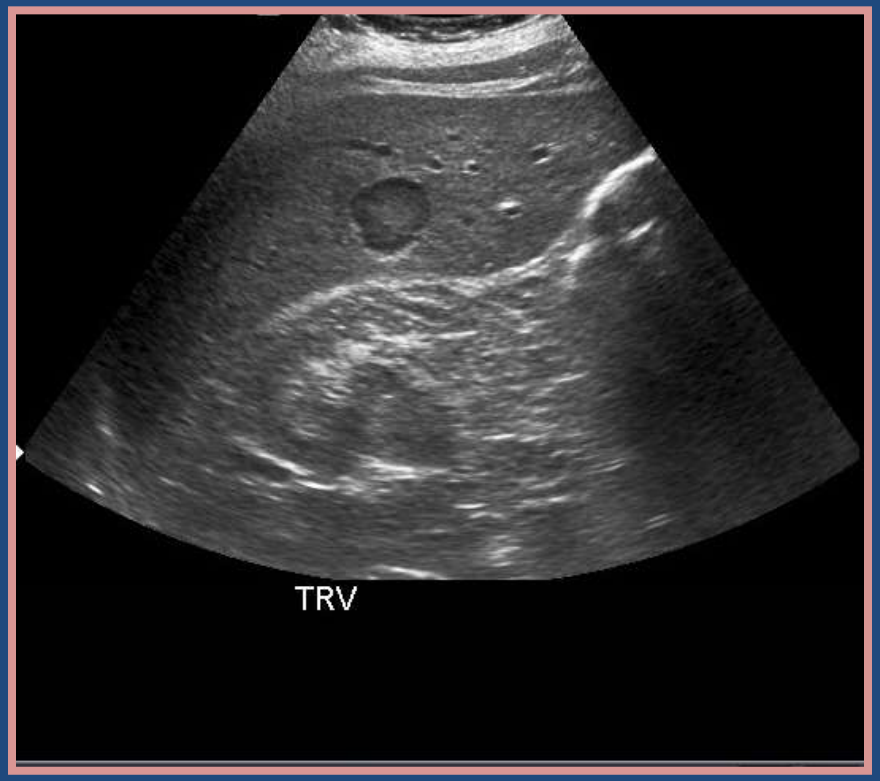
Sustained Enhancement - BENIGN

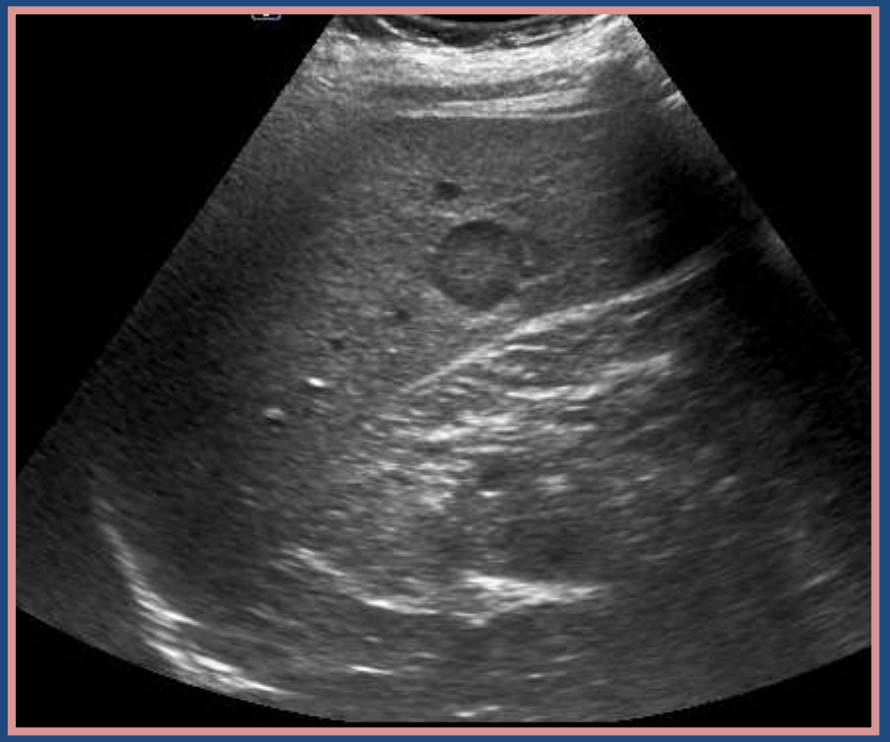
AP

PVP









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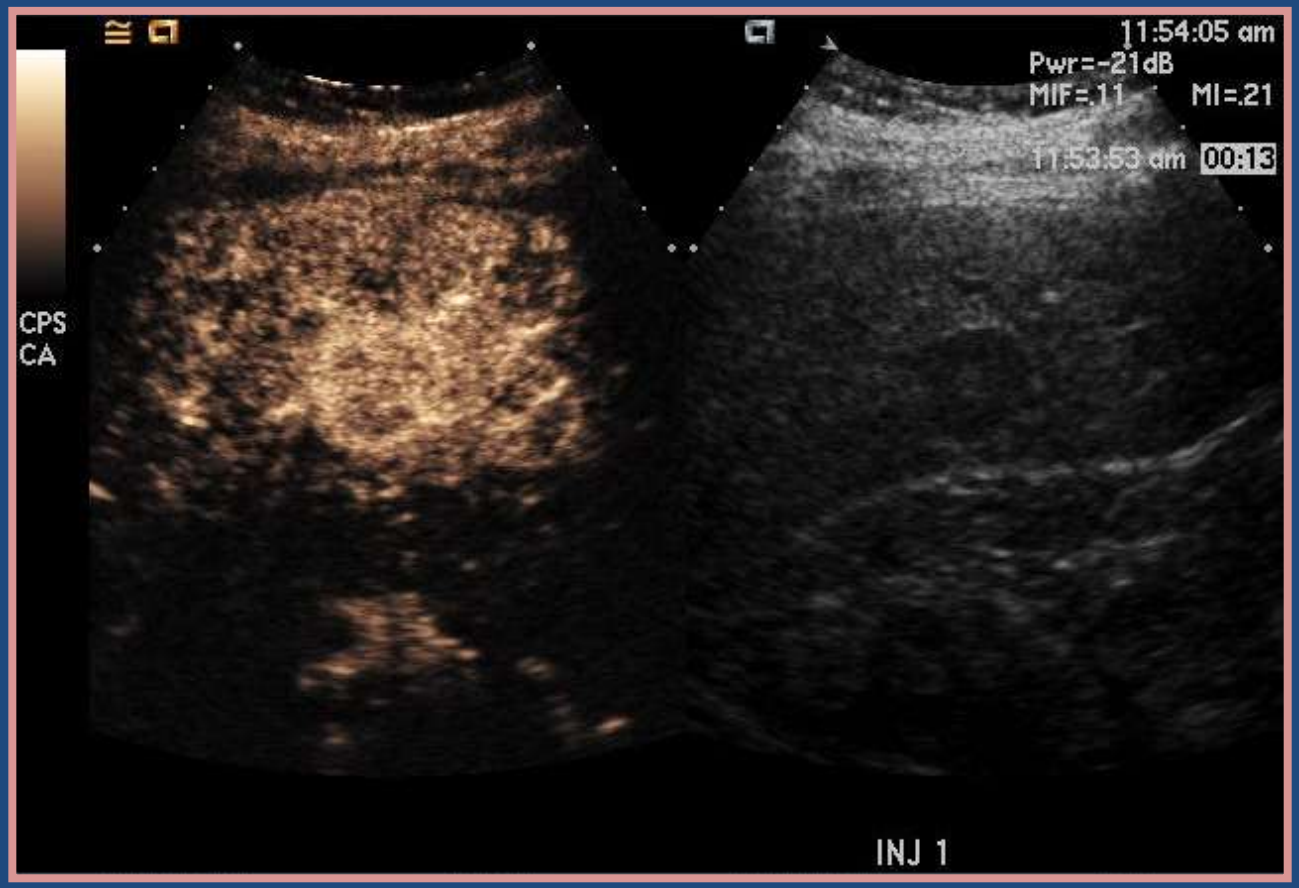
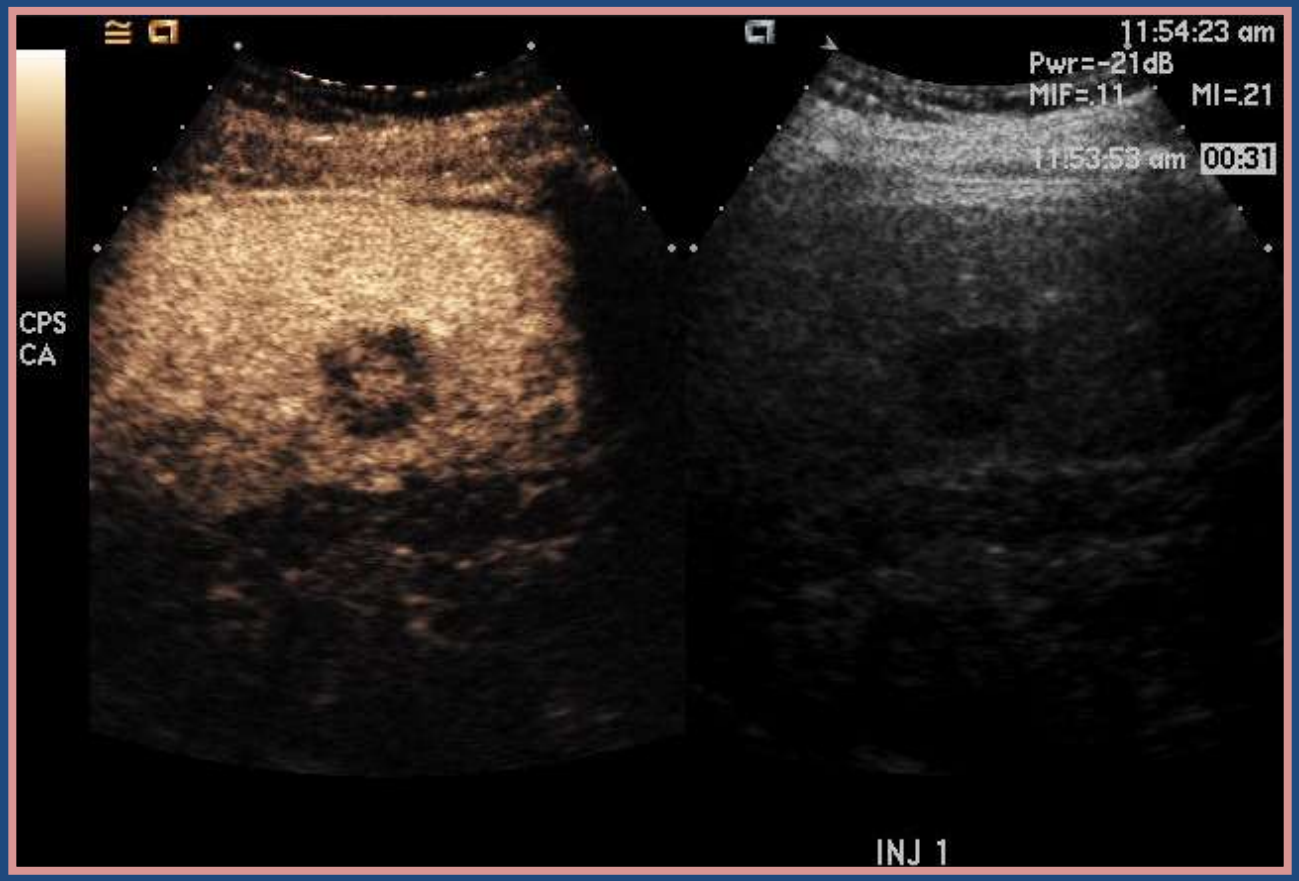
13 S

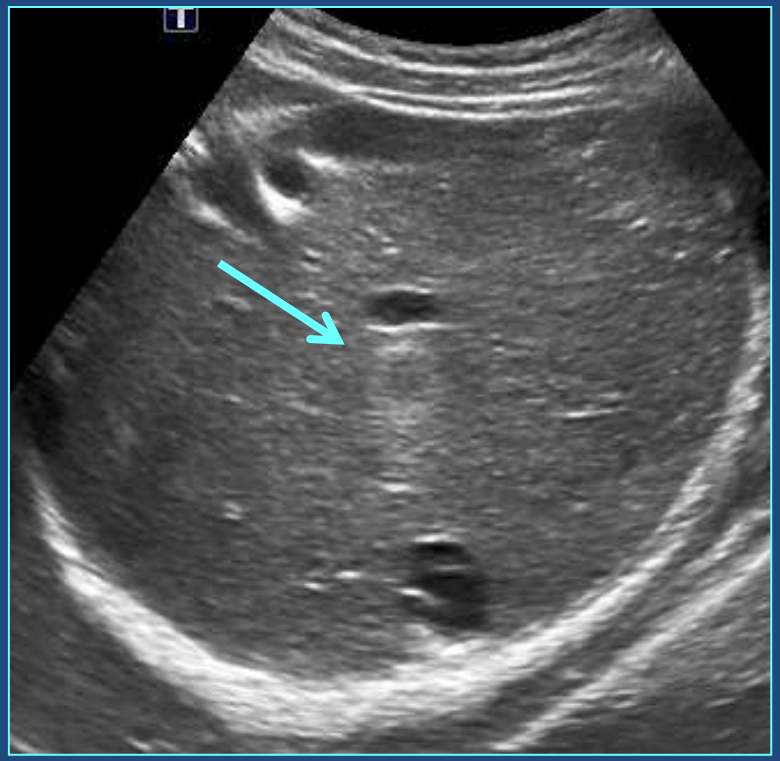


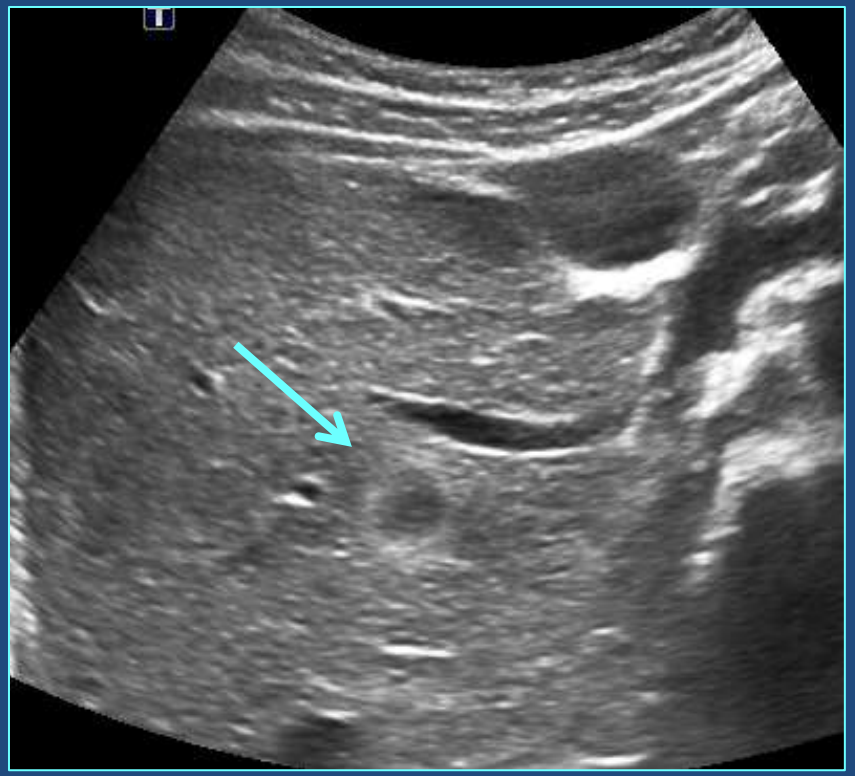
31 S



Rapid Washin and Washout = Metastasis

59/F HBV Surveillance





Nodule with an echogenic rim in liver
Above threshold size of 1 cm - do CEUS

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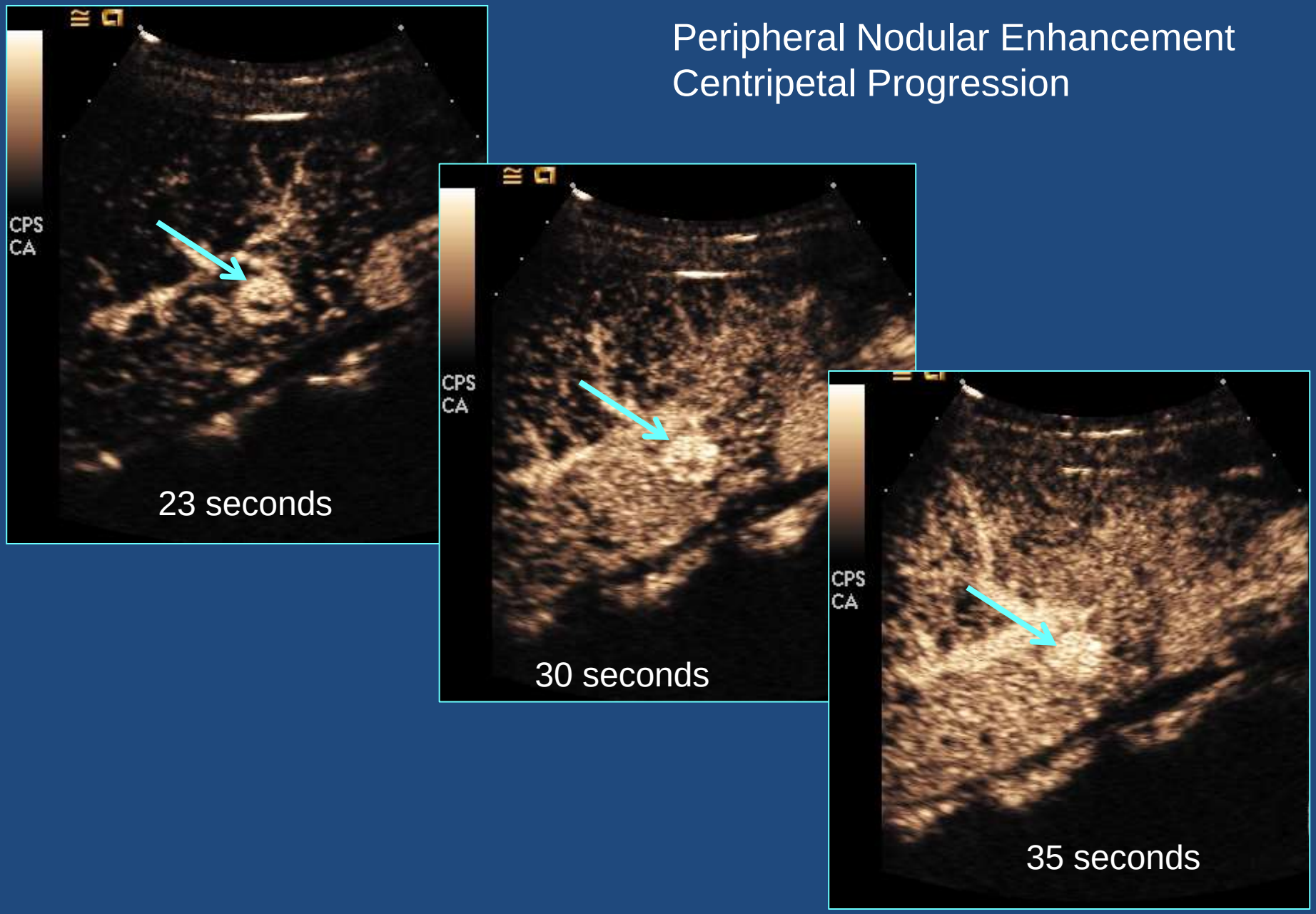
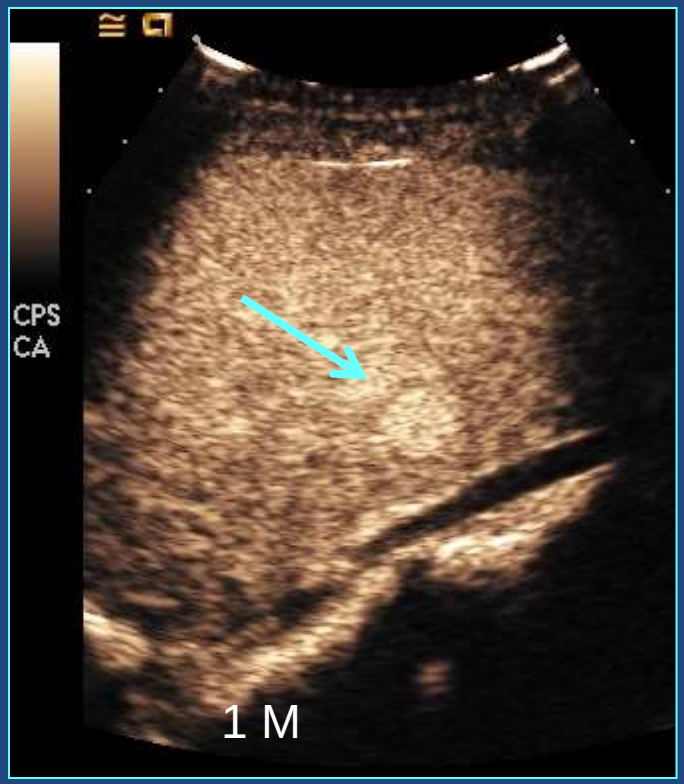
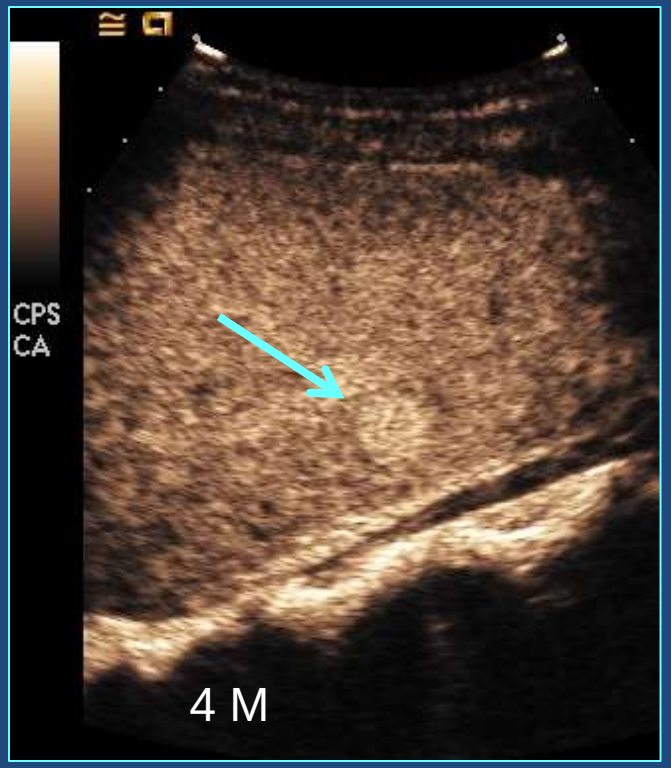
Peripheral Nodular Enhancement
Centripetal Progression



Flash Filling Hemangioma





Sustained Enhancement to 4 M
STOP – no further imaging.

67/M HCV Surveillance US

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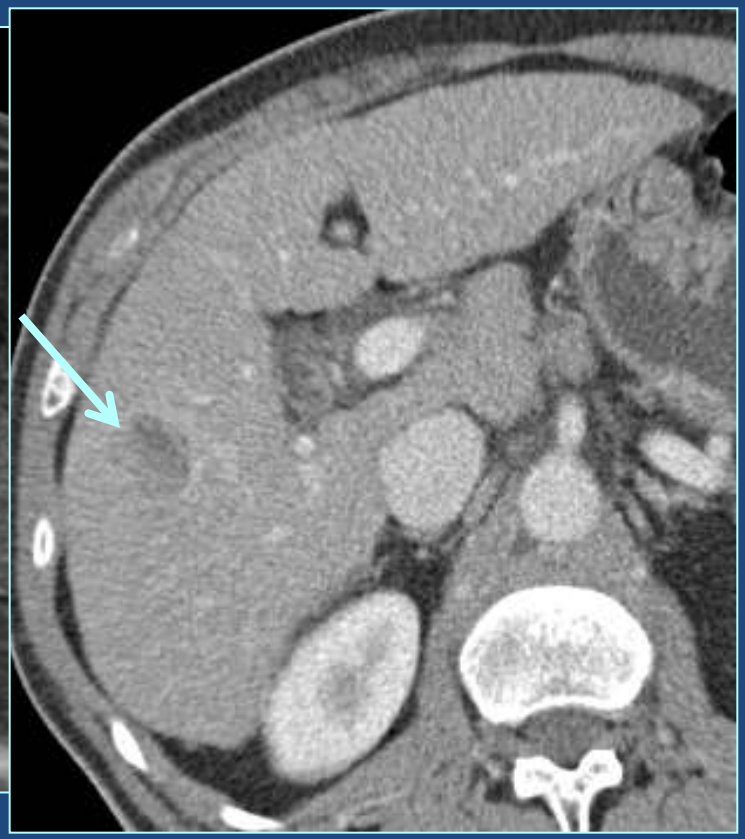
67/M HCV
US 4.2cm Mass

Triphasic CT
Mass 2.5 cm

AP Hypervascular



PVP Washout

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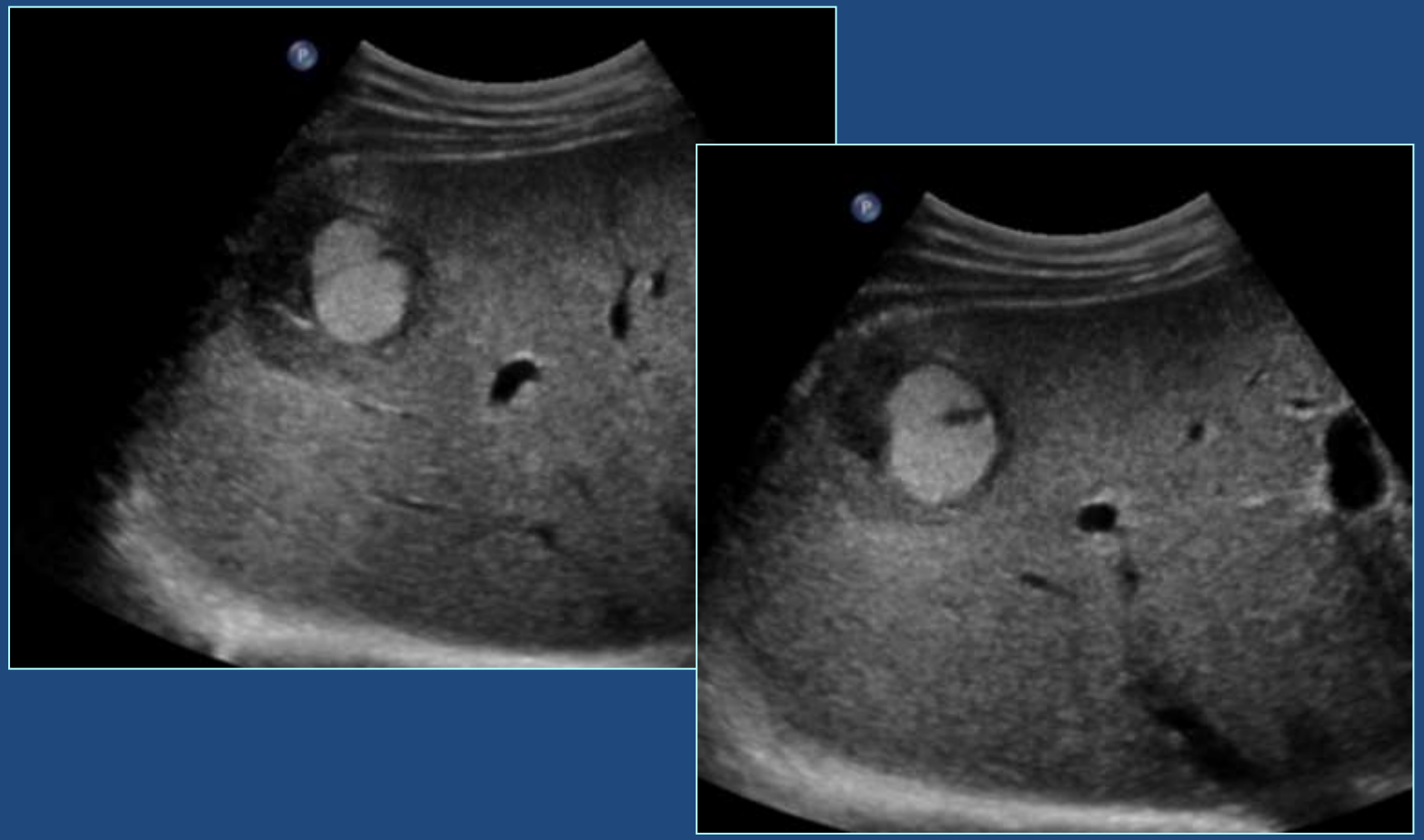
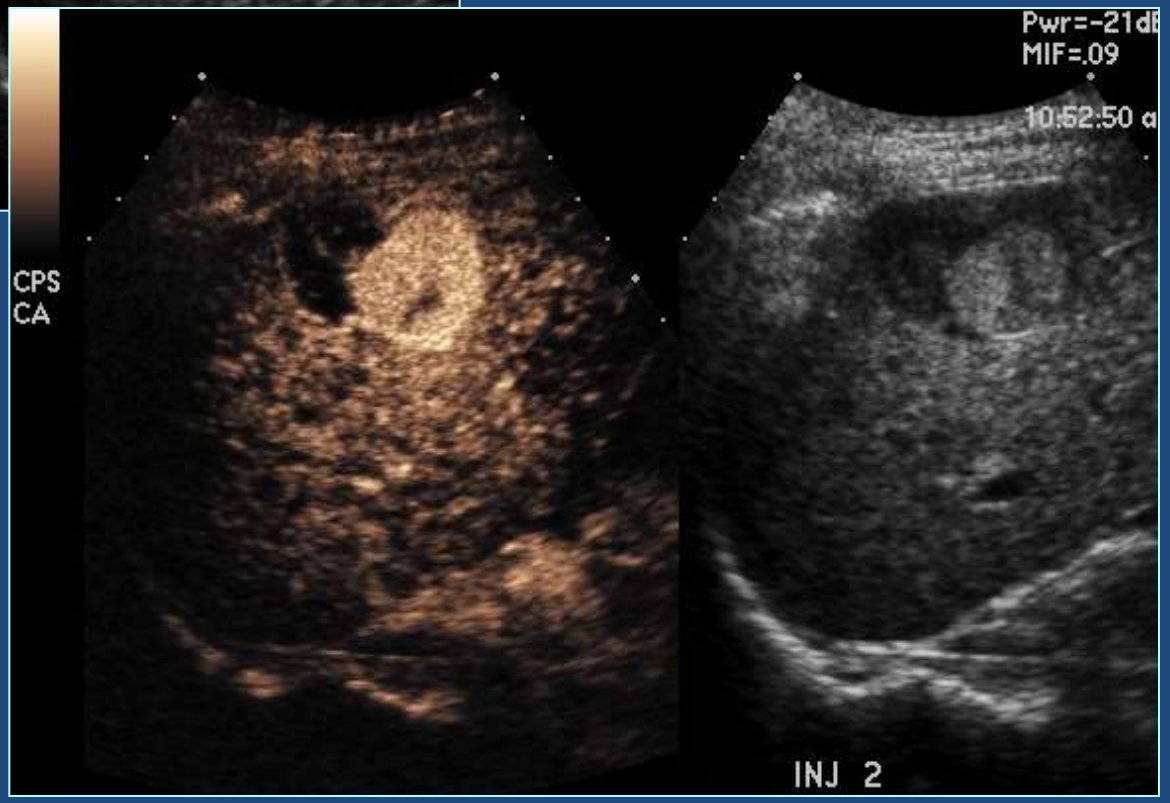
Referral to CEUS to resolve SIZE Discrepancy

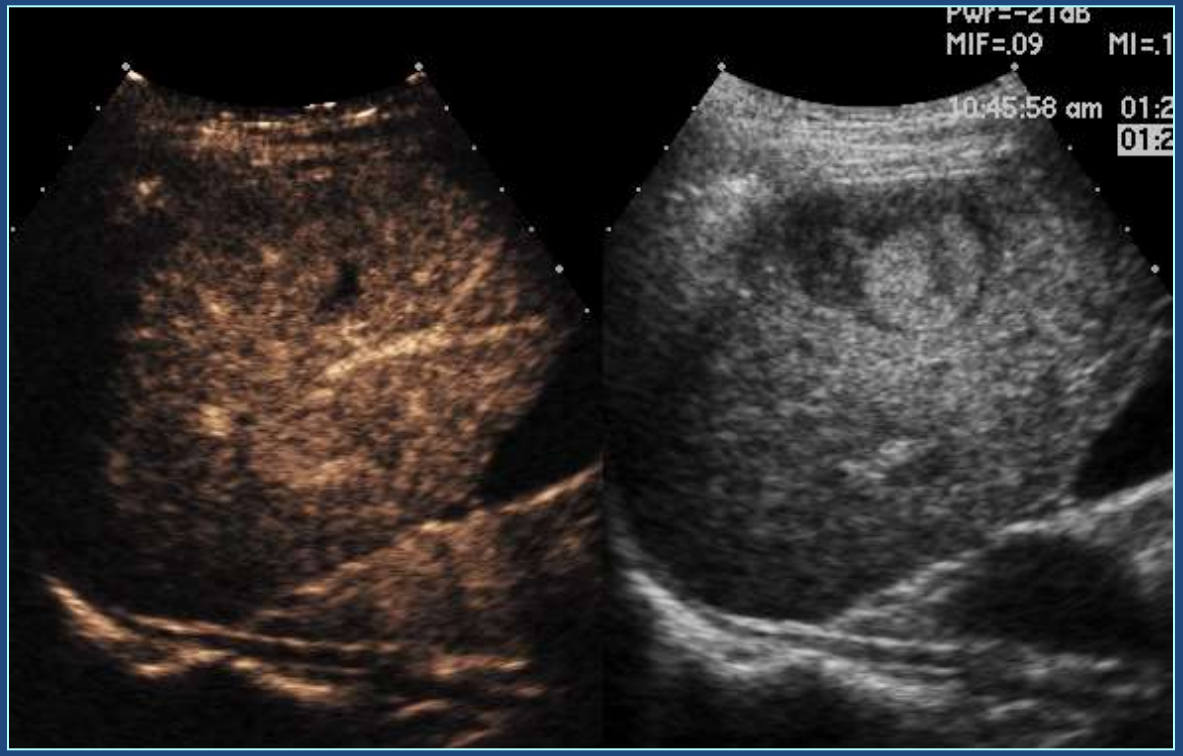
“Nodule in Nodule” Appearance



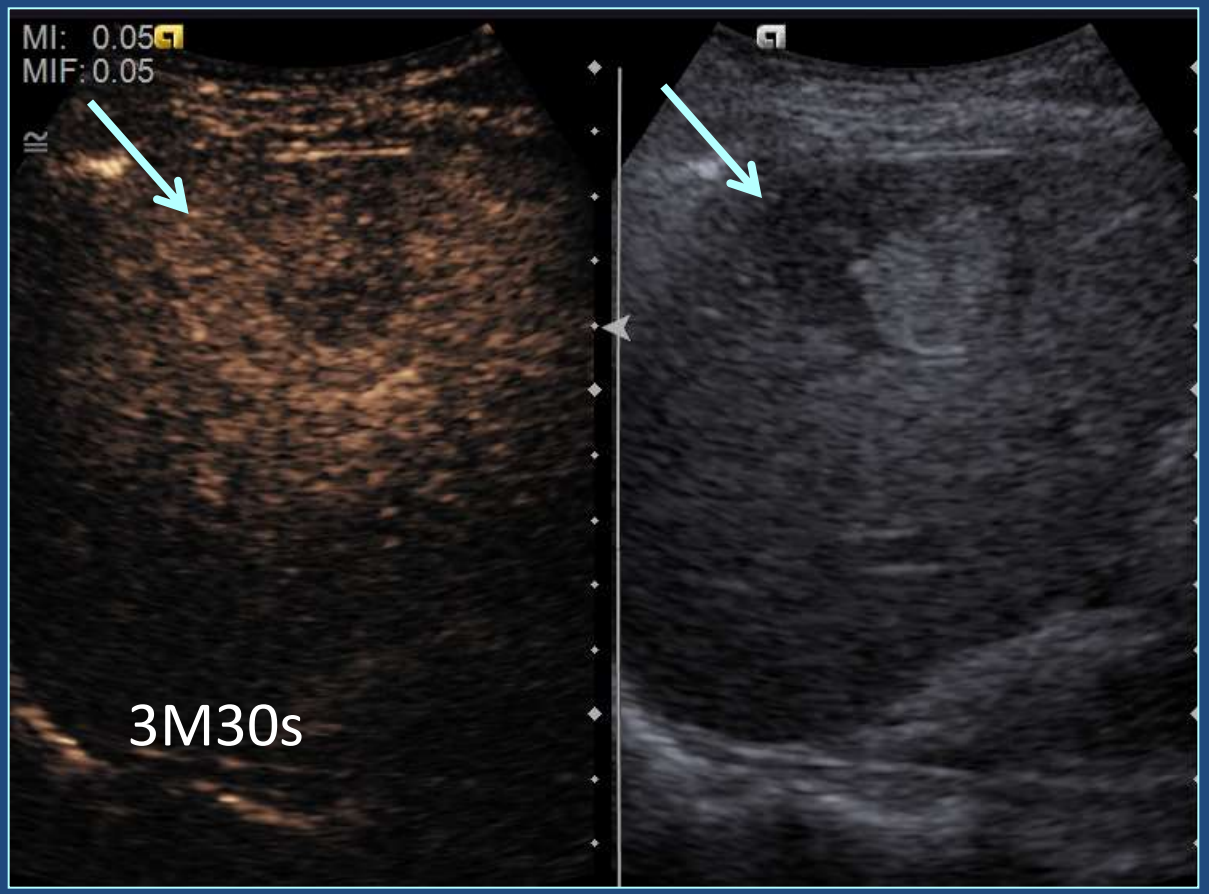
Peak AP



Isovascular at 90 s



Washout HCC
Sustained Enhancement DN



IMPACT: HCC in DN or higher grade focus HCC within lower grade nodule

CEUS in the Kidney

- Solid Mass characterization- equivalent to CT for Clear cell RCC, and superior for Papillary (showed minimal flow better than CT) (1)
- Bosniak II lesions seen with CEUS (31 patients, accuracy 74% by CT, 90% by US, US tended to upstage lesions (thicker septae)- (2)

(1)Tamai H, Takiguchi Y, Oka M, et al. *Contrast-enhanced ultrasonography in the diagnosis of solid renal tumors. J Ultrasound Med 2005;24(12):1635–1640*

*(2)*Park BK, Kim B, Kim SH, Ko K, Lee HM, Choi HY. *Assessment of cystic renal masses based on Bosniak classification: comparison of CT and contrast-enhanced US. Eur J Radiol 2007;61(2):310–314.*

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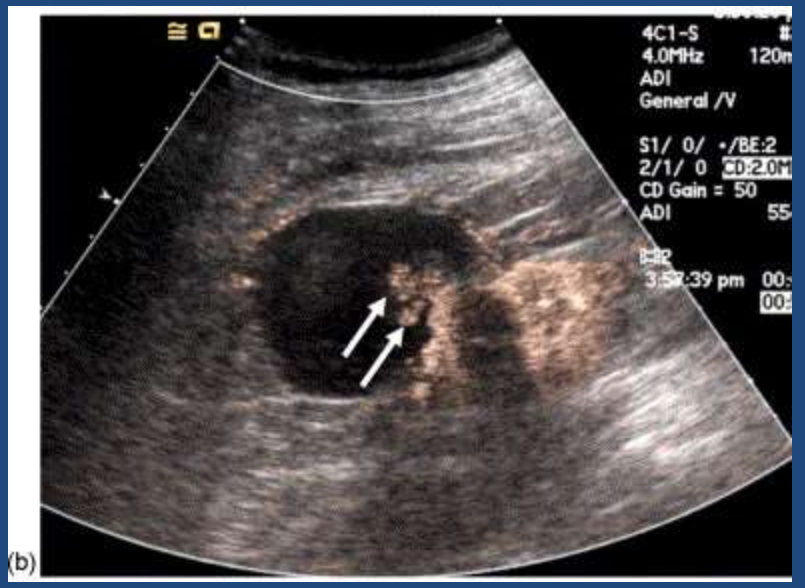


Park BK, Kim B, Kim SH, Ko K, Lee HM, Choi HY. *Assessment of cystic renal masses based on Bosniak classification: comparison of CT and contrast-enhanced US. Eur J Radiol 2007;61(2):310–314.*

Number of Septae US >CT

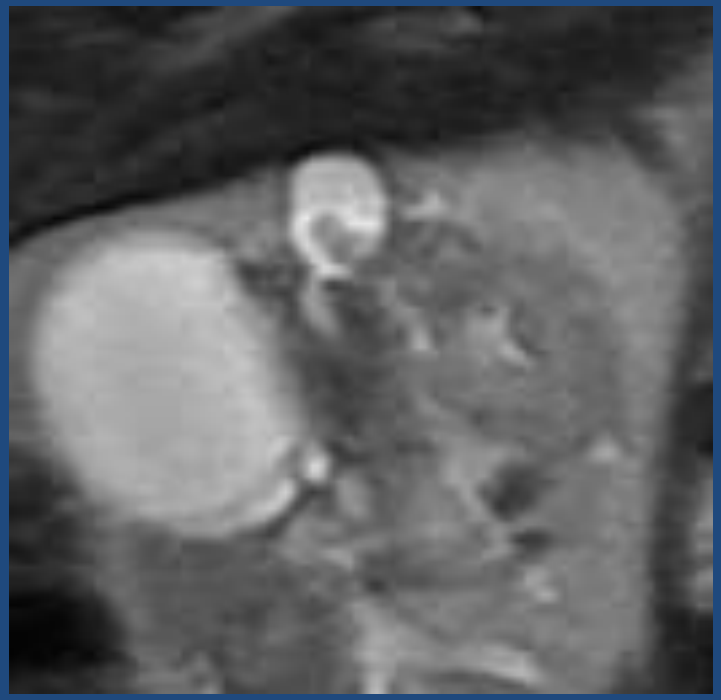
Park BK, Kim B, Kim SH, Ko K, Lee HM, Choi HY. *Assessment of cystic renal masses based on Bosniak classification: comparison of CT and contrast-enhanced US. Eur J Radiol 2007;61(2):310–314.*

Prospective CEUS vs CT Complex Cysts

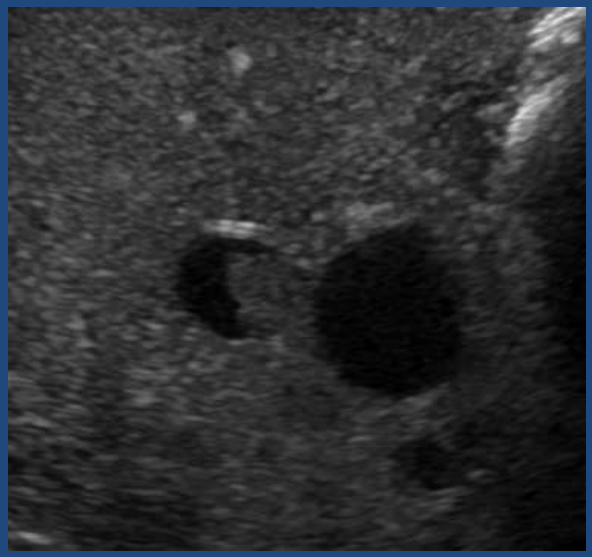
- 40 patients with complex cystic masses detected by CT
- 3 readers
- Path outcome or 24 mo F/U
- 21 RCCs, 9 complex cysts, 2MCNs, 8 simple cysts
- CEUS accuracy 80-83%, vs 63-75% CT
- Non-enhanced US accuracy only 30%

Quaia E, Bertolotto M, Cioffi V, et al. ***Comparison of Contrast-Enhanced Sonography with Unenhanced Sonography and Contrast-Enhanced CT in the Diagnosis of Malignancy in Complex Cystic Renal Masses*** *AJR* 2008; 191:1239-1249

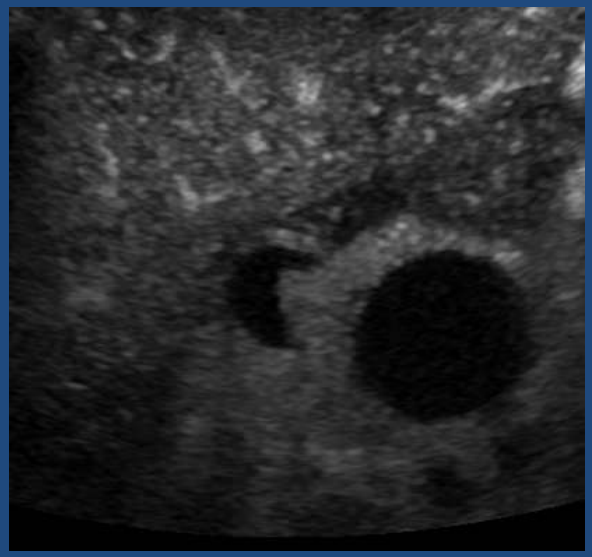
Patient with Indeterminate Mass (MR) who cannot get CT or MR contrast



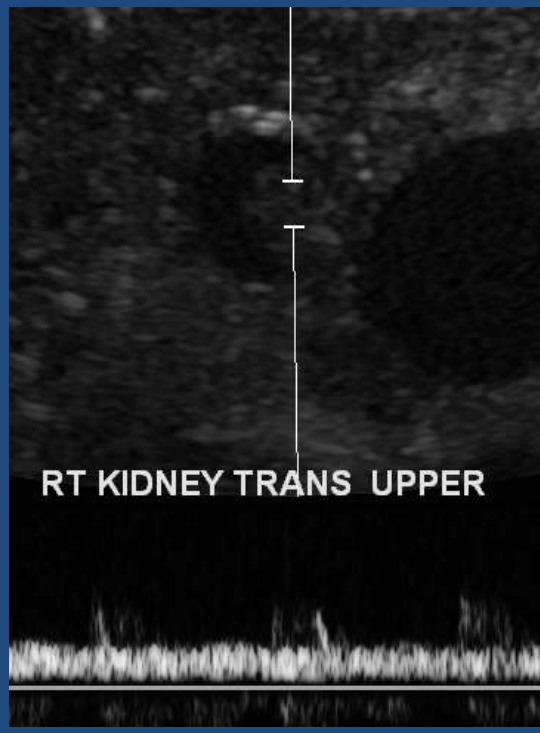
Patient with Indeterminate Mass on MR who cannot get CT or MR contrast



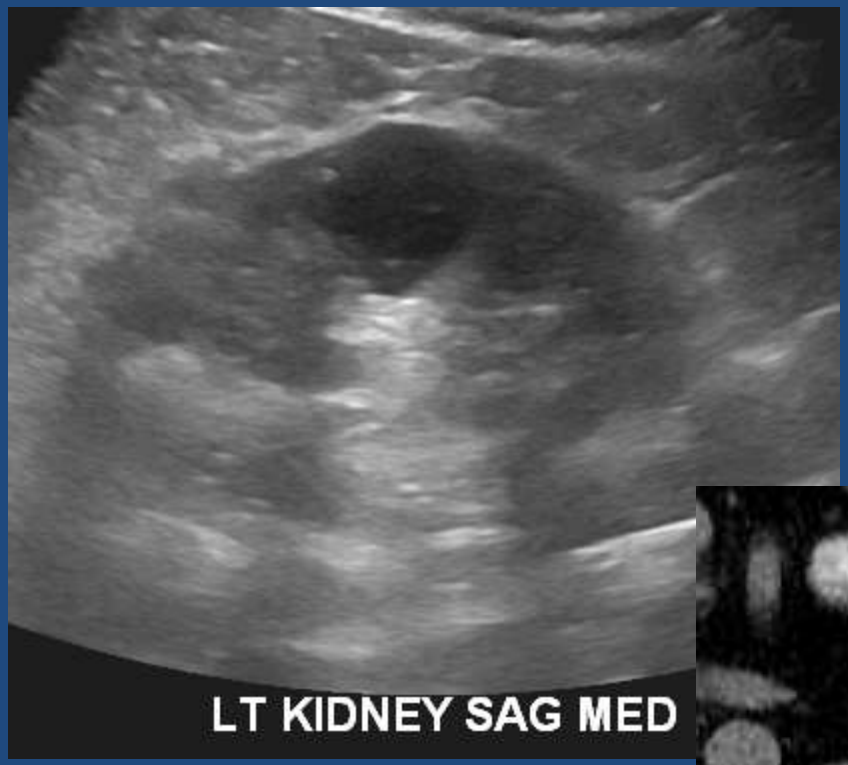
Pre Contrast

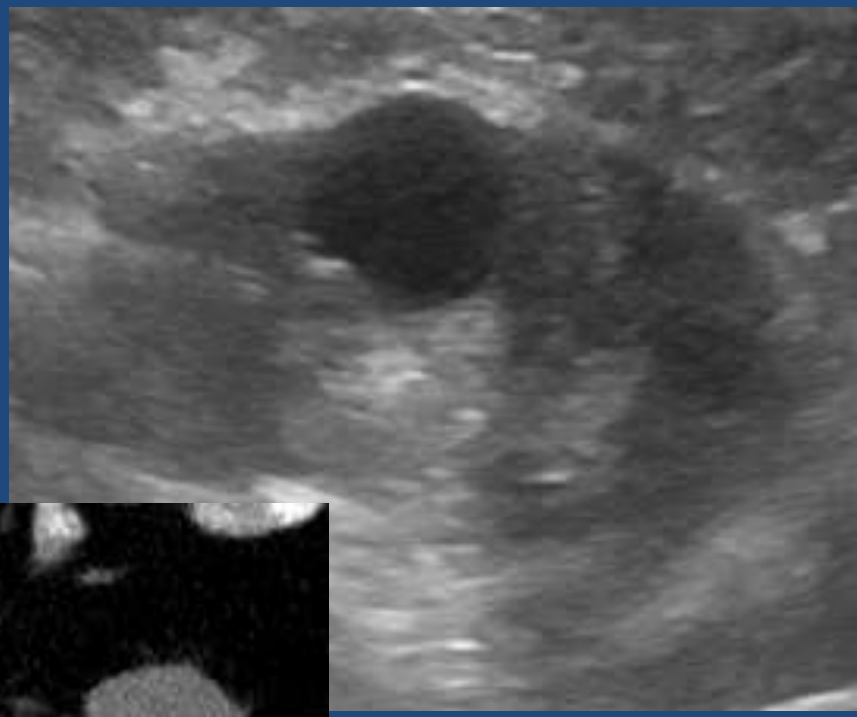


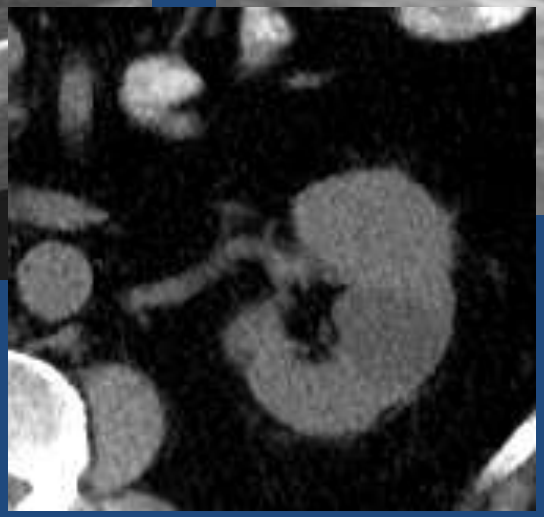
Post Contrast



Patient with CRF suspected Mass on CT and unenhanced US.







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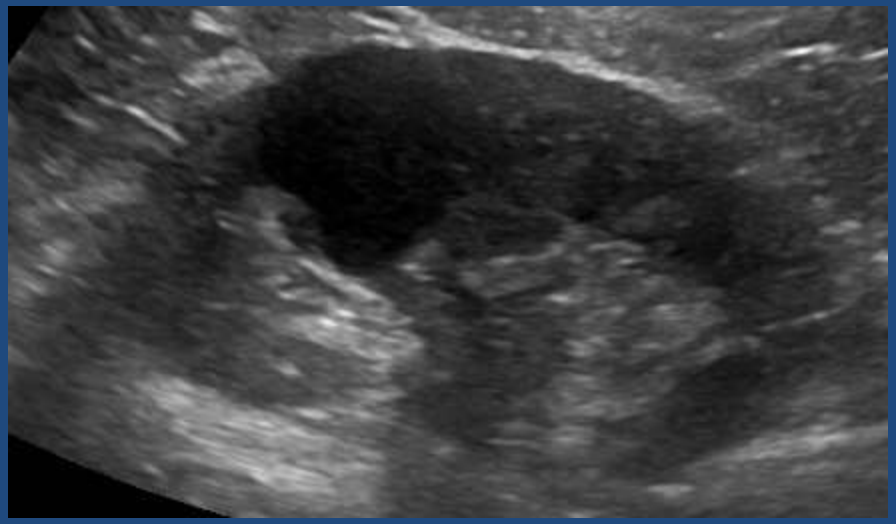
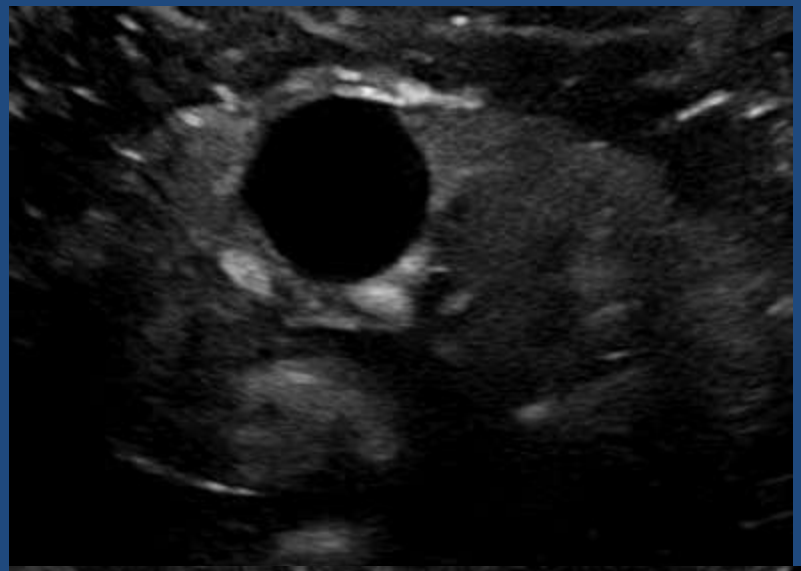
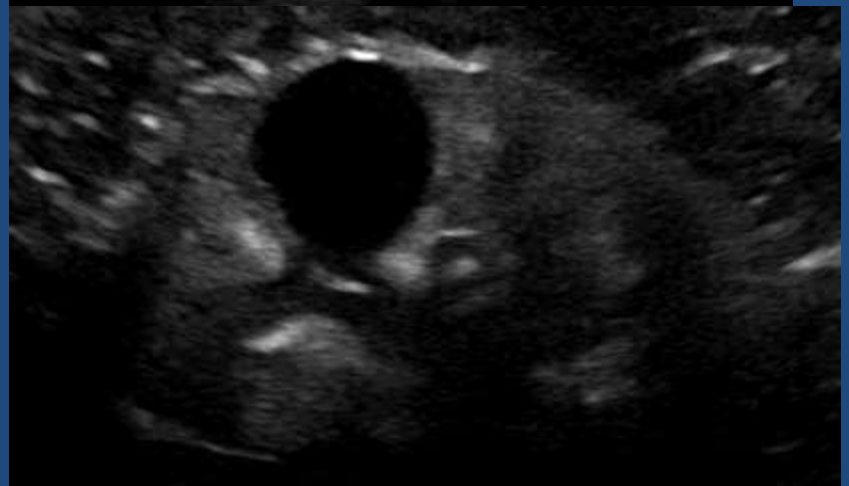
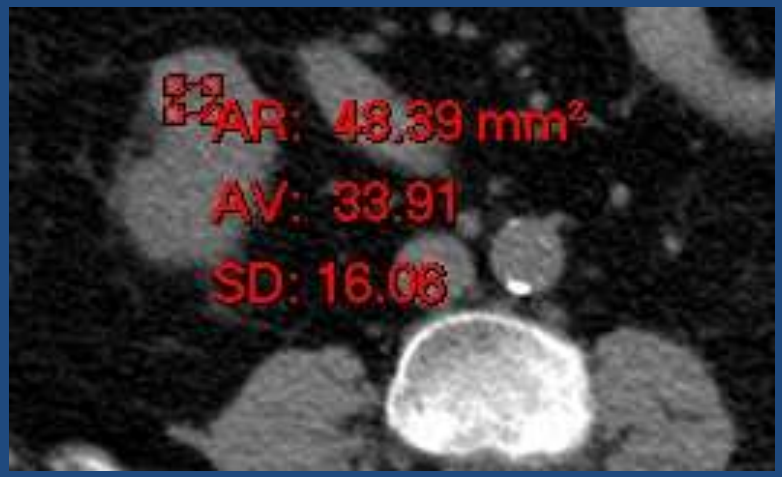
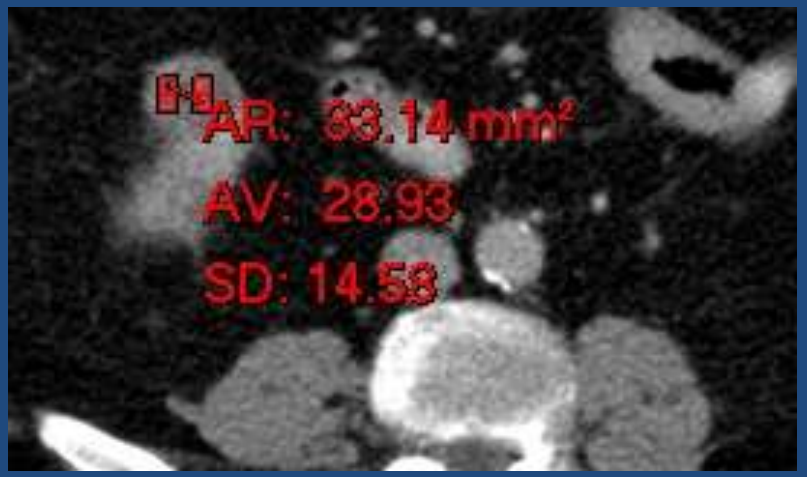


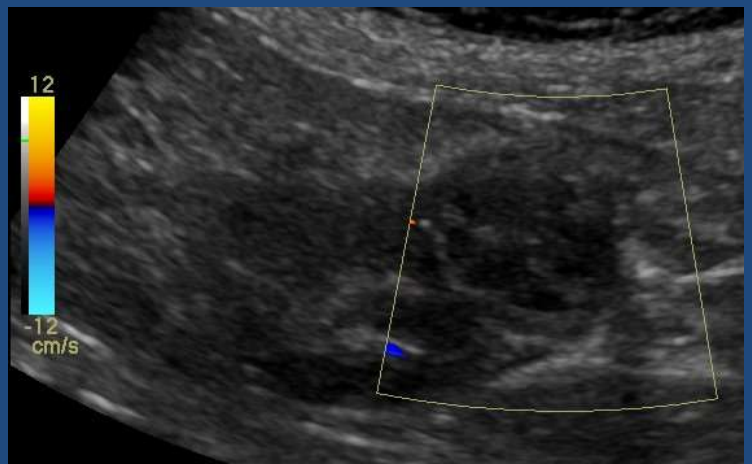




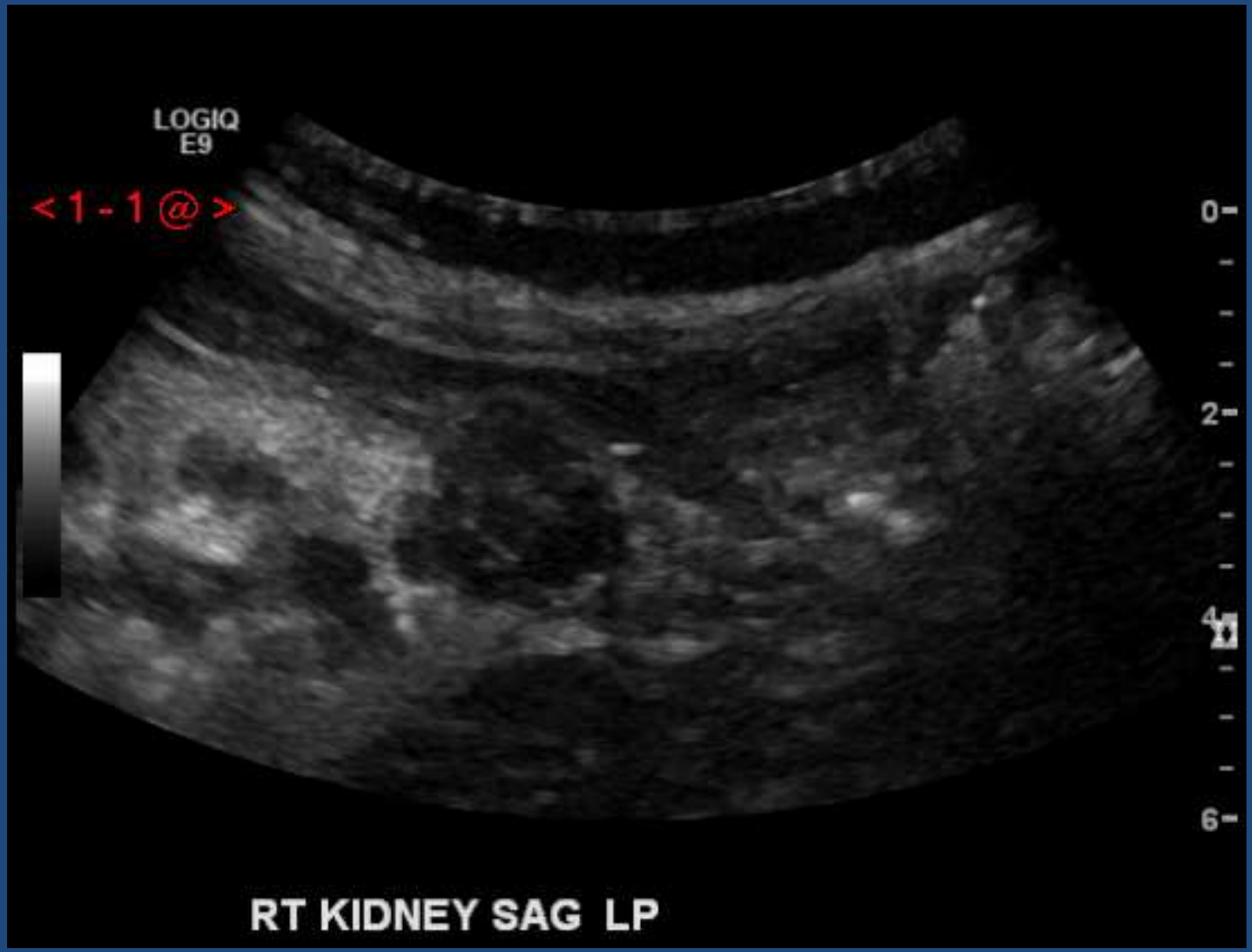
Patient with Indeterminate Mass on Contrast CT- 86 yo female







US Contrast 2nd bolus combined phases

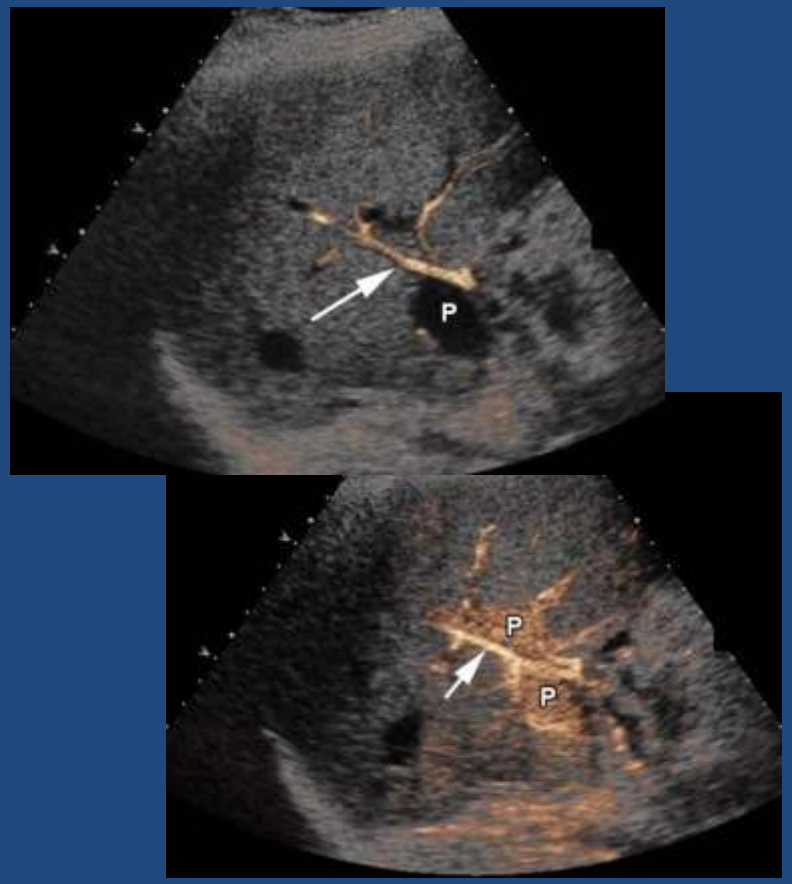


Vascular/Interventional Applications

- Hepatic/Renal transplants- confirm vascular patency
- Endografts- diagnose leaks/monitor therapy
- Monitor ablations

IMPROVED HA VISUALIZATION WITH US CONTRAST

- 8/72 no flow on CDUS
- 6 flow on CEUS (Optison .5ml)
  - confirmed with angio or nl f/u US.
- 2 no flow, angiography confirmed
- US sensitivity rose from .91 to 1.0 ($p<.014$)



Benjamin K. Hom, BS, Ruchi Shrestha, MD, Suzanne L. Palmer, MD, Michael D. Katz, MD, R. Rick Selby, MD, Zhanna Asatryan, BA, Jabali K. Wells, BS and Edward G. Grant, MD **Prospective Evaluation of Vascular Complications after Liver Transplantation: Comparison of Conventional and Microbubble Contrast-enhanced US *Radiology* 2006;241:267-274**

AAA ENDOGRAFT SURVEILLANCE AND THERAPY: ROLE OF US

- CT preferred to assess graft anatomy, and to dx stent migration, leaks
- CEUS equally effective to CT and DSA for endoleaks in small groups of selected patients: 20(a), 30(b) and 24(c) but less effective in overall literature review (d)
- Occasionally better for delayed and/or small leaks
- US potentially useful to guide therapy

a) Bendick PJ. Bove PG. Long GW. Zelenock GB. Brown OW. Shanley CJ. **Efficacy of ultrasound scan contrast agents in the noninvasive follow-up of aortic stent grafts.** *Journal of Vascular Surgery. 37(2):381-5, 2003 Feb.*

b) Napoli V. Bargellini I. Sardella SG. Petruzzi P. Cioni R. Vignali C. Ferrari M. Bartolozzi C. **Abdominal aortic aneurysm: contrast-enhanced US for missed endoleaks after endoluminal repair.** *Radiology. 233(1):217-25, 2004 Oct.*

c) Dill-Macky MJ, **Aortic Endografts: Detecting Endoleaks Using Contrast-enhanced Ultrasound**. *Ultrasound Quarterly. 22:49-52, 2006*

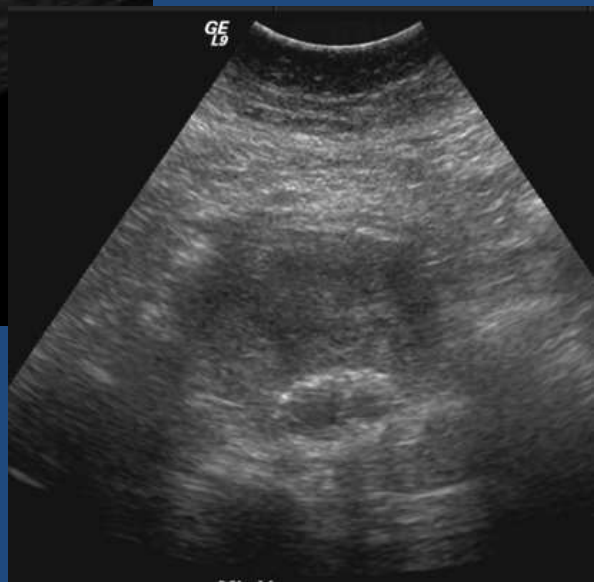
d) Sun Z, Diagnostic value of color duplex ultrasonography in the follow-up of endovascular repair of abdominal aortic aneurysm. Journal of vascular and interventional radiology [1051-0443] 2006 vol:17 iss:5 pg:759 -64

84 YO DIABETIC WITH ENDOGRAFT AORTIC REPAIR

endoleak AAA 5cm attempted angiographic rx.

8 mo later persistent endoleak AAA 5.6cm

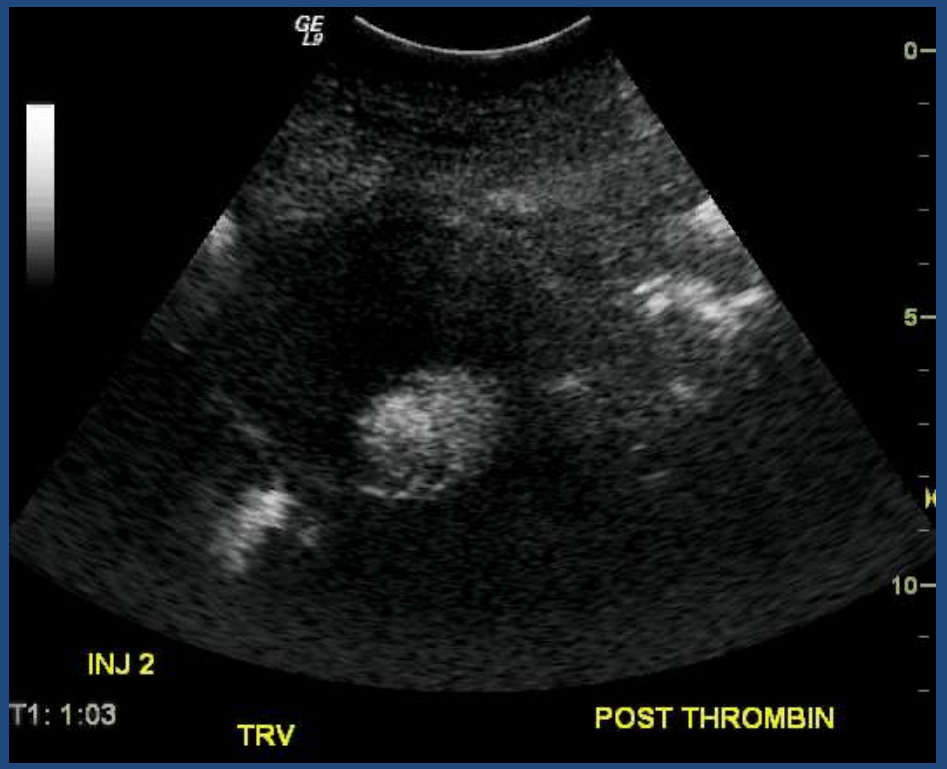
2 yrs later AAA 6.3cm with renal insufficiency –angio same time shows no endoleak



Gray scale and color Doppler show AAA

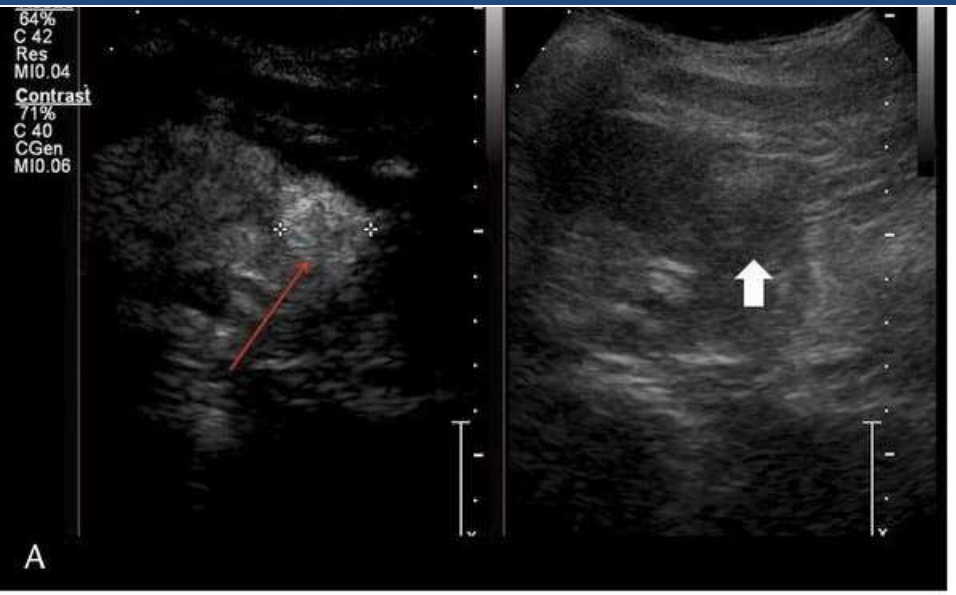
Only contrast study shows endoleak

POST THROMBIN



After initial1000u thrombin injection the leak is no longer seen with repeat contrast bolus (Definity .75cc/bolus)

Contrast guided and monitored RFA of Renal Tumors



[Contrast-Enhanced Ultrasound-Guided Radiofrequency Ablation of Renal Tumors]

Lackey, Logan II; Peterson, Cynthia; Barr, Richard G.

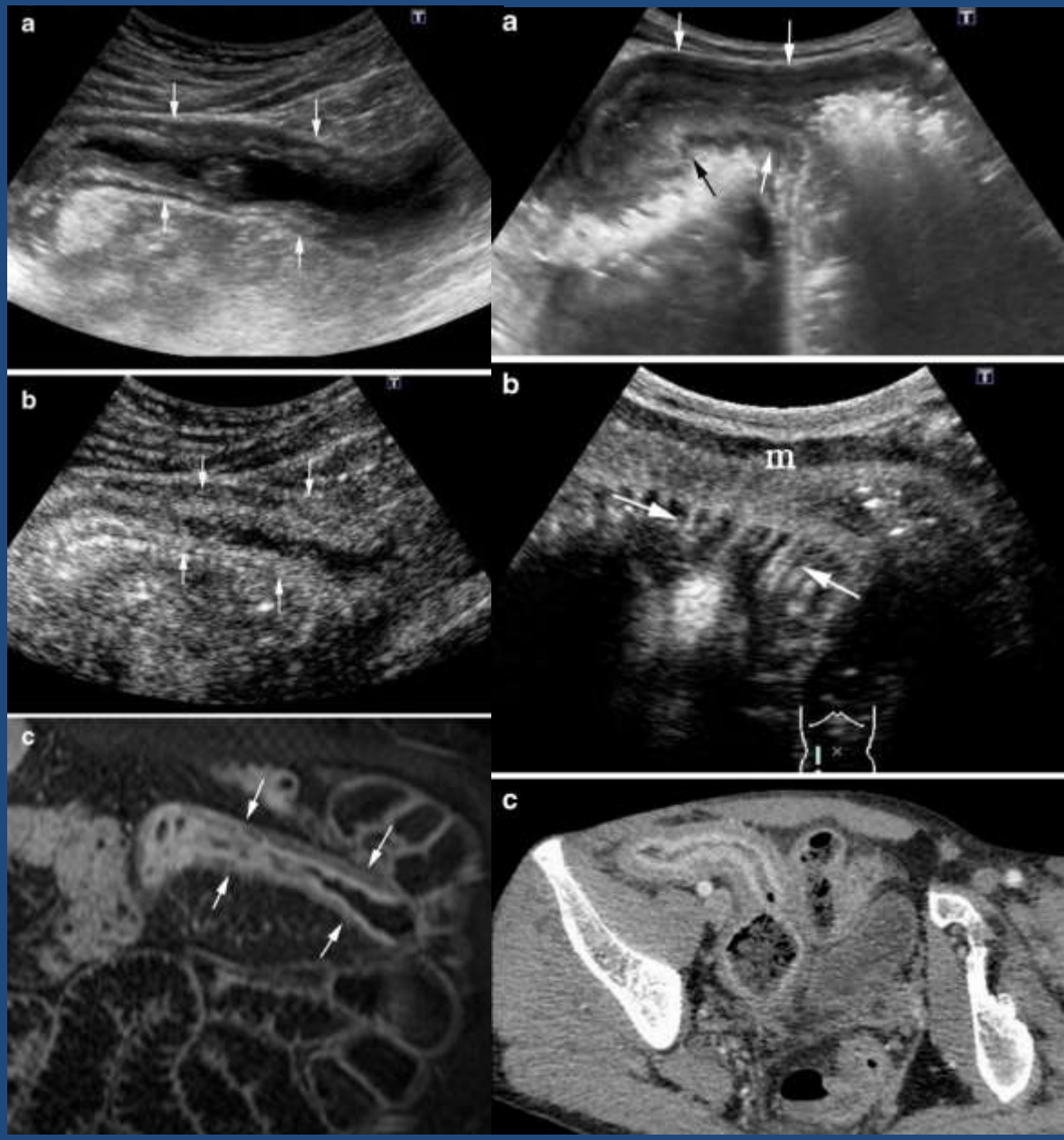
Ultrasound Quarterly. 28(4):269-274, December 2012.

doi: 10.1097/RUQ.0b013e318274de66

c/o Richard Barr

Other Applications

- Bowel (IBD, Ischemia)
- Cystoscopy (VCUG)
- Trauma
- Ovary, Prostate?



CEUS in Crohn's Disease Ripolles et al Insights Imaging Dec 2011

Conclusions

- US Contrast a powerful tool to enhance US diagnosis
- Primary use in characterizing focal lesions (liver-Wilson et al)
- Useful in assessing ablation margins (Liver, kidney-european studies)
- Vascular agent for intra-abdominal vessels (transplants, vascular stents)
- Applications in bowel (Wilson), ovary, prostate?
- Great potential use in patients who cannot receive CT or MR contrast due to allergy, renal function or location (interventional, OR, etc)