

Responses to the reviewers

We are very grateful about the reviewers' valuable comments. We believe that these comments have made our manuscript more comprehensible. We have made all the changes as required. We have made the required changes in the main text, abstract, references, legends and figures. We tracked the changes in the text.

Reviewer 1: Specific Comments to Authors: Contrast-enhanced ultrasound (CEUS) represents a significant breakthrough in ultrasonography (US), and it is being increasingly used for the evaluation of focal liver lesions (FLLs). CEUS is unique in that it allows non-invasive assessment of liver perfusion in real time throughout the vascular phase, which has led to dramatic improvements in the diagnostic accuracy of US in the detection and characterization of FLLs, the choice of therapeutic procedures, and the evaluation of response. CEUS is sensitive in detecting small MLC and provides information of tumor features, such as size, number, location, focal infiltration, central necrosis and blood supply. This information is critically helpful in selecting candidates and planning protocol for RFA. Therefore, CEUS may serve as an important auxiliary method for RFA in improving the tumor necrosis outcome and reducing recurrence rate of RFA in MLC. The treatment efficiency of local thermal ablation therapy (including through percutaneous, laparoscopic or intraoperative approaches) on hepatic malignant tumors, both HCC and liver metastases, has been emphasized and affirmed. Unenhanced US is commonly used to guide ablation it is easy to use and widely available. However, CEUS can provide more important information and plays a more significant role in ablation therapy. Therefore, author should write the relationship between CEUS and RFA.

Reply: Thanks for your professional comments and questions. We have added the relationship between CEUS and RFA to the manuscript (Discussion, second paragraph). The details are as follows:

The majority of HCCs are not suitable for curative resection at the time of treatment, and difficulties of surgical resection may be related to size, site, and number of tumors, vascular and extrahepatic involvement as well as liver function of the patient (Minami Y, Kudo M. *Review of dynamic contrast-enhanced ultrasound guidance in ablation therapy for hepatocellular carcinoma. World J Gastroenterol.* 2011;17(45):4952-4959. PMID: 22174544. doi:10.3748/wjg.v17.i45.4952).

Radiofrequency ablation (RFA) is another effective treatment for liver cancer, which have emerged in clinical practice to expand the pool of patients considered for liver-directed therapies (Shiina S, Teratani T, Obi S, Hamamura K, Koike Y, Omata M. *Nonsurgical treatment of hepatocellular carcinoma: from percutaneous ethanol injection therapy and percutaneous microwave coagulation therapy to radiofrequency ablation. Oncology.* 2002;62 Suppl 1:64-68. PMID: 11868788.

doi:10.1159/000048278). Traditionally, RFA is usually performed under B-mode US guidance. In recent years, some scholars have reported the treatment technique of RFA guided by CEUS for HCC. Miyamoto et al. exhibited the complete ablation rate after a single treatment session was significantly higher in CEUS group than in the B-mode US group (Miyamoto N, Hiramatsu K, Tsuchiya K, Sato Y. *Contrast-enhanced sonography-guided radiofrequency ablation for the local recurrence of previously treated hepatocellular carcinoma undetected by B-mode sonography. J Clin Ultrasound.* 2010;38(7):339-345. PMID: 20572066. doi:10.1002/jcu.20720).

Moreover, Masuzaki et al. reported in a large-scale study that the detectability of tumor nodules was 83.5% in B-mode US and 93.2% in CEUS ($P = 0.04$) (Masuzaki R, Shiina S, Tateishi R, et al. *Utility of contrast-enhanced ultrasonography with Sonazoid in radiofrequency ablation for hepatocellular carcinoma. J Gastroenterol Hepatol.* 2011;26(4):759-764. PMID: 21054516. doi:10.1111/j.1440-

1746.2010.06559.x). Therefore, the use of CEUS guidance in RFA for liver cancer is an efficient approach. (Page 12-13)

Reviewer 2:

1. Results, first paragraph: "Approximately 22 of the remaining studies were

removed" – what is meant by "approximately" in this context?

Reply: Thanks for your professional comments and questions. According to the standard of retrieval literature, the word of “approximately” is redundant. The replacement sentence is as follows: “Twenty-two of the remaining studies were removed, including 19 articles that were unrelated to the field of interest and 3 review articles.” (Page 9)

2. Please check the numbers (Table 1: "48" + "228" is not "272").

Reply: Thank you for your careful review. We are sorry for the error in recording data. The error in the table has been corrected.

First Author	Publication Year	Country	Study Design	Enrollment Method	US System	Number of Patients (Male/Female)	Age (Mean Year \pm SD)	Number of FLLS (Benign/Malignant)	LI-RADS Version	Reference Standard
Hai-Qing Chen	2017	China	Retrospective	Consecutive	Hitachi HI VISION Preirus; Siemens S3000 Siemens S2000; GE	377 (207/170)	43.56 \pm 11.48	429 (96/333)	2016	Pathology and SCRS
Barbara Schellhaas	2018	Germany	Retrospective	Consecutive	Logiq E9; Toshiba Aplio 500	55 (44/11)	65.90 (53 - 86) ^a	55 (5/50)	2016	Pathology and SCRS
Wen-Wu Ling	2018	China	Retrospective	Consecutive	Philips IU22	56 (44/12)	52.5 ^b	56 (10/46)	2016	Pathology
Qian-Yu Liu	2019	China	Prospective	Consecutive	Philips IU22; Toshiba Aplio 500	82 (61/21)	58.15 \pm 10.97	82 (34/48)	2017	Pathology and SCRS
Ya-Nan Zhou	2019	China	Retrospective	Consecutive	GE Logiq E9	241 (166/75)	56 \pm 10	272 (44/228)	2016	Pathology and SCRS
Zehao Tan	2020	Singapore	Retrospective	Selective	GE Logiq E9; Toshiba Aplio 500	45 (32/13)	63.1 (34 - 84)	46 (9/37)	2017	Pathology and SCRS
Jia-Yu Wang	2020	China	Retrospective	Consecutive	Hitachi Hi Vision Avius	258 (200/58)	52 \pm 11	355 (235/120)	2017	Pathology and SCRS
Xin-Wu Cui ^c	2020	China	Retrospective	Selective	Hitachi Hi Vision Avius	63 (47/16)	56 \pm 8	84 (35/49)	2017	Pathology and SCRS

Note. US: ultrasound; SCRS: synthesized clinical reference standard

a: this study only included age range and mean. b: this study used the median of age.

3. Figure 1: From this figure, it is not clear how the reduction from 54 to 35 records was done.

Reply: Thanks for your advice. This part of Figure 1 has been supplemented. The modified picture is as follows:

5. Discussion, fifth paragraph: "Barbara Schellhaas et al. used 3 reviewers for interobserver agreement and achieved a satisfactory Kappa value using pairwise comparisons, which is a lower kappa value than the other articles" – "Kappa value"/"kappa value" – please be consistent.

Reply: This sentence was revised. "Barbara Schellhaas et al. used 3 reviewers for interobserver agreement and achieved a satisfactory Kappa value using pairwise comparisons, which is a lower Kappa value than the other articles (0.39 vs 0.79, $p < 0.01$)."

 (Page 13)

6. References: Parts of the reference list are not according to the guidelines of the journal.

Reply: Thanks for your advice. We checked the references, and supplement PMID and DOI numbers to some references. However, three references in this article are dissertations from the database of China National Knowledge Infrastructure (CNKI), which did not have PMID and DOI numbers. In this paper, meta-analysis needs to calculate these references. According to *Guidelines for Manuscript Preparation and Submission: Meta-Analysis*, we have provided a printed copy of the first page of each article and upload them as the supplementary material.

Three dissertations are as follow:

1. Chen H-Q. The Clinical Application of Liver Ultrasound Imaging Reporting and Date System Classification Method of Liver Occupying Lesions. Fujian Medical University, 2017
 2. Liu Q-Y. The clinical application Value of liver imaging reporting and data system with contrast-enhanced ultrasound in the diagnosis of hepatocellular carcinoma. Zhengzhou University, 2019
 3. Zhou Y-N. Contrast-enhanced ultrasound (CEUS) liver imaging reporting and data system (LI-RADS) LR-5 for Hepatocellular carcinoma-diagnostic value in clinical practice. Jilin University, 2019
7. Some language polishing is recommended (e.g., Figure 1: "repeat published"; Discussion, third paragraph: "Notably, the CEUS LI-RADS criteria require consideration of the combination two major features to distinguish benign and

malignant FLLs, arterial phase hyperenhancement (APHE) and washout"; Discussion, fifth paragraph: "The low Kappa value may because the calculation of Kappa relies on the assumption that a significant proportion of agreement is due to chance, and if a feature is observed very frequently, then a low Kappa value between the observers results"; Discussion, eighth paragraph: "Notably, substantial interobserver agreements for LI-RADS categorization on CEUS were observed i LI-RADS version 2016 and version 2017").

Reply: Thank you for your careful review. These sentences all have been revised in manuscript, which have been marked in red.

- (1). Repeated "Figure 1" has been delete.
- (2). "Notably, the CEUS LI-RADS criteria...hyperenhancement (APHE) and washout" has been revised to "Notably, the CEUS LI-RADS criteria requires the combination of two major features, including arterial phase hyperenhancement (APHE) and washout, to distinguish benign and malignant FLLs.". (Page 13)
- (3). "The low Kappa value may...the observers results" has been revised to "The low Kappa value may be because the calculation of Kappa relies on the assumption that a significant proportion of agreement is due to chance, and if a feature is observed very frequently, then a low Kappa value between the observers results.". (Page 13)
- (4). "Notably...and version 2017" has been revised to "Notably, reliable interobserver agreements for LI-RADS categorization on CEUS were also observed LI-RADS version 2016 and version 2017 (0.74 vs 0.78, $p = 0.66$).". (Page 14)