

Point-by-Point Responses

Manuscript ID: 81125

Title: Ablative Strategies for Recurrent Hepatocellular Carcinoma

Dear editor,

Thanks very much for giving us the opportunity to revise and resubmit our manuscript (81125). We really appreciated your and the reviewers' helpful comments. We have carefully revised our manuscript as you suggested to improve the quality of the manuscript.

In response to the reviewers' comments, we have revised the original manuscript in the following ways:

1. We have clarified all the questions raised by the reviewers.
2. Following the reviewers' comments, we have improved our abstract, introduction, methods, results, and discussion.

If there are any other problems, please feel free to contact us.

Below we include detailed responses to the reviewers' comments and suggestions.

The numberings of the sections and parts refer to the revised manuscript.

Responses to the reviewer 1

We feel great thanks for your valuable comments concerning our manuscript. According to your suggestions, we have revised the manuscript carefully. Thank you very much for your help.

Comment 1: This manuscript provided evidence of combination therapy including RFA/MWA+TACE and RFA+PEI, but then the authors do not present both comparisons.

Response 1: Thank you for your comment. We appreciate it very much for this valuable comment. The direct comparison of the efficacy of RFA/MWA+TACE and RFA+PEI has not been performed. We have found that the 2-year OS was slightly higher in the RFA-PEI than in the RFA group, and current evidence was difficult to draw a definite conclusion regarding the therapeutic management in terms of , Local recurrence free proportion and complete tumor necrosis ^[1]. However, TACE-RFA is comparable to repeat hepatectomy in both OS and RFS for recurrent HCC (rHCC), and has a lower complication rate and hospital stay than repeat hepatectomy ^[2]. Therefore, in rHCC patients with liver function compensation, TACE-RFA local therapy may be considered as a preferred option.

Comment 2: The authors should discuss whether RFA+TACE and RFA+PEI are the better combination therapy for 3 to 5cm lesions with liver function compensation.

Response 2: Thank you for your comment. We appreciate it very much for this valuable comment. The direct comparison of the efficacy of RFA/MWA+TACE and RFA+PEI has not been performed. PEI-RFA has comparable OS and RFS, shorter hospital stay and a lower major complication rate for small HCC compared to hepatic resection^[3, 4]. TACE-RFA has comparable 1-/3-year OS and 1-/3-year RFS to repeated resection but lower long-term survival than surgical resection^[5]. Therefore, the treatment of rHCC patients with 3 to 5cm lesions and liver function compensation

should be determined according to the tumor characteristics and patients' condition.

Responses to the reviewer 2

We feel grateful for your valuable comments concerning our manuscript. Thank you very much for your help.

Comment 1: The authors may wish to consider the differences (if any) in the use of ablation in HCC recurrence versus primary, since this is part of the stated goal of the paper.

Response 1: Thank you for your comments. We appreciate it very much for this valuable comment. A retrospective study found that RFA provided similar long-term survival rates for isolated hepatocellular carcinoma 5 cm or less regardless of whether the treatment was initial or salvage therapy^[6]. Therefore, we consider there is no difference between the use of ablation in HCC recurrence versus primary.

Comment 2: The authors may also wish to discuss a comparison between other locoregional treatment modalities and ablation for recurrent HCC

Response 2: Thank you for your comments. We appreciate it very much for this valuable comment. Apart from ablation, non-operative local treatment of HCC includes TACE, stereotactic body radiation therapy (SBRT) and Proton beam radiotherapy (PBT). Many articles have shown that RFA has long-term benefits comparable to repeat hepatectomy (RH) for tumours less than 3 cm. The study showed that RFA has better OS and RFS advantages than TACE for rHCCS in both ≤3cm and > 3cm lesions^[7]. RFA and SBRT showed considerable therapeutic benefit

for rHCC \leq 3cm, better OS but lower RFS rate for rHCC $>$ 3cm [7]. A prospective randomized study showed that the local progression-free survival rate of PBT was comparable to that of RFA observed in rHCC patients with \leq 2 tumor(s) of <3 cm^[8]. We add this content to the part of **ABLATION VS OTHER LAGICAL TREATMENT** in the main text. Thank you for your suggestions.

Comment 3: The authors may also wish to include a discussion about the different approaches to ablation (percutaneously, open, minimally invasive).

Response 3: Thank you for your comment. We appreciate it very much for this valuable comment. Thermal ablation can be performed safely using percutaneous, laparoscopic techniques. Percutaneous RFA is commonly used to eliminate percutaneous tumors and is the most appropriate method for HCC masses far from the intestine, bile duct, ureter, or diaphragm^[9]. In contrast, LRFA performed better than PRFA in the deep-seated liver cancers, such as subphrenic lesions^[10], and those located in the subcapsular area or those in nearby hollow viscous or vessels^[9]. According to Min's study^[11] on subphrenic HCC, the local tumor progression (LTP) rate of the LRFA group was significantly lower than that of the PRFA group, the cumulative OS rate of the LRFA group was significantly higher than that of the PRFA group, and there was no statistical difference in DFS rate between the two groups. Another study showed that laparoscopic MWA (LMWA) seemed to have a tendency to be more effective than percutaneous MWA (PMWA) in the treatment of subcapsular HCC^[12]. However, the laparoscopic approach has a higher rate of postoperative complications than the percutaneous approach^[9, 11, 13]. In addition, there

are few reports of open surgical ablation for rHCC. Consequently, LRFA can be a valuable treatment option for subphrenic and subcapsular HCC if accessible using the laparoscopic approach. We add this content to the part of **PERCUTANEOUS VS LAPAROSCOPIC TECHNIQUES** in the main text. Thank you for your suggestions.

Responses to Editorial Office's comments

We feel grateful for your valuable comments concerning our manuscript. Thank you very much for your help.

Comment 1: The author(s) must add a table/figure (medical imaging) to the manuscript.

Response 1: Thank you for your comments. The table is as follows.

Table 1

Application of various minimally invasive treatments in HCC

Tumour size	Patients condition	Treatment
sub-centimeter	percutaneous tumors	PRFA
	local ablation therapy is not feasible	TACE
<3cm	percutaneous tumors	PRFA
	subphrenic and subcapsular tumors	LRFA
	perivasculat tumors	MWA
	can't endure thermal ablation	CRA
	MVI(+)	TACE-RFA
3-5cm	with liver function compensation	TACE-RFA
	liver failure	MWA,CRA

PRFA: Percutaneous radiofrequency ablation; LRFA: Laparoscopic radiofrequency ablation;

TACE: Transarterial chemoembolization; MWA: microwave ablation; CRA: Cryoablation;

MVI: microvascular invasion.

Comment 2: The author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript.

Response 2: Thank you for your comment. We appreciate it very much for this valuable comment. This review methodically describes the treatment of rHCC by various ablation procedures in recent years. Moreover this study compares the indications, advantages and survival analysis of various ablative treatments. Therefore, we summarize how to choose the appropriate ablation therapy for different rHCC patients.

Moreover, we have invited a native English-speaker to polish the writing of our manuscript. Thank you!

[Reference]

- 1 Lu DE, Cheng SW, Lin YS, Tu MW, Lee CH, Chen C, Chen KH. Combination of radiofrequency ablation and percutaneous ethanol injection versus radiofrequency ablation alone for hepatocellular carcinoma: a systematic review and meta-analysis. *Ann Hepatol* 2022; **27**(5): 100729 [PMID: 35700935 DOI: 10.1016/j.aohep.2022.100729]
- 2 Peng Z, Wei M, Chen S, Lin M, Jiang C, Mei J, Li B, Wang Y, Li J, Xie X, Kuang M. Combined transcatheter arterial chemoembolization and radiofrequency ablation versus hepatectomy for recurrent hepatocellular carcinoma after initial surgery: a propensity score matching study. *Eur Radiol* 2018; **28**(8): 3522-3531 [PMID: 29536241 DOI: 10.1007/s00330-017-5166-4]
- 3 Chen S, Peng Z, Xiao H, Lin M, Chen Z, Jiang C, Hu W, Xie X, Liu L, Peng B, Kuang M. Combined radiofrequency ablation and ethanol injection versus repeat hepatectomy for elderly patients with recurrent hepatocellular carcinoma after initial hepatic surgery. *Int J Hyperthermia* 2018; **34**(7): 1029-1037 [PMID: 28974113 DOI: 10.1080/02656736.2017.1387941]
- 4 Chen S, Peng Z, Lin M, Chen Z, Hu W, Xie X, Liu L, Qian G, Peng B, Li B, Kuang M. Combined percutaneous radiofrequency ablation and ethanol injection versus hepatic resection for 2.1-5.0 cm solitary hepatocellular carcinoma: a retrospective comparative multicentre study. *Eur Radiol* 2018; **28**(9): 3651-3660 [PMID: 29600474 DOI: 10.1007/s00330-018-5371-9]
- 5 Yi PS, Huang M, Zhang M, Xu L, Xu MQ. Comparison of Transarterial Chemoembolization Combined with Radiofrequency Ablation Therapy versus Surgical Resection for Early Hepatocellular Carcinoma. *Am Surg* 2018; **84**(2): 282-288 [PMID: 29580359]
- 6 Bai XM, Cui M, Yang W, Wang H, Wang S, Zhang ZY, Wu W, Chen MH, Yan K, Goldberg SN. The 10-year Survival Analysis of Radiofrequency Ablation for Solitary Hepatocellular Carcinoma 5 cm or Smaller: Primary versus Recurrent HCC. *Radiology* 2021; **300**(2): 458-469 [PMID: 34003058 DOI: 10.1148/radiol.2021200153]
- 7 Zheng J, Cai J, Tao L, Kirih MA, Shen Z, Xu J, Liang X. Comparison on the efficacy and prognosis of different strategies for intrahepatic recurrent hepatocellular carcinoma: A systematic review and Bayesian network meta-analysis. *Int J Surg* 2020; **83**: 196-204 [PMID: 32980518 DOI: 10.1016/j.ijsu.2020.09.031]
- 8 Kim TH, Koh YH, Kim BH, Kim MJ, Lee JH, Park B, Park JW. Proton beam radiotherapy vs. radiofrequency ablation for recurrent hepatocellular carcinoma: A randomized phase III trial. *J Hepatol* 2021; **74**(3): 603-612 [PMID: 33031846 DOI: 10.1016/j.jhep.2020.09.026]
- 9 Eun HS, Lee BS, Kwon IS, Yun GY, Lee ES, Joo JS, Sung JK, Moon HS, Kang SH, Kim JS, Shin HJ, Kim TK, Chun K, Kim SH. Advantages of Laparoscopic Radiofrequency Ablation Over Percutaneous Radiofrequency Ablation in Hepatocellular Carcinoma. *Dig Dis Sci* 2017; **62**(9): 2586-2600 [PMID: 28744835 DOI: 10.1007/s10620-017-4688-6]
- 10 Song KD, Lim HK, Rhim H, Lee MW, Kang TW, Paik YH, Kim JM, Joh JW. Hepatic resection vs percutaneous radiofrequency ablation of hepatocellular carcinoma abutting right diaphragm. *World J Gastrointest Oncol* 2019; **11**(3): 227-237 [PMID: 30918595 PMCID: PMC6425331 DOI: 10.4251/wjgo.v11.i3.227]
- 11 Kwak MH, Lee MW, Ko SE, Rhim H, Kang TW, Song KD, Kim JM, Choi GS. Laparoscopic radiofrequency ablation versus percutaneous radiofrequency ablation for subphrenic

hepatocellular carcinoma. *Ultrasonography* 2022; **41**(3): 543-552 [PMID: 35430787 PMCID: PMC9262669 DOI: 10.14366/usg.21241]

12 Della Corte A, Ratti F, Monfardini L, Marra P, Gusmini S, Salvioni M, Venturini M, Cipriani F, Aldrighetti L, De Cobelli F. Comparison between percutaneous and laparoscopic microwave ablation of hepatocellular carcinoma. *Int J Hyperthermia* 2020; **37**(1): 542-548 [PMID: 32469252 DOI: 10.1080/02656736.2020.1769869]

13 Jin S, Tan S, Peng W, Jiang Y, Luo C. Radiofrequency ablation versus laparoscopic hepatectomy for treatment of hepatocellular carcinoma: a systematic review and meta-analysis. *World J Surg Oncol* 2020; **18**(1): 199 [PMID: 32787883 PMCID: PMC7425008 DOI: 10.1186/s12957-020-01966-w]