CEUS (Contrast Enhanced Ultrasonography) in liver

Yun Jung Lee
Bracco Imaging Korea
Outline

• Background information
• Key characteristics of Ultrasound contrast agent
  ▪ Composition
  ▪ Distribution after injection
  ▪ Technical imaging aspects
• Clinical evidence
  ▪ FLL characterization
  ▪ FLL detection
  ▪ CEUS-guided interventions
  ▪ Safety
• Conclusions
• Work in progress (R&D)
• CEUS code 소개
The acronym CEUS as the official term describing Contrast-enhanced ultrasound (ultrasonography) techniques in general

A separate term is dynamic contrast-enhanced ultrasound (DCE-US) which describes time intensity (TIC) analyses used for quantification of tumor perfusion → assessment of treatment response.

CEUS guidelines were first introduced by the EFSUMB in 2004, entered on liver applications.
The liver CEUS guideline were then updated in 2008 and 2012.
Current version was a joint venture between WFSUMB and EFSUMB → The guideline was published simultaneously in EJU and UMB.
The CEUS LI-RADS Working Group has adopted the terminology of these guideline and adapted the terminology of CT and MR LI-RADS to CEUS.
CEUS perfusion parameters as biomarkers for disease status and therapy.
Ultrasound Contrast Agents

= Microbubbles

- consists of gas $\rightarrow$ high echogenicity
- surrounded by a shell $\rightarrow$ stabilization
US Contrast agent

- Current clinical use is as a drug (medical imaging agent) to enhance the diagnostic performance of ultrasonography.
- Interaction between microbubbles and ultrasound waves that are reflected, which generates a specific and enhanced backscattered ultrasound signal.
- Enhances visualization of cardiac cavities, large extra-cardiac vessels, small vessels, and of the urinary tract.
US Contrast Agent oscillation

Microbubbles microscopical picture

Microbubbles behaviour under an ultrasound field
US Contrast Agent oscillation

High Mechanical Index (MI) Technique

Destructive Mode:
- Microbubble
- Destruction
- Transient Imaging

Low MI technique

Conservative Mode Low:
- Microbubble
- Conservation
- Real Time Imaging
US Contrast agent characteristic

X-ray and MRI extracellular contrast agents

Intravascular pixel  extravascular pixel
Ultrasound Contrast Agents are administered by intravenous injection and they remain in the vascular space (blood-pool agents) where they strongly enhance the ultrasound signal of the blood. CEUS visualizes “MACROcirculation” and “MICROcirculation.”
US Contrast Agents

- **Levovist™**: air, galactose/palmitic acid (Schering 1996)
  - Indications: Cardiac, abdomen, ureteric reflux, TC doppler
- **Optison™**: octafluoropentane, albumin shell (GE 1998)
  - Indications: Cardiac
- **SonoVue™**: SF$_6$, phospholipid shell (Bracco 2001)
  - Indications: Cardiac, macrovascular, liver and breast lesions
- **Luminity™**: Octafluoropropane, lipid shell (Bristol-Myers Squibb 2006)
  - Indications: Cardiac
- **Sonazoid™**: C4F10, hydrogenated egg phosphatidy serine (GE 2007)
  - Indications: Liver specific late phase
- **Lumason™ (SonoVue™)**: SF$_6$, phospholipid shell (Bracco 2016)
Composition of the microbubbles

**SONOVUE**

- **SOFT SHELL**
  - Phospholipids
  - Sulphur hexafluoride

Monolayer of phospholipids (DSPC, DPPG-Na) + palmitic acid as stabilizer – gas: sulphur hexafluoride ($\text{SF}_6$), inert gas also used in respiratory physiology and vitreoretinal surgery

SonoVue SPC

**SONAZOID**

- **STIFF SHELL**
  - Perfluorobutane ($\text{C}_4\text{F}_{10}$)

Monolayer of phospholipids obtained from hydrogenated egg phosphatidylserine – gas: perfluorobutane ($\text{C}_4\text{F}_{10}$)

Hvattum et al, 2006, Sonazoid brochure, GE Healthcare
Distribution after IV injection

SONOVUE IS A PURE BLOOD-POOL AGENT
Following IV injection, the SonoVue microbubbles remain in the vascular compartment and follow the distribution kinetics of the red blood cells, as their size prevent them from leaving the vascular system (unless in case of active bleeding).

SONAZOID IS TAKEN UP BY THE MONONUCLEAR PHAGOCYTE SYSTEM
• Following IV injection of Sonazoid, uptake by the mononuclear phagocyte system (MPS) starts at ~ 1 min

Injected Sonazoid microbubbles are taken up by the Kupffer cells in the liver.
Microbubble (SonoVue)circulation in liver
CEUS Technique

Contrast-specific Imaging

Siemens Sequoia CPS
Siemens S2000 CPS
Philips iU22 PM/PI
GE Logiq E9/9/7 TAD
Toshiba Aplio CHI

Esaote MyLab CN Ti
Aloka Alpha 10 CHI
Hitachi HI VISION dCHI
BK Medical Pro Focus CI
Supersonic AIxplorer

CEUS+
Helpful diagnostic images with outstanding quality and performance

CEUS+ (VesselMax)
Improved vessel and blood flow visualization
Accumulating contrast images & Motion correction

CEUS+ (FlowMax)
Improved vessel and blood flow visualization
Compensation image uniformly, decreasing saturated signal
Clinical Evidence
FLL Characterization
When should CEUS need to be used to characterize FLL?

- Patients with incidental findings at unenhanced US
- Patients at high risk for HCC after lesion detection at unenhanced US
- Patients with indeterminate lesions at CT/MRI
- Patients who should avoid radiation or the risk of nephrotoxicity
- In conjunction with certain interventional procedures

Chung YE, Kim KW Ultrasonography 2015
CEUS LI-RADS® v2017 CORE
Claudon et al. Ultraschall Med 2012
Nolsoe CP et al. J Ultrasound Med 2018
## FLL Characterization – Available Evidence

<table>
<thead>
<tr>
<th>Meta-analysis</th>
<th>N of studies</th>
<th>N of lesions with SonoVue</th>
<th>Pooled Sensitivity (range)</th>
<th>Pooled Specificity (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Friedrich-Rust M 2013</td>
<td>45 (35 with SonoVue†)</td>
<td>7231</td>
<td>93% (91-95)</td>
<td>90% (88-93)</td>
</tr>
<tr>
<td>Niu Y * 2013</td>
<td>15 (12 with SonoVue)</td>
<td>878</td>
<td>84% (77-90)</td>
<td>89% (81-94)</td>
</tr>
<tr>
<td>Guang Y ** 2011</td>
<td>10 (all with SonoVue)</td>
<td>2981</td>
<td>88% (87-90)</td>
<td>81% (79-84)</td>
</tr>
</tbody>
</table>

† 1 Sonazoid study qualified for inclusion
* small HCCs ≤ 2 cm
** also included 9 studies with CECT and 10 studies with CEMR

### CECT
<table>
<thead>
<tr>
<th>Pooled Sensitivity (range)</th>
<th>Pooled Specificity (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90% (88-92)</td>
<td>77% (71-82)</td>
</tr>
</tbody>
</table>

### CEMR
<table>
<thead>
<tr>
<th>Pooled Sensitivity (range)</th>
<th>Pooled Specificity (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>86% (83-88)</td>
<td>81% (76-85)</td>
</tr>
</tbody>
</table>

*Friedrich-Rust M – Liver Int 2013; 33:739
*Niu Y – Tumor Biol 2013; 34:3667
*Guang Y – J Cancer Res Clin Oncol 2011; 137:1595*
Clinical Evidence
FLL Detection
When should CEUS be used to detect FLLs?

- Oncology patients
  - When CT/MRI is not feasible or available
  - Monitor tumor treatment
- Pediatric patients to avoid radiation exposure

Claudon M et al. Ultraschall Med 2013
<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Title</th>
<th>Year</th>
<th>Sensitivity CEUS</th>
<th>Sensitivity CT</th>
<th>Specificity CEUS</th>
<th>Specificity CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quaia E, D’Onofrio M, Palumbo A, Rossi S, Bruni S, Cova M.</td>
<td>Eur Radiol 2006; 16: 1599-609</td>
<td>2006</td>
<td>83%</td>
<td>89%</td>
<td>84%</td>
<td>89%</td>
</tr>
<tr>
<td>Cantisani V, Ricci P, Pagliara E, Drudi F et al.</td>
<td>Ultraschall in Med 2010;31:500-505</td>
<td>2010</td>
<td>93.4% - 95.8%</td>
<td>95.8% - 96.8%</td>
<td>76.7% - 83.3%</td>
<td>83.3% - 86.7%</td>
</tr>
<tr>
<td>Rafaelsen SR, Jakobsen A</td>
<td>Colorectal Disease 2011;13: 420-425</td>
<td>2011</td>
<td>85.7%</td>
<td>85.7%</td>
<td>97.6%</td>
<td>95.6%</td>
</tr>
<tr>
<td>Dietrich CF, Kratzer W, Strobe D, Danse E, et al.</td>
<td>World J Gastroentrol 2006; 12: 1699-1705</td>
<td>2006</td>
<td>88.5%</td>
<td>92.3%</td>
<td>94.0%</td>
<td>89.2%</td>
</tr>
</tbody>
</table>
Detection of Metastase—Available Evidence

• NICE guidelines report SonoVue to be similar to CECT and CEMRI for the diagnosis of liver metastases in 4 studies analyzed
  • Sensitivities 83% across modalities
  • Conclusion: “....contrast enhanced ultrasound alone may be adequate to rule out liver metastases in people with known primary malignancies.”
• Rafaelsen et al. compared SonoVue CEUS to CE-MDCT for the diagnosis of metastases
  - Sensitivity 85.7% for both modalities, specificity 97.6% vs. 95.6%, respectively
  - Conclusion: “CEUS has potential as a diagnostic alternative to MDCT in the detection of Liver metastases.”
• Cantisani et al. also compared SonoVue CEUS to CE-MDCT
  - No significant differences in sensitivity or specificity between CEUS and MDCT
  - Conclusion: “CEUS is...highly comparable with MDCT in the detection of liver metastases from colorectal cancer
HCC imaging systems: updates in 2018

- LI-RADS v2018
- AASLD v2018
  - EOB-MR, incorporate LI-RADS
- EASL v2018
  - EOB-MR, CEUS (Intravascular CMs)
- KLCSG-NCC v2018
  - CEUS (Intravascular CMs)

- All major guidelines include EOB-MR as a first line diagnostic modality
- CEUS reported as first line modality after detection by B-mode ultrasound in Chinese HCC guideline
- CE-US added as a second line diagnostic modality in EASL, KLCSG-NCC, & APASL
Technical Aspects – Imaging Phases
LI-RADS

- **Recommendations – in cirrhosis**

- **LIRADS only for CEUS with Pure Blood Pool Agents**

<table>
<thead>
<tr>
<th>Arterial phase hyperenhancement (APHE)</th>
<th>No APHE</th>
<th>≥ 20</th>
<th>&lt; 10</th>
<th>≥ 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodule size (mm)</td>
<td>&lt; 20</td>
<td>≥ 20</td>
<td>&lt; 10</td>
<td>≥ 10</td>
</tr>
<tr>
<td>No washout of any type</td>
<td>CEUS LR-3</td>
<td>CEUS LR-3</td>
<td>CEUS LR-3</td>
<td>CEUS LR-4</td>
</tr>
<tr>
<td>Late and mild washout</td>
<td>CEUS LR-3</td>
<td>CEUS LR-4</td>
<td>CEUS LR-4</td>
<td>CEUS LR-5</td>
</tr>
</tbody>
</table>

*a. CEUS LR-M criteria – any of following:*
- rim APHE OR early (< 60 s) washout OR marked washout
**Algorithm for CEUS**

**CEUS LI-RADS**

<table>
<thead>
<tr>
<th>LR-1</th>
<th>LR-2</th>
<th>LR-5V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely benign</td>
<td>Probably benign</td>
<td>Tumor in vein</td>
</tr>
<tr>
<td>LR-1</td>
<td>LR-2</td>
<td>LR-5V</td>
</tr>
<tr>
<td>definitely or probably malignant, not specific for HCC&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Observation in high-risk patient on pre-contrast US**

**Inadequate assessment**

**Treated observation**

**Untreated observation**

**Arterial phase hypo/isoenhancement**

<table>
<thead>
<tr>
<th>Dimension (mm)</th>
<th>&lt; 20</th>
<th>≥ 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>No washout of any type</td>
<td>LR-3</td>
<td>LR-3</td>
</tr>
<tr>
<td>Late and mild washout&lt;sup&gt;2&lt;/sup&gt;</td>
<td>LR-3</td>
<td>LR-4</td>
</tr>
</tbody>
</table>

**Arterial phase hyperenhancement**

<table>
<thead>
<tr>
<th>Dimension (mm)</th>
<th>&lt; 10</th>
<th>≥ 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>No washout of any type</td>
<td>LR-3</td>
<td>LR-4</td>
</tr>
<tr>
<td>Late and mild washout&lt;sup&gt;2&lt;/sup&gt;</td>
<td>LR-4</td>
<td>LR-5</td>
</tr>
</tbody>
</table>

**Kinetics of CEUS Washout LR-M**

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>Arterial</th>
<th>Portal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid WO</td>
<td>&lt; 60 sec</td>
<td>Any degree of WO</td>
</tr>
<tr>
<td>Any APHE</td>
<td>Rapid WO</td>
<td>Any degree of WO</td>
</tr>
<tr>
<td>Marked Punched out WO</td>
<td>Marked WO</td>
<td>Marked WO</td>
</tr>
<tr>
<td>Rim enhancement</td>
<td>Rim enhancement</td>
<td>Rim enhancement</td>
</tr>
</tbody>
</table>

1. Arterial phase hyperenhancement: whole or in part, not rim or peripheral discontinuous globular enhancement
2. Late in onset (≥ 60 seconds) and mild in degree: in whole or in part, with no part showing early or marked washout
3. Early onset washout (< 60 seconds) and/or marked (punched out) appearance and/or arterial phase rim enhancement

---

**Concept:**
Observation is probably or definitely malignant, but imaging features are not specific for HCC

**Definition:**
Distinct solid nodule with one or more imaging features that favor non-HCC malignancy

**Criteria:**
- Distinct solid nodule with at least some enhancement in the arterial phase (regardless of morphological pattern or degree) with either or both of the following:
  - Early washout relative to liver within 60 seconds of contrast injection
  - Marked washout resulting in a "punched out" appearance
  - Arterial phase rim enhancement, followed by washout (regardless of onset or degree)

**Management:**
- Variable, depending on type of malignancy suspected
- Biopsy is frequently needed for a LR-M categorization as there is a lack of specificity for a diagnosis

**CEUS LR-M: Definitely or Probably Malignant, not specific for HCC**

**Arterial phase enhancement**
- Rim enhancement

---

**Acknowledgments**

Feedback? Email nordr@acr.org
Clinical Evidence
CEUS-guided Interventions
# CEUS-guided Liver Biopsy – Available Evidence

<table>
<thead>
<tr>
<th></th>
<th>Contrast Agent</th>
<th>Lesions N</th>
<th>Technical Success %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sparchez 2015</td>
<td>SonoVue</td>
<td>86</td>
<td>98</td>
</tr>
<tr>
<td>Eso 2016</td>
<td>Sonazoid</td>
<td>65</td>
<td>92</td>
</tr>
<tr>
<td>Park 2015</td>
<td>Sonazoid</td>
<td>41</td>
<td>95</td>
</tr>
<tr>
<td>Kang 2016</td>
<td>Sonazoid</td>
<td>16</td>
<td>88</td>
</tr>
</tbody>
</table>

When should CEUS be used to Monitor Ablation Procedures?

- Guide ablation
- Intra-operative monitoring
- Monitoring after ablation treatment

Claudon M et al. Ultraschall Med 2013
Liu F et al. Int J Hypertherm 2011
CEUS is important to guide biopsy and improve successful sampling in:
- Liver (during arterial phase to sample areas of viable phase)
- Thyroid (biopsy during arterial phase)
- Lung
- Pediatric patients
- Lymph node
- Sarcomas
- Prostate
CEUS for local treatment follow up – Available Evidence

Postprocedural CEUS

- Follow up after local ablation
- Concordance compared to standard imaging modality in follow up

<table>
<thead>
<tr>
<th></th>
<th>Contrast Agent</th>
<th>Treated Lesions N</th>
<th>Accuracy %</th>
<th>Follow up Time</th>
<th>Reference Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Du 2015</td>
<td>SonoVue</td>
<td>78</td>
<td>97</td>
<td>20-30 min</td>
<td>MRI 1 mth</td>
</tr>
<tr>
<td>Luo 2010</td>
<td>Sonazoid</td>
<td>63</td>
<td>97</td>
<td>1 day</td>
<td>CT 1 mth</td>
</tr>
<tr>
<td>Zheng 2013</td>
<td>SonoVue</td>
<td>221</td>
<td>93</td>
<td>1 – 31 months</td>
<td>CT 1- 31 mth</td>
</tr>
<tr>
<td>Bo 2014</td>
<td>SonoVue</td>
<td>73</td>
<td>96</td>
<td>1 month</td>
<td>CT/MRI 1 mth</td>
</tr>
<tr>
<td>Frieser 2011</td>
<td>SonoVue</td>
<td>91</td>
<td>96</td>
<td>1 - &gt;3 months</td>
<td>CT/MRI &gt;6m</td>
</tr>
</tbody>
</table>

CEUS Safety
<table>
<thead>
<tr>
<th></th>
<th>Contrast Agent</th>
<th>Patients Exposed N</th>
<th>AEs N (%)</th>
<th>Serious AEs N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piscaglia 2006</td>
<td>SonoVue</td>
<td>23,188</td>
<td>29 (0.125)</td>
<td>2 (0.0086)</td>
</tr>
<tr>
<td>Tang 2017</td>
<td>SonoVue</td>
<td>30,222</td>
<td>6 (0.020)</td>
<td>2 (0.007)</td>
</tr>
</tbody>
</table>

Piscaglia UMB 2006, Tang J Ultrasound Med 2017
Conclusions

• A large body of published study data demonstrate that SonoVue has high sensitivity and specificity for the characterization of FLLs, based on the assessment of vascular phase enhancement patterns.
• In studies evaluating FLL detection, SonoVue demonstrated sensitivity between 83%–95% for detection of metastases versus 78% for Sonazoid
• Technical success rate for biopsy and liver ablation guidance was reported to be similar in studies with SonoVue (92%–98%) vs Sonazoid (70%–92%)
  – key is the identification of viable tumor tissue
• The safety record of SonoVue has been extensively studied, with large-scale studies confirming low incidence of AEs/serious AEs
“Work in progress (R&D)”

- **Ultrasound Contrast Agents**
  - “**imaging**” applications
  - “**therapeutic**” applications
    - Drug Delivery Ultrasound mediated
    - Sonoporation & Gene Delivery
Nanomedicine and Molecular Imaging research at Bracco

- Nano & Micro constructs
  - Microparticle or capsules
  - Liposomes
  - Nanoparticle
  - Micelle
- Ultrasound Guided Technology
- Molecular Imaging
- Prodrug
- Antibody conjugate
- Polymer conjugate
- Biotechnology and bioengineering
- Drug & Gene delivery
**CEUS 검사행위코드**

<table>
<thead>
<tr>
<th>수가코드</th>
<th>분류번호</th>
<th>한글명</th>
<th>영문명</th>
</tr>
</thead>
<tbody>
<tr>
<td>EB421020</td>
<td>나-942</td>
<td>유방. 액와부 초음파</td>
<td>Breast Axilla US</td>
</tr>
<tr>
<td>EB433020</td>
<td>나-943</td>
<td>경흡부 심초음파 전문</td>
<td>Transthoracic Echo (Advanced)</td>
</tr>
<tr>
<td>EB448020</td>
<td>나-944</td>
<td>신장.부신.방광</td>
<td>Kidney. Adrenal Gland Bladder (Adult)</td>
</tr>
<tr>
<td>EB449020</td>
<td>나-944</td>
<td>신장.부신</td>
<td>Kidney Adreal Gland</td>
</tr>
<tr>
<td>EB449320</td>
<td>나-944</td>
<td>신장.부신</td>
<td>Kidney Adreal Gland</td>
</tr>
<tr>
<td>EB451020</td>
<td>나-944</td>
<td>전립선,정낭</td>
<td>Prostate Seminal Vesicle (Transrectum)</td>
</tr>
<tr>
<td>EB451320</td>
<td>나-944</td>
<td>전립선,정낭</td>
<td>Prostate Seminal Vesicle (Transrectum)</td>
</tr>
<tr>
<td>EB452020</td>
<td>나-944</td>
<td>전립선,정낭 (경복부로실시할 경우)</td>
<td>Prostate Seminal Vesicle (Transabdominal)</td>
</tr>
<tr>
<td>EB490020</td>
<td>나-948</td>
<td>대동맥 도플러초음파</td>
<td>Aorta Doppler US</td>
</tr>
<tr>
<td>EB561020</td>
<td>나-956가</td>
<td>유도초음파(I)</td>
<td>Guiding US for Procedure</td>
</tr>
<tr>
<td>EB562320</td>
<td>나-956나</td>
<td>유도초음파(II)</td>
<td>Guiding US for Procedure</td>
</tr>
<tr>
<td>EB563020</td>
<td>나-956다</td>
<td>유도초음파(III)</td>
<td>Guiding US for Procedure</td>
</tr>
<tr>
<td>EB564020</td>
<td>나-956라</td>
<td>유도초음파(IV)</td>
<td>Guiding US for Procedure</td>
</tr>
</tbody>
</table>

✅ CEUS 검사 비용 → 일반 초음파 검사비 30% 가산 (도플러: 10%, 소아:20%)
✅ 초음파조영제 급여 진행중 (소노뷰)
✅ 소노뷰급여적용대상: CEUS 검사 행위코드 분류와 동일
Thank you for your attention

Not compatible as contrast agent!