Peer Review file

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Reviewer A

This is an interesting topic on TAE vs DEB-TACE of the very early and early HCC. The common recommendation by BCLC guideline is ablation, and yet the authors treated these lesions with transarterial embolization. The authors had significant number of patients in both DEB-TACE (n=53) and TAE group (n=51). Showed there was no difference in outcome and complications.

Comment 1:
The patients in both groups were very heterogenous:
- TAE: microparticles or microspheres with a size of 100µm up to 700µm
- DEB-TACE: all 100-300, 300-500, 500-700 µm beads are used, unclear which brands, unclear to what endpoint, loaded with heterogenous dose of dose of 25-150mg Doxorubicin or a dose of 75mg Adriblastin.
The authors need to perform extensive subanalysis to break down this heterogenicity or show no difference in the outcome.
Reply 1: Thank you very much for this important comment. To address the heterogeneity issue of our study population, we conducted further sub-group analyses. In the DEB-TACE group we compared embolization with DC beads (300-700um) with dose of doxorubin ≥100mg versus <100mg; and in the TAE-group embolization with microparticles ≥250µm versus <250µm in respect to local response.
Changes in the text (p.11, line 197): Further sub-group analyses according to the size of DC beads and the doses of doxorubin within the DEB-TACE-group as well as the comparison of size of microparticles in the TAE-group in respect to local response were performed and showed no difference (see supplementary data).

Abstract
Background:
Fine

Comment 2:
Methods:
Need to detail on HCC population/size and mRECIST
Reply 2: Thank you for this remark. We changed the description of the HCC population and size in the methods section accordingly.
Changes in the text (p. 3, line 53): Clinical data of totally 95 patients with very early and early HCC not amenable for surgery or ablation, treated between 2009 and 2019 at the Department of Visceral Surgery and Medicine and Interdisciplinary Center of Vascular Interventions, University Hospital Bern, Switzerland, were retrospectively analyzed (52 patients in DEB-TACE and 42 patients in TAE grou, respectively). All imagine were assessed using the

modified Response Evaluation Criteria in Solid Tumors (mRECIST).

Comment 3:
Results:
debTACE (n=53) and TAE group (n=51) should be mentioned in method.
Reply 3: We changed the methods section and now present the numbers there (with the new numbers, see Reviewer C)
Changes in text (p. 3, line 57): (52 patients in DEB-TACE and 43 patients in TAE group, respectively).

Comment 4:
No significant differences were detected between DEB-TACE and TAE. What do the authors mean? In response or complication? Difference happened in something and the authors need to clarify that.
Reply 4: Thank you for this important comment. We removed this sentence completely since it was redundant.
Changes in the text (p.3, line 63): Results: Most patients presented with Child-Pugh - A, thrombocytes were significantly lower in patients treated by TAE. Minor side effects occurred equally in both groups. No differences were detected in terms of overall survival, local tumor recurrence and response rate.

Comment 5:
Conclusion:
Please replace “infeasible” with “not amenable”
Reply 5: We replaced infeasible with not amenable also in the title of the manuscript
Changes in the text (p. 4, line 68): Compared with DEB-TACE, TAE is an equally effective and save therapy for very early and early HCC not amenable for resection or ablation without differences in local tumor control and overall survival.

Comment 6:
Introduction
This section is long and focus on comparting the results of TAE and DEB-TACE or cTACE which are more suitable for discussion.
Please keep it short and reason why it was necessary to this study.
Reply 6: Thank you very much. We completely agree with your important remark and shortened the introduction tremendously only focusing on TAE and DEB-TACE.
Changes in the text (p. 6, line 80): Please see the revised Introduction section in the main manuscript.

Comment 7:
Methods
Please break down this section to following subtitles: study design, study population, Angiogram and embolization technique, Image analysis, outcome and variables, statistical

analysis.

Reply 7: We really appreciate this important comment and changed the methods section according to your suggestion.

Changes in the text (p.8, line 110): Please see the completely revised methods section.

Comment 8:

Were the lesions biopsy proven or just imaging diagnosis?

Reply 8: Thank you for this important question. HCC diagnosis were either made histologically or radiological according to the current EASL guidelines.

Changes in the text (p.8, line 120): Patients were included with either histologically proven HCC or HCC diagnosis based on radiological non-invasive criteria according to the European Association of the Study of the Liver (EASL) guidelines

Comment 9:

How many were treatment naïve?

Reply 9: In our cohort, 73 (77.7%) patient were treated naïve. This information was only given in Table 2 and we now also included a sentence in the Results section.

Changes in the text (p. 13, line 234): Totally, 73 (77.7%) patients were treatment naïve, 41 (78.8%) patients in the TACE-group and 32 (76.2%) in the TAE-group, respectively (Table 2).

Comment 10:

What systemic therapy was used?

Reply 10: Thank you for this important remark. Patients received Sorafenib since this was the recommended first line treatment at the time..

Changes in the text (p.16, line 288): Fifty-four (44.3%) lesions with residual activity received either MWA, systemic therapy (sorafenib) or were operated including atypical resection, hemihepatectomy or LT.

Comment 11:

Concurred systemic therapy?

Reply 11: No patients were included which had systemic therapy.

Changes in the text (p. 8, line 131): Furthermore, patients receiving both kind of embolizations, or patients with simultaneous systemic therapy were excluded.

Comment 12:

Resection?

Reply 12: We performed either atypical resection or hemihepatectomy, but changed the wording in this section completely

Changes in the text (p. 8, line 124): Embolization was recommended as treatment whenever the tumor was deemed unresectable and/or unablatable including patients awaiting liver transplantation (LT).

Comment 13:

Description of the angiogram, selective and subselectivity are very limited.

Reply 13: We specified the description of the angiogram.
Changes in the text (p. 9, line 137): See methods, paragraph 2.3 angiogram and embolization technique.

Comment 14:
Specify which brand of beads were used for DEB-TACE and same for TAE.
Reply 14: We specify the brand of the embolization material (DC Beads, Boston Scientific®, Embozene, Varian®; Hydropearls, Terumo®; PVA foam embolization particles, Cook®).
Changes in the text (p. 9, line 138): DEB-TACE was the standard embolization technique at our hospital between 2009 and 2014 and was performed using doxorubicin as the chemotherapeutic agent, applicated by drug-eluting beads (DC Beads, Boston Scientific®, supplementary data). The loaded bead size was between 300-700µm. For small and large supplying arteries, bead sizes of 100-300µm and 500-700µm were applied, respectively. Per embolization, a dose of 25-150mg doxorubicin was administered. Since 2014, TAE became the standard embolization technique at our institution using microparticles or microspheres with a size of 100µm up to 700µm (Embozene, Varian®; Hydropearls, Terumo®; PVA foam embolization particles, Cook®; supplementary data).

Comment 15:
Missing end point for embolization
Reply 15: Thank you for this important observation. We described the end point of the embolization, which is depending on the type of embolization.
Changes in the text (p. 10, line 156): For the TAE approach the embolization was done as superselective as possible, meaning embolization in a subsegmental position as close to the tumor as possible. In general, for TAE the smallest possible particle size was used to achieve distal/intratumoral vessel occlusion, as this was thought to produce more necrosis. Overall goal was to use 100µm microspheres, if considered safe by the interventionalist, judged by the angiography and previous imaging. If considered unsafe larger spheres or PVA were used. For DEB-TACE, on the other hand, a more central embolization position was usually accepted. DC-Beads were used in all cases for DEB-TACE with a standard size of 300-500µm or 500-700µm. Endpoint of the embolization was the lack of tumor blush with obtained antegrade perfusion for DEB-TACE and complete stasis of the superselective tumor feeder for TAE, respectively.

Comment 16:
Page 11, lines 178 to 182 should be summarized in a Table.
Reply 16: We really appreciate your comment and summarized this part in a table and removed it from the text.
Changes in the text (p. 11, line 186): See Table 1.

Comment 17:
Mann-Whitney-U test cannot be sued, since the study has enough power.
Reply 17: We discussed the statistics again with a statistician. For nominal variables with size $n<120$ we took the Fisher's exact test. According to our statistician, we performed Mann-Whitney-U test only for continuous variables.

Changes in the text: The entire calculation was revised (see results).

Comment 18:

Results

The first paragraph belongs to method section, to study population subtitle.

Reply 18: Thank you for this comment. We deleted this sentence and integrated it in the sub-section study population.

Changes in the text (p.8, line 119): see methods, study population.

Comment 19:

Discussion

Omit the first line.

The statement of "no difference in any of the analyzed endpoints" is too vague and lack significance. No difference in what?? Response??? Overall survival?? Complication??

Reply 19: We omitted the first line and concrete "no difference of the analyzed endpoints".

Changes in the text (p.18, line 131): Our retrospective single-center analysis showed no significant differences in terms of local tumor control and overall survival in patients treated with DEB-TACE or TAE for very early and early HCC.

Comment 20:

Conclusion

Please break down this to two separate sentence.

Reply 20: Thank you for this important comment. We broke the conclusion down into two sentences.

Changes in the text (p.22, line 419): In conclusion, our present monocentric retrospective study showed no difference in local tumor control and overall survival between DEB-TACE and TAE. These findings indicate that TAE might be a valid treatment alternative for patients with very early and early HCC.

Reviewer B

The paper is interesting to read, and helps add to the sparse body of evidence in the therapy area. I am also aware that the general evidence base for TACE is not the greatest, and this is summarised well in the introduction so I have been pragmatic in my review of the paper and not expected perfection.
Overall, I think this would be of interest to the readers of JGO but I do have a couple of minor concerns that it would be good to hear the authors view on to reassure me.

Comment 21:
1. The study collection period was 2009 to 2019 which means that some of the information is potentially 14 years old and some only 4 years old. Has general clinical practice changed over the ten year time frame? I am wondering if there has been some sort of inadvertent confounding going on due to changing general practices. The discussion mentions changes in policy that have affected length of stay and I wonder if there are other things that need to be thought about.
Reply 21: Thank you very much for this important comment. In the discussion we changed the following sentence and added one sentence:
Changes in the text (p. 21, line 405): Clearly the retrospective character of the study, the potential bias due to the change in our treatment algorithm and the change of clinical practice over time as well as the small patient collective with no possible matching limits the interpretation of our results. In particular, the further development of minimal invasive procedures, imaging modalities and also the compounds and devices used for embolotherapies in the treatment landscape of HCC most likely limit the interpretation of the current study results.

Comment 22:
2. L148 to 149. Is this a valid reason for exclusion of patients, and how many did it effect? Again, I am wondering if there is any inadvertent confounding/ selective patient choice going on. I'm not a clinician but is there any relationship between image quality and clinical variables such as tumour size? When I first read this it did seem odd.
Reply 22: Thank you for this important comment. The exclusion of patients receiving simultaneous treatment with systemic therapy and those with other kinds of embolization material was performed in order to reduce confounding factors that could affect the analysis. The exclusion of 10 patients from the analysis due to poor imaging quality was necessary in order to ensure the correct analysis and interpretation of the follow-up imaging. Because the tumor might appear differently in the pre-interventional images, during the embolization and in the post-interventional CT/MRI patients had to be excluded whenever the radiologists were not able to interpret the images sufficiently. In addition. factors such as ascites or insufficient use of contrast might affect the image quality of CT/MRI. In general, the quality of images and/or the visibility in particular of very small lesions can vary tremendously between different image modalities. This is why for any prospectively designed trial the quality of the study would increase when only one imaging modality would be used.
Changes in the text (p. 21, line 405): In order to acknowledge this limitation we changed this section of the discussion (see changes comment 21).

Comment 23:

3. The title is slightly misleading in my opinion. It implies that it's all very early and early HCC patients but the text qualifies it to individuals who infeasible for surgery or ablation (I believe). Can the authors check the title is accurate.

Reply 23: Thank you for this important comment! We specified the title. Reviewer A and you made two different suggestions: not amenable and infeasible. We decided to take the term "not amenable", which is more general as infeasible.

Changes in the text (title of the paper, p. 1, line 1): Comparison of transarterial bland embolization and drug-eluting beads transarterial chemoembolization for very early and early HCC not amenable for surgery or ablation: a single center retrospective data analysis

Comment 24:

4. I understand how statistics works, and accept that the results in table are all p=NS due to small sample size but the absolute gaps time to local recurrence and progression are large and surely a signal of some real difference. Do the authors think this is worth talking about in the discussion, or is there a genuine biological reason why these differences would still not statistically significantly different if there were a lot more patients. To this non-clinical eye, there seems to be potential benefits associated with the treatment that was stopped being used in 2014.

Reply 24: Thank you for this interesting observation. We absolutely agree that the results suggest that patients treated with TAE have a much longer time to local recurrence which could be at least partly explained by the more selective and therefore maybe longer-lasting embolization. But due to the small sample size this would have to be validated in a separate and ideally prospective study.

Changes in the text (p.20, line 390): We added this to the discussion: The much longer time to progression in the TAE group might be, at least partly, explained by the more selective and therefore maybe longer-lasting embolization. Due to the small sample size this would have to be validated in a separate and ideally prospective study.

Reviewer C

Title: OK

Comment 25:

Abstract: would enhance to add the specific TAE (?) and DEB-TACE devices (DC Beads) used

Reply 25: Thank you for this important comment. We specify, that we only investigated DEB-TACE as a specific technique of TACE.

Changes in the text (p. 3, line 48): We aimed to compare the outcome of patients with early HCC treated by drug-eluting beads TACE (DEB-TACE), a specific technique of the TACE using DC Beads, and TAE using microparticles with a size of 100µm up to 700µm.

Comment 26:

Highlights: final line is misleading as it states "TACE" rather than DEB-TACE. No comparison was made to lipiodol TACE, which is the world-wide standard technique. DEB-TACE has already been discredited in multiple RCTs, so results are unsurprising, but only imply that DEB-TACE should not be used.

Reply 26: We really appreciate your remark. TACE was replaced by DEB-TACE.

Changes in the text (p. 5, line 78): TAE might be safe and equally effective as DEB-TACE for very early and early HCC.

Comment 27:

Intro:

Caution is required in writing this section to distinguish between conventional Lipiodol TACE, upon which guidelines are based, and DEB-TACE, a discredited technique shown in multiple RCTs to be no different from TAE in clinical outcomes yet with higher hepatobiliary toxicity. The term "TACE" cannot be used indiscriminately.

Reply 27: We really appreciate your comment. We shortened the introduction (see Reviewer A). Further, concentrated on DEB-TACE and emphasize, that this study only compare DEB-TACE with TAE.

Changes in the text (p. 6, line 80): See Introduction.

Comment 28:

Line 95 incorrectly cites reference 5; reference 6 does not conclude that DEB-TACE has better outcomes than cTACE, reporting no difference in immediate and one-year responses.

Reply 28: Thank you for this important remark. Ref. 5 and 6 comes to a different conclusion, therefore the sentence were adapted to a more general statement.

Changes in the text (p. 6, line 97): Up to date, only few studies addressed the non-inferiority of TAE compared with DEB-TACE in patients with HCC.

Comment 29:

Methods:

Line 145 states embolization was a second-line therapy. What was the first line? It would be unusual to have another therapy precede LDT in these patients.

Reply 29: Thank you very much. Our wording was misleading since it suggests that another

first-line therapy was performed. We simply wanted to state that not the recommended treatment for BCLC 0 and A was performed (Ablation or resection).
Changes in the text 29 (p. 8, line 124): Embolization was recommended as treatment whenever the tumor was deemed unresectable and/or unablatable including patients awaiting liver transplantation (LT).

Comment 30:
Line 153 – specify DEB-TACE was the standard embolization technique (not "TACE", which in most of the world means lipiodol).
Reply 30: We clarified that DEB-TACE was used as standard technique in this study. Patients with lipiodol or ethanol were excluded.
Changes in the text: The entire calculation was revised (see results).

Comment 31:
Line 155 – specify the brand of embolic used for DEB-TACE.
Reply 31: We specify the brand of the embolization material (DC Beads, Boston Scientific®, Embozene, Varian®; Hydropearls, Terumo®; PVA foam embolization particles, Cook®). Further, we added a table (see supplementary data).
Changes in the text (p. 9, line 138): DEB-TACE was the standard embolization technique at our hospital between 2009 and 2014 and was performed using doxorubicin as the chemotherapeutic agent, applicated by drug-eluting beads (DC Beads, Boston Scientific®, supplementary data). The loaded bead size was between 300-700µm. For small and large supplying arteries, bead sizes of 100-300µm and 500-700µm were applied, respectively. Per embolization, a dose of 25-150mg doxorubicin was administered. Since 2014, TAE became the standard embolization technique at our institution using microparticles or microspheres with a size of 100µm up to 700µm (Embozene, Varian®; Hydropearls, Terumo®; PVA foam embolization particles, Cook®; supplementary data).

Comment 32:
Lines 156-57 – typo, should read "small and large", not "large and small"
Reply 32: We changed the row of these two words.
Changes in the text (p. 9, line 142): For small and large supplying arteries, bead sizes of 100-300µm and 500-700µm were applied, respectively.

Comment 33:
Line 160 – specify brand(s) of embolic(s) used.
Reply 33: See above comment 31.
Changes in the text: See comment 31.

Comment 34:
Line 201 – transplantation should be censored, not considered the same as death. This is a methodological error.
Reply 34: Thank you for this important comment. We take death or end of the study as overall

survival. The survival analysis with OLT as end point can be found in the supplementary data.
Changes in the text (p. 16, line 305): Mean overall survival (OS) was 42.4 (3-132) months for DEB-TACE patients and 34.7 (1-102) months for TAE patients until death or end of the study period (p = 0.42; Kaplan Meier-Curve; Figure 2B). Additionally, mean survival considering transplantation or death as endpoint was not different (see supplementary data).

Comment 35:
Results:
Line 231 please define "intervention time".
Reply 35: We define intervention time (in "material and methods", in the paragraph: "angiogram and embolization technique")
Changes in the text (p. 10, line 168): Intervention time was considered as time between the first angiography and the final one.

Comment 36:
Line 237, typo, 300-500
Reply 36: We corrected typo.
Changes in the text (p. 14, line 251): In the DEB-TACE-group, one lesion (1.4%) was embolized with DC beads 100-300 µm, 30 lesions (41.7%) with DC beads 300-500µm, one (1.4%) with DC beads 500-700 µm and 36 lesions (50.0%) with DC beads 300-500 µm and 500-700 µm.

Comment 37:
Line 239, typo 700-900
Reply 37: There are 36 embolization, which used DC Beads 300-500µm and 500-700µm. We summarized as 300-700 µm. We clarified in the text.
Changes in the text (p. 14, line 251): In the DEB-TACE-group, one lesion (1.4%) was embolized with DC beads 100-300 µm, 30 lesions (41.7%) with DC beads 300-500µm, one (1.4%) with DC beads 500-700 µm and 36 lesions (50.0%) with DC beads 300-500 µm and 500-700 µm.

Comment 38
Line 243, please report what "microparticles" were used (brand, size). Were these not microspheres?
Reply 38: In the text, microparticles act as a summary.
Changes in the text: We give the detailed information on each material in table 1 in the supplementary data.

Comment 39:
Line 243 – Lipiodol is not a therapeutic embolic agent and has no anti-cancer effect if used alone.
Reply 39: We removed all embolizations with lipiodol.
Changes in the text (p. 13, line 220): See results.

Comment 40:
Line 243 – use of ablative ethanol embolization should be excluded from this analysis.
Reply 40: In this study, DEB-TACEwas considered as standard chemoembolization. Therefore, all interventions using lipiodol or ethanol were excluded.
Changes in the text (p. 13, line 220): See results.

Comment 41:
Line 252-53. Please report hospital admission and discharge criteria. This is an outpatient or 23-hour observation status procedure in the U.S.
Reply 41: Thank you very much for this important comment. We specified this in "material and methods", in the paragraph "outcome and variables".
Changes in the text (p. 12, line 204): At the beginning of the study period, embolizations were performed as outpatient procedures, what changed over time due to the changes in the reimbursement policy requiring a minimum 2-night hospital stay in order to not be deficient. Patients were admitted the day before the intervention and discharged one day after the intervention when pain-free and in an adequate general condition.

Comment 42:
Lines 268-69 state that 17 and 13 patients recurred after a CR; then lines 274-75 state only 10 and 7 patients had local progression. Please reconcile this apparent discrepancy.
Reply 42: Recurrence refers to the fact that the primary lesion completely responded, in contrast to local progression, which was defined as progressive lesion after partial response. We specified the text.
Changes in the text (p. 16, line 290): In the longtime follow-up, local progressive disease occurred in 9 (24.3%) of 37 DEB-TACE-lesions with PR and 6 (31.6%) of 19 TAE-lesions with PR (p= 0.74; chi-square Test; Table 4).

Comment 43:
Line 272. Lesions undergoing subsequent ablation or resection become inevaluable for progression. Were these censored in the local progression analysis? Please report the number treated in each group and add "Subsequent Treatment" to Table 3. Subsequent curative-intent therapies could bias PFS and OS if not applied similarly in the two arms.
Reply 43: Lesions ablated or resected were censored in the local progression analysis. We specified the text (methods; in the paragraph: outcome and variables). Further, we add "subsequent treatment" to table 3.
Changes in the text (p. 11, line 194): All hepatic lesions were followed until recurrence or progressive disease (PD) and re-treatments like additional TACE or TAE, surgery or additional interventions were documented and were censored for the follow-up analysis.

Comment 44:
Discussion:
Lines 345-350 Reimbursement policy cannot solely account for the mean >3 day hospitalization in the TAE arm. TAE is well known to be more painful, cause worse PES and

increased rate of hospitalization and re-hospitalization due to the harder embolic endpoint and severe ischemia achieved. This should be acknowledged.

Reply 44: Thank you for this important comment. Even though it is well known, that TAE is more painful, our data did not show any differences in adverse events. Some of the patients received in-hospital liver transplantation evaluation examination during the same hospital stay during some time of the analyzed time period which might also contribute to the longer hospital stay.

Changes in the text (p. 19, line 372): Further reasons may include the fact that TAE is a painful procedure, even this study found no differences in the adverse event.

Comment 45:

Line 359 What is the reference supporting dissolution of DC beads in 2 weeks? They are PVA, which is a permanent embolic.

Reply 45: Thank you very much for this comment. You are right, the embolic is permanent. We removed this section

Changes in the text (p. 18, line 331): See discussion.

Comment 46:

Two RCTs have shown the same results in intermediate HCC:
Malagari, CVIR 2010;33:541-51
Brown K, J Clin Oncol. 2016 Jun 10;34(17):2046-53

Malagari should be added to the references and both should be discussed in context with this study.

Reply 46: In the revised paper, we now discussed these two studies in the discussion and added the study of Malagari to the references..

Changes in the text (p. 18, line 335): In 2009, Malagari et al. compared DEB-TACE with TAE finding better local response, fewer recurrences and a longer time to progression in favor of DEB-TACE without a survival benefit within one year. In contrast, the more recently published randomized controlled trial by Brown et al. found no difference in terms of response rates and survival comparing bland embolization with DEB-TACE. Our data support the latter results for patients with early and very early HCC.

Comment 47:

Conclusion:
Some modification to acknowledge that no comparison to cTACE was made would be appropriate.

Reply 47: Thank you for this important comment. As cTACE is a widely used embolization technique we mentioned as a limitation of this study, that no comparison to cTACE is available.

Changes in the text (p. 21, line 411): On top of that, no comparison to conventional TACE is available.

Comment 48:

References:

Several are review articles, not primary sources.
Citations in the text are not used accurately and should be verified.
Reply 48: We revised all references.
Changes in the text: See references.

Tables & Figs: good