Contrast Enhanced Ultrasound in Pediatric Oncology

M. Beth McCarville, MD
St. Jude Children’s Research Hospital
Memphis, TN
Overview

- Contrast enhanced ultrasound (CEUS)
  - Benefits in children
  - Measuring tumor blood flow
  - Problem solving tool in pediatric oncology
Benefits of CEUS in children

- Small body habitus reduces artifact
- Well tolerated, no sedation
- Portable
- Less expensive
- No ionizing radiation!
CEUS improves visualization of tumor margins, invasion, adenopathy

<table>
<thead>
<tr>
<th>Trial cohort</th>
<th>US-CT agreement score precontrast</th>
<th>US-CT agreement score postcontrast</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conspicuity</td>
<td>Tumor margin</td>
</tr>
<tr>
<td>1</td>
<td>5.00</td>
<td>3.89</td>
</tr>
<tr>
<td>2</td>
<td>4.22</td>
<td>3.00</td>
</tr>
<tr>
<td>3</td>
<td>4.78</td>
<td>4.44</td>
</tr>
<tr>
<td>4</td>
<td>5.00</td>
<td>3.89</td>
</tr>
<tr>
<td>Average</td>
<td>4.75</td>
<td><strong>3.81</strong></td>
</tr>
</tbody>
</table>

Each parameter was scored on a scale of 1 to 5. The individual parameter US-CT agreement score was defined as 5 minus the absolute difference of scores between US and CT. The higher the score, the better the agreement. 5 is the highest score, indicating identical scores for US and CT (e.g., US = 4 and CT = 4, then US-CT agreement score = 5-|4-4|=5); 1 is the lowest score, indicating polar opposite scores by US and CT (e.g., US = 5 and CT = 1, then US-CT agreement score = 5-|5-1|=1).
17 yo boy with renal rhabdoid, pelvic recurrence
6 yo boy with Wilms tumor
Tumor angiogenesis

- Angiogenesis is critical for:
  - Tumor growth
  - Survival
  - Metastasis

Kerkar SP. Cancer Res 2012;72:3125-3130
Targeted anti-angiogenic therapy

- Interfere with steps in angiogenic signaling pathways
- Inhibit binding of factors required for structural integrity of immature vessels
- Cytostatic not cytotoxic
- Conventional methods of assessing tumor response not suitable
Assessing tumor response to anti-angiogenic agents

• Crucial need for functional modalities, quantitative methods
  – Dynamic contrast enhanced CT
  – $^{15}$O-labeled water PET-CT
  – Dynamic contrast enhanced MRI
  – Dynamic contrast enhanced US (CEUS)
Ultrasound Contrast Agents

- Outer shell
  - Lipid
  - Protein
  - Polymer
- Inner Gas
  - Perfluorocarbon
- Remain in vascular space
- Highly reflective, very small doses (<1 mL)
- Contrast specific software allows quantitation

Optison™; GE Healthcare, Milwaukee, WI
5 yo girl with recurrent Wilms tumor
Dynamic CEUS Tumor Imaging

- First, confirm lesion is visible on grey-scale
- Identify landmarks for follow-up CEUS
Quantitating the data

Time-intensity curve

Limitations of CEUS in Assessment of Anti-angiogenic Therapy

- Limits number of target lesions that can be followed
- Not all lesions will be visible with US
- Motion artifact
CEUS as a problem solving tool in pediatric oncology

- Tumor vs. post-op change
- Focal liver lesions
Adrenal Tumor vs. Hemorrhage

Pre-operative

Post-operative

Post-op hematoma

# Liver lesions in children after cancer therapy

TABLE 1: Primary Malignant Diagnoses in Patients With New Liver Lesions by Group

<table>
<thead>
<tr>
<th>Focal Nodular Hyperplasia</th>
<th>Metastasis</th>
<th>Other Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroblastoma (7)</td>
<td>Neuroblastoma (2)</td>
<td>Neuroblastoma (6)</td>
</tr>
<tr>
<td>Wilms tumor (2)</td>
<td>Wilms tumor (2)</td>
<td>Wilms tumor (5)</td>
</tr>
<tr>
<td>Primitive neuroectodermal tumor (2)</td>
<td>Rhabdomyosarcoma (1)</td>
<td>Hepatoblastoma (4)</td>
</tr>
<tr>
<td>Rhabdomyosarcoma (2)</td>
<td>Ewing sarcoma (1)</td>
<td>Rhabdomyosarcoma (2)</td>
</tr>
<tr>
<td>Hepatoblastoma (1)</td>
<td>Hepatoblastoma (1)</td>
<td>Primitive neuroectodermal tumor (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Malignant germ cell tumor (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clear cell sarcoma (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ganglioneuroblastoma (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatocellular carcinoma (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Undifferentiated sarcoma (1)</td>
</tr>
</tbody>
</table>

Note—Data in parentheses are number of patients.
Lesions classified as other

**TABLE 2: Etiology of Lesions Classified as Other Lesions**

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfusion abnormalities</td>
<td>11</td>
</tr>
<tr>
<td>Posttherapy effects</td>
<td>3</td>
</tr>
<tr>
<td>Focal fat</td>
<td>5</td>
</tr>
<tr>
<td>Hepatic cysts</td>
<td>2</td>
</tr>
<tr>
<td>Subcentimeter low-attenuation lesions</td>
<td>4</td>
</tr>
</tbody>
</table>
13 yo boy, previously treated for stage 4 neuroblastoma. Liver lesions found incidentally on imaging obtained for SBO.
CEUS Features of Focal Nodular Hyperplasia

Arterial Phase

Centrifugal enhancement
Portal Venous Phase

“Lightbulb” appearance

Portal vein

Delayed Phase: Isoenhancing

7 yo girl treated for neuroblastoma at age 13 months
Regenerative nodule

Arterial phase
Regenerative nodule

Portal venous phase
Regenerative nodule

Delayed phase

25 yo girl treated for AML at age 16 years
Visible on grey scale

Adenomas

Early arterial

Late arterial
Adenomas

Portal venous phase
Adenomas

Delayed phase
20 yo woman diagnosed with gastric carcinoid at age 14 years. Currently symptomatic flushing.
Possible metastasis
Possible metastasis

Arterial phase
Possible metastasis

Portal venous phase
Possible metastasis

Delayed phase

Conclusions

• CEUS is uniquely suited for pediatric imaging
• Within pediatric oncology
  – Measurement of tumor blood flow
  – Distinguishing tumor from abscess, hematoma, other benign process
  – Characterizing focal liver lesions