ROUND 1

March 23, 2022

The Editorial Office

World Journal of Clinical Cases

Re: 72762

Neoadjuvant transcatheter arterial chemoembolization and systemic chemotherapy for treatment of undifferentiated embryonal sarcoma of liver in children.

Dear Editor:

We wish to re-submit the manuscript titled “Neoadjuvant transcatheter arterial chemoembolization and systemic chemotherapy for treatment of undifferentiated embryonal sarcoma of liver in children”. The manuscript ID is 72762.

We thank you and the reviewers for your thoughtful suggestions and insights. The manuscript has benefited from these insightful suggestions. We look forward to working with you and the reviewers to move this manuscript closer to publication in the *WJCC*.

The manuscript has been rechecked and the necessary changes have been made in accordance with the reviewers’ suggestions.

The responses to all comments have been prepared and attached herewith/given below.

Thank you for your consideration. We look forward to hearing from you.

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RESPONSE TO JOURNAL EDITORIAL OFFICE AND REVIEWERS

(All comments are in italics)

Reviewer #1:

1.It should be considered as a case series report and conclusions should be toned down, since methods are not adequate to claim such results.

Response: Thanks for your suggestion and the conclusions have been rewritten.

2.Methodology : TACE has significantly evolved in such a large time span (2006 - 2019) and in recent years drug eluting beads have been made available, which reduce systemic chemotherapy dispersion and toxicity. Why the authors did not use drug eluting beads?

Response: The drug eluting beads are in the approval process and are expected to be put into use in the near future

3.The technique they described in performing TACE is not the standard; moreover they administered an unconventional chemotherapy cocktail: on what scientific basis was this protocol applied?

Response: The process and chemotherapy emulsion were created by the former director of our center. It has been proved to have good efficacy in liver tumor and kidney tumor, and papers have been published.

4.Methodology and result interpretation : The protocol applied by the authors relied on a complete cycle of neoadjuvant treatment and then disease restaging. Systemic chemotherapy was given at least 3 weeks after TACE. In my opinion this raises two main concerns : the firs is related to the assessment of diaease response, which cannot be definitely attributed to TACE or systemic chemotherapy. It is impossibile to evaluate the real prognostic impact of TACE in the absence of a control population or an early imaging liver assessment.

Response: This study mainly evaluated the efficacy of neoadjuvant treatment for the treatment of UESL. There was no control group due to the small number of cases. Further investigations with a larger cohort and prospective study are needed to compare the efficacy of TACE, systemic chemotherapy and NAT for UESL.

5.Furthermore, the delay in the administration of systemic chemotherapy, due to pre-treatment TACE, may promote tumor progression in extrahepatic sites. Of note, two of six patients presented extrahepatic disease at diagnosis and presented favorable outcomes thanks to the efficacy of systemic chemotherapy at extrahepatic sites.

Response: When infusion into the hepatic artery, chemotherapy drugs will still flow through the hepatic vein to the heart and the whole body, thus the extra-hepatic lesions can also be suppressed. However, intravenous chemotherapy is still essential, as the dose of chemotherapy drugs flowing into the body from the TACE is limited,

which cannot achieve effective concentration.

6.All these aspects must be highlighted in the discussion and the conclusions must be toned down consequently.
Response: Thanks for your suggestion and all these aspects have been highlighted in the discussion and the conclusions have been toned down consequently.

7.Finally, due to the retrospective nature and non rigorous design, the study does not have enough robustness to claim the safety and efficacy of the proposed tratment that must be validated in a prospective and randomized trial. With such a study design the authors cannot provide any evidence of the benefit of TACE over standard systemic chemotherapy.
Response: Thanks for your suggestion and further investigations with a larger cohort and prospective study have been designed and are being carried out to compare the efficacy of TACE, systemic chemotherapy and NAT for UESL.

Reviewer #2:
1.A comparison between study patients and patients uniquely undergoing preoperative CHT (without TACE) and surgery and postop-CHT may add to this study and allow the authors to really assess the role of NAT as an alternative treatment for UESL before surgery.
Response: Thanks for your suggestion. There was no control group due to the small number of cases. Further investigations with a larger cohort and prospective study have been designed and are being carried out to compare the efficacy of TACE, systemic chemotherapy and NAT for UESL.

2.The manuscript contains both orthographic and grammatical errors and needs to be reviewed by an English mother-tongue Scientific Editor.
Response: Thanks for your suggestion and the manuscript has been sent to an English-language professional editing service for improved English usage to meet the high standards of *WJCC*.

3.Abstract: o It is not clear if the patients included patients undergoing NAT or patients who underwent NAT and subsequently surgery. Please clarify.
Response: The patients in the study were underwent NAT and subsequently surgery, it has been clarified in the manuscript.

4.o the study aim is not clearly defined: the authors say that the study aims to evaluate the efficacy of NAT as an alternative treatment for UESL. Alternative treatment to what? Actually, the authors are reporting on characteristics and outcomes of NAT + surgery + postoperative CHT in their experience.
Response: Thanks for your suggestion and the study aim has been revised.

5.o The term NAT indicates the combination of TACE + systemic chemotherapy: this

should be better explained in the abstract.
Response: Thanks for your suggestion and the term NAT has been better explained in the abstract.

6.o The Tumor characteristics of treated patients should be reported in the abstract, as well as rates of response to NAT. IN contrast, drugs administered during NAT may not be shown in the abstract.
Response: Thanks for your suggestion and the above contents have been modified.

7.o In the results, when reporting on post-NAT complications, the authors should avoid terms like "almost all" and report, instead, numbers or rates of patients.
Response: Thanks for your suggestion and the above contents have been modified.

8.- Material and Methods, section "Toxicity evaluation": the authors should be consistent with the use of the term NAT to indicate the use of TACE and intravenous chemotherapy.
Response: Thanks for your suggestion and the above contents have been modified.

9.- Discussion: o Needs to be deeply reviewed because in its actual form lacks a proper organization : different paragraphs are not adequately connected with each other (for example, the authors initially speak about TACE story and benefits, then report on response to CHT + TACE, then go back to TACE complications) and contains notions with are not fully assessed (for example in the paragraph reporting on TACE benefits, the authors should expand on technical benefit for future liver resection, like for example the tumor shrinkage, which is not induced uniquely by CHT).
Response: Thanks for your suggestion and the order of the paragraphs has been adjusted, and some content has been added.

10.o The important role of preoperative CHT is almost totally neglected: the authors should expand on CHT role before surgery and after surgery, on primary tumor and control of distant metastases.
Response: Thanks for your suggestion and the benefits of CHT before surgery and after surgery have been added in discussion.

11.The role and aims and advantages of the combination of TACE and CHT in NAT should be better assessed.
Response: Thanks for your suggestion and further investigations with a larger cohort and prospective study have been designed and are being carried out to compare the efficacy of TACE, systemic chemotherapy and NAT for UESL.

12.o in the sentence "They achieved SD (shrunk by about 20%) after one cycle of NAT, and still had large tumors with PRETEXT stage III in radiography", authors should cite the manuscript describing the pretext staging classification.
Response: Thanks for your suggestion and the manuscript describing the pretext

staging classification has been cited.

13. - Conclusion: should be rewritten, in order to highlight the benefits of the combination of TACE and CHT before surgery. In addition, the study limitations should be enlisted in the discussion, not in the conclusion.
Response: Thanks for your suggestion and the conclusions have been rewritten, and the study limitations have been moved to the discussion.

ROUND 2

April 30, 2022

The Editorial Office

World Journal of Clinical Cases

Re: 72762

Neoadjuvant transcatheter arterial chemoembolization and systemic chemotherapy for the treatment of undifferentiated embryonal sarcoma of liver in children.

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The manuscript has been rechecked and the necessary changes have been made in accordance with the reviewers’ suggestions.

The responses to all comments have been prepared and attached herewith/given below.

Thank you for your consideration. We look forward to hearing from you.

Jinhu Wang, MD. PhD.
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RESPONSE TO JOURNAL EDITORIAL OFFICE AND REVIEWERS

(All comments are in italics)

1. Further language polishing is required to fix all grammatical, syntactical, formatting and other related errors, in order to meet the publication requirement

Response: The revised manuscript has been sent to a professional English language editing company for language polishing in order to meet the publication requirement. And a new language certificate has been submitted along with the revised manuscript.

2. Please provide the Figures cited in the original manuscript in the form of PPT.

Response: The Figures cited in the original manuscript have been integrated in the form of PPT.

3. Please provide this funding document Supported by Youth Program of Natural Science Foundation of Zhejiang Province, No. LQ20H160027; and National Natural Science Foundation of China, No. U20A20137

Response: The funding documents have been submitted with the revised manuscript.

4. Please provide the Tables.

Response: The Tables have been submitted with the revised manuscript.

Reviewer #1:

1. Methodology: TACE has significantly evolved in such a large time span (2006 - 2019) and in recent years drug eluting beads have been made available, which reduce systemic chemotherapy dispersion and toxicity. The authors should state in the manuscript limitations why they did not perform DEBTACE.

Response: Thanks for your suggestion. In recent years Drug-eluting beads (DEBs) have been introduced as novel drug-delivery agents for TACE, allowing for higher concentrations of drugs to the target tumor and lower systemic concentrations. Studies showed lower incidence of systemic toxicity and improved tolerance with DEB-TACE， but overall survival did not differ from conventional lipiodol-TACE. DEB-TACE has been widely used for the treatment of hepatocellular carcinoma in adults, but it has not been reported in pediatric liver malignancies so far, and its clinical safety needs to be confirmed by further clinical trials in children. Besides, DEB-TACE reduces systemic complications by lowering extrahepatic drug concentrations, but it also decreases the inhibition of extrahepatic lesions. Therefore, DEB-TACE was not used in this study. In the near future, DEB-TACE is expected to be applied in treatment of pediatric unresectable intrahepatic malignancy. This limitation has been added in discussion section.

hen infusion into the hepatic artery, chemotherapy drugs will still flow through the hepatic vein to the heart and the whole body, thus the extra-hepatic lesions can also be suppressed. However, intravenous chemotherapy is still essential, as the dose of chemotherapy drugs flowing into the body from the TACE is limited, which cannot achieve effective concentration.

2. The technique they described in performing TACE is not the standard; moreover they administered an unconventional chemotherapy cocktail: in the response to reviewers file the authors said that there are published papers about the chemotherapy cocktail they used. They must include those references in the methods section. It is not acceptable just the explanation that the protocol was set up by the former director.

Response: Thanks for your suggestion. The procedure of TACE we described was adapted from published reports and has been shown to be effective in the treatment of pediatric tumors in our center. Vindesine, ifosfamide, pirarubicin, cisplatin and etoposide are commonly used, and combined of more than 3 drugs, in the chemotherapy of UESL. The chemoembolic emulsion consisted of vindesine, cisplatin and pirubicin used in this study have all been proved to be effective and safety in the treatment of UESLs and also other tumors in our center. All the references have been added in the methods section.

3. Methodology and result interpretation : The protocol applied by the authors relied on a complete cycle of neoadjuvant treatment and then disease restaging. Systemic chemotherapy was given at least 3 weeks after TACE. In my opinion this raises two main concerns : the firs is related to the assessment of diaease response, which cannot be definitely attributed to TACE or systemic chemotherapy. It is impossibile to evaluate the real prognostic impact of TACE in the absence of a control population or an early imaging liver assessment. This point must be stressed in discussion. The authors have no scientific elements to claim the utility of TACE as neoadjuvat therapy.

Response: Thanks for your suggestion. We have recognized the limitation of this study, and the conclusions have been rewritten, which highlighted the efficacy of NAT as a whole. Controlled study is difficult to perform due to the low incidence of UESL, and this point was emphasized in the limitations section of the discussion. Further prospective and controlled studies with a larger cohort are needed and under way to compare the efficacy of TACE, systemic chemotherapy and NAT for UESL, respectively.