Format for ANSWERING REVIEWERS

February 7, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 8004-review.doc).

Title: Hepatocellular carcinoma treated by conventional transarterial chemoembolization in field-practice: serum sodium predicts survival.

Author: Marco Biolato, Luca Miele, Vittoria Vero, Simona Racco, Carmine Di Stasi, Roberto Iezzi, Andrea Zanché, Maurizio Pompili, Gian Ludovico Rapaccini, Giuseppe La Torre, Antonio Gasbarrini, Antonio Grieco.

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 8004

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

2 Revision has been made according to the suggestions of the reviewer

(1) I'd recommend including AUROC for the 5 staging systems as stand-alone predictors of survival and compare the AUROCs statistically

The statistical analysis on the AUROC of staging systems was performed and is described in the methods section and in the results section.

(2) In table 2 the Authors report that 11.1% of the patients was BCLC-C (Advanced Stage, portal invasion, extrahepatic spread, Child Pugh class A/B, PS 1-2) according to the most recent update of the BCLC staging system (Forner A, Llovet JM, Bruix J. Lancet. 2012); furthermore, according to this system, these patients should be treated with Sorafenib. The Authors also report in the inclusion criteria that all the patient was CTP Class A or B7 and PS 0. I suggest to clarify this point in the paper.

Our study included patients treated with conventional TACE in the period 1997-2008, while in our center sorafenib has been available only since 2009. In detail, 30 patients classified as BCLC-C included 25 patients with extrahepatic metastases and Child A status and 5 patients with a performance status of 1 or 2 and Child B8-9. These data have been included in Table 2. The decision to perform TACE in these patients was made on an individual basis in an era when sorafenib was not available, and it is somehow supported by the 19-month median survival reported in Table 2.

(3) How do the Authors explain that alkaline phosphatase is a significant predictor of survival at univariate and multivariate analysis?

Our interpretation about the prognostic role of alkaline phosphatase was added in the discussion section.

(4) After first-time TACE, how many patients were treated with repeated TACE or RFA? Authors should mention about them clearly in the text, please.

The retrospective nature of the study does not allow us to know in detail the treatments after the first TACE, with the exception of an eventual liver transplant. This limitation of the study is acknowledged and made clearer in the discussion section.

(5) Although authors stressed serum sodium concentration, how was the treatment by diuretics? Authors should also describe them at the baseline and during the follow-up period.

The retrospective nature of the study does not allow us to know the drug therapy practiced by patients at the time of the TACE procedure. To overcome this limitation, we repeated the analysis excluding 61 patients with radiological ascites that would have been an indication to diuretic therapy, and univariate and multivariate analysis confirmed the role of serum sodium as an independent predictor of survival, as reported and made more explicit in the results section.

(6) In ABSTRACT section, …Patients with hepatocellular carcinoma (HCC)…. Is it right?

As suggested, we had defined the abbreviations when first appeared.

(7) In Core tip, …..270 hepatocellular carcinoma (HCC)-patients with….. …..in this field. Our study is……in patients with HCC….. Is it right?

As suggested, we had defined the abbreviations when first appeared.

(8) In Patients and Methods section, What is "spleen diameter >12 cm on ultrasound"? Authors should explain this or refer the proper article(s).

12 centimeters is the cut-off used to define splenomegaly on ultrasound in italian patients (Sillabus of Italian Society of Ultrasound in Medicine and Biology, 2010). Splenomegaly could also be defined by other radiological methods, apart from the ultrasound. For this reason, the definition of cirrhosis is defined in more detail in the methods section.

(9) In Exclusion criteria were ...portal vein thrombosis (partial or complete) of the main trunk or…?

These conditions are relative contraindications to conventional TACE at our Institution, and are evaluated on an individual basis. This was pointed out in the methods section and proper references were included.

(10) Presence of a transjugular intrahepatic porto-systemic shunt, Esophageal varices F2…….. Authors should refer the proper article(s)…….

These conditions are relative contraindications to conventional TACE at our Institution, and are evaluated on an individual basis. This was pointed out in the methods section and proper references were included.
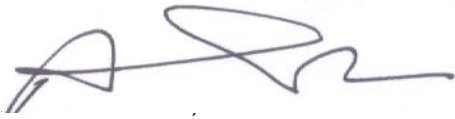
(11) How did authors diagnose Hepatitis C or B?

Hepatitis C and B were diagnosed by detecting antibodies to hepatitis C virus (HCV) and Serum hepatitis B surface antigen (HBsAg), respectively, through standardized tests. Details have been included in the methods section.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology.*

Sincerely yours,

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