

Tuesday, October 24, 2023

Dear Editorial Board and Reviewers,

I would like to express my gratitude to the reviewers for their insightful comments and recommendations regarding our manuscript, titled **“Any Role For Transarterial Radioembolization (TARE) In Unresectable Intrahepatic Cholangiocarcinoma (iCCA) In The Era Of Advanced Systemic Therapies?”** submitted for consideration in *World Journal of Hepatology*. We appreciate the time and effort invested in evaluating our work.

In this letter, we address each of the reviewers' points and outline the revisions we have made in response to their feedback.

Reviewer #1:

The manuscript offers a comprehensive overview of the epidemiology, clinical manifestations, and therapeutic approaches for intrahepatic cholangiocarcinoma (iCCA). Specifically, the manuscript delineates the technology of transhepatic arterial radioembolization (TARE), both as a standalone modality and in conjunction with systemic chemotherapy, CT-HDRBT, among other treatments. Furthermore, the work delves into the therapeutic strategy of TARE in managing unresectable iCCA, highlighting its efficacy, safety, and the variables contributing to prognostic determinations. The article's clinical implications are evident, with a commendably coherent structure and succinct prose.

We thank the Reviewer for his comment regarding the depth of our manuscript's discussion on the application of TARE in iCCA. In response, we have expanded our discussion on the operational complexities of TARE tailored specifically for iCCA scenarios, including unresectable iCCA, highlighting its efficacy, safety. We believe that these additions enhance the manuscript's comprehensiveness and provide valuable insights into the nuanced application of TARE in iCCA (see below).

However, there are several points that warrant further elaboration and clarification:

1.While the manuscript provides an introduction to the TARE technology, there's a noticeable dearth of specific insights into its nuanced application in iCCA. The authors are encouraged to delve deeper into the operational complexities of TARE, tailored specifically for iCCA scenarios, such as lobar or segmental perfusion?

2.It's widely recognized that iCCA is frequently associated with lymph node metastasis, an occurrence that is even more pronounced in advanced-stage patients. Given that TARE is primarily designed to address intrahepatic lesions, the authors should clarify their stance on concurrent management strategies. Specifically, how would one approach the treatment of patients presenting with both intrahepatic lesions and lymph node metastasis?

Reviewer #1 correctly highlights the importance of addressing concurrent management strategies for patients with intrahepatic lesions and lymph node metastasis in TARE.

We acknowledge this point and we expanded upon these aspects in the revised manuscript.

We delved deeper into the operational complexities of tailoring TARE specifically for iCCA scenarios, ensuring that the readers gain a better understanding of how TARE can be customized to address the intricacies of this particular disease. We have completely revised the section “TARE AS A THERAPEUTIC STRATEGY IN iCCA” which provides a more comprehensive discussion of concurrent management strategies highlighting the challenges for patients presenting with both intrahepatic lesions and lymph node metastasis (page 9, lines 8-15).

3.The manuscript does not shed light on the optimal radiation dosing guidelines for iCCA patients undergoing TARE. This omission is significant and should be rectified.

We appreciate the feedback from reviewer #1. We have incorporated this important information into the manuscript to provide readers with guidance on optimal radiation dosing for iCCA patients undergoing TARE (page 10, lines 1-10).

4. An essential aspect that requires elaboration is the identification of specific clinical attributes of iCCA that make patients viable candidates for TARE. The authors should contemplate incorporating this information into the manuscript.

The reviewer's suggestion to include information about the specific clinical attributes that make patients viable candidates for TARE is well-taken. We have added a section that discusses when TARE is indicated for iCCA patients, providing a comprehensive understanding of patient selection criteria, together with the challenges of this selection (Page 9, lines 8-14).

5. A finer point, yet of potential clinical significance, is the selection of embolic agents and their infusion methodologies tailored for TARE in the context of iCCA. It would be beneficial if the authors could shed light on this aspect.

Reviewer #1's comment on the selection of embolic agents and their infusion methodologies is valid. We have expanded the discussion in this regard, providing insights into the selection of embolic agents and their infusion methods tailored for TARE in the context of iCCA (pages 10 and 11).

6. The information provided in Table 1 concerning the Median OS and radiologic response in iCCA treated with TARE is valuable. However, to provide a more robust understanding, the table should be expanded to encompass the number of cases, inclusion criteria, and operational techniques from various studies. Moreover, a nuanced analysis discussing the potential reasons behind the observed OS variations across studies would add depth to the research. In closing, while the manuscript is robust in its current form, addressing the aforementioned areas of concern will undeniably enhance its depth, comprehensiveness, and overall clinical relevance.

We have revised Table 1 as suggested, incorporating the number of cases, inclusion criteria, and operational techniques from various studies to provide a more comprehensive understanding of the Median OS and radiologic response in iCCA treated with TARE.

Furthermore, we have included a nuanced analysis that discusses the potential reasons behind observed OS variations across studies.

Reviewer #2:

It is a high quality mini-review. Authors reviewed more than 30 published papers and concluded that TARE may have a role in the treatment of iCCA, either as a standalone treatment or in combination with systemic chemotherapy. However, I have some comments.

1. "Epidemiology, clinical characteristics and treatment of CCA" should be condensed as it is a mini-review. The repetitious details need not be given here.

Reviewer #2 suggests condensing the section on "Epidemiology, clinical characteristics, and treatment of CCA". We have revised the entire section to make it more concise and focused on the essential details (see Page 3).

2. "TARE as a therapeutic strategy in hepatocellular carcinoma (HCC)" should be an essential part, which is helpful for readers to get a better understanding of TARE. As the knowledge of foreshadowing, this part needn't to be long, just be concise and to the point.

We have modified this part accordingly to ensure that it is more succinct while still providing readers with a clear understanding of TARE's role in HCC, also including the comments of Reviewer#1.

3. The first column in Table 1 & 2 should be written with reference number (in brackets).

According to Reviewer #2's request, we included reference numbers in the first column of Tables 1 and 2 and revised both the Tables.

4. The latest papers should be cited (10.1016/j.jvir.2023.07.028, 10.1016/j.jvir.2023.05.026). The α -particle-emitting transarterial radioembolization (α TARE) should be generically mentioned (10.1186/s41181-023-00205-3).

We appreciate the reviewer's suggestion to cite the latest papers (10.1016/j.jvir.2023.07.028, 10.1016/j.jvir.2023.05.026) and mention α -particle-emitting transarterial radioembolization (α TARE). We have included these citations as recommended (page 4, lines 10-16).

We hope that these revisions adequately address the concerns raised by the reviewers and enhance the quality and comprehensiveness of our manuscript. We believe that the changes made will contribute positively to the scientific literature in the field of TARE for iCCA. Thank you for your time and consideration.

Sincerely,

Alessandra Elvevi