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**Transarterial chemoembolization combined with radiofrequency ablation in the treatment of large hepatocellular carcinoma with stage C**

The authors would like to thank the associate editor and all anonymous reviewers for their support and constructive comments on this manuscript. The authors have followed up all the comments carefully and have made every possible effort to clean up all the issues. In the following sections, we provide detailed explanations on modifications we've made in response to the comments raised by the editor and reviewers. The responses are presented respectively.

**Reviewer #1:**

**1. *The abstract should be re-written.***

Response: Thanks for the suggestion. We have re-written the abstract in the revised paper. It is as follows:

**Abstract**

***Background***

The combination therapy of transarterial chemoembolization and radiofrequency ablation (TACE-RFA) s shows promising efficacy in large hepatocellular carcinoma (HCC). Data on the clinical efficacy and safety of TACE-RFA for large HCC with Barcelona Clinic Liver Cancer (BCLC) stage C are lacking in China.

***Aim***

To determine the safety and efficacy of TACE-RFA for large, advanced HCC.

***Methods***

Patients of HCC with BCLC stage C who were treated with TACE-RFA or TACE alone at our institute from August 2008 to January 2017 were retrospectively reviewed. The complications were observed. The associations between overall survival (OS) and treatment method were analysed.

***Results***

Data were collected from 102 HCC patients. Among them, 64 underwent

TACE-RFA and 38 underwent TACE. The combination of TACE and RFA was safe. All complications were controllable. The median OS in the TACE-RFA group was significantly longer than that in the TACE group (8.0 months vs. 4.0 months,  $P=0.000$ ). The 6-, 12- and 24-month survival rates of the combination group were 68.8%, 34.4%, and 10.9%, respectively, while those of the TACE group were 36.8%, 7.9%, and 0% ( $P < 0.05$ ).

### ***Conclusion***

*TACE-RFA has an advantage over TACE alone in improving OS in large HCC patients with BCLC stage C.*

### ***2. Some minor language polishing should be corrected.***

Response: Thanks for the suggestion. The English grammar and tense have been revised carefully in the revised paper.

### ***3. Some radiological images can be added to the results.***

Response: Thanks for the suggestion. We think your suggestion is very good. However, due to the recent transformation and upgrading of our hospital, many patients' imaging examinations before 2020 cannot be consulted, which leads to our temporary inability to provide. We are sorry for this and hope you can understand. We can draw inspiration from your suggestions to make progress in future research.

### **Reviewer #2:**

### ***1. Radiological images, before and after treatments, would be useful and interesting.***

Response: As the reviewer said, radiological images, before and after treatments, would be useful and interesting. However, due to the recent transformation and upgrading of our hospital, many patients' imaging examinations before 2020 cannot be consulted, which leads to our temporary inability to provide. We are sorry for this and hope you can understand. Thanks.

***2.Regarding follow-up, it is reported that in the first 6 months all patients were evaluated every month with chest X-ray, abdominal computed tomography or magnetic resonance imaging. It means 6 CT or MR in 6 months; it seems a quite***

*aggressive follow-up. Why?*

Response: Thanks for the suggestion. We are very sorry for your misunderstanding caused by our clerical error. Regarding follow-up, in the first 6 months all patients were evaluated every 4-6 weeks with chest X-ray, abdominal computed tomography or magnetic resonance imaging. Such follow-up frequency is due to the poor prognosis of these patients with advanced liver cancer. Especially in the first half of the year, tumor progression is likely to occur, and the disease condition is hidden. At the same time, patients cannot apply systemic treatment due to personal reasons.

*3. Tumors were very large, so why ablations were always performed with CT guide, instead of ultrasonography guide? Please discuss.*

Response: Thanks for the question. Based on our clinical experience, the therapeutic effect of radiofrequency ablation with CT guidance in large tumors is better than that of ultrasound guidance, which may be related to more needle placement times and longer ablation time under CT guidance.

*4. Every patient presented tumour thrombus; this significantly increase the risk of major complications during TACE, like liver failure or abscess formation. Surprisingly these never occurred. Why? Please discuss.*

Response: Thanks for your question. The types of portal vein tumour thrombus were Cheng's classification type I or II, and the liver function were mostly child A. So, these patients had no liver failure. Abscess formation usually occurred in older patients with basic diseases such as diabetes. The median age of this group was 52 years old, and there are fewer basic diseases in the crowd. Thus, abscess formation never occurred. This was also a retrospective study, and a large clinical trial is necessary to assess curative effects.

*5. Consider to read and cite: "Large Multifocal Hepatocarcinoma: Technical Details of Treatment with Combined Transarterial Chemoembolization, Microwave and Radiofrequency Ablation" 2021, J Gastrointest Cancer, doi: 10.1007/s12029-020-00416-w*

Response: Thanks for the suggestion. we have read the article and discussed it.

It was about the treatment with combined TACE, microwave ablation and RFA, and just a case report. This was not similar to our study.

**Reviewer #3:**

**Sun reported a retrospective study comparing RFA-TACE and TACE alone. They compared two groups with different liver function and tumor progression populations, although the background did not present statistical differences. Therefore, no one would be interested in the results with severe selection biases. In addition, no one selected RFA-TACE for the treatment anymore except in very few cases.**

Response: Thanks for the reviewer's comments. Indeed, the study is a retrospective research, selection bias is the main limitation. In China, There are some patients with HCC whose liver function cannot reach child A, even after liver protection treatment. These advanced HCC patients are more willing to accept minimally invasive treatment due to the economic factors.

**Reviewer #4:**

**The revision has been made inappropriately. The background of the patient is too heterogenous to conclude anything. The survival difference could be due to the potential difference in liver function. Economic reasons cannot justify the clinical strategy. It is unlikely to change current guidelines for multiple HCCs.**

Response: Thanks for the reviewer's comments. Indeed, the study is a retrospective research, selection bias is the main limitation. In China, there are some patients with HCC whose liver function cannot reach child A, even after liver protection treatment. These advanced HCC patients are more willing to accept minimally invasive treatment due to the economic factors. Sometimes economic reasons could influence the clinical strategy. The observations need to be further validated by prospective, multicenter, randomized studies.