Novel Kidney Imaging

Contrast-enhanced ultrasound

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Disclosures

• Contract with Lantheus Medical Imaging (Definity)

Objectives

• Current kidney surveillance guidelines and potential areas for improvement
• Review of ultrasound
• Contrast-enhanced ultrasound
  » Kidney applications
• Potential application in VHL
• From nephrology perspective

Imaging surveillance in VHL

• Annual high quality ultrasound of the kidneys
• Every other year contrast-enhanced MRI (age 16+)
• In addition to contrast-enhanced MRI for central nervous system every 2-3 years (age 16+)
• Cost, time and lifetime gadolinium doses are high
Gadolinium - safety issues

- Gadolinium very low adverse event rate
- 2006: Nephrogenic sclerosing fibrosis reported in patients with severe kidney disease
- Stage 4 and higher kidney disease requires informed consent -> RARE!

Gadolinium – safety issues

- 2015: Gadolinium deposition disease reported, but clinical significance not clear
- 2017: FDA issues class warning
  - no direct linkage to adverse effects
  - requires New Patient Medication Guide
  - requires manufacturers to conduct animal and human studies to further assess safety

Ultrasound

Advantages
- Accessibility
- Cost
- Patient tolerability
- Lack of radiation

Disadvantages
- Single organ imaging
- User dependent
- Despite better resolution, interpretation is not intuitive to clinicians
- Lack of contrast

How ultrasound works

Transducer produces high frequency sound waves
When sound interfaces with surfaces
- Transmission
- Reflection
Air causes impedance mismatch
Coupling Gel
- Reduce interface between air and skin
**B-Mode image of the kidney**

- Standard ultrasound images
  - B = brightness
- Longitudinal and transverse
- Can add Doppler
  - Large vessel flow only

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**Contrast-enhanced Ultrasound CEUS**

- Microbubble contrast agents
- Blood flow & tissue perfusion
- Advantages: cost efficient, safe, images in real time
- Disadvantages: *Not yet FDA approved for kidneys*, short enhancement and circulation time, single plane

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**Ultrasound contrast agents**

- Microbubbles
  - Gas core
    - Highly compressible
  - Stabilizing shell (lipid, albumin)
    - Biocompatible
  - Size: 1-5 microns, similar to RBC
    - Activated by mixing
    - Injected into bloodstream

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**Perflutren lipid microspheres**
- Definity
**Sulfur hexafluoride lipid microspheres**
- Lumason (Sonovue)

**Perflutren protein microspheres**
- Optison
Microbubble properties

- **Nonlinear response to ultrasound not produced by tissue**
  - Microbubble echoes can be separated from tissue
- **No extravasation**
  - Reflect blood flow
- **Can be destroyed with ultrasound – FLASH**
  - Bubble signal can be cleared and reperfusion visualized

Microbubble clearance

- After minutes of circulation, breathed off
- NOT cleared through the kidney
- NOT nephrotoxic

How CEUS works (rat kidney)

- Microbubbles oscillate in size in ultrasound field
- Contrast-enhanced ultrasound images show contrast only

Kidney ultrasound Cumulative Contrast Image vs MRI

*Images are not from the same animal*
Kidney Lesion Diagnosis

- 6 studies comparing sensitivity of CEUS to other modalities

<table>
<thead>
<tr>
<th>Modality</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Biopsy</th>
<th>CEUS</th>
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</thead>
<tbody>
<tr>
<td>US</td>
<td>46-70%</td>
<td>13-94%</td>
<td>33-90%</td>
<td>89-100%</td>
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<tr>
<td>Contrast CT</td>
<td>83-100%</td>
<td>51-96%</td>
<td>61-100%</td>
<td>71-99%</td>
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<tr>
<td>Contrast MR</td>
<td>81-100%</td>
<td>71-100%</td>
<td>90-100%</td>
<td>71-99%</td>
</tr>
</tbody>
</table>

- One study with 950 cystic lesions, others 30-80 lesions

E Chang, et al., Urology 2014

UNC Study

All comers (n=48)

<table>
<thead>
<tr>
<th>Diagnosis Type</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Overall Accuracy</th>
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<tbody>
<tr>
<td>Tissue diagnosis</td>
<td>96%</td>
<td>96%</td>
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<tr>
<td>Tissue/clinical diagnosis</td>
<td>96%</td>
<td>57%</td>
<td>78%</td>
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</table>

CKD patients (n=27)

<table>
<thead>
<tr>
<th>Diagnosis Type</th>
<th>Sensitivity</th>
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<th>Overall Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue diagnosis</td>
<td>100%</td>
<td>NA</td>
<td>100%</td>
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<tr>
<td>Tissue/clinical diagnosis</td>
<td>92%</td>
<td>57%</td>
<td>65%</td>
</tr>
</tbody>
</table>

E Chang, et al., BMC Nephrology 2017

Indeterminate lesion

- B-mode indeterminate internal echoes
- Clearly no enhancement from start to finish
- Simple cyst

Heterogeneous mass

- Clear enhancement from start to finish
- Showed on Doppler
- Quantify enhancement characteristics
What about CEUS for VHL?

Current Surveillance
- Costly
- Time consuming
- Contrast exposure
  - Particularly if kidney is already compromised

CEUS
- Less expensive
- Less time intensive
- No iodinated or gadolinium contrast exposure
- Microbubbles are safe for kidneys

Vision for updated surveillance
- NOT a complete replacement of MRI
- Reduction in the total lifetime MRI requirement and gadolinium exposure by reducing frequency of MRI

Hurdles
- Accuracy – screening vs diagnosis
- Variability in number of lesions
- Tolerability
- Patient and provider acceptance
- Not yet widely available
- Clinical implementation
  - Requires expertise and training
Future directions

- Molecular imaging
- Directed therapies
- Surveillance for other organs
- Opportunities for collaboration!

Conclusions

- Contrast-enhanced ultrasound is a potential novel imaging tool that may prove useful in kidney cyst/mass surveillance in VHL patients
  - Screening
  - Diagnosis
- Requires studies to determine feasibility and accuracy

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- Lantheus Medical Imaging

Thank you!

- Questions?
Cumulative Contrast Images (CCI)

Standard B-Mode

Live Contrast Image

Sum together frames of video clips

Time