

SF02-S2

Practical Guidelines for HCC Diagnosis Using Sonazoid

09:40-10:00

GBR 103

Chairperson(s): **Jeong Min Lee** (Seoul National University Hospital, Korea)  
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## Development of KSR-KSAR Guidelines for HCC Diagnosis Using Sonazoid: A General Review

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### Introduction

Sonazoid® (perfluorobutane, GE Healthcare, Oslo, Norway), a combined blood-pool and Kupffer-cell agent, different from pure blood-pool contrast agents. Two fundamental questions regarding diagnostic criteria of hepatocellular carcinoma (HCC) on Sonazoid CEUS remained unanswered. One is whether major imaging features of HCC, arterial phase hyperenhancement (APHE) and washout, could be applied in the Sonazoid CEUS. The second question is about the Kupffer phase. To conduct reliable research about Sonazoid, the standardization of terminology and the guideline of CEUS study for the patients at risk of HCC should be established.

In 2021, support from the Korean Society of Radiology (KSR) and the Korean Society of Abdominal Radiology (KSAR), 20 Korean abdominal radiologists with expertise in CEUS contributed to developing the Sonazoid CEUS guideline focusing on the diagnosis of HCC and made guideline statements about eight key questions. It takes about one year (from May 2021 to May 2022) for the guideline development. In addition, it was looked around the related associations such as Korean Association of the Study of Liver (KASL), Korean Liver Cancer Association (KLCA), and Korean Society of Ultrasound in Medicine (KSUM). The goal of this guideline is to provide an evidence-based standard for the diagnosis of HCC using Sonazoid.

### Guideline Development Methodology

#### Searching publication

A systematic literature search of publications in English was performed by an expert radiologist (S.H.C) and an experienced research librarian. The databases used for searching were MEDLINE, EMBASE, and COCHRANE library. The search keywords were set based on the following terms HCC, ultrasound, and Sonazoid (or Kupffer phase). Finally, 241 papers assessed for eligibility were assigned to the literature pool.

#### Recommendation and Evidence levels

##### Recommendation levels

Strongly recommended

Conditionally recommended

##### Evidence levels

I	Systematic review of cross-sectional studies with consistently applied reference standard and blinding
II	Individual cross sectional studies with consistently applied reference standard and blinding
III	Non-consecutive studies, or studies without consistently applied reference standards
IV	Case-control studies or poor or non-independent reference standard

#### Developing key questions

Seven teams (developing groups) developed key questions. Each team looked for relevant pieces of literature from the literature pool (n=241) and

designated the works of literature included in the evidence table. After relevant evidence selection, the total number of pieces of literature finally chosen by the developing groups was 45. All the literature chosen was evaluated by a radiologist who experienced many guideline developments (W.K.J.) using quality assessment of diagnostic accuracy studies-II (QUADAS-II).

### Questions and Recommendations

#### Summary of recommendation statements

### Recommendation statements

Recommendation statements and their levels were made by the developing group based on the chosen evidence. Evidence levels of the statements referred to Oxford Centre for Evidence-based Medicine [4].

### Consensus

For the consensus, two times of consensus meetings were held (Apr 21, 2022, and May 11, 2022) by teleconference (Zoom, Zoom Video

Key Questions	Recommendations	Recommendation level	Evidence level	Agreement
1-1. Is it appropriate that 'nonrim APHE' and 'late (≥ 60 sec) and mild washout' are major imaging features of HCC in Sonazoid CEUS?	Nonrim APHE' and 'late (≥ 60 sec) and mild washout' are an appropriate major imaging features in SZ-US for diagnosing HCC in at-risk patients.	Strongly	2	100% (18/18)
1-2. Can 'Kupffer phase wash-out' be used a major feature of HCC diagnosis using Sonazoid CEUS?	'Kupffer phase wash-out' can be considered as another major imaging feature in SZ-US for diagnosing HCC in at-risk patients if lesions do not show either early or marked washout during the vascular phase.	Conditionally	2	100% (18/18)
2. What is the appropriate diagnostic criteria for diagnosis of HCC using Sonazoid CEUS in the patients at risk?	The diagnosis of HCC can be made in a nodule ≥ 1 cm detected in at-risk patients when 'nonrim arterial phase hyperenhancement' with 'late (≥ 60 seconds) and mild washout' or 'washout in the Kupffer phase' are present.	Conditionally	2	100% (18/18)
3. Can Sonazoid-CEUS be used to characterize inconclusive nodules detected at CT or MRI in patients with high risk for HCC?	Sonazoid-CEUS is useful for the characterization of inconclusive nodules at CT or MRI, as it can detect arterial hypervascularity of nodule in a real-time fashion and show Kupffer cell activity within the nodule.	Conditionally	3	88.9% (16/18)
4. Can Sonazoid CEUS differentiate HCC from non-HCC malignancies in patients at risk?	Sonazoid CEUS is able to differentiate HCC from non-HCC malignancies such as ICC and metastasis.	Conditionally	3	88.8% (16/18)
5. Can Sonazoid-enhanced US be used as a surveillance tool for HCC in patients at risk?	Sonazoid-enhanced US can be used as a surveillance tool in the patients at risk.	Conditionally	3	88.8% (16/18)
6. Is Sonazoid CEUS helpful for the guidance of local ablation therapy for HCC?	Sonazoid CEUS is helpful for the guidance of local ablation therapy by increasing detectability and conspicuity for small inconspicuous HCC on conventional B-mode US.	Strongly	2	100% (18/18)
7. Is it appropriate that treatment response for HCC is assessed with Sonazoid CEUS in the patients who underwent TAC or RFA?	As far as 2 or 3 index tumors that can be observed with CEUS, Sonazoid CEUS is useful to evaluating treatment response after TACE or RFA.	Conditionally	3	94.5% (17/18)

Communications, San Jose, CA). For blinded voting, a web-voting system (Naver office, Korea) was used. All recommendation statements were discussed and approved by all developing members by using the Delphi method. Then, the grade of the agreement was divided into six steps: 1) strongly disagree; 2) disagree with major reservation; 3) disagree with minor reservation; 4) agree with major reservation; 5) agree with minor reservation, and 6) strongly agree. If more than 80% of participants scored either agree with minor reservation or strongly agreed (e.g., 5) or 6)), it was decided that the consensus about the topic was reached, and the recommendation was accepted.

### **Presentation and external evaluation**

The consensus recommendation statements were presented at the annual conference of KSAR on May 21, 2022. And the guideline draft will be evaluated by KLCA and KSUM.

### **Conclusion**

As the number of countries available for Sonazoid CEUS, the number of research is increasing and need for guidelines for diagnostic criteria using Sonazoid CEUS is also growing. This guideline was developed through an in-depth review and fair consensus process by experts in the field by collecting as much of the literature on Sonazoid CEUS published so far, so it would help the clinicians to perform the Sonazoid CEUS for the patients at risk of HCC and make a clinical decision for further treatment.