

## Format for ANSWERING REVIEWERS



February 2, 2016

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 23918-review.doc).

**Title:** Impact of biliary stent-related events (SRE) in patients diagnosed with advanced pancreaticobiliary tumours receiving palliative chemotherapy.

**Author:** Angela Lamarca, Christina Rigby, Mairéad G McNamara, Richard A Hubner, Juan W Valle

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 23918

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

### General comments

1. Some syntactic/orthographic mistakes remain in the text and tables/figures
  - Replace "stent blockage" by "stent obstruction"

Reply: amended as suggested by reviewer

- Replace "multivariable" by "multivariate"

Reply: We would prefer to retain the term multivariable in our paper, since this is technically more appropriate. In the paper by Hidalgo and Goodman (January 2013, Vol 103, No. 1 | American Journal of Public Health; full text provided as supplementary material for the Editor's information) "Statistically speaking, multivariate analysis refers to statistical models that have 2 or more dependent or outcome variables, 1 and multivariable analysis refers to statistical models in which there are multiple independent or response variables.". The most frequent example of multivariate analysis, as explained by Hidalgo and Goodman, is "modeling of data that are often derived from longitudinal studies, wherein an outcome is measured for the same individual at multiple time points (repeated measures), or the modeling of nested/clustered data, wherein there are multiple individuals in each cluster. A multivariate linear regression model would have the form  $Y_{n \times p} = X_{n \times (k+1)} \beta_{(k+1) \times p} + \epsilon$  where the relationships between multiple dependent variables (i.e.,  $Y_s$ )—measures of multiple outcomes—and a single set of predictor variables (i.e.,  $X_s$ ) are assessed." Since no repeated measures and only one dependent /outcome (OS or SRE, depending on which analysis we are referring to) are used, the technically correct term for our analysis is multivariable and not multivariate.

We would be happy to include this reference into our paper should the Editor find this necessary.

2. Do not use "SRE-cohort" and "no-SRE cohort". There is only one cohort, which was produced according to your inclusion/exclusion criteria. To discriminate your patients, use "cases" and "controls" or "SRE group/patients" and "no-SRE group/patients"

Reply: amended. We have used the terms "SRE-group" and "no-SRE group" all through this reviewed version of our manuscript.

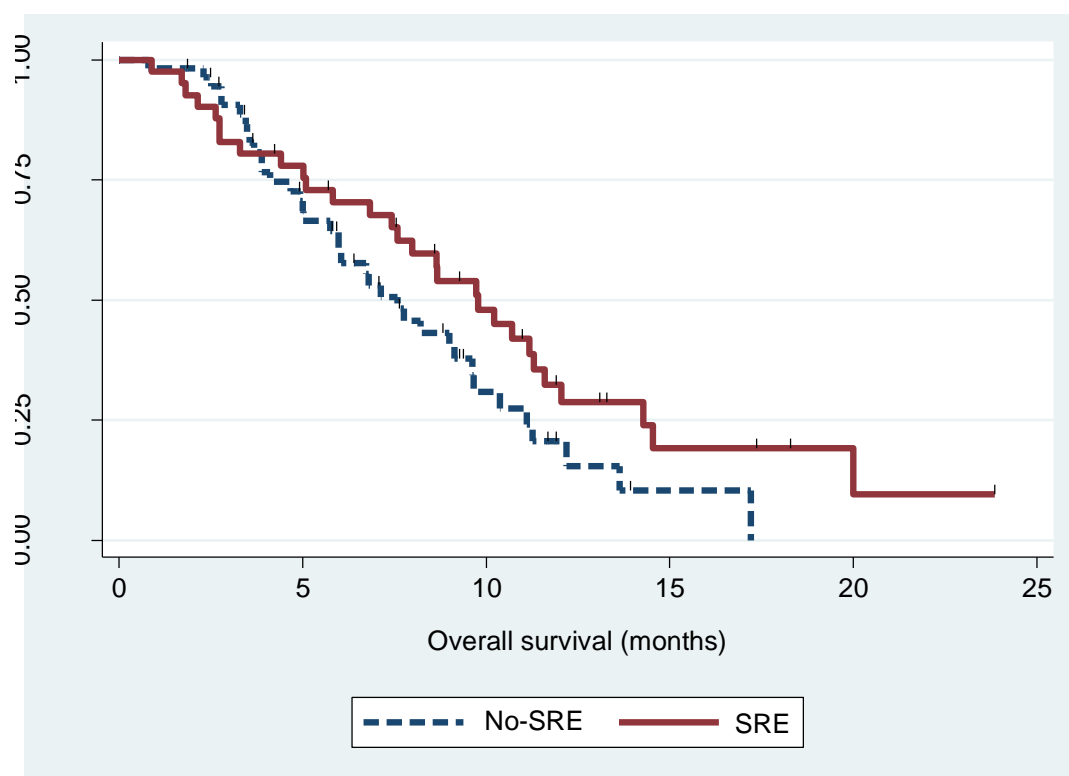
3. "p<0.05" and not "p-value<0.05"

Reply: amended as suggested by reviewer

4. A Kaplan-Meier survival curve depicting survival without SRE/time would be welcomed

Reply: Due to the fact that death acts as a competing event, as discussed in our manuscript, the Kaplan Meier curve for SRE vs no-SRE may mislead the readers to incorrect conclusions. Unless they read the manuscript completely, readers may understand that development of SRE is a favorable prognostic factor and may lose the message of "time at risk" widely discussed in our manuscript. We would, personally, try to avoid any confusion and would prefer not to display it. We would be grateful for Editor's opinion regarding this.

The Kaplan Meier curve is as below.



5. Did you encounter any other complication than obstruction/cholangitis ? (hemorrhage, perforation, ...)

Reply: One patient had an episode of cholangitis with secondary gallbladder perforation and was classified as "cholangitis". No other type of complications were recorded.

## Abstract

6. Do not abbreviate SRE more than once

Reply: This mistake has been corrected

7. The origin of the 693 screened patients have to be mentioned, as well as the inclusion/exclusion criteria

Reply:

- Inclusion criteria are mention in the abstract: "advanced pancreatico-biliary cancer and a biliary stent in-situ prior to starting palliative chemotherapy" which correspond to the following inclusion criteria:
  - advanced pancreatico-biliary cancer
  - biliary stent in-situ
  - due to start palliative chemotherapy
- Information regarding the origin of the 693 screened patients: this information was not available in the abstract but has been added as per reviewer's suggestion.

8. Chemotherapy does not need to be mentioned in the abstract

Reply: this information has been omitted from the abstract as suggested by the reviewer

9. Please state how long the follow-up was

Reply: this information has been included in the abstract as suggested by the reviewer

## Introduction

10. Do not mix objectives and perspectives. The "feasibility of developing an adequately-powered clinical trial" is clearly not one of the objectives of your study, as it was not explored

Reply: This section has been amended in the reviewed version of the manuscript as suggested. Assessing the feasibility was not one of the primary objectives and the paragraph has been reworded accordingly.

## Materials and Methods

11. Do not mix cancer localizations and histological types (gallbladder vs. cholangiocarcinoma)

Reply: the term "bile duct" as primary site has been included in the manuscript

12. Rewrite the sentence about your inclusion criteria : "had previous biliary obstruction treated with biliary stenting; had a biliary stent in-situ at the time of starting palliative chemotherapy" could be : ""had an in-situ biliary stent for biliary obstruction at the time of ..."

Reply: this suggestion has been included into the manuscript

13. The section "The primary objective of this study was to... and overall survival (OS) should belong to the end of the introduction

Reply: this information has been added to the last paragraph of the introduction

14. It should be indicated that you did not include patients on long-term antibiotics or ursodeoxycholic acid

Reply: this information is available in the results section – patients' demographic. "None of the patients included were on long-term antibiotics or ursodeoxycholic acid." Since this was not one of the exclusion criteria defined at the beginning of this study, it would not be correct for us to add this to the exclusion criteria.

## Results

15. How was your follow-up defined?

Reply: this information has been added into the methods section: "Time on follow-up was defined as the time from first biliary stent insertion to date of last follow-up available."

16. Do not indicate range, but SD or SEM, as appropriate

We are aware that the WJG guidelines suggest provision of results as "mean  $\pm$  SD or mean  $\pm$  SE." However, mean is an accurate descriptive data in case of normal distribution of variables only (in which case mean and median are similar). Since, as specified in table 1, most of our variables did not follow a normal distribution, medians (providing range for information of variable distribution) are given in order to be more accurate.

17. Are the numbers you indicate (45%) means or medians? Similarly, SEM or SD should be mentioned

Reply: 45% are absolute percentages, not estimations or pooled mean or medians.

18. "Cholangiocarcinoma" is not a primary tumour site

Reply: We have changed "cholangiocarcinoma" for "bile duct" as primary site.

19. Please mention the etiologies of deaths

Reply: Since all patients were diagnosed with advanced malignancy, all deaths were cancer related. Out of all patients who died during the follow-up, only 9 patients had SRE-related death, as specified in table 2 and in the results section.

## Discussion

20. The discussion is of very good quality

Reply: We thank the reviewer for this positive feedback.

## Figures

21. Figure 1: The flowchart should not contain useless abbreviations. The legend should be rewritten.

Reply: We thank the reviewer for picking this up. Unnecessary abbreviations have been omitted.

22. Table 2: What does "unknown" mean? Should not it be excluded?

Reply: "unknown" refers to "not specified". This has been amended for clarity.

## Editor's comments

23. Author names should be given first, then author title, affiliation, the complete name of institution, city, postcode, province, country, and email.

Reply: this information has been provided

24. Please put the reference numbers in square brackets in superscript at the end of citation content or after the cited author's name.

Reply: this has been amended

25. Please add PubMed citation numbers and DOI citation to the reference list and list all authors.

Reply: this information is provided below:

1. Valle JW. - Advances in the treatment of metastatic or unresectable biliary tract cancer. - Ann Oncol 2010;21 Suppl 7:vii345-vii348.  
PubMed link: <http://www.ncbi.nlm.nih.gov/pubmed/20943640>
2. Hidalgo M. - Pancreatic cancer. - N Engl J Med 2010;362(17):1605-1617.  
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4. Von Hoff DD, Ervin T, Arena FP et al. Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine. N Engl J Med 2013.  
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PubMed link: <http://www.ncbi.nlm.nih.gov/pubmed/?term=Ballinger+AB%2C+McHugh+MFAU%2C+Catnach+SMFA%2C+Alstead+EMFA%2C+Clark+ML.+Symptom+relief+and+quality+of+life+after+stenting>
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PubMed link: <http://www.ncbi.nlm.nih.gov/pubmed/10625815>
9. Costamagna G, Mutignani M, Rotondano G et al. Hydrophilic hydromer-coated polyurethane stents versus uncoated stents in malignant biliary obstruction: a randomized trial. Gastrointest Endosc 2000;51(1):8-11.  
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PubMed link: <http://www.ncbi.nlm.nih.gov/pubmed/25442083>

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<http://www.rtog.org/LinkClick.aspx?fileticket=oClaTCMufRA%3D&tabid=290>. <http://www.rtog.org/LinkClick.aspx?fileticket=oClaTCMufRA%3D&tabid=290>, 5 A.D. (Accessed January 1, 15).

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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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