

Responses to Reviewers' comments

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1. Manuscript ID: [WJG_42301_R1](#)
2. Manuscript title: [Percutaneous ablation for perivascular hepatocellular carcinoma: Refining the current status based on emerging evidence and future perspectives](#)

Comments to the Author:

Reviewer 1: While the authors provide several valid points regarding various modalities of HCC ablation, I have several concerns with this review

R1-1) There is no mention of the relative ubiquity of the 4 described ablation technologies as they relate to modern practice. For example, in our opinion, in the United States, cryoablation is of historical interest only. Similarly, RFA is gradually losing ground to microwave ablation, which has proven to be superior in ablating liver lesions. This review presents these technologies as equally viable options, albeit with their individual strengths and weaknesses. A review of which techniques are actually being used would be a vital component of this discussion.

→ We also agree that microwave ablation is superior to other ablation methods for ablating large tumors. However, RF ablation and cryoablation are still being widely used worldwide and we think that they may be still effective for small hepatic tumor (less than 2 or 3 cm). According to the most recent 2018 EASL guidelines (J Hepatol 2018; 69: 182-236), only RF ablation is the standard of care for patients with BCLC 0 and A tumors that are not suitable for surgery and liver transplantation. Although microwave ablation showed promising results for local tumor control and survival, the evidence is still low due to relatively low number of published reports.

Various ablation techniques that can curatively treat HCC have been developed that need to be available in each center dealing with HCC in order to maximize the chance of curative treatment if possible. Moreover, we are also observing a change in paradigm in the role of ablation in the complex discussion of curative treatment. Overall, the question of RF ablation, cryoablation, and microwave ablation should not be seen as a cause for disagreement but rather as a puzzle for personalized medicine that will lead to a safe curative treatment.

R1-2) The authors briefly touch on the technical workings of the 4 discussed modalities, but

give no sense to how they have evolved and are evolving over time. There are many, exciting new developments in the newer generation devices, but these are not addressed at all. A discussion to this effect would illuminate the ways in which readers can expect ablation to affect their practices in the coming years.

→ During the manuscript editing, we wanted to give the information regarding recent clinical outcomes of various ablation methods rather than describing detailed historical technical advances of the ablation treatments. As you recommended, we added the brief history of technical advances of cryoablation and microwave ablation to the manuscript (R1-2). The advanced of RF ablation was already described in our manuscript.

R1-3) The authors present ablation as a "non surgical" percutaneous technique. While it is true that many centers (to varying degrees depending on the country in question) relegate ablation to interventional radiology departments, many surgeons are actively employing RFA and microwave ablation in conjunction with intraoperative ultrasound (either via laparoscopy or laparotomy). Percutaneous vs. surgical ablation is a contentious issue, and one that mandates mention in a review of this kind.

→ As you pointed out, we also perform intraoperative RF ablation via laparoscopy with surgeon' assistance, especially for subcapsular tumors. If the topic of this review is overview of ablation treatment, comparison of the approach methods for ablation would be an important issue.

However, in cases of perivascular tumors, laparoscopic approach is relatively limited due to difficulty of tumor localization. So, we mainly focused on the percutaneous treatment of perivascular tumors in this review. In addition, based on the previous meta-analysis investigating the approach methods of ablation treatment, percutaneous approach is mainly performed for minimal invasiveness (Ann Surg 2005;242:158–171). This meta-analysis study included ninety-five independent series of 5,224 treated liver tumors. Tumors were coagulated percutaneously (67.9%), laparoscopically (11.6%), or by laparotomy (20.5%).

Reviewer 2: The authors made a great effort preparing and writing this article. Here are some comments: the current study included most available percutaneous treatment methods available for perivascular HCC. it is important for clinicians to compare available treatment

options then deciding the best for their patients and searching behind it guided by this manuscript.

Title. Yes, the title reflect the main subject/hypothesis of the manuscript

Abstract. Yes, the abstract summarize and reflect the work described in the manuscript

Key words. Yes, the key words reflect the focus of the manuscript

Background. Yes, the manuscript adequately describe the background, present status and significance of the study Yes, the manuscript is highlighting the key points concisely, clearly and logically. They are accurate and discuss the paper's scientific significance with relevance to clinical practice sufficiently the figures, are of good quality and appropriately illustrative of the paper contents the manuscript cite appropriately the latest, important and authoritative references the manuscript is well, concisely and coherently organized and presented? Is the style, language and grammar accurate and appropriate? There is no page number in the manuscript to refer to thus iam mentioning the paragraphs

R2-1) The authors mentioned that: RF or microwave ablation uses thermal energy from the RF electric current or microwave field to destroy cancer cells.[12] However, when the index tumor is near large blood vessels, the blood flow carries thermal energy away from the targeted tissue, resulting in reduced ablation volume; this considerably modifies the size and shape of the ablation zone, especially during RF ablation. The authors should mention here that heat sink effect is much less in MWA.

→ We already described the relative advantage of MWA over RF ablation in terms of “heat-sink effect” due to difference of physical activity in the section “Microwave ablation”.

R2-2) The authors mentioned that: post-operative adjuvant transarterial chemoembolization (TACE) after surgical resection improved outcomes among patients who exhibit HCC with microvascular invasion, there remains uncertainty with respect to adjuvant therapy after curative treatment for HCC, with either micro- or macro-vascular invasion because a potent anticancer drug for HCC is not well established in clinical practice. Is there a role for adjuvant TACE in combination with microwave ablation in perivascular tumors?

→ Yes, we also think combination of TACE and microwave ablation can be a problem

solving tool for perivascular tumor with regard to decrease in heat sink effect. We added corresponding issue to the Section of microwave ablation for more clarification of the manuscript (R2-2). Although several retrospective case series were reported investigating this method, there was no study regarding adjuvant TACE in combination with microwave ablation in perivascular tumors. So, the clinical significance of the corresponding treatment still uncertain.

R2-3) The authors mentioned that: considering the more powerful ablation performance of microwave ablation, relative to RF ablation, microwave ablation may be more vulnerable to the risk of vascular complications. Thus far, there has been no study directly comparing RF ablation and microwave ablation for perivascular HCCs. In addition, whether the ability of microwave ablation to induce a broader ablation zone can lead to a real survival benefit remains unclear. As there is no study yet to confirm that microwave ablation may be more vulnerable to the risk of vascular complications, I think the authors should take this with caution as in experienced hands this should not happen.

→ In general, microwave ablation can create much larger ablation zones. Thus, theoretically there may be increased risk of vascular complications when perivascular tumor is treated with microwave ablation. As you recommended, we deleted the corresponding contents based on our anecdotal evidence (R2-3).

R2-4) In the conclusion: To overcome these potential risks, a modified RF ablation technique, cryoablation, or combined treatment with TACE have been used recently Add microwave ablation in the conclusion, it is now an alternative guideline to RFA since EASL 2018.

→ We agree with your opinion. We added it to the corresponding sentence (R2-4).

Reviewer 3: A well-written and exhaustive review on a topic of high interest for interventional oncologists.

R3-1) I have just a minor suggestion: please, add to the conclusions some consideration about

the potential prospective role of microwasve ablation of perivascular tumors.

→ We added it as you suggested (R3-1).

Thank you!