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Editors-in-Chief

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Dear Editors:

Thank you for your comments and efforts concerning our manuscript entitled:
“Application of Ablative Therapy for Intrahepatic Recurrent Hepatocellular Carcinoma following Hepatectomy” (No. 80161)

The comments are all valuable and helpful for revising and improving our paper. We have studied the comments carefully and have made the following point-by-point modifications to the manuscript (our responses are shown in blue):

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors:

1.It is a well written article. A good summary of ablative techniques. But MWA is more widely used due to its advantages. You may write it in more detail.

Response: Thank you for your valuable advice. We added the technique improvement of different generation MWA in more detail in part of “Microwave ablation (MWA)”.

2.And comparative results of ablative techniques may be mentioned in article.

Response: Thank you for your comment. The advantages and limitations of different techniques have been briefly discussed in each technique section. And we added Table1 to summary characteristics of different ablation modalities.

Table1 Description characteristics of different ablation modalities.

Ablation modalities	Advantages	Limitations
RFA[13, 14]	●Most widely used and mature technology	●Limited zone of monopolar centrifugal ablation

MWA[13, 14]	<ul style="list-style-type: none"> •Multibipolar RFA for larger and more modulable ablation zones •Higher temperature and faster heating of larger target over RFA •Less sensitive to heat sink effect •Less influenced by tissue conductance 	<ul style="list-style-type: none"> •Sensitive to heat sink effect •Influenced by tissue conductance •Complex and technically demanding operation •Thermal injury from higher temperature
PEI[41]	<ul style="list-style-type: none"> •Simple to perform, inexpensive •Chemo-ablation: no thermal injury 	<ul style="list-style-type: none"> •Small size of ablation zone •High local recurrence rate
HIFU[46]	<ul style="list-style-type: none"> •Noninvasive operation: no worry of needle tract seeding 	<ul style="list-style-type: none"> •Time consuming •Influenced by ultrasound propagation and artifacts, respiration motion •Burns from high-intensity ultrasound
CRA[13, 47]	<ul style="list-style-type: none"> •Less pain •Well-visualized ice ball on imaging for precise monitoring 	<ul style="list-style-type: none"> •High cost •Cryoshock (more often in early device)
IRE[13, 14]	<ul style="list-style-type: none"> •Nonthermal ablation: low risk of thermal injury •Less sensitive to heat-sink effect •Well preserved connective tissue, blood vessels and bile ducts •Less frequent liver failure 	<ul style="list-style-type: none"> •Risk of myoclonia and arrhythmias •Limited clinical data

RFA, radiofrequency ablation; MWA, microwave ablation; PEI, percutaneous ethanol injection; HIFU, high-intensity focused ultrasound ablation; CRA, cryoablation; IRE, Irreversible electroporation.

3. Microwave ablation (MWA) was developed several years after RFA had become established as the nonsurgical standard of care for early HCC.

Response: Thank you for your comment. We agree that microwave ablation (MWA) is an emerging alternative modality to RFA and has become established as the nonsurgical standard of care for early HCC. So we written it more detail about the technique improvement of different generation MWA in part of “Microwave ablation (MWA)”.

Reviewer #2:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: I read with interest the article by Rong Cong et al "Application of Ablative Therapy for Intrahepatic Recurrent Hepatocellular Carcinoma after Hepatectomy", in which the authors make a narrative review of this interesting topic. This is a very good review, with very good definitions, and includes many options for the management of recurrence of HCC after surgical resection. There are good explanations of various percutaneous options that address this common scenario in HCC. The order of the presentation, the main techniques and the references are very well presented.

[Response: Thank you for your positive comment.](#)

Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: The purpose of this article is to review ablation for recurrent hepatocellular carcinoma. The authors have reviewed a great deal of literature and have written in much more detail. However, this article still has several problems that need to be addressed.

1.Many techniques or principles introduced in the article are not cited with references, and the authors should recheck the article in detail.

[Response: Thank you for your suggestions. Some references of techniques or principles were cited at the end of the whole paragraph previously. In addition, we have added more references to introduce the technique and principles.](#)

[Reference 12: Hong K, Georgiades C. Radiofrequency ablation: mechanism of action and devices. J Vasc Interv Radiol 2010; 21\(8 Suppl\): S179-186 \[PMID: 20656227 DOI: 10.1016/j.jvir.2010.04.008\]](#)

[Reference 33: Lubner MG, Brace CL, Hinshaw JL, Lee FT, Jr. Microwave tumor ablation: mechanism of action, clinical results, and devices. J Vasc Interv Radiol 2010; 21\(8 Suppl\): S192-203 \[PMID: 20656229 PMCID: PMC3065977 DOI: 10.1016/j.jvir.2010.04.007\]](#)

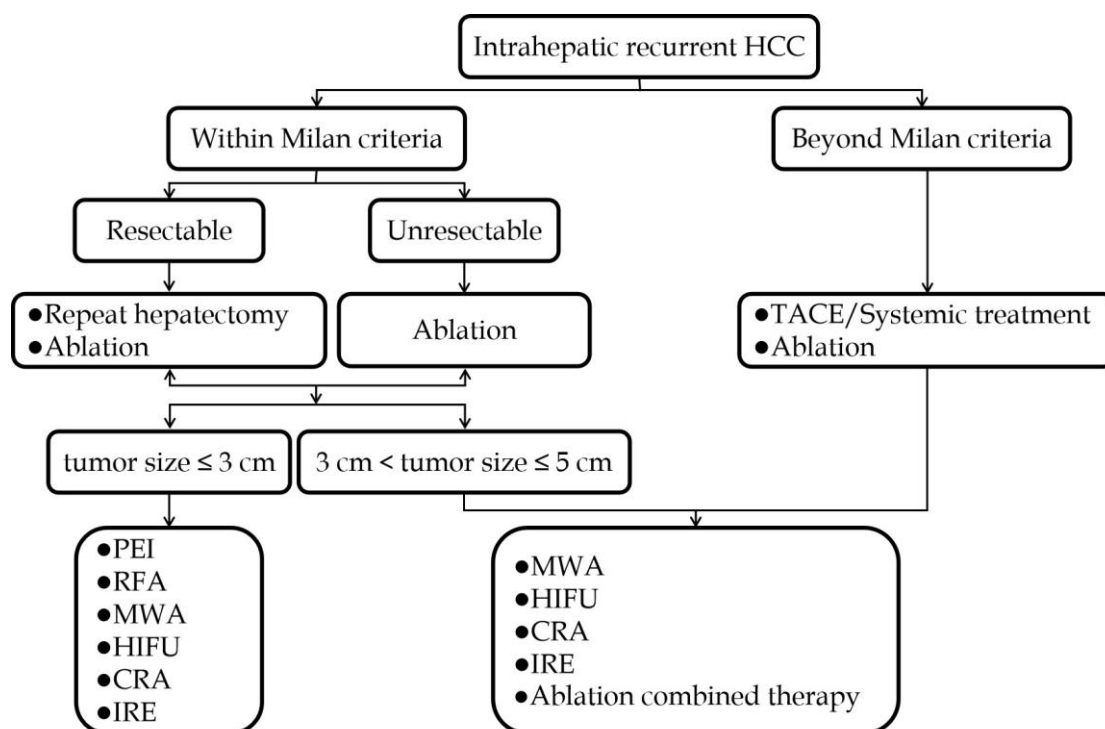
[Reference 43: Feng W, Wang ZB, Chen WZ, Hui Z, Jin B, Zou JZ, Li KQ, Jin CB, Xie FL, Su HB. Extracorporeal high intensity focused ultrasound ablation in the treatment of patients with large hepatocellular carcinoma. Annals of Surgical Oncology 2004; 11\(12\): 1061-1069 \[PMID: WOS:000225475400007 DOI: 10.1245/aso.2004.02.026\]](#)

2.It is difficult for me to quickly understand the focus of the article based on the descriptions of multiple techniques and comparisons of different treatment options presented in the article. It would be helpful if the authors divided the article into several parts and summarized the key points in each part clearly and concisely.

Response: Thank you for your advice. This minireview aimed to review the current experience on different ablation modalities in treating recurrent HCC, so we divided the article into these parts. We have bolded the title and subtitle and added Table1 to summary characteristics of different ablation modalities for clear show.

3.The meaning of Figure 1 is not clear. Please explain each box's meaning and the picture's meaning, and add a legend.

Response: Thank you for your valuable advice. We have modified the figure for clearly demonstrating the current potential role of ablation in intrahepatic recurrent HCC.



4.Overall, this paper has not yet reached the requirements of publication and needs to be revised as a whole, such as the logic and innovation of the article.

Response: Thank you for your comment. We revised the manuscript carefully, including its logic and innovation.

Reviewer #4:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors:

1.This manuscript is interesting in revising this topic, however minor language editing is required.

Response: Thank you for your comment. We sent our manuscript to Editage LTD. and had a native language editing again.

2.Additional adding some data about management of recurrent HCC with post surgical resection decompensation could be improve the quality of this manuscript based on the importance of liver decompensation post HCC resection.

Response: Thank you for your valuable advice. Decompensation post HCC resection exactly needs to be taken into account, especially for recurrent HCC with probably inadequate residual liver volume. Furthermore, the ablation modalities could be the appropriate method for the recurrent HCC instead of repeat hepatectomy. Therefore, we added the details into our "Introduction".

Reviewer #5:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: The authors summarized the application of ablative therapy for intrahepatic recurrent hepatocellular carcinoma following hepatectomy. The paper is well written; however, the paper lacks a bold message. Here are the comments.

1.Local ablation therapy can also be applied for treatment-naïve HCC. The authors did not emphasize enough why they focused on recurrent HCC.

Response: Thank you for your comment. As you said, local ablation therapy has been well applied for treatment-naïve HCC. However, we received the topic from the BPG as follow "Treatment strategy of recurrent hepatocellular carcinoma". Therefore, this minireview just focus on recurrent HCC.

2.The authors can refer to specific post-operative conditions such as adhesion to the GI tract and skin operation scars.

Response: Thank you for your valuable advice. Considering that postoperative intra-abdominal adhesions increase difficulty of re-resection,

only a small part of well-selected patients can receive secondary surgery in clinical practice. We have mentioned this key point in “Introduction” as the limitation of repeat hepatectomy.

3.Second generation of MWA should be mentioned compared to previous version.

Response: Thank you for your valuable advice. We have added the technique improvement of different generation MWA in more detail in part of “Microwave ablation (MWA)”.

4.Surgical resection for a recurrent HCC should be mentioned.

Response: Thank you for your comment. The minireview focuses on application of ablative therapy for intrahepatic recurrent HCC. We mentioned the limitation of repeat resection and comparison between surgery and RFA in “Introduction” and “Radiofrequency ablation(RFA)”.

5.The mechanism and literature of HIFU and IRE can be described in more detail since they are still not approved and available in most countries.

Response: Thank you for your comment. This minireview aims to review the current experience on different ablation modalities in treating recurrent HCC. As you said, HIFU and IRE have not get widespread adoption yet, and there was limited experience published .

We introduced the mechanism of HIFU as follow: “HIFU ablation is an extracorporeal conformal therapy that can achieve heat-induced coagulation necrosis without the need for surgical exposure or probe insertion. Heat generation is mediated by focusing high-intensity ultrasound beams on the target using the extracorporeal motion of a multi-element ultrasound transducer. HIFU, which is noninvasive and conformal, can ablate a large volume of tumor with no worry of tumor seeding along the needle tract”, “HIFU have not get widespread adoption yet, probably as ultrasound propagation influenced by different tissues, ultrasound artifacts and respiration motion add time consumption and technical challenge relative to other ablation modalities”

We introduced the mechanism of IRE as follow: “IRE works by short pulses of high intensity delivered between two electrodes (convergent centripetal technique), which produce irreversible pores in the cellular bilayer membrane for cell death, while the connective tissue, blood vessels, and bile ducts are preserved. It is a nonthermal ablative method with no influence of the “heat-sink effect”, a lower risk of thermal injury, and less frequent liver failure”

6.Lastly, TKI and ICI should be mentioned for the treatment of HCC combined with local ablative therapy.

Response: Thank you for your valuable advice. We added the part of “RFA and systemic treatment” in combination therapy as follow: “The combination with systemic therapy has been considered effective to impede rapid progression of residual tumors due to inadequate RFA and control advanced HCC[56]. Peng et al.[57] investigated the role of Sorafenib combined with TACE-RFA in the treatment of advanced RHCC after initial hepatectomy and proved its safety, efficacy and superior survival outcomes over sorafenib alone. These benefits might be due to Sorafenib suppressing angiogenesis induced by TACE or inadequate RFA. The combination of RFA and immunotherapy is also considered rationale. Ablation boosts the T cell immune response to improve the efficacy of immunotherapy and immune checkpoint inhibitors block immune escape to reduce recurrence after ablation[58]. A retrospective study[59] reported that patients with RHCC had significantly better RFS and OS outcomes in the RFA plus anti-PD-1 group than in the RFA alone group. However, additional trials are required to confirm these interesting findings.”

Reviewer #6:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: 20220927 Reviewer on F6Publishing

1.You focused on ablation in treating RHCC. Why do you exclude surgical resections in treating RHCC? Surgery might be still effective in treating RHCC, which especially existing the limited intrahepatic area. You should add the negative aspects of hepatic surgeries in the introduction part more clearly.

Response: Thank you for your comment. This minireview aims to review the current experience on different ablation modalities in treating recurrent HCC. The negative aspect of surgery has been rewritten more clearly in “ Introduction” according to reviewer #4 and reviewer #5.

2.You mentioned, “other available ablative techniques” in this article. It includes MWA, PEI, HIFU, CRA, and IRE. Those treatment options are not popular depending on the country, and fewer evidence that show clinical efficacy. You should make sure and revise these parts.

Response: Thank you for your comment. This minireview aims to review the current experience on different ablation modalities in treating recurrent HCC.

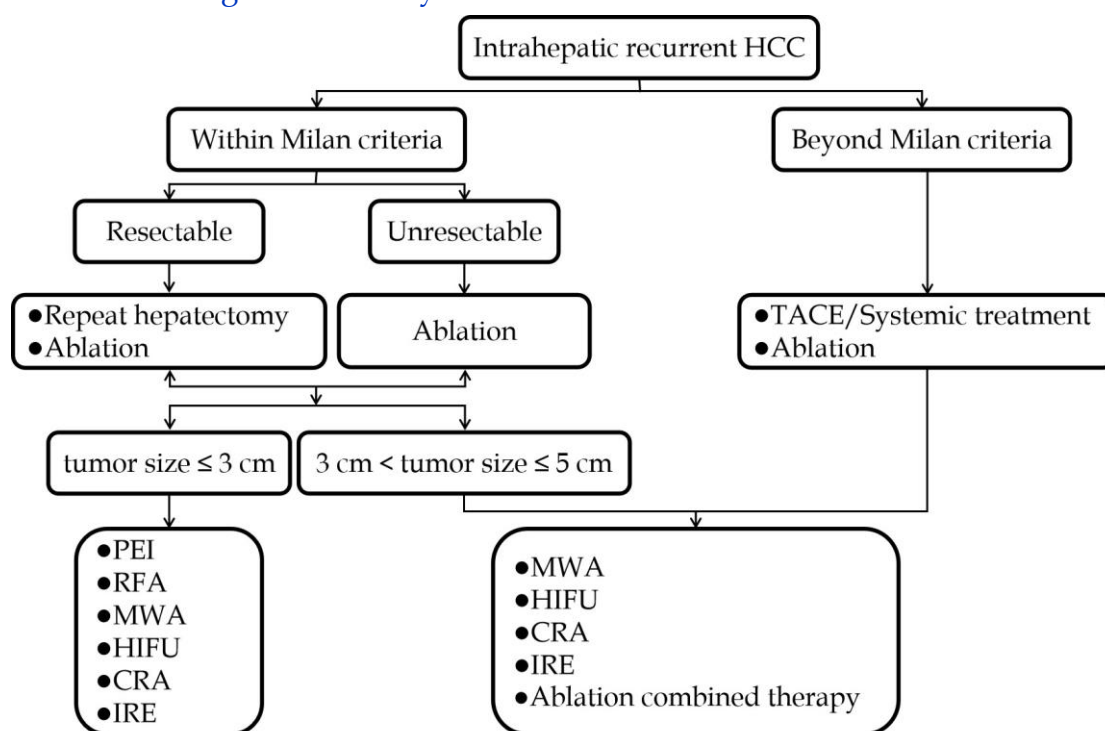
As you said, the other available ablative techniques have not get widespread adoption yet , but there have been limited experience published previously. So we mentioned these parts in this artical and expected more evidence. We will pay more attention to those fields and follow-up newly published articles to improve our understanding.

3.You also explained ablation combination therapy as an treatment option for RHCC. Those may not develop efficacy and safty by the phase III trials. You could make sure these parts and revise better explanation.

Response: Thank you for your comment. This minireview aims to review the current experience on different ablation modalities in treating recurrent HCC. We reviewed current clinical data on ablation combination therapy for recurrent HCC and added the content of systemetic treatment according to reviewer #5.

4.Figure 1 is hard to understand if I look it as a hepatology expart. Because most part of the treatment options are immature or have less evedences for efficacy and safety. You could make sure these parts and revise better explanation.

Response: Thank you for your comment. The figure aims to demonstrate the current potential role of ablation in intrahepatic recurrent HCC. We have modified the figure for clearly show.



We very much appreciate the Editor's and Reviewers' helpful comments, and hope

that the amendments will be acceptable.

Yours sincerely,

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