

Reviewer #1:

**Scientific Quality:** Grade B (Very good)

**Language Quality:** Grade A (Priority publishing)

**Conclusion:** Minor revision

**Specific Comments to Authors:** The authors have presented significant insights and data that support the role of contrast-enhanced ultrasonography in HCC treatment. Below are some comments that the authors are required to revise in order to improve the quality of the review:

1. Abstract: there should be no reference and in-text citation; kindly remove. Also, punctuations should be revised.

Response: thank you for the comment. We have deleted the reference. We have also revised the punctuations.

2. a. Introduction part should be named background.

Response: thank you for the comment. We have renamed the Introduction part as requested (Background)

b. "Unfortunately, HCC, still today, is a pathology with a great mortality and morbidity, even with great efforts in term of primary prevention, surveillance and multidisciplinary approach" paragraph needs to be rephrased and cited.

Response: thank you for the comment. We have changed the following paragraph:

*"Unfortunately, HCC, still today, is a pathology with a great mortality and morbidity, even with great efforts in term of primary prevention, surveillance and multidisciplinary approach"*

Into:

“Unfortunately, HCC is known to be a multicentric tumor, often with a poor prognosis. Despite great efforts in term of primary prevention, surveillance and multidisciplinary approach, incidence and mortality continue to rise <sup>[4-6, 37]</sup>.”

We have also added the following reference

4. **Balogh J**, Victor III D, Asham EH, Burroughs SG, Boktour M, Saharia A, Li X, Ghobrial RM, Monsour Jr HP. Hepatocellular carcinoma: a review. *J Hepatocell Carcinoma*. 2016;3:41-5 <https://doi.org/10.2147/JHC.S61146>

6. **El-Serag HB**. Hepatocellular carcinoma. *N Engl J Med*. 2011; **365**:1118-27. [PMID: 21992124. doi: 10.1056/NEJMra1001683.]

37. **Llovet JM**, Real MI, Montaña X, Planas R, Coll S, Aponte J, Ayuso C, Sala M, Muchart J, Solà R, Rodés J, Bruix J; Barcelona Liver Cancer Group. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002 ;**359**:1734-9. [PMID: 12049862. doi: 10.1016/S0140-6736(02)08649-X]

c. "RFA induces thermal injury to tumoral tissue by creating resistive ionic heating (50 - 100°)", the authors need to specify the type of temperature measuring scale.

Response: thank you for the comment. We have added the symbol C, standing for “centigrade” according to the International Measurement System

3. Authors did not specify the figures (2 and 3) locations in-text.

Response: thank you for the comment. We have specified the figure (2 and 3) locations in-text

4. number of references need to be updated, if possible.

Response: thank you for the comment, we updated the number of references.

5. As it is a review, it should include even a brief background about HCC as a disease and pathophysiology.

Response: thank you for the interesting comment. As requested, we have added the following sentences as well as the pertaining references:

“It occurred more often in males than females (2,4:1) and the worldwide incidence is heterogeneous because of the variable prevalence of the risk factors, with a higher incidence in Eastern and Southern Asia and Middle and Western Africa [6].

Chronic liver disease and cirrhosis remains the most important risk factor for the development of HCC regardless of etiology. Hepatitis B and C, alcohol and nonalcoholic fatty liver disease, autoimmune or genetic conditions, are independent risk factors for the development of cirrhosis. [3, 4].

Development of HCC is a complicated multistep process that involves inflammatory liver damage, hepatocyte necrosis and regeneration and fibrotic deposition, leading to increasing liver function impairment. The accumulation of somatic genomic alterations in addition to epigenetic changes runs in parallel with the progression to low-grade dysplastic nodules, high-grade dysplastic nodules, early HCC and advanced HCC. [6].

Also, should state LRT in the era of any other therapy such as targeted and immunotherapy and how it could help.

Response: thank you for the very interesting comment. As requested, we have added the following sentences as well as the pertaining references:

“Finally, much hope has been placed in the recognition of novel targets and prognosis predictors through molecular profiling. The combinations of immunotherapy with LRT are under investigation, representing a promising treatment strategy in advanced HCC <sup>[10]</sup>. In several preclinical studies this combination has demonstrated increased antitumor immune response due to LRTs effect to increment tumor immunogenicity by inducing inflammation and by releasing tumor-associated antigens. <sup>[11 - 12]</sup>.

Furthermore, observational and small non-randomized studies have demonstrated the safety of TACE in combination with sorafenib, with manageable toxicities, in patients with intermediate stage HCC and good liver function. However, the combination did not provide meaningful clinical benefit compared with DEB-TACE alone <sup>[13]</sup>”.

Reviewer #2:

**Scientific Quality:** Grade B (Very good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Minor revision

**Specific Comments to Authors:** Very well written paper. few minor edits, but otherwise, excellent topic. Page 7 last paragraph: "The enhanced area around the tumor may obscured by the artifacts created from the dense accumulation of the ethiodized oil in TACE", please add "be" next to may "be" obscured. Page 11:

Response: thank you for the comment. We added “be” next to may “be” obscured.

"We think 3D CEUS is an increasingly technique". Increasingly what?

Response: thank you for the comment. We added "used" at the sentence: "We think 3D CEUS is an increasingly used technique"

**1) *Science editor:*** 1 Scientific quality: The manuscript describes a minireview of the loco-regional treatment of hepatocellular carcinoma. The topic is within the scope of the WJH. (1) Classification: Two Grades B; (2) Summary of the Peer-Review Report: The authors have presented significant insights and data that support the role of contrast-enhanced ultrasonography in HCC treatment. The questions raised by the reviewers should be answered; (3) Format: There are 3 figures; (4) References: A total of 53 references are cited, including 17 references published in the last 3 years; (5) Self-cited references: There are 6 self-cited references. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations (i.e. those that are most closely related to the topic of the manuscript) and remove all other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated; and (6) References recommendations: The authors have the right to refuse to cite improper references recommended by the peer reviewer(s), especially references published by the peer reviewer(s) him/herself (themselves). If the authors find the peer reviewer(s) request for the authors to cite improper references published by him/herself (themselves), please send the peer reviewer's ID number to [editorialoffice@wjgnet.com](mailto:editorialoffice@wjgnet.com). The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately. 2 Language evaluation: Classification: Grade A and Grade B. 3 Academic norms and rules: No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an invited manuscript. No financial support was obtained for the study. The topic has not previously been published in the WJH. 5 Issues raised: (1) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; and (2) If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide

documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, “Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]”. And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable. 6 Recommendation: Conditional acceptance.

**(2) Editorial office director:**

**(3) Company editor-in-chief:** I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Hepatology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office’s comments and the Criteria for Manuscript Revision by Authors.