



PEER-REVIEW REPORT

Name of journal: *World Journal of Clinical Cases*

Manuscript NO: 72762

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

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05569437

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Adjunct Professor, Attending Doctor, Postdoctoral Fellow, Surgical Oncologist

Reviewer's Country/Territory: Italy

Author's Country/Territory: China

Manuscript submission date: 2021-11-11

Reviewer chosen by: Jin-Lei Wang

Reviewer accepted review: 2022-02-07 06:57

Reviewer performed review: 2022-02-12 12:23

Review time: 5 Days and 5 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection



Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

In this manuscript the authors report on short and long-term results of six pediatric patients affected by undifferentiated embryonal sarcoma of liver (UESL) who underwent one/two cycles of Neoadjuvant transcatheter arterial chemoembolization and systemic chemotherapy (NAT), followed by liver resection and by subsequent postoperative chemotherapy. The combination of TACE (which favours tumor shrinkage and local tumor control, facilitating tumor resection) with CHT (which controls and limits eventual tumor extrahepatic dissemination) seems to be of benefit for this category of patients. This single center series contains only 6 patients, however the management homogeneity of patients included and the UESL extreme rarity may increase clinical relevance of this manuscript. 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. However, many comments are due: -

The manuscript contains both orthographic and grammatical errors and needs to be reviewed by an English mother-tongue Scientific Editor. - Abstract: o It is not clear if the patients included patients undergoing NAT or patients who underwent NAT and subsequently surgery. Please clarify. 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



**Baishideng
Publishing
Group**

7041 Koll Center Parkway, Suite
160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

experience. o The term NAT indicates the combination of TACE + systemic chemotherapy: this should be better explained in the abstract. 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. 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. -

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. - 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). 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. The role and aims and advantages of the combination of TACE and CHT in NAT should be better assessed. 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. - 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.



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Reviewer's code: 06118556

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor, Staff Physician

Reviewer's Country/Territory: Italy

Author's Country/Territory: China

Manuscript submission date: 2021-11-11

Reviewer chosen by: Jin-Lei Wang

Reviewer accepted review: 2022-02-08 08:59

Reviewer performed review: 2022-02-14 15:54

Review time: 6 Days and 6 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection



Re-review	[<input checked="" type="checkbox"/>] Yes [<input type="checkbox"/>] No
Peer-reviewer statements	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No

SPECIFIC COMMENTS TO AUTHORS

The authors present an interesting report of TACE performed as neoadjuvant treatment in a rare form of tumor in 6 pediatric patients. The manuscript is clear and well written, but in my opinion the scientific merit is poor due to a non-rigorous methodology. It should be considered as a case series report and conclusions should be toned down, since methods are not adequate to claim such results. Specific comments :

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? 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? Was TACE administered with compassionate use? If this was the case, did the Ethical Committee approved the study as experimental or retrospective report?

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 first is related to the assessment of disease response, which cannot be definitely attributed to TACE or systemic chemotherapy. It is impossible to evaluate the real prognostic impact of TACE in the absence of a control population or an early imaging liver assessment. 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



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7041 Koll Center Parkway, Suite
160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
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and presented favorable outcomes thanks to the efficacy of systemic chemotherapy at extrahepatic sites. All these aspects must be highlighted in the discussion and the conclusions must be toned down consequently. 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 treatment 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.



RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Reviewer's code: 06118556

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor, Staff Physician

Reviewer's Country/Territory: Italy

Author's Country/Territory: China

Manuscript submission date: 2021-11-11

Reviewer chosen by: Jia-Ru Fan

Reviewer accepted review: 2022-03-29 21:09

Reviewer performed review: 2022-03-29 21:35

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection



Peer-reviewer statements	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No
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SPECIFIC COMMENTS TO AUTHORS

I wish to thank the authors for having improved their manuscript following my previous suggestion. However I think that some critical points have not been adequately addressed. Therefore I ask the authors to revise their paper including the following limitations (from my previous review) :

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. The authors should state in the manuscript limitations why they did not perform DEBTACE.

3.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.

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 first is related to the assessment of disease response, which cannot be definitely attributed to TACE or systemic chemotherapy. It is impossible 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 neoadjuvant therapy.