Jiaping Yan

Dear Reviewer, Thank you so much for review, rating and comments. We have tried to make corrections according to the suggestions and requests made throughout the document. However, we were unable to answer and attach CONSORT 2010. This is because our study is an observational prospective nonrandomized study, not a randomized trial. How should we proceed in the absence of this document, is there any file / document that replaces CONSORT 2010?

1) Please don't include abbreviations in the title. The title should be no more than 12 words.
   -Thank you for the comment. We modify the title.

2) A short running title of no more than 6 words should be provided. It should state the topic of the paper
   -Thank you for the comment. We include the running title.

3) Designation of co-first authors and co-corresponding authors is not permitted. Author names (unabbreviated) should be given as first name, middle name (acronym, with no period) and family (sur) name, and typed in bold with the first letter capitalized
   -Thank you for the comment. We include this.

4) Author names (unabbreviated) should be given first as first name, middle name (acronym, with no period) and family (sur)name, and typed in bold with the first letter capitalized, with a hyphen included between the syllables of Chinese names, followed by the complete name of the affiliated institution, city, province/state, postcode and country typed in non-bold.
   -Thank you for the comment. We include this.

5) ORCID provides a persistent digital identifier that distinguishes you from every other researcher and, through integration in key research workflows such as manuscript and grant submissions, supports automated linkages between you and your professional activities, thereby ensuring that your work is recognized.
   -Thank you for the comment. We include this.

6) The format of this section will be as follows: Author contributions
   -Thank you for the comment. We include this.

7) Please provide the approval file of Institutional review board, and state it on the title page
   -Thank you for the comment. We include this in title page and submitted this.

8) Please provide the primary version (PDF) of the Informed Consent Form that has been signed by all subjects and investigators of the study, prepared in the official language of the authors' country to the system
-Thank you for the comment. We submitted this.

9) Any research study (clinical trial) that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes must be registered. Authors have 6 mo from the first patient enrollment to register the trial, but BPG recommends registration prior to enrollment. This registration policy applies to prospective, randomized, controlled trials only. Authors must provide the registration identification number and the URL for the trial's registry. In addition, the registration information must be provided in a PDF format, and the registered URL and registration identification number must also be mentioned as a footnote in the manuscript text.
-Thank you for the comment. There is no Clinical trial registration statement, it is a prospective nonrandomized study.

10) Please download the Conflict of Interest (PDF), fill it in, and then upload the completed PDF version to the system.
-Thank you for the comment. We submitted this.

11) Authors must state on the title page of the manuscript that the guidelines of the CONSORT 2010 Statement have been adopted (see below). Authors must upload the PDF version of the completed checklist to the system.
-Thank you for the comment. There is no Clinical trial registration statement, it is an observational prospective nonrandomized study. We were unable to answer and attach CONSORT 2010. How should we proceed in the absence of this document, is there any file / document that replaces CONSORT 2010? We sent an email asking that also.

12) Only one corresponding author is allowed. Designation of co-corresponding authors is not permitted. The corresponding author's contact information should be provided in the following format: Author names (unabbreviated) should be followed by the author's title in bold, and the affiliation, complete name of institution, present address, city, province/state, postcode, country, and E-mail. The corresponding author's E-mail address must be issued by his/her institution. All the letters in the E-mail address should be typed in lowercase, and separated from the country by a period and a space.
-Thank you for the comment. We include this.

13) Telephone and fax numbers should consist of +, country number, district number and telephone or fax number.
-Thank you for the comment. We include this.

14) The 5 sections of the structured abstract are: Background, Aims, Methods, Results, and Conclusion
-Thank you for the comment. We include this.

15) This section should clearly describe the rationale for the study. It should end with a statement of the specific study hypothesis
-Thank you for the comment. We include this.

16) The purpose of the study should be stated clearly, with no or minimal background information, following the format of: “To investigate/study/determine…”
-Thank you for the comment. We include this.

17) Please write a summary of no more than 100 words to present the core content of your manuscript, highlighting the most innovative and important findings and/or arguments. The purpose of the Core Tip is to attract readers’ interest for reading the full version of your article and increasing the impact of your article in your field of study.
-Thank you for the comment. We include this.

18) Please offer the audio core tip
-Thank you for the comment. We include this.

19) The guidelines for writing and formatting Article Highlights are as follows:
-Thank you for the comment. We include this.

20) Please check and confirm that there are no repeated references! Please add PubMed citation numbers (PMID NOT PMCID) and DOI citation to the reference list and list all authors. Please revise throughout. The author should provide the first page of the paper without PMID and DOI
-Thank you for the comment. We modified the references.

21) Regarding the figures (1): Please provide the decomposable figure of figures, whose parts are all movable and editable, organize them into a PowerPoint file, and submit as “Manuscript No. -Figures.ppt” on the system, we need to edit the words in the figures. All submitted figures, including the text contained within the figures, must be editable. Please provide the text in your figure(s) in text boxes.
-Thank you for the comment. We modified this and submitted this as power point.

22) Regarding the figures (2): Please provide the decomposable figure of figures, whose parts are all movable and editable, organize them into a PowerPoint file, and submit as “Manuscript No. -Figures.ppt” on the system, we need to edit the words in the figures. All submitted figures, including the text contained within the figures, must be editable. Please provide the text in your figure(s) in text boxes.
-Thank you for the comment. We modified this and submitted this as power point.

23) Please explain all the abbreviations of each figure/table under each piece of figure/table legends. (Fig 2)
-Thank you for the comment. We modified this and submitted this as power point.

24) Regarding the figures (3):Please provide the decomposable figure of figures, whose parts are all movable and editable, organize them into a PowerPoint file, and submit as “Manuscript No. -Figures.ppt” on the system, we need to edit the words in the figures. All submitted figures, including the text contained within the figures, must be editable. Please provide the text in your figure(s) in text boxes.
-Thank you for the comment. We modified this and submitted this as power point.

25) Please explain all the abbreviations of each figure/table under each piece of figure/table legends (Fig 3).
-Thank you for the comment. We modified this and submitted this as power point.

26) Regarding the figures (4):Please provide the decomposable figure of figures, whose parts are all movable and editable, organize them into a PowerPoint file, and submit as “Manuscript No. -Figures.ppt” on the system, we need to edit the words in the figures. All submitted figures, including the text contained within the figures, must be editable. Please provide the text in your figure(s) in text boxes.
-Thank you for the comment. We modified this and submitted this as power point.

27) Please explain all the abbreviations of each figure/table under each piece of figure/table legends (Fig 4)
-Thank you for the comment. We modified this and submitted this as power point.

28) Please provide the decomposable TABLE, whose parts are movable and words can be edited. Please don’t include abbreviations in the title of the figure/table.Please explain all the abbreviations in the figure/table legends: full name (abbreviation) Please explain all the abbreviations of each figure/table under each piece of figure/table legends. (Table 1)
-Thank you for the comment. We modified this. You can decomposable with a double clink on table.

29) Please provide the decomposable TABLE, whose parts are movable and words can be edited. Please don't include any *, #, †, §, ‡, ¥, @….in your manuscript; Please use superscript numbers for illustration; and for statistical significance, please use superscript letters. Statistical significance is expressed as $^{a}P < 0.05$, $^{b}P < 0.01$ ($P > 0.05$ usually does not need to be denoted). If there are other series of P values, $^{c}P < 0.05$ and $^{d}P < 0.01$ are used, and a third series of P values is expressed as $^{e}P < 0.05$ and $^{f}P < 0.01$. Please don't include abbreviations in the title of the figure/table. Please explain all the abbreviations in the figure/table legends: full name (abbreviation) Please explain all the abbreviations of each figure/table under each piece of figure/table legends. (Table 2)

-Thank you for the comment. We modified this. You can decomposable with a double clink on table.

30) Please provide the decomposable TABLE, whose parts are movable and words can be edited. Please don't include any *, #, †, §, ‡, ¥, @….in your manuscript; Please use superscript numbers for illustration; and for statistical significance, please use superscript letters. Statistical significance is expressed as $^{a}P < 0.05$, $^{b}P < 0.01$ ($P > 0.05$ usually does not need to be denoted). If there are other series of P values, $^{c}P < 0.05$ and $^{d}P < 0.01$ are used, and a third series of P values is expressed as $^{e}P < 0.05$ and $^{f}P < 0.01$. Please don't include abbreviations in the title of the figure/table. Please explain all the abbreviations in the figure/table legends: full name (abbreviation) Please explain all the abbreviations of each figure/table under each piece of figure/table legends. (Table 3)

-Thank you for the comment. We modified this. You can decomposable with a double clink on table.

31) Please provide the decomposable TABLE, whose parts are movable and words can be edited. Please don't include abbreviations in the title of the figure/table.Please explain all the abbreviations in the figure/table legends: full name (abbreviation) Please explain all the abbreviations of each figure/table under each piece of figure/table legends. (Table 4)

-Thank you for the comment. We modified this. You can decomposable with a double clink on table.

32) Please provide the decomposable TABLE, whose parts are movable and words can be edited. Please don't include any *, #, †, §, ‡, ¥, @….in your manuscript; Please use superscript numbers for illustration; and for statistical significance, please use superscript letters. Statistical significance is expressed as $^{a}P < 0.05$, $^{b}P < 0.01$ ($P > 0.05$ usually does not need to be denoted). If there are other series of P values, $^{c}P < 0.05$ and $^{d}P < 0.01$ are used, and a third series of P values is expressed as $^{e}P < 0.05$ and ^{f}P

< 0.01. Please don’t include abbreviations in the title of the figure/table. Please explain all the abbreviations in the figure/table legends: full name (abbreviation) Please explain all the abbreviations of each figure/table under each piece of figure/table legends. (Table 5)

-Thank you for the comment. We modified this. You can decomposable with a double clink on table.

33) Please provide the decomposable TABLE, whose parts are movable and words can be edited. (table 6)

- Thank you for the comment. We modified this. You can decomposable with a double clink on table.

34) Please provide the decomposable TABLE, whose parts are movable and words can be edited. (table 7)

- Thank you for the comment. We modified this. You can decomposable with a double clink on table.

35) Please provide the decomposable TABLE, whose parts are movable and words can be edited. (table 8)

- Thank you for the comment. We modified this. You can decomposable with a double clink on table.

Reviewer’s code: 00761439

Dear Reviewer, Thank you so much for review, rating and comments.

1) How the authors decided to create and evaluate group 4 pts. In addition, the number of patients in this group was too small for final conclusions

-Thank you for the comment. These groups were created for better understanding and organization of the downstaging group given the wide variation in tumor diameters. Within our series, we found this small number of patients with criteria beyond the criteria of responding patients (tumors larger than 5 cm), but with low tumor volume (below 8 cm) that obtained a good response after treatment. We think it is important to highlight this group for future research.

2) Can the authors clarify the terms “coagulopathy” and thrombocytopenia”?

-Thank you for the comment. We considered coagulopathy as patients with an INR greater than 1.2; and patient thrombocytopenia with a platelet count below 150,000 / mm3. Included information in the text and reference. Modified page 5 line 22.

3) AUC should be provided regarding the discriminative ability of max HCC diameter

-Thanks for the comment. We used AUC.

4) Page 6: "…Post-transplantation recurrence occurred more frequently in the downstaging group 25% (5/20) than in the bridging group 5.81% (5/86) (p=0.020); however, these events did not significantly affect recurrence-free survival (p=0.874)." However, in the same page: "…Kaplan-Meier's 1, 3, and 5-year post-transplant recurrence-free survival probability were 95%, 82.8%, 62.1% in the downstaging group, and 80.2%, 76.5%, 74.8% in the bridging group (P=0.935).." . Why the p values were different?

-Thanks for the comment. The p values (0.935) in "..Kaplan-Meier`s 1, 3 and 5-year post-transplant recurrence-free survival probability were 95%, 82%, 62.1% in the downstaging group, and 80.2%, 76.5%, 74.8% in the bridging group (p=0.935).."is the same value presenting in table 8 for unadjusted analysis. While in the text we quote the value of "p" after the adjustment (p=0.874).

5) Did the authors provide the drop out rates in each group?

-Thanks for the comment. We performed the total drop out analysis (Groups Bridging and Downstaging), 105 patients underwent transplantation, and the other 92 were not transplanted due to clinical contraindication to transplantation, HCC progression and exclusion of the milan criteria or failure in downstaging therapy. We did not do individual analysis of each subgroup.

6) The authors should provide the median values for variables without normal distribution. For example, AFP in Table 3?

-Thanks for the comment. We modified the values.

7) Was AFP an exclusion criterion for LT or TACE?

-Thanks for the comment. AFP analysis was excluded because AFP values did not influence tumor response results.

8) An update in Refs is needed (e.g. Sinha J, et al. Hepatology. 2019)

-Thanks for the comment. I`m sorry but we don`t understand that update.

Reviewer's code: 00051373

Dear Reviewer, Thank you so much for review, rating and comments.

Reviewer's code: 00053950

Dear Reviewer, Thank you so much for review, rating and comments.

1. The title is long-term outcome of HCC. However, the follow-up was only 3 years in the mean and as we well know HCC often recurs after this time period in LT patients.

-Thanks for the comment. We use Kaplan-Meier's 1, 3, and 5-year post-transplant overall survival probability were 95%, 88.2%, 73.5% in the downstaging group, and 82.8%, 76.5%, 72.3% in the bridging group (P=0.317), respectively and for post-transplant recurrence-free survival probability were 95%, 82.8%, 62.1% in the downstaging group, and 80.2%, 76.5%, 74.8% in the bridging group (P=0.935), respectively.

2. The abstract summarizes adequately the work, but the conclusion is rather simplified and should be presented better in details.
-Thanks for the comment. We modified the conclusion in abstract.

3. Methods. Patients in the bridging group are within the Milan criteria and in the downstaging group there were patients even with the total tumor diameter beyond 8cm. Both groups were treated with TACE preLT and only patients within Milan criteria after TACE were transplanted. This fact should be clearly pointed out in the paper and in the abstract.
-Thanks for the comment. we include in the text and abstract.

4. Results. The major finding of the study was that LT after downstaging of HCC to Milan criteria would give the same results as TACE in patient within Milan from the beginning. Could it be concluded that TACE is not needed for patients within Milan criteria?
-Thanks for the comment. In Brazil, the supply of organ is lower than the demand, so it is necessary the careful use and a cut number for patients who will benefit at the end of treatment and liver transplant at lower cost. However we have seen that we can offer selected patients the same long term outcome, although the drop out rate is higher in the DS group.

5. How are the tumor status in the explanted livers taken in account?
- Thanks for the comment. We do not consider tumor status in explanted liver for analysis of results.

6. The number of dropouts was high, 1/3 also in the MC-group. Why is that as they were treated with TACE?
-Thanks for the comment. We performed the total drop out analysis (Groups Bridging and Downstaging), 105 patients underwent transplantation, and the other 92 were not transplanted due to clinical contraindication to transplantation, HCC progression and exclusion of the milan criteria or failure in downstaging therapy.

7. There were about 7% Child C patients in the both groups. It is quite expected that such patients end readily up to dropouts?
-Thanks for the comment. These patients (Child C) may be expected to have a higher drop out rate due to clinical contraindications.

8. Table 2. The level of AFP was as high as 22000 in some patient. Was AFP used as a criterion for treatment response?
-Thanks for the comment. AFP analysis was excluded because AFP values did not influence tumor response results.

9. Table 2. The highest amount of nodules was 9 and the maximal tumor diameter 17cm in the downstaging group. Was it realistic to get these patients to the Milan criteria?
-Thanks for the comment. It is very unlikely that a patient in these parameters (9 nodules or maximum diameter of 17 cm) will achieve values compatible with the milan criteria. However, during the study period, several patients evaluated by the liver transplantation team were referred for chemoembolization. Our article was written with all patients involved in the period, not excluding even those with a low probability of actual reduction to the Milan criteria.

10. Table 4. Quite many patients died in 30 days after LT even in the bridging group. Was any of these related to the TACE. The two columns right in the table seem to be unnecessary.
-Thanks for the comment. We modified the table.

11. Table 7. It should be stated that patients with Child C or with AFP >1000 were not transplanted? P-values?
AFP greater than 1000 in a patient with CHILD C was 15.4% while A and B were respectively 1.1 and 6.1 with p = 0.043 significant.
In transplant patients, CHILD A, B, C were 55.2, 59.3, 46.2 with p = 0.64 not significant.

Variável	**CHILD**						**Total**		**p**
	A		B		C				
	n	%	n	%	n	%	**n**	**%**	
TxHep									0,646
Não	43	44,8	33	40,7	7	53,8	83	43,7	
Sim	53	55,2	48	59,3	6	46,2	107	56,3	
AFP1000									**0,043**
Não	92	98,9	77	93,9	11	84,6	180	95,7	
Sim	1	1,1	5	6,1	2	15,4	8	4,3	
Total	93	100	82	100	13	100	188	100	

12. The discussion is clear and the shortages of the study have been noted.
-Thanks for the comment.

Reviewer's code: 00181520

Dear Reviewer, Thank you so much for review, rating and comments.

1) Page 3 line 8 : Could you please rephrase this sentence to clarify what you mean to say ? "It was identified a subgroup never before described, Group 4"
-Thank for the comment. We include in the text “It was identified a subgroup never before described, Group 4 which has a low tumor volume (less than 8 cm) but with 2 or 3 lesions above 5 cm.”

2) Page 4 "DEB-TACE protocol was previously described". This gives the impression that it was described in your manuscript above. Could you please clarify that it was previously described "in the literature" or by "Cavalcante et al and Nasser et al " or "by other investigators"?
-Thanks for the comment. This has been modified in the text.

3) Page 5 "Eligibility". Could you please write "Eligibility for transplantation" ?
-Thanks for the comment. This has been modified in the text.

4) Page 6 "Receiver operating characteristic curve analysis revealed that patients with maximal tumor diameter up to 7.05 cm are more likely ...". Please write "were" instead of "are".
-Thanks for the comment. This has been modified in the text.

5) Page 9 line 4" Please replace " suchlike " with "just like"
-Thanks for the comment. This has been modified in the text.

6) Page 9 last line "We recognize that the subgroup analysis is strongly limited by the low number of patients included in each subgroup." Try to complete this paragraph with "But " or "Nevertheless" and say the strengths of your study.
-Thanks for the comment. We include the text in the paragraph.

7) I am surprised you performed DEB TACE for CTP score till 15. Didn't they decompensate further?
-Thanks for the comment. We evaluated that 7.4% of the cases were CTP score C, but we do not have the maximum patient score. The highest maximum MELD of 28 without clinical decompensation. We can say with certainty that there were no cases with score 15. In cases with CTP score C treatment was performed in superselective. In addition, all cases were previously evaluated and followed up by the liver transplantation clinical team, so patients were not referred in borderline clinical conditions.

8) In table 2 please correct "trombocytopenia" to read "thrombocytopenia"
-Thanks for the comment. This has been modified in the text.

9) Table 3: Please remove the column of "Total"

-Thanks for the comment. This has been modified in the text.