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OPEN PEER REVIEW

Treatment Benefits and Side Effects of Transarterial Chemoembolization with Drug-Eluting Bead Microspheres (DEB-TACE) in Hepatocellular Carcinoma Patients with Conventional TACE Resistance: A Retrospective Study

Zhangping Zhao, Ying Xie, Xingming Xu, Yinbao Hu, Youjian Zou

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

6 comments · 31 Oct 2020 – 20 Feb 2021

Referee 1 Reviewer

REJECT 31 Oct 2020

Hi
Despite the efforts of respected researchers to conduct a high-quality study, unfortunately, it should be said that the design of this study is not appropriate to evaluate the effectiveness of a treatment. This is because, in this study, past data that were recorded for the care of patients were used, whereas a clinical trial study should be used to evaluate a treatment method.

Mahyar Mohammadifard Reviewer

ACCEPT 30 Nov 2020

Proper article TITLE, structured ABSTRACT, accurate RESULTS and relevant DISCUSSION... I think it is Approved.

mohammad momeni Reviewer

MINOR REVISION 4 Jan 2021

The manuscript follows a good structure and gives useful information; however, I would suggest the following:

1-As DEB-TACE is a new method in comparison to the conventional method, what was your plan for the management of probable adverse reactions and follow-up treatment? (Please mention this in the method section.)

2-Please mention the chemotherapy drugs used in this study.

3-In the TACE procedure, it is important to achieve complete occlusion of the target artery, and it is recommended to use Gelfoam after C-TACE for this reason. If there is no need to use Gelfoam in DEB-TACE, please mention this as a benefit in the discussion section.

4-Please add the patient's final angiography photo to the patient's figures to allow comparison of angiographic changes.

Referee 2 Reviewer

MAJOR REVISION 11 Feb 2021

1-The authors mentioned: "…….. in patients with conventional transarterial chemoembolization (c-TACE) resistant." I think it should be "resistance," not "resistant."
2-Please add an objective section to the paper according to the journal format.
3-At the beginning of the methods section, please move the term "Definition of c-TACE resistance:" to a later part. It is not good style to begin the methods section this way. In addition, please write "Inclusion criteria:" as "Inclusion criteria were as follows".
4-In the definition of -TACE resistance, the authors mentioned 4 conditions. It is unclear whether all these conditions must be present simultaneously or whether even one of them indicates resistance.
5-Please add to the paper that the ethics committee approved the study.
6-How did the authors determine the volume of DEB and microspheres needed for DEB-TACE in each patient?

Did they use a single volume of the agent?
7-What was the method of embolization regarding the advancement of the catheter tip? Did the authors inject the mixture at the beginning of the hepatic artery, or did they advance the catheter tip to the origin of the specific vascular bed of the tumor? A patient could have more than one lesion, and superselective TACE of a mass could be effective only for that mass, while other masses would need to be treated separately. Please explain this further in the paper.
8-Did the authors consider hepatic vein or artery thrombosis an exclusion criterion?
9-The authors did not mention the size of the microspheres used in patients. Did they select the size of DEB based on the angiographic vascular blush of the tumor? Or did they use a single form for all patients?
10-Please add the full terms for abbreviations as footnotes in the tables. In addition, please provide the full terms for abbreviations at their first occurrence in the text.
11-If a patient had more than one lesion, one lesion could show CR while another could show PR, SD, or DP. It would then be unclear how the authors determined whether the patient had CR, SD, PR, or DP. Please explain this in the paper.
12-It would be better for the authors to determine the distribution of lesion responses per patient. I mean that it would be better to determine the response status of the lesions in all patients. [It would be better to add this in a table.] [For example: patient 1 had 2 lesions, 3 and 4 cm in diameter, at week 6; the first lesion showed PR and lesion 2 showed SD; at week 12, lesion 1 showed PR and lesion 2 showed PR too.] This report could provide better insight for readers.
13-What imaging evaluation methods were used for the patients? [How many underwent CT, and how many underwent MRI?]
14-It would be better if the authors evaluated the lesion response [response rate based on size reduction, response rate based on CR+PR] in relation to important independent variables such as age, sex, previous treatments, metastasis, baseline pathology [HBV, HCV, ...], Child-Pugh staging, number of lesions, lesion size, enhancement pattern, etc. This analysis could be performed on a per-patient and per-lesion basis and requires linear regression and/or logistic regression analysis. [The analysis at 12 weeks would be better.]
15-Please state in the statistical analysis section whether the normality of the data was checked before the tests.
16-The statistical test for table 3 should be a paired t-test [if the data are normally distributed]. Please correct this. [When the data are not normally distributed, it should be a Wilcoxon test.] In addition, I think the authors should analyze the variables in table 3 at the three time points—before treatment, 1 week, and 6 weeks—using repeated-measures ANOVA [three repeated measurements] if the data are normally distributed, or the Friedman test [if the data are not normally distributed].
17-Please describe or mention the severity scoring system for complications in table 4. [As a footnote in the table and a description in the text.]
18-Did the authors use sorafenib therapy? Please add the data.
19-Did the authors have lesions with PR or SD at 6 weeks that showed DP at 12 weeks? Please add the data in a table.
20-As DEB causes considerable stagnation of blood in the vascular bed, it could cause thrombus formation at the tumor site. This could result in a lack of perfusion on follow-up imaging and thus be interpreted as CR, even though the reason is not the disappearance of the tumor but rather a lack of perfusion at the tumor site, which presents as no enhancement [while the tumor remnant is viable]. How could the authors rule out such an event? [This could interfere with the correct interpretation of the response rate.]
21-Is the definition of resistance patient-based or lesion-based? Please describe this in the paper.
22-It would be good if the authors mentioned the mean size reduction [and the mean percentage reduction of lesions at 6 and 12 weeks].

Associate Editor

MAJOR REVISION 17 Feb 2021

dear Editorial
Regarding the manuscript entitled: The clinical application of DEB-TACE for c-TACE resistant hepatocellular carcinoma patients
The reviewers commented as follows:

1-The authors mentioned: "…..…. in patients with conventional transarterial chemoembolization (c-TACE) resistant." I think it should be "resistance," not "resistant."
2-Please add an objective section to the paper according to the journal format.
3-At the beginning of the methods section, please incorporate the heading "Definition of c-TACE resistance:" into a later part of the section. It is not good style to begin the methods section this way. In addition, please write Inclusion criteria: as "Inclusion criteria were as follows".
4-In the definition of -TACE resistance, the authors mentioned 4 conditions. It is unclear whether all these conditions must be present simultaneously or whether even one of them means resistance.
5-Please add a statement to the paper that the ethics committee approved the study.
6-How did the authors determine the volume of DEB and microspheres needed for DEB-TACE in each patient? Did they use the same volume of the agent for all patients?
7-What was the method of embolization regarding the advancement of the catheter tip? Did the authors inject the mixture at the beginning of the hepatic artery, or did they advance the catheter tip to the origin of the specific vascular bed of the tumor? A patient could have more than one lesion, and superselective TACE of a mass could be effective only for that mass; other masses should be treated separately. Please explain this further in the paper.
8-Did the authors consider hepatic vein or artery thrombosis an exclusion criterion?
9-The authors did not mention the size of the microspheres used in patients. Did they select the size of DEB based on the angiographic vascular blush of the tumor? Or did they use a single form for all patients?
10-Please add the full forms of abbreviations as footnotes to the tables. In addition, please add the full forms of abbreviations at their first occurrence in the text.
11-If a patient had more than one lesion, it is possible that one lesion could show CR while another could show PR, SD or DP. It would then be unclear how the authors determined whether the patient had CR, SD, PR or DP. Please explain this in the paper.
12-It would be better for the authors to determine the distribution of lesion responses per patient. I mean that it would be better for them to determine the status of the lesions regarding the response rate in all patients. [It would be better to add this information in a table.] [For example: patient 1 had 2 lesions, 3 and 4 cm in diameter, at week 6; the first lesion showed PR and lesion 2 showed SD; at week 12, lesion one showed PR and lesion 2 showed PR too.] This report could provide better insight for readers.
13-What imaging evaluation methods were used for the patients? [How many underwent CT, and how many underwent MRI?]
14-It would be better if the authors evaluated the relationship between lesion response [response rate based on size reduction, response rate based on CR+PR] and important independent variables such as age, sex, previous treatments, metastasis, baseline pathology [HBV, HCV, …], Child-Pugh staging, number of lesions, size of lesions, enhancement pattern, etc. This analysis could be performed on a patient basis and a lesion basis and requires linear regression and/or logistic regression analysis. [The 12-week analysis would be better.]
15-Please state in the statistical analysis section whether the normality of the data was checked before the tests.
16-The statistical test for table 3 should be a paired t-test [if the data are normal]. Please correct this. [When the data are not normal, it should be the Wilcoxon test.] In addition, I think the authors should analyze the variables in table 3 at the three time points—before, 1 week and 6 weeks—using repeated-measures ANOVA

[three repeated measurements] if the data are normal, or the Friedman test [if the data are not normal].
17-Please describe or mention the severity scoring system for complications in table 4. [As a footnote in the table and a description in the text.]
18-Did the authors use sorafenib therapy? Please add the data.
19-Were there lesions with PR or SD at 6 weeks that showed DP at 12 weeks? Please add the data to the table.

20-Is the definition of resistance patient-based or lesion-based? Please describe this in the paper.
21-It would be good if the authors reported the mean size reduction [and the mean percentage reduction in lesion size at 6 and 12 weeks].
22. Please note the type of chemotherapy drugs.

Editor-in-Chief

MAJOR REVISION 20 Feb 2021

Dear authors,
Your article needs Major Revision.
Regards

2

Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Prof. Kavous Firouznia,

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "**The efficacy and safety of DEB-TACE for the hepatocellular carcinoma patients with c-TACE resistance: a retrospective study**" (**ID: 110538**). These comments are valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our study.

We have studied comments carefully and have made correction item by item which we hope to meet with approval. Revised portions are marked in red in the paper. Point-by-point responses to the reviewers' comments are listed below this letter.

We hope that the revised version of the manuscript is now acceptable for publication in your journal. I look forward to hearing from you soon.

Yours sincerely,

Responses to comments from reviewers

Reviewer 1:

1. Proper article TITLE, structured ABSTRACT, Accurate RESULTS and relevant DISCUSSION ...I think it is Approved.

Response: We have revised the title, results, discussion, etc. according to the reviewer's request.

Reviewer 2:

The manuscript follows a good structure and gives useful information, however, I would suggest the following:

1. As DEB-TACE is a new method in comparison to the conventional method what was your plan for the management of probable adverse reaction and the follow-up treatment (please mentioned in the method section)

Response: We have added corresponding content in the new section (in Page 7):
Prevention and treatment of adverse reactions and complications of DEB-TACE.

We should prevent and deal with adverse reactions and complications. The common adverse reactions of DEB-TACE are mainly post-embolization syndrome, which mainly manifests as liver pain, fever, nausea and vomiting. Other adverse reactions include liver damage and bone marrow suppression caused by chemotherapy drugs.

If the patient has an adverse reaction, we will deal with it as follows:

Pain: We evaluate the patient's pain level according to the visual analogue

scale (VAS). If the patient has pain, it can be treated with tramadol 100 mg by intramuscular injection and parecoxib 40 mg by intravenous bolus injection.

Fever: If the patient has a low fever, physical cooling can be taken. If the patient has moderate and high fever, non-steroidal anti-inflammatory drugs such as indomethacin suppository 50 mg orally can be used. If fever exceeds 39°C, be wary of co-infection and give antibiotics if necessary.

Nausea and vomiting: Once the patient has nausea, vomiting and other discomforts, we can give the patient gastrointestinal protection drugs and antiemetic drugs, such as ondansetron hydrochloride 8 mg or tropisetron hydrochloride 5 mg by intramuscular injection for treatment.

Liver damage: If the patient has liver damage, we routinely give the patient liver protection drugs and drugs to reduce transaminase for treatment.

Bone marrow suppression: If the patient has bone marrow suppression, we treat it symptomatically according to the degree of bone marrow suppression.

2. Please mention the drugs Chemotherapy drugs used in this study.

Response: In the section of Drugs loading methods, the drug epirubicin contained in CalliSpheres drug-loaded microspheres has been added (in Page 5).

3. In TACE procedure it is important to achieve complete occlusion of target artery and that's recommended to use Gelfoam after C-TACE for this reason, if there is no need for using Gelfoam in DEB-TACE please mentioned it as a benefit in the discussion section.

Response: Generally, gelatin sponge is not added. If hepatic artery-portal fistula or hepatic artery-hepatic venous fistula is found on hepatic arteriography, try to super-select intubation, and the microcatheter goes over the fistula to reach the tumor blood vessel for embolization treatment. If the microcatheter cannot pass through the fistula, select the gelatin sponge particles with the appropriate diameter according to the type, location and size of the fistula. Generally, the particle size is used to close the fistula as much as possible. Observe closely to prevent the microspheres from entering the portal vein or hepatic vein through the fistula.

4. Please add the patient's final angiography photo to the patient's figures that provide comparable angiographic changes.

Response: We have added **Figure1** in the article.

Reviewer 3:

1. the authors mentioned: "…… in patients with conventional transarterial chemoembolization (c-TACE) resistant." I think it is resistance not resistant.

Response: We revised it as suggested (in Page 1, 2, 3).

2. Please add objective part to the paper according to journal format.

   Response: We revised it as suggested (in Page 2).

3. At the beginning of method section, please combine the term: “Definition of c-TACE resistance:” in the later part. it is not a good style to begin method section. I addition, please write Inclusion criteria: as “Inclusion criteria were as follows”.

   Response: We revised it as suggested (in Page 4).

4. In the definition of the -TACE resistance, the authors mentioned 4 condition. It is unknown if all these conditions should be seen simoultaneously or even one of them mean resistance.

   Response: The definition of c-TACE resistance uses the standards recognized by the Japan Liver Cancer Research Association in 2014. The presence of one of the four conditions in the definition of the patient is regarded as c-TACE resistance (in Page 4).

5. Please add in the paper that the ethics committee has approved the study.

   Response: We revised it as suggested (in Page 13).

6. How did the authors determine the volume of DEB and microspheres needed for DEB-TACE in each patient? Did they use a single volume of the agent?

   Response: In this study, the particle size of the drug-loaded microspheres was selected according to the size of the tumor and the blood supply of the tumor. Due to individual differences, the particle size used in this study is inconsistent.

7. What was the method of embolization regarding the advancement of catheter tip? Did the authors injected the mixture at the beginning of hepatic artery or they advanced the catheter tip up to the specific vascular bed origin of tumor? As the patient could have more than one lesion and superselective TACE of a mass could be effective only for the mass and other masses should be treated separately. Please explain more in this regard in the paper.

   Response: We use a microcatheter to superselect to the tumor supplying artery. After confirming that the tumor supplying artery is in the correct position, we use a microcatheter with a slow and stable (1ml/min) flow rate (determined according to the tumor location, patient age, patient pain threshold, etc.) Intermittently and slowly inject the suspension of drug-loaded microspheres, chemotherapeutics and

contrast agents into the tumor supply artery. If there is an obvious arteriovenous shunt, suitable embolic materials, such as gelatin sponge or PVA particles, should be used first, and the shunt should be blocked, and then the drug-loaded microspheres should be injected. In the process of bolus injection of microspheres, keep the microspheres evenly distributed in the syringe to avoid precipitation of the microspheres. We use a 1 ml syringe each time, using the pulse injection method, while injecting and shaking the syringe. We embolized the tumor branch by branch according to the blood supply of the tumor, observed the flow rate of the chemotherapeutic drug and contrast medium suspension, and stopped the bolus injection when the embolization endpoint was reached (Contrast agent is not drained for 3 to 4 cardiac cycles, which can be regarded as complete embolism rather than blood flow stagnation). After stopping for 5 minutes, angiography was performed again. If tumor staining still exists, embolization is continued until the end point of embolization is reached (the tumor staining disappears).

8. Did the authors consider hepatic vein or artery thrombosis as an exclusion criteria?

   Response: The patients included in this article were determined according to the inclusion criteria of the 2019 Primary Liver Cancer Diagnosis and Treatment Guidelines. The guidelines stipulate that the patients, who with the main portal vein is not completely blocked, or the hepatic artery and the portal vein are completely blocked but compensatory collateral blood vessels are formed, can be included in this study (in Page 4).

9. The authors did not mention the size of microspheres used in patients. Did the select the size of DEB based on the angiographic vascular blush of the tumor? Or they used a single form for all patients?

   Response: All patients in the group used microspheres with a diameter of 100-300 μm.

10. Please add abbreviations in full term in tables as footnote. In addition please add full term of abbreviations in first time in the text.

    Response: We revised it as suggested (in Page 12).

11. If a patient had more than one lesion, it is probable that one lesion show CR while the other could show PR, SD or DP. Then it would be questionable how did the authors determine if the patient is CR, SD, PR or DP. Please explain in this regard in the paper.

    Response: The evaluation criteria (mRECIST) for solid tumors used in this article are recommended by the 2012 EASL liver cancer guidelines (*European Association For The Study Of The L, European Organisation For R Treatment Of EASL-EORTC*

clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908–43). We have reason to believe in its reliability and practicality (in Page 6).

12. It is better the authors determine the distribution of the lesion responses per patient. I mean it is better they determine in all patients what was the situation of the lesions regarding the response rate. [it is better to be add in a table] [for example: patient 1 had 2 lesions, 3 and 4 cm in diameters in week 6; first lesion showed PR and lesion 2 showed SD, in weeks 12 lesion one was in PR and lesion 2 was PR too]. This report could make a better insight for readers.

    Response: In Table 2, we have provided the patient's tumor remission in the 12th week after DEB-TACE treatment mRECIST (in Page 21).

13. What were the imaging evaluation methods among the patients? [how many CT, how many MRI?]

    Response: In this study, 16 patients were evaluated by CT, and 3 patients were evaluated by MRI.

14. It is better if the authors evaluate the lesion response [response rate based on size reduction, response rate based on CR+PR] with important independent variables such as age, sex, previous treatments, metastasis, baseline pathology [HBV, HCV, ..], child-pugh staging, number of lesion, size of lesion, enhancement pattern, etc. this analysis could be performed patient based and lesion based and needs linear regression and/or logistic regression analysis. [The 12 weeks analysis is better]

    Response: On the one hand, this study has a shorter evaluation time for tumors. Second, this study aims to explore the efficacy and safety of DEB-TACE. Therefore, we did not use baseline age, sex, previous treatments, metastasis, baseline pathology [HBV, HCV, ..], child-pugh staging, number of lesion to analyze independent risk factors for tumor progression.

15. Please add in statistical analysis if the normality of data were cecked before tests?

    Response: This study aims to explore the efficacy and safety of DEB-TACE. Therefore, only data related to the baseline and the efficacy after DEB-TACE treatment were selected.

16. The statistical test for table 3 should be paired t-test [if the data is normal]. Please correct. [whan the data is not normal, it should be wilcoxon] in addition, I think the authors should analyze three sessions of before, 1 week and 6 weeks variables in table 3 by repeated measure ANOVA [three measurements that are repeated] if the data are normal or by Friedman test [if the data are not normal]

Response: Statistical differences (liver enzymes, blood routine, and AFP levels) between groups were assessed by paired t-test (in Page 22).

17. Please describe or mention the severity score system of complications in table 4. [as a footnote in table and description in text]

    Response: In this study, the Common Terminology Criteria Adverse Events （CTCAE V5.0）（*Common Terminology Criteria for Adverse Events (CTCAE) Version 5. Published: November 27. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute*） was used to evaluate the safety of DEB-TACE, which has been added in the part of Assessment of clinical safety (in Page 6-7).

18. Did the authors have sorafenib therapy? Please add the data.

    Response: None of the patients included in this study were treated with sorafenib.

19. Did the authors had lesions with PR or SD in 6 week while the lesion showed DP in 12 weeks? Please add data in table.

    Response: We revised it as suggested (in Page 21).

20. As the DEB make a considerable stagnation of blood in the vascular bed, it could make thrombus in the tumor location and this can make lack of perfusion in follow up imaging and thus be interpreted as CR while the reason is not vanishing of the tumor, rather it could be due to lack of perfusion in the tumor location that present itself as no enhancement [and tumor remnant is viable]. how did the authors could rule out such event? [this could interfere with correct interpretation of response rate].

    Response: For tumor lesions lacking blood supply, we can determine whether the tumor is progressing by puncturing the liver of the suspicious lesion.

21. Is definition of resistance patient based or lesion based? Please describe in paper.

    Response: The definition of resistance based on lesion (in Page 4).

22. It would be good if the authors mention mean size reduction [and mean reduction percent of lesions in 6 and 12 weeks]

    Response: Since the size of the tumor is irregular, we have measured it in accordance with the evaluation criteria of the international guidelines.

Associate Editor's Comments:
Associate Editor 1:
dear Editorial
according to manuscript entiteld as: The clinical application of DEB-TACE for c-TACE resistant hepatocellular carcinoma patients
Manuscript ID: 110538
the reviewers commented as:

1. The authors mentioned: "…… in patients with conventional transarterial chemoembolization (c-TACE) resistant." I think it is resistance not resistant.

   Response: We revised it as suggested (in Page 1, 2, 3).

2. Please add objective part to the paper according to journal format.

   Response: We revised it as suggested (in Page 2).

3. At the beginning of method section, please combine the term: "Definition of c-TACE resistance:" in the later part. it is not a good style to begin method section. I addition, please write Inclusion criteria: as "Inclusion criteria were as follows".

   Response: We revised it as suggested (in Page 4).

4. In the definition of the -TACE resistance, the authors mentioned 4 condition. It is unknown if all these conditions should be seen simoultaneously or even one of them mean resistance.

   Response: The definition of c-TACE resistance uses the standards recognized by the Japan Liver Cancer Research Association in 2014. The presence of one of the four conditions in the definition of the patient is regarded as c-TACE resistance (in Page 4).

5. Please add in the paper that the ethics committee has approved the study.

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6. How did the authors determine the volume of DEB and microspheres needed for DEB-TACE in each patient? Did they use a single volume of the agent?

   Response: In this study, the particle size of the drug-loaded microspheres was selected according to the size of the tumor and the blood supply of the tumor. Due to individual differences, the particle size used in this study is inconsistent.

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   Response: We use a microcatheter to superselect to the tumor supplying artery. After confirming that the tumor supplying artery is in the correct position, we use a microcatheter with a slow and stable (1ml/min) flow rate (determined according to the tumor location, patient age, patient pain threshold, etc.) Intermittently and slowly inject the suspension of drug-loaded microspheres, chemotherapeutics and contrast agents into the tumor supply artery. If there is an obvious arteriovenous shunt, suitable embolic materials, such as gelatin sponge or PVA particles, should be used first, and the shunt should be blocked, and then the drug-loaded microspheres should be injected. In the process of bolus injection of microspheres, keep the microspheres evenly distributed in the syringe to avoid precipitation of the microspheres. We use a 1 ml syringe each time, using the pulse injection method, while injecting and shaking the syringe. We embolized the tumor branch by branch according to the blood supply of the tumor, observed the flow rate of the chemotherapeutic drug and contrast medium suspension, and stopped the bolus injection when the embolization endpoint was reached (Contrast agent is not drained for 3 to 4 cardiac cycles, which can be regarded as complete embolism rather than blood flow stagnation). After stopping for 5 minutes, angiography was performed again. If tumor staining still exists, embolization is continued until the end point of embolization is reached (the tumor staining disappears).

8. Did the authors consider hepatic vein or artery thrombosis as an exclusion criteria?

   Response: The patients included in this article were determined according to the inclusion criteria of the 2019 Primary Liver Cancer Diagnosis and Treatment Guidelines. The guidelines stipulate that the patients, who with the main portal vein is not completely blocked, or the hepatic artery and the portal vein are completely blocked but compensatory collateral blood vessels are formed, can be included in this study (in Page 4).

9. The authors did not mention the size of microspheres used in patients. Did the select the size of DEB based on the angiographic vascular blush of the tumor? Or they used a single form for all patients?

   Response: All patients in the group used microspheres with a diameter of 100-300 μm.

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term of abbreviations in first time in the text.

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Response: The evaluation criteria (mRECIST) for solid tumors used in this article are recommended by the 2012 EASL liver cancer guidelines (European Association For The Study Of The L, European Organisation For R Treatment Of EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908–43). We have reason to believe in its reliability and practicality (in Page 6).

12. It is better the authors determine the distribution of the lesion responses per patient. I mean it is better they determine in all patients what was the situation of the lesions regarding the response rate. [it is better to be add in a table] [for example: patient 1 had 2 lesions, 3 and 4 cm in diameters in week 6; first lesion showed PR and lesion 2 showed SD, in weeks 12 lesion one was in PR and lesion 2 was PR too]. This report could make a better insight for readers.

Response: In Table 2, we have provided the patient's tumor remission in the 12th week after DEB-TACE treatment mRECIST (in Page 21).

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Response: In this study, 16 patients were evaluated by CT, and 3 patients were evaluated by MRI.

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Response: On the one hand, this study has a shorter evaluation time for tumors. Second, this study aims to explore the efficacy and safety of DEB-TACE. Therefore, we did not use baseline age, sex, previous treatments, metastasis, baseline pathology [HBV, HCV, ..], child-pugh staging, number of lesion to analyze independent risk factors for tumor progression.

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    Response: This study aims to explore the efficacy and safety of DEB-TACE. Therefore, only data related to the baseline and the efficacy after DEB-TACE treatment were selected.

16. The statistical test for table 3 should be paired t-test [if the data is normal]. Please correct. [whan the data is not normal, it should be wilcoxon] in addition, I think the authors should analyze three sessions of before, 1 week and 6 weeks variables in table 3 by repeated measure ANOVA [three measurements that are repeated] if the data are normal or by Friedman test [if the data are not normal].

    Response: Statistical differences (liver enzymes, blood routine, and AFP levels) between groups were assessed by paired t-test (in Page 22).

17. Please describe or mention the severity score system of complications in table 4. [as a footnote in table and description in text].

    Response: We revised it as suggested (in Page 6-7).

18. Did the authors have sorafenib therapy? Please add the data.

    Response: None of the patients included in this study were treated with sorafenib.

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    Response: We revised it as suggested (in Page 21).

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    Response: The definition of resistance based on lesion (in Page 4).

21. It would be good if the authors mention mean size reduction [and mean reduction percent of lesions in 6 and 12 weeks].

    Response: Since the size of the tumor is irregular, we have measured it in accordance with the evaluation criteria of the international guidelines.

22. Please note the type of chemotherapy drugs.

    Response: In the section of Drugs loading methods, the drug epirubicin contained in CalliSpheres drug-loaded microspheres has been added (in Page 5).

2 Revision 1

3 comments · 29 Aug 2021 – 15 Sep 2021

Referee 2 Reviewer

MINOR REVISION 29 Aug 2021

1-Please add or separate the objective section of the paper before the method section.
2-The response and explanation to question 4 should be added to the paper. [I mean the definition of c-TACE; the authors should add the following part to the paper: "The presence of one of the four conditions in the definition of the patient is regarded as c-TACE resistance"]
3-It is better for the authors to mention the phrase ethics committee approval in the paper [they mentioned only hospital approval].
4-Please add this explanation to the paper: “In this study, the particle size of the drug-loaded microspheres was selected according to the size of the tumor and the blood supply of the tumor. Due to individual differences, the particle size used in this study is inconsistent.”
5-I asked a question regarding the angiography technique [Q7: What was the method of embolization regarding the advancement of catheter tip? Did the authors injected the mixture at the beginning ….] and the authors replied to this question and mentioned many points in this regard, but they did not mention the important points of the response in the paper. Please add the important points of the response to the paper [I mean this response: "We use a microcatheter to superselect to the tumor supplying artery. After confirming that the tumor ……."]
6-Please add this part of the response to question 8 to the paper: “The guidelines stipulate that the patients, who with the main portal vein is not completely blocked, or the hepatic artery and the portal vein are completely blocked but compensatory collateral blood vessels are formed, can be included in this study”
7-Please add this part to the paper: “All patients in the group used microspheres with a diameter of 100-300 µm.”
8-The response to question 11 ["If a patient had more than one lesion, it is probable that one lesion show CR while the other could show PR, SD or DP. ……."] is not related to the question. Please add a relevant response to the question.
9-Please define the abbreviations used in the tables in the table footnotes. [For example, CR, PR, …. in table 2]
10-Please add this part to the paper: “16 patients were evaluated by CT, and 3 patients were evaluated by MRI”
11-This response to question 15 is not related to the question: “This study aims to explore the efficacy and safety of DEB-TACE. Therefore, only data related to the baseline and the efficacy after DEB-TACE treatment were selected.”
12-Please add this explanation to the paper: “None of the patients included in this study were treated with sorafenib”
13-Please add the explanation in response to question 20 to the paper and discuss it [this response should be added with further explanation: “For tumor lesions lacking blood supply, we can determine whether the tumor is progressing by puncturing the liver of the suspicious lesion.”]

Associate Editor

MINOR REVISION 15 Sep 2021

1-Please add or separate the objective section of the paper before the methods section.
2-The response and explanation to question 4 should be added to the paper. [I mean the definition of c-TACE; the authors should add the following part to the paper: “The presence of one of the four conditions in the definition of the patient is regarded as c-TACE resistance”]
3-It is better for the authors to mention ethics committee approval in the paper [they mentioned only

hospital approval].
4-Please add this explanation to the paper: “In this study, the particle size of the drug-loaded microspheres was selected according to the size of the tumor and the blood supply of the tumor. Due to individual differences, the particle size used in this study is inconsistent.”
5-I asked a question regarding the angiography technique [“Q7: What was the method of embolization regarding the advancement of catheter tip? Did the authors injected the mixture at the beginning ….”], and the authors replied to this question and mentioned many points in this regard, but they did not mention the important points of the response in the paper. Please add the important points of the response to the paper [I mean this response: “We use a microcatheter to superselect to the tumor supplying artery. After confirming that the tumor ….…..”].
6-Please add this part of the response to question 8 to the paper: “The guidelines stipulate that the patients, who with the main portal vein is not completely blocked, or the hepatic artery and the portal vein are completely blocked but compensatory collateral blood vessels are formed, can be included in this study”
7-Please add this part to the paper: “All patients in the group used microspheres with a diameter of 100-300 µm.”
8-The response to question 11 [“If a patient had more than one lesion, it is probable that one lesion show CR while the other could show PR, SD or DP. ….…..”] is not related to the question. Please add a relevant response to the question.
9-Please write out the abbreviations used in the tables in full in the table footnotes. [For example, CR, PR, …. in table 2]
10-Please add this part to the paper: “16 patients were evaluated by CT, and 3 patients were evaluated by MRI”
11-This response to question 15 is not related to the question: “This study aims to explore the efficacy and safety of DEB-TACE. Therefore, only data related to the baseline and the efficacy after DEB-TACE treatment were selected.”
12-Please add this explanation to the paper: “None of the patients included in this study were treated with sorafenib”
13-Please add and discuss the explanation given in response to question 20 in the paper [this response should be added with more explanation: “For tumor lesions lacking blood supply, we can determine whether the tumor is progressing by puncturing the liver of the suspicious lesion.”]

Editor-in-Chief MINOR REVISION 15 Sep 2021

Dear authors,
Your article needs Minor Revision.
Regards

3

Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Editor,

The efficacy and safety of DEB-TACE for the hepatocellular carcinoma patients with c-TACE resistance: a retrospective study

The manuscript has been improved according to the suggestions of reviewers:

1-Please add or separate objective part of paper before method section.

Reply: Thank you very much for your comments. We have added "This study was aimed to investigate the clinical efficacy and safety of transarterial chemoembolization with drug-eluting beads microspheres (DEB-TACE) in hepatocellular carcinoma patients with conventional transarterial chemoembolization (c-TACE) resistance."

2-the response and explanation to question 4 should be added in paper. [I mean definition of c-TACE, the authors should add following part to the paper: The presence of one of the four conditions in the definition of the patient is regarded as c-TACE resistance]

Reply: Thank you very much for your comments. We have added "The presence of one of the four conditions in the definition of the patient is regarded as c-TACE resistance".

3-it is better the authors mention the word ethics committee approval in paper [they mentioned only hospital approval]

Reply: Thank you very much for your comments. We have added the statements.

4-please add this explanation to the paper: "In this study, the particle size of the drug-loaded microspheres was selected according to the size of the tumor and the blood supply of the tumor. Due to individual differences, the particle size used in this study is inconsistent."

Reply: Thank you very much for your comments. We have added it in our methods

part.

5-i asked a question regarding the angiography technique [Q7: What was the method of embolization regarding the advancement of catheter tip? Did the authors injected the mixture at the beginning ….] and the authors replied to this question and mentioned many points in this regard but they did not mention the important points of response in paper. please add the important points of response to the paper [I mean this response: We use a microcatheter to superselect to the tumor supplying artery. After confirming that the tumor ……..…]

Reply: Thank you very much for your comments. We have added it in the part of "Treatment procedure of DEB-TACE".

6-please add this part of response to question 8 to the paper: "The guidelines stipulate that the patients, who with the main portal vein is not completely blocked, or the hepatic artery and the portal vein are completely blocked but compensatory collateral blood vessels are formed, can be included in this study"

Reply: Thank you very much for your comments. We have added it in the Inclusion criteria:

7-please add this part to paper: "All patients in the group used microspheres with a diameter of 100-300 μm."

Reply: Thank you very much for your comments. We have added it in the methods part.

8-Response to question 11 [If a patient had more than one lesion, it is probable that one lesion show CR while the other could show PR, SD or DP. ……..] is not related to question. Please add a relevant response to question.

Reply: Thank you very much for your comments. We have reviewed our data, this situation was not found in our study. However, we considered that if a patient had more than one lesion with different remission, this patient would be defined as a

serious kind.

9-please add the abbreviations in tables as full term in footnotes of tables. [for example, CR, PR, ….. in table 2]

Reply: Thank you very much for your comments. We have added the abbreviations in footnotes of tables.

10-please add this part to paper: "16 patients were evaluated by CT, and 3 patients were evaluated by MRI"

Reply: Thank you very much for your comments. We have added this in the results part.

11-this response to question 15 is not related to the question: "This study aims to explore the efficacy and safety of DEB-TACE. Therefore, only data related to the baseline and the efficacy after DEB-TACE treatment were selected."

Reply: Thank you very much for your comments. We have added "Normality of the data was evaluated with the Shapiro-Wilks test." in our methods part.

12-please add this explanation to paper: "None of the patients included in this study were treated with sorafenib"

Reply: Thank you very much for your comments. We have added this in our results part.

13-please add and discuss the explanation to question 20 to the paper [this response should be added with more explain: "For tumor lesions lacking blood supply, we can determine whether the tumor is progressing by puncturing the liver of the suspicious lesion."]

Reply: Thank you very much for your comments. We have added in the discussion part as "As the DEB lead a considerable stagnation of blood in the vascular bed, it could cause thrombus in the tumor location, which can lead to the lack of perfusion in

the follow up imaging. Thus, the evaluation on the patient could be interpreted as CR, the reason is not vanishing of the tumor, rather it could be due to lack of perfusion in the tumor location that present itself as no enhancement. Therefore, in this situation, we should be very carefully and determine whether the tumor is progressing by puncturing the liver of the suspicious lesion."

We have tried our best to revise and improve the manuscript and made great changes in the manuscript according to the Reviewers' good comments. We appreciate for Editors/Reviewers' warm work earnestly and hope that the corrections will meet with approval. Once again, thank you very much for your comments and suggestions.

Yours sincerely,

3 Revision 2

1 comment · 26 Feb 2022

Editor-in-Chief

MINOR REVISION 26 Feb 2022

Dear authors,
Your article needs Minor Revision.
Regards

4

Revision 3

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Editor,

The efficacy and safety of DEB-TACE for the hepatocellular carcinoma patients with c-TACE resistance: a retrospective study

The manuscript has been improved according to the suggestions of reviewers:

Associate Editor 1:

Accept

Reply: Thank you very much for your comments.

Associate Editor 2:

1-please mention and arrange references in a sequential order in the text. [for example, we can see the reference 25 has been mentioned after reference 3]

Reply: Thank you very much for your comments. We have modified the reference.

2-As the study is not a randomized trial or prospective before-after trial [the study is retrospective], it is better the authors apply some changes in the paper:

Reply: Thank you very much for your comments. We have made the corrections.

2-I-In the title: it is better the title be changed as follows: [please note that the first characters should be capitalized]: "Treatment Benefits and Adverse Reactions of Transarterial Chemoembolization with Drug-Eluting Beads Microspheres (DEB-TACE) in the Hepatocellular Carcinoma Patients with c-TACE Resistance: A Retrospective Study"

Reply: Thank you very much for your comments. We have corrected the title.

2-II-In the conclusion of abstract: Please correct the conclusion of abstract as follows: "In this study, DEB-TACE in patients with c-TACE resistance in hepatocellular carcinoma can bring treatment benefits and low adverse reactions."

Reply: Thank you very much for your comments. We have corrected it.

2-III-In the objective part of abstract and paper, please apply following corrections: in objective part of abstract: "This retrospective study aims to investigate the treatment benefits and adverse reactions of transarterial chemoembolization with drug-eluting beads microspheres (DEB-TACE) in HCC patients with conventional TACE (c-TACE) resistance."

And in objective part of paper: "This study aims to investigate the treatment benefits and adverse reactions of DEB-TACE in HCC patients with c-TACE resistance."

Reply: Thank you very much for your comments. We have corrected it.

3-the authors mentioned: "According to the modified response evaluation criteria in solid tumors (mRECIST), the efficacy evaluation was divided into complete remission (CR), partial remission (PR), stable disease (SD) and progressive disease (PD), objective remission rate (ORR) and disease control rate (DCR), at Week 1and Week 6 after the DEB-TACE treatment." While they have mentioned later: "At Week 6 and Week 12 after DEB-TACE for -TACE resistance patients" it is confusing what were the time of follow up assessments? Weeks 1 and 6 or weeks 6 and 12? Please clarify this point and correct it in all parts of paper.

Reply: Thank you very much for your comments. We have corrected it as "at Week 6 and Week 12 after the DEB-TACE treatment."

4-the objective part of paper should be separately mentioned and numbered from background.

Reply: Thank you very much for your comments. We have corrected it.

5-in line 72; please correct: "who were c-TACE resistant."

Reply: Thank you very much for your comments. We have corrected it.

6-in line 73, please correct: "Inclusion criteria were as follows:"

Reply: Thank you very much for your comments. We have corrected it.

7-in line 81, please correct: "Exclusion criteria were as follows:"

Reply: Thank you very much for your comments. We have corrected it.

8- in line 83, please correct: "Definition of c-TACE resistance was as follows:"

Reply: Thank you very much for your comments. We have corrected it.

9-this sentence is unclear: "A 2.7F Progreat microcatheter (Terumo, Japan) was superselected to the tumor blood supply arteriography"

Reply: Thank you very much for your comments. We have corrected it as "A 2.7F Progreat microcatheter (Terumo, Japan) was selected for the tumor blood supply arteriography".

10-in line 108, this part is unclear: "slow pulsed injection (about 1ml/min),"

Reply: Thank you very much for your comments. We have deleted "slow pulsed injection (about 1ml/min)".

11-the SPSS manufacturer data is wrong. Please use the IBM site for this purpose [https://www.ibm.com/support/pages/how-cite-ibm-spss-statistics-or-earlier-versions-spss]

Reply: Thank you very much for your comments. We have corrected it as "SPSS Statistics package (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp)".

12-pleaser ad the unites for variables for ; example year for age.

Reply: Thank you very much for your comments. We have corrected it.

13-in the line 188, the authors mentioned: "The success rate of the DBE-TACE procedure in 17 patients was 100%." I think they mean the technical success rate …..

Reply: Thank you very much for your comments. We have corrected it as "The

techn*ical* success rate of the DBE-TACE procedure in 17 patients was 100%".

14-in line 190, the part "(Figure A-D)," is better to be transferred to the end of sentence.

Reply: Thank you very much for your comments. We have corrected it.

15-in line 244, the authors mentioned "low effective rate" it seems to be "low effectiveness rate"

Reply: Thank you very much for your comments. We have corrected it.

16-please correct the DED-TACE in line 254.

Reply: Thank you very much for your comments. We have corrected it.

17- only 7 references have been mentioned in this version.

Reply: Thank you very much for your comments. We have corrected it.

18-In table 3, footnotes a and b seems confusing and these could be improved as below [or something like these]:

a Comparison between before DEB-TACE and 1 Week after DEB-TACE using paired t-test

b Comparison between before DEB-TACE and 6 Weeks after DEB-TACE using paired t-test

Reply: Thank you very much for your comments. We have corrected it.

19-please change the (Figure A-D) to (Figure 1 A-D), and mention the figure legend as figure 1.

Reply: Thank you very much for your comments. We have corrected it.

20-the authors mentioned in figure 1C legend: Figure C. At Week 6 after the DBE-TACE treatment, CT showed that the tumor was significantly reduced, …. It is better

the authors mention: ….. showed that the tumor size was ….. please apply similar change in figure 1D legend.

Reply: Thank you very much for your comments. We have corrected it.

21-In figure legends part B, its better mentioned 'DSA angiography confirmed the CT signs mentioned in figure A.

Reply: Thank you very much for your comments. We have corrected it.

We have tried our best to revise and improve the manuscript and made great changes in the manuscript according to the Reviewers' good comments. We appreciate for Editors/Reviewers' warm work earnestly and hope that the corrections will meet with approval. Once again, thank you very much for your comments and suggestions.

Yours sincerely,

4 Revision 3

1 comment · 11 Apr 2022

Editor-in-Chief

MINOR REVISION 11 Apr 2022

Dear authors,
Before starting the review process for your article, it is necessary to clarify the following item:
Given the importance of “conflict of interest” clarification, the corresponding author should fill out the “ICMJE form” and upload it during the submission process. (The form is available in the “conflict of interest” section of the site:
https://brief.land/iranjradiol/knowledgebase/category/tree.html#conflicts_of_interest.html).
Regards

5

Revision 4

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Editor,

> EIC Decision:

Dear authors,

Before starting the review processing of your article, it is necessary to clarify the following item:

Regarding the importance of “conflict of interest” clarification, the corresponding author should fill out the “ICMJE form” form and upload in the submission process. (The form exists in “conflict of interest” section of the site: https://brief.land/iranjradiol/knowledgebase/category/tree.html#conflicts_of_interest.html).

Regards

Reply: I have fill in the the“ICMJE form”.

Yours sincerely,

5 Revision 4

1 comment · 18 Apr 2022

Editor-in-Chief

MINOR REVISION 18 Apr 2022

Dear authors,
Your article needs Minor Revision.
Regards

6

Revision 5

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

May 5, 2022

Dear Editor,

Treatment Benefits and Adverse Reactions of Transarterial Chemoembolization with Drug-Eluting Beads Microspheres (DEB-TACE) in the Hepatocellular Carcinoma Patients with c-TACE Resistance: A Retrospective Study

The manuscript has been improved according to the suggestions of reviewers:

Reviewer 1:

This paper is suitable for publication in IJR.

Reply: Thank you very much for your comments.

Associate Editor 1:

1-please add full term of abbreviations in abstract and paper separately for example AFP, ALT, AST, TB, and WBC….

Reply: Thank you very much for your comments. We have added the full term of abbreviations.

2-in line 113, Child-Pugh is usually mentioned as score not grade and stage.

Reply: Thank you very much for your comments. We have corrected it as “Child-Pugh score < 10”

3-this part is unclear. Please write it better: “The guidelines stipulate that the patients, who with the main portal vein is not completely blocked, or the hepatic artery and the portal vein are…..”

Reply: Thank you very much for your comments. We have corrected it as “T*he p*atients, whose main portal vein is not completely blocked, or the hepatic artery and the portal vein are completely blocked but compensatory collateral blood vessels are formed, can be included in this study.”

4-in line 118, please correct Excluded to Exclusion

Reply: Thank you very much for your comments. We have corrected it.

5-what is the meaning of 8 in "8Spheres polyethylene microspheres" [line 154]

Reply: Thank you very much for your comments. It is a typo error, we have corrected it as "Spheres polyethylene microspheres".

6-this sentence is unclear: "In the process of bolus injection of microspheres, keep the microspheres evenly distributed in the syringe to avoid precipitation of the microspheres."

Reply: Thank you very much for your comments. We have corrected it as "For bolus injection of microspheres, the microspheres were kept evenly distributed in the syringe to avoid precipitation of the microspheres."

7-the sentences in the method part [especially in section treatment procedure of DEB-TACE] have been written in present time while it is better the authors write them in past tenses.

Reply: Thank you very much for your comments. We have corrected it

8-please correct: "……. experienced radiologists (more than 5 years working experience)……"

Reply: Thank you very much for your comments. We have corrected it

9-this sentence is unclear: "If fever exceeds 39°C, be wary of co-infection and give antibiotics if necessary."

Reply: Thank you very much for your comments. We have corrected it as "If body temperature exceeds 39°C, co-infection and antibiotics treatment should be considered."

10-in line 327, liver function damaged is better to be written as abnormal liver function or elevated liver function.

Reply: Thank you very much for your comments. We have corrected it as “abnormal liver function”.

11-figure 1 legend: please correct as: Curative effect of DBE-TACE procedure

Reply: Thank you very much for your comments. We have corrected it.

Associate Editor 2:

Thanks to the authors for their appropriate edition. Currently, this manuscript is ready for publication in the IJR.

Reply: Thank you very much for your comments.

We have tried our best to revise and improve the manuscript and made great changes in the manuscript according to the Reviewers’ good comments. We appreciate for Editors/Reviewers’ warm work earnestly, and hope that the corrections will meet with approval. Once again, thank you very much for your comments and suggestions.

Yours sincerely,

6 Revision 5

1 comment · 11 Jun 2022

Editor-in-Chief

ACCEPT 11 Jun 2022

Dear authors,
Your article is acceptable for publication in IJR.
Regards