Contrast Enhanced Ultrasound of Liver Lesions: A Children’s Cancer Center Experience

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Disclosures

• I receive product support from GE Healthcare and royalties from Springer publishers
Objectives

• Review history of contrast enhanced ultrasound (CEUS) in pediatrics in the United States
• Share St. Jude experience with CEUS of liver disease
• Discuss clinical impact of CEUS for assessing focal liver lesions in pediatric oncology
• Future directions
CEUS in Pediatrics in the United States

- Until recently, CEUS in children had been off-label in the US
- Most advances in pediatric CEUS occurred in Europe
- 2011:
  - Society for Pediatric Radiology (SPR) formed CEUS Taskforce
  - SPR wrote position letter to FDA regarding value of CEUS in children
- 2013:
  - SPR and ICUS join forces
ICUS-SPR Collaboration

- April, 2013: Joint SPR-ICUS briefing of FDA on pediatric CEUS
- July, 2013: Publish joint review article

![Image of a review article](Pediatr Radiol (2013) 43:1063–1073)

**Safety of contrast-enhanced ultrasound in children for non-cardiac applications: a review by the Society for Pediatric Radiology (SPR) and the International Contrast Ultrasound Society (ICUS)**

Kassa Darge • Frederica Papadopoulou • Aikaterini Ntoulia • Dorothy I. Bulas • Brian D. Coley • Lynn A. Fordham • Harriet J. Palfiel • Beth McCarville • Frank M. Volberg • David O. Cosgrove • Barry B. Goldberg • Stephanie R. Wilson • Steven B. Feinstein
Bracco Focal Liver Lesions Trial

• June 2009 – July 2013: Conducted 2 parallel, multi-institutional Phase 3 trials of Lumason (SonoVue) in the US and Europe
  – 33 centers
  – 702 patients
• Retrospective safety study of Lumason in 44 children in Europe
• Submitted to the FDA in mid 2015
2016 FDA Approval!

• March, 2016: FDA approves Lumason (Sonovue) for adult and pediatric liver imaging

• December, 2016: FDA approves Lumason for intravesical use and removes contraindication for use in right-to-left, bi-directional or transient right-to-left cardiac shunts
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The St. Jude Experience

• Used CEUS in clinical cancer trials since 2001
• In 2013 began using CEUS clinically
  – Main indication, imaging of the liver
    • Hepatic veno-occlusive disease
    • Primary liver tumors
    • Focal liver lesions
Hepatic Veno-Occlusive Disease

- Occurs in first 2 weeks after stem cell transplant
- Fibrinous occlusion of hepatic sinusoids
  - Obstructs portal vein flow
    - Slows PV velocity
    - Bi-directional PV flow
    - Reversal of PV flow
    - PV thrombus
9 yo Girl Two Weeks After Bone Marrow Transplant for Relapsed AML

August 4th

August 6th

Complicating Issues

• Portal vein thrombus would require intravascular TPA
  – Bleeding risk (thrombocytopenia, coagulopathy)
• Need to confirm thrombus
  – Renal insufficiency
    • Computed tomography angiography contraindicated
    • Patient in ICU not a good candidate for MRA
• Ideal candidate for contrast enhanced ultrasound
Contrast Enhanced Ultrasound
Primary Pediatric Liver Tumors

- Infantile hemangioma
- Hepatoblastoma
- Fibrolamellar hepatocellular carcinoma
Primary Pediatric Liver Tumors

- Infantile hemangioma
- Hepatoblastoma
- Fibrolamellar hepatocellular carcinoma

Overlapping age groups
Both may have elevated AFP
3 mo with Liver Mass Found on US for Pyloric Stenosis
Arterial Phase
Peripheral Hyper-Enhancement
Portal Venous Phase
Central Filling/Iso-Enhancing
Delayed Phase
Central Filling/Hyper-Enhancing
Delayed Phase
Central Filling/Hyper-Enhancing

Infantile Hemangioma
Focal Liver Lesions (FLL)

• Commonly encountered “incidentalomas”
  – 7.2 – 33% on computed tomography
  – 10.2 – 34.5% on MRI
  – 2.3 – 6.2% on screening ultrasound
  – 20 – 50% (benign lesions) on autopsy

• Probability FLL is benign
  – Healthy person: > 95%
  – History of malignancy/chronic liver disease: 65% if lesion < 1.5 cm
Follow-up imaging 273 solid tumor patients

- 17% (46/273) developed new liver lesion
  - 30% (14/46) focal nodular hyperplasia
    - 86% (12/44) had multiple lesions
  - 15% (7/46) metastases
    - 57% (4/7) had multiple lesions
  - 54% (24/46) had other lesions
Management of FLLs in Pediatric Oncology

• Leads to further investigations
  – Detailed medical history
  – Review of prior imaging
  – Size, number, morphology of FLLs

• Often requires additional imaging

• Adds cost, time, anxiety

• Work-up should be:
  – Prompt
  – Effective
  – Non-invasive
  – Preferably avoids radiation and sedation
### CEUS vs CECT

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CEUS of Focal Liver Lesions

Figure 5. Algorithm used to diagnose a liver mass.
Retrospective Review
CEUS of Liver Lesions at St. Jude

• 25 patients:
  – 10 males, 15 females
  – Avg. age 15.5 yrs
  – 2 primary liver tumors
  – 23 had FLLs
• Detected on
  • CT (n = 14)
  • MRI (n = 7)
  • Ultrasound (n = 4)
• No adverse reaction to ultrasound contrast agent
Results

• Primary diagnoses
  – Leukemia (n = 5)
  – Brain tumor (n = 3)
  – Other solid tumor (n = 17)

• On average 5 years after therapy (range 0 -17 years)

• 23 patients with FLLs
  – 2 had too numerous to count lesions
  – 21 had average of 2.5 lesions (range 1 – 8)
Results cont’

• On CEUS, 21/25 subjects had lesions with benign features:
  – FNH (n=11)
  – Adenoma (n=5)
  – FNH vs. adenoma (n=3)
  – Perfusion defect, regenerative nodule, and infantile hemangioma (n=1 each)

• Clinical follow-up confirmed benign disease
Results cont’

• 4/25 subjects suspicious for malignant disease
  – Metastatic disease (n=2)
    • One biopsied: granuloma (sampling error?—multiple lesions). Patient later recurrent carcinoid
    • Local recurrence (head/neck rhabdo): liver lesion presumed metastatic (no biopsy)
  – Primary liver malignancies (n=2)
    • One biopsied: HCC
    • One resected: FNH

• 100% sensitivity
• 96% specificity
7 yo Girl Treated for Neuroblastoma at Age 13 Months. FLL Found on CT for Abdominal Pain
Arterial Phase
Iso-Enhancing

Portal Venous Phase
Iso-Enhancing
Delayed Phase
Iso-Enhancing
Delayed Phase
Iso-Enhancing

Regenerative Nodule
11 yo Boy with Desmoplastic Small Round Cell Tumor

T1W C+ Axial MRI
On Therapy Disease Evaluation

T1W C+
Axial MRI

Early Arterial Hyperenhancing
Portal Venous Washout
Delayed Phase

Metastases

18 yo Boy
Previously Treated for Medulloblastoma

T1W C+ Spine MRI

C+ CT

Arterial Phase
Hyper-Enhancing
Portal-Venous Phase
Hypo-Enhancing/Washout
Delayed Phase
Hypo-Enhancing/Washout
Delayed Phase
Hypo-Enhancing/Washout

Focal Nodular Hyperplasia
Management of Patient with Focal Liver Lesion

FLL discovered on routine surveillance

Off therapy
- Return in 3 months
  - Repeat imaging
    - No growth
      - Continue routine follow-up
    - Growth
      - ? More imaging
        - ? Follow
        - ? Biopsy

On therapy
- Return 4 – 6 weeks
  - Repeat imaging
    - No growth
      - Continue routine follow-up
    - Growth
      - Biopsy

Confirmatory imaging
- ? Biopsy
Management of Patient with Focal Liver Lesion

FLL discovered on routine surveillance

Off therapy
- Return in 3 months
  - Repeat imaging
    - No growth
      - Continue routine follow-up
    - Growth
      - ? More imaging
        - ? Follow
          - ? Biopsy
  - Growth
    - ? More imaging
      - ? Follow
        - ? Biopsy

On therapy
- Return 4–6 weeks
  - Repeat imaging
    - No growth
      - Continue routine follow-up
    - Growth
      - Biopsy
  - Confirmatory imaging
    - ? Biopsy

Management of Patient with Focal Liver Lesion

FLL discovered on routine surveillance

Off therapy

On therapy

Same day/next day

Contrast enhanced ultrasound

Make informed management decisions

Proceed

CEUS of FLLs
Game Changer in Pediatric Oncology!

- Provides immediate resolution (usually)
- Alleviates patient/physician anxiety
- Cost effective
- No sedation
- No radiation
Future Directions
Pediatric Liver Imaging

• Instrumental in evaluating FLLs
• Distinguishing liver hemangioma from hepatoblastoma
• Guide biopsy
• Assess response to therapy
  – Chemotherapy
  – Trans-arterial chemoembolization
  – Radiofrequency ablation
Thank-you!

Questions?