Author's response to reviews

Title: TACE performed in patients with single nodule of hepatocellular carcinoma

Authors:

Eleonora Terzi (eleonora_terzi@yahoo.it)
Fabio Piscaglia (fabio.piscaglia@unibo.it)
Ludovica Forlani (ludovica.forlani@studio.unibo.it)
Cristina Mosconi (cristina.mosconi@aosp.bo.it)
Matteo Renzulli (dr.matteo.renzulli@gmail.com)
Luigi Bolondi (luigi.bolondi@unibo.it)
Rita Golfieri (golfieri@aosp.bo.it)

Version: 3
Date: 3 July 2014

Author's response to reviews: see over
Dear Editors,

we would like to thank you for your comments which allow us the opportunity to improve our manuscript. Here below please find the answers to your requests. All changes in the manuscript are underlined and striked through.

Reviewer’s comment to the Author(s):

Reviewer #1:
This is a well written paper with a well defined question, appropriate methods, sound data (though retrospective in nature), and balanced conclusions on the basis of their data. With a few revisions which are delineated below, I believe that the work would merit publication:

Major Compulsory Revisions –

1. I would like to have more technical information regarding the actual TACE procedure. 
Specifically, how much Lipiodol was used, what is the dose of Epirubicin which was used, etc.

Re: For both selective/superselective TACE, a mixture of epirubicin (Farmorubicin; Pfizer, Latina, Italy) and iodized oil (Lipiodol; Guerbet, Milan, Italy) was injected under fluoroscopic control followed by embolizating gelatin sponge particles (Gelita-Spon; Gelita Medical, Amsterdam, Netherlands) cutted into approximately 1-mm cubes, mixed with few milliliters of contrast media. The mean chemotherapeutic agent dose administered per treatment was approximately 40 mg of epirubicin (range, 20–75 mg) and the mean Lipiodol dose administered was approximately 8 mL (range, 4–15 mL) (this information has been added into the manuscript). In all superselective transarterial chemoembolization procedures, the angiographic embolic endpoint was to reduce the residual antegrade blood flow in the artery reaching the tumor with no residual tumor blush.

Parasitic tumor blood supply through accessory arteries was tested in all cases in which the nodules showed extrahepatic feeding arteries on CT or MR imaging performed before treatment, in cases of Lipiodol accumulation different in shape on imaging performed before treatment (ie, no nodular shape), and in cases in which the lesion demonstrated on imaging performed before treatment was not found on hepatic arteriography. If extra hepatic feeding arteries were found, additional superselective treatment (chemotherapeutic mixture plus
embolization) was performed. The extrahepatic collateral vessels were examined according to the tumor location and the more frequent vessels were the right inferior phrenic artery, the omental branch, the adrenal artery, and the intercostal and subcostal artery.

2. The authors conclude on the basis of their results that TACE is a valid treatment option in patients with single HCC not suitable for curative treatment. Ablation modalities are commonly used in patients with single HCC who are not eligible for transplantation or surgery. In the discussion, it would be very helpful for the authors to discuss published studies on ablation for solitary HCC and compare and contrast data for TACE vs ablation. The reader may also be curious to know what the authors' treatment of choice is for a solitary HCC < 5 cm (and < 3 cm) on the basis of their data - TACE or ablation (in patients not eligible for transplant or surgery)

Re: Thank you for your suggestion. It would be very interesting comparing our results with that reported in literature for solitary HCC treated with ablation modalities. Unfortunately, an accurate comparison with published studies is not possible since those studies generally included either patients with single nodule < 5 cm or patients with both single and multiple lesions, making it impossible to identify selectively the outcome of only those with single lesions.

According to our clinical practice, patients not eligible for transplant or surgery are first routinely evaluated for percutaneous ablation as indicated in the international guidelines. However, patients are considered optimal candidates for percutaneous ablation if the single lesion is <2 cm, good candidates if the lesion is <3 cm and questionable candidates if the lesions is in the range 3 to 5 cm, especially if >3.5 cm. However, even though theoretically patients might be good or optimal candidates, location of the nodule or other factors (e.g. mild ascites) may prevent percutenous ablation. If patients are not eligible for percutaneous ablation, than are usually evaluated for TACE treatment according to the “stage migration” concept. Unfortunately, at the moment, no data are available to evaluate the exact percentage of patients with single HCC <5 and <3 cm submitted to RF or TACE in our whole department. Nonetheless, as reported in the manuscript, a considerable percentage of patients submitted to TACE (156/344, 45%) in our interventional Radiology Unit had single HCC.

Minor Essential Revisions:

1. What was the median or mean length of stay after TACE procedure
Re: Patients were generally admitted to the hospital the day before TACE when they underwent clinical examination, laboratory tests and ultrasound assessment. After TACE, patients were generally managed with bed rest for 6 hours and discharged the second day after the session if no complications appeared. The median recovery stay was 4 days.

2. *It is our practice to not routinely obtain labs on the day after TACE. It would be useful if the authors can discuss their protocol for obtaining labs and whether they believe it should be obtained in all patients on the basis of their results.*

Re: In our clinical practice, patients undergo clinical examination and laboratory tests the morning after TACE in order to exclude the development of procedure-related complications. Quite often also a simple ultrasound scan is performed to confirm absence of complications before discharge back home. On the basis of our results, 56 patients (38%) and 93 patients (63%), developed CPT or MELD increase $\geq 1$ point respectively the day after TACE. Interestingly, an increase of $\geq 1$ point of CPT or MELD score the day after TACE was significantly associated with lower survival ($P=0.003$) (Table 5). Those data suggest that the assessment of laboratory tests the day after the procedure may be useful to identify patients with liver decompensation and consequently patients with worst prognosis who might not be good candidates for further treatments (see below, next answer).

3. *A change in Child Pugh or MELD is not going to change whether the patient is treated; it would be helpful if the authors can address if there is any significance to these results other than being poor prognosticators for survival*

Re: thank you for the suggestion. The analysis has been performed comparing variables with the $\chi^2$ test. In particular, we found that patients with a CPT score increase $\geq 1$ point more likely underwent a single TACE cycle rather multiple cycles (70% vs. 30% of patients, $P=0.006$), on the opposite, a MELD score increase $\geq 1$ point did not impact on number of TACE cycles ($P=1.000$). As pointed out by the reviewer such changes have no impact on the decision already take to perform or not TACE, but appear of relevance on the possibility to perform repeated TACE cycles. Therefore, an increase in CPT score immediately after TACE should alert the physician to reconsider the treatment strategy having in mind the possible situation that patients will not be any more fit for repeated TACE (new sentence
added in the manuscript, discussion section, see reply to reviewer 2, point 13). Conversely the number of TACE sessions was not associated with survival \((P=0.407)\).

Reviewer #2:

**Reviewer's report:**

Dear authors,

Congratulations on an interesting study of TACE in solitary HCC. My comments (all are minor essential revisions except some discretionary revisions as noted):

**ABSTRACT**

1. First sentence of Background is unclear and poorly worded. “Patients with single hepatocellular carcinoma (HCC) are usually submitted to transarterial chemoembolization (TACE) even if TACE is not the first expected treatment in that patients.” I would disagree with this statement. Patients with single HCC are very often treated with surgery, OLT or ablation rather than TACE. Would change wording to “Patients with solitary hepatocellular carcinoma (HCC) usually undergo transarterial chemoembolization (TACE) if they are not candidates for curative surgical or ablative therapy.”

**Re:** we thanks the reviewer for his suggestion, which we agree upon. The sentence has been corrected now according to the suggestion

2. 2nd sentence: “The primary aim” not “Aim”. Also, “submitted” is not the ideal verb for TACE. Prefer “undergo” (present tense) or “underwent” (past tense). Please make this change throughout the manuscript. In this sentence: “The primary aim of the study was to assess the overall survival and clinical determinants of survival in patients with single HCC who underwent TACE.”

**Re:** the sentence has been corrected according to the suggestion and the verb “submit” changed with “undergo” throughout the text.

3. Methods sentence: The outcomes… were retrospectively…

**Re:** the sentence has been corrected according to the suggestion

4. Results, 3rd sentence: … 93 (63%) had a MELD increase…
Re: the sentence has been corrected according to the suggestion

5. Results, 5th sentence: unclear regarding “mild impairment of PS had some but minor impact on prognosis”- please clarify in exact terms- was this statistically significant? What was the exact magnitude? Reword for clarity.

Re: The exact terms are reported in detail in Table 5, where the survival of patients with different PS is reported either in the total population or patients within the Milan criteria. The sentence has been reworded in the manuscript as follow: “even a mild impairment of PS had an impact on prognosis. In fact, survival in PS-1 patients (thus qualified as BCLC-C) was worse than that in PS-0 patients, especially considering only the two groups within Milan criteria (corresponding to BCLC 0-A in case of PS-0). Nonetheless, the impact of PS on survival was smaller in comparison to that of the tumour burden, since survival in PS-1 patients (BCLC-C) was better than that of PS-0 patients beyond Milan criteria (BCLC-B) (Table 5 and 6, Fig. 3)”.

BACKGROUND
6. 3rd sentence: remove “many”

Re: the sentence has been corrected according to the suggestion

PATIENTS AND METHODS
7. Last sentence of “patient population”: … as the cohort for the study

Re: the sentence has been corrected according to the suggestion

8. TACE protocol and technical procedure, 3rd paragraph: “Very few patients were submitted to TACE despite moderate liver dysfunction in the perspective of transplantation.” This sentence is unclear, I don’t understand what you mean. Please re-word for clarity.

Re: We apologize for our insufficient clarify. Following the reviewer’s suggestion the sentence has been re-worded and now is more extensively explained, as follows: very few patients underwent TACE despite a CPT function B8-B9, which usually contraindicates TACE due to the risk of irreversible rapidly evolving liver failure. These patients were treated because they were on
the waiting list for liver transplantation and they could undergo salvage liver transplantation in case of severe liver failure

9. TACE protocol and technical procedure, last paragraph, 2nd sentence: “separated by” not “performed at”

Re: the sentence has been corrected according to the suggestion

DISCUSSION

10. 2nd sentence: remove “many”

Re: “many” has been removed

11. 2nd paragraph, 2nd to last sentence: “BCLC” not “BLCL”

Re: thanks for pointing out this misspelling, which has been corrected

12. It may be worth briefly explaining the “stage migration” concept since many readers will not be familiar with this term. A single sentence explaining the concept would suffice.

Re: the sentence has been added in “background” section, 6th row. The sentence reads as follows: “according to the “stage migration” concept, patients who cannot receive the recommended treatment allocation within their stage should be offered treatment according to the recommendations for the next stage”

13. 3rd paragraph, last sentence: I do not believe you have the evidence to make this claim. Your study suggested that worsening of hepatic function after TACE is a negative prognostic factor, I agree; but I disagree that they should be switched to a different treatment or no treatment based on this alone, since there is no evidence that a different treatment or no treatment would improve their survival compared to repeat TACE. Please change this sentence accordingly.

Re: the sentence has been eliminated. In addition, we found that patients with a CPT score increase ≥1 point more likely underwent single TACE cycle vs. multiple (70% vs 30%, \( P=0.006 \)), on the opposite, a MELD score increase ≥1 point did not impact on number of
TACE cycles ($P=1.000$). The result suggests that liver decompensation after TACE is an indicator of sustained liver decompensation which usually prevents further treatments (added in the manuscript, results and discussion sections) (see also question #3, minor revisions, reviewer 1). The results now include the following: “Patients with a CPT score increase $\geq 1$ point after the first TACE underwent more often one single rather than multiple TACE courses (70% vs 30% of cases respectively, $P=0.006$) in our routine clinical practice. This difference suggests that the immediate liver function worsening after TACE may either elicit a fear of sustained liver decompensation in case of a new TACE cycle are to be planned or indicate the occurrence of persistent liver functional deterioration, both turning into abstention from further TACE course”. The discussion has been modified, leading to the following sentence: “As expected, we also found that patients with a CPT score increase $\geq 1$ point more likely underwent a single rather than multiple TACE cycles. Furthermore, both CPT and MELD score $\geq 1$ point increase were found to be associated with a significant worse prognosis (Table 4). Such findings do not affect the initial choice of recommending TACE, but seem to alert clinicians to consider the risk that patients will be no more candidate for future repeated TACE in case of early CPT score worsening after the procedure, deserving an even more careful assessment of treatment strategy”

14. 4th paragraph: “… patients with bland thrombosis are candidates for TACE…and a selective approach is feasible”

Re: the sentence has been corrected according to the suggestion

15. 5th paragraph. As you state, I believe that BCLC intends that performance status be used for cancer-related symptoms; it seems that you included performance status for any reason to allocate patients into BCLC stage C or D, but it should really only be if the reduced performance status is due to cancer symptoms. See your reference #1, J Hepatology, page 921, first column, which states: “Advanced HCC (BCLC stage C): Patients with cancer related-symptoms (symptomatic tumors, ECOG 1-2), macrovascular invasion… etc”. Since you yourself state that the PS1 patients were very unlikely to have PS1 related to cancer symptoms, perhaps these patients should not have been considered PS1 for the purposes of BCLC classification. You seem to agree with this based on your statements; a re-analysis of the data with these patients re-classified into BCLC A or B would be interesting though not required – up to the authors.
Re: In principle we agree with the reviewer, but the critical problem with the use of PS1 in the BCLC is that it is impossible to distinguish whether PS1 is only related to cirrhosis or to HCC or to both. Moreover, once a patient has PS1 due to cirrhosis, he/she will never qualify as PS1 due to HCC, but he could be classified as symptomatic only when symptoms become so relevant to be judged as PS2, which means a worsening over the previous condition. Thus, having in mind the impossibility to clearly distinguish with certainty the origin of symptoms, whether cirrhosis or HCC, we pooled together all patients with PS1. However, in order to highlight the fact that PS1 is most likely not tumour related, a re-analysis has been performed including patients with PS-1 in the subgroup of patients BCLC A-0 (all patients had tumour within MC). As expected, BCLC 0-A patients had a median survival of 51 months (95% CI=38.7-63.3) vs. 12 months (95% CI=0.3-23.7) with a p<0.001. Those results further suggest that patients with PS1 with tumour within MC liken BCLC0-A patients considering the symptoms as related to liver function rather than cancer related and therefore with no major impact on survival. This is a critical issue of the BCLC staging system that cannot be extended further in the present analysis, but is matter of a separate article we are submitting on a much larger patient population whose results are in line with those reported here.

16. 5th paragraph, last sentence is unclear, please re-word for clarity.

Re: In our study, all patients with PS-1 had HCC within Milan Criteria and were classified in BCLC-C stage for the impossibility to distinguish between cancer and cirrhosis-related symptoms. According to the survival analysis, those with PS-1 and tumour within Milan criteria had better survival with respect to patients with PS-0 beyond Milan Criteria (BCLC-B) so that it can be argued that the former patients (theoretically held BCLC-C if not detailed speculation about the origin of the symptoms is made) can be considered as early stage HCC (BCLC 0-A) according to treatment allocation intents (considering the PS-1 as cirrhosis-related). On the opposite, considering patients with same tumour burden (within MC), PS-1 and consequently the liver function, certainly impact on survival so that BCLC-C patients (PS-1) had significant worse survival with respect to BCLC 0-A patients (PS-0). The issue has been clarified in the manuscript now.

17. 6th paragraph, 3rd sentence: “those reporting” not “those reported evaluating”
Re: the sentence has been corrected according to the suggestion

18. 7th paragraph: I agree that the day 1 decline in liver function is interesting, but were these changes persistent? You make a statement that we should avoid overtreatment and detrimental effects on liver function, but was this actually shown in your study? That is, were the lab parameters still abnormal 1 month after treatment, and did patients who underwent multiple TACE treatment fare worse in regards to liver function compared to those who only underwent one treatment? These data would be interesting if available.

Re: unfortunately the data are not available but the aim of our study was to have a rapid indicator of prognosis after liver treatment which can also guide allocation policy for further treatments. We removed the phrase alluding to the fact the patients with worsening of CPT immediately after TACE could have suffered persistent liver deterioration (since we do not show this findings as the reviewer correctly pointed out) and we just stated that these patients are at risk of being considered no more fit for further TACE cycles (see previous points)

19. Last sentence “… in the treatment of HCC.”

Re: the sentence has been corrected according to the suggestion

TABLES

20. Table 1: “Within Milan criteria” not “Milan criteria within”. Also make this change in other tables.

Re: tables have been corrected according to the suggestion

21. Table 4: I’m quite surprised that the very small absolute difference in INR and MELD scores proved to be statistically significant, especially with the wide range of the scores… please double check to ensure accuracy.

Re: We agree with you that the changes on laboratory tests after TACE are very small. Anyway, our intent was to evaluate whether there was a negative impact of TACE on laboratory tests the day after the procedure analyzing if a significant number of patients
showed a worsening of some labs post TACE.
The statistical analysis was double checked. We used the Wilcoxon signed-rank test whose significance is primarily related to the number of patients who met a decrease/increase of post-TACE laboratory tests (Tab 1) rather than the relative magnitude of laboratory changes (even if also the entity of changes certainly influences the result of the test). Thus statistically significance was produced by the fact that, despite changes were relatively small, they tended to go all in the same direction in the majority of patients.

We thank the reviewers once more for the effort dedicated to our manuscript allowing highly relevant improvement and the editor for the possibility to resubmit a revised version.
We hope that this version could be considered improved to an extent deserving publication in your prestigious journal.
We remain at your disposal for any further explanation.

Yours sincerely
Fabio Piscaglia