May 16, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (Complications and Survival in Patients Undergoing Colonic Stenting for Malignant Obstruction: 3202 -revised.doc).

Title: Complications and Survival in Patients Undergoing Colonic Stenting for Malignant Obstruction

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 3202

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) **Reviewer No. 1**

- Reviewers comment
This is a well-written manuscript on an important topic. I have two recommendations.

- Response
We thank the reviewer for his impression about the article and the effort to enhance the article content.

- Reviewers comment
1. The guidelines mentioned in the last paragraph of the discussion section and listed as reference 36 should be discussed in the body of the manuscript. They may even be attached as a figure/table to the manuscript.

- Response
We have taken the reviewers suggestion into consideration and listed all the statements in the guideline that pertain to colonic stents in the management of obstructive colonic lesions.

- Reviewers comment
2. The last sentence on page 12, discussion section, is "SEMS insertion for malignant colorectal obstruction is the best option when technical skills...". This is incorrect. It should read "SEMS insertion for malignant colorectal obstruction is the best option FOR PALLIATION OR AS A BRIDGE TO SURGERY when technical skills..."

- Response
We agree with the reviewer that the statement we had made needs further specification. We have incorporated his suggestion.

(2) Reviewer No. 2

- Reviewers comment

The authors aimed to predict complications after stent placement for colonic obstruction either in a palliative or a curative attempt. The purpose of the study is interesting and could help to select patients who could be good candidate for stent. The authors should nevertheless indicate in the manuscript that there is currently a debate on the oncological safety of the stent (Sabbagh et al, ann surg, 2013).

- Response

We agree with the reviewer. We had stated the following in the introduction "Although there are risks associated with the use of SEMS like perforation[2-6], migration[2-6] and reobstruction[2-4] as well as a debate whether there is an added benefit from the use of SEMS when compared to surgery as an initial management strategy[7, 8], ***and even possibly a negative effect on survival***[8], however, there are study design considerations that might account for such results[8]"

We had added the article suggested by the reviewer.

- Reviewers comment

Major comments: 1/ In the material and methods chapter, the authors should define what an unresectable cancer is. Idem for palliative vs curative intent.

- Response

We thank the reviewer for his note. We added the following clarification in the material and methods section.

"Based on a computerized tomography (CT) scan that was performed for the patients, the stage of the tumor was determined and the SEMS insertion would be either as a bridge to surgery in patients that were deemed resectable or as a palliative procedure in those who had metastatic disease or were poor surgical candidates."

- Reviewers comment

2/ The authors should revise the statistics in the results chapter. There is a mistake in this part "On univariable analysis, none of the following variables predicted the development of complications from SEMS insertion: age of the patients OR 1.02 (95%CI; 0.95 to 1.10), patients sex OR 2.37 (95%CI; 0.69 to 8.14), the time between the onset of symptoms to SEMS insertion OR 1.01 (95%CI; 0.99 to 1.03), the time between SEMS insertion and surgery OR 1.02 (95%CI; 0.85 to 1.22), the length of the stenosis OR 1.12 (95%CI; 0.70 to 1.80), location of the stenosis OR 1.03 (95%CI; 0.97 to 1.08), albumin level OR 0.98 (95%CI; 0.90 to 1.06), receiving neoadjuvant chemotherapy OR 1.38 (95%CI; 0.39 to 4.88)". Odd ratio are multivariate analysis and not univariate analysis if the authors mean multivariate they should give the outcomes of the univariate first and then included only significant variables in the multivariate analysis.

- Response

We do respect the opinion of the reviewer, but it is well known that odds ratios, relative risks, hazard ratios, etc.. are all measures of effect and are not related to whether the regression is a univariable or a multivariable one. We initially perform a univariable analysis and those variables that are clinically relevant or are significant on univariable analysis are entered into the multivariable model and a stepwise regression is performed.

We refer the reviewer to the text book by Szklo and Nieto "Epidemiology: Beyond The Basics"

- Reviewers comment

3/ Most importantly what is the primary criteria of the study.

- Response

In the methods section we have made the following statements

For the inclusion criteria" The medical records of consecutive patients who underwent an attempted SEMS insertion between November 2006 and March 2013 were included"

For the exclusion criteria "Patients with any of the following were excluded: clinical evidence of bowel perforation or peritonitis, free intraperitoneal air on abdominal imaging, significant coagulopathy, hemodynamic or pulmonary instability, non-malignant strictures (e.g. those with inflammatory strictures due to diverticulitis), those where the endoscopist found a patent lumen not requiring SEMS insertion, or rectal cancer within 5 cm from the anocutaneous line."

- Reviewers comment

4/ Do you really think that patients with extracolonic tumors must be selected for the purpose of this study? For me they corresponded to another issue.

- Response

In our cohort only 4.76% of patients had extracolonic tumors, thus an effect on the study analysis is very unlikely. In other series 27% to 41% of patients who underwent colonic SEMS insertion with a palliative intent had extracolonic tumors

see :

1- Yoon JY et al. Gastrointest Endosc 2011;74:858-68.
2- Im JP et al. Int J Colorectal Dis 2008;23:789-94.
3- Kim JY et al. Surg Endosc 2013;27:272-7.

Furthermore, the literature is unclear with regards to SEMS inserted for malignant colonic obstruction from extraintestinal origins as the insertion was more likely to be unsuccessful, but in those receiving SEMS with a palliative intent there was no difference in the SEMS patency and reobstruction rate (21.9% vs. 30%, *P*-value =0.29). This was mentioned in the discussion.

Also, for practical reasons, in some cases the clinician is faced with an obstructing lesion and it might not be obvious from the initial imaging whether the tumor is of colonic origin or not prior to obtaining a tissue diagnosis, which is not possible in cases where there is an acute bowel obstruction.

Thus for the purpose of this study we do not think that the exclusion of these patients from the study cohort would be warranted.

- Reviewers comment

5/ your univariate analysis for complication is very unclear : - what are the corresponding complications (perforation, failure, migration?) you are speaking about? - Why don't you test all your variable (as example localisation of the stenosis has not been selected

- Response

We apologies that the term "complication" was not defined. In table 1 there is a breakdown of what the term "complications" that have been associated with SEMS insertion are comprised of; perforation 4.10% (955 CI; 0.01%- 8.77%), migration 8.21% (95%CI; 0.02%-14.67%) and stent re-occlusion 2.74% (95%CI; 0.01%-6.57%).

We have added these to the heading in table 2 as well as in the results section under the heading of ***Predictors of complications from SEMS insertion.***

We did test all the variables including the location of the obstruction but due to constrains of space we only included selected variables to report in the table. As there was a small number of cases in each location of the colon apart from the sigmoid (69.6%) thus there was no much variability and there was no association between the development of "complications" and the location of the tumor whether on univariable or multivariable analysis.
In the results section there is a statement with that regards "*location of the stenosis OR 1.03 (95%CI; 0.97 to 1.08)*"

- Reviewers comment
6/ Table 1 is unclear and it should be more standardized.

- Response
For the first table there is only a simple description of the study population with the mean and 95% confidence intervals. We cannot by any means make it any simpler. If the reviwer meant that the subheadings for the variables are unclear we have made them in *italics* but eventually this will be determined by the publisher and the style of the journal.

- Reviewers comment
7/ The conclusion doesn't answer to the question of the title.

- Response
We agree with the reviewer and thank him for pointing that out. This was an oversight on our part and have modified the conclusion to include the following statement "In conclusion, none of the variables in our study could predict the occurrence of complications (perforation, migration, and stent re-occlusion) from the insertion of SEMS or long-term survival in cases with malignant colonic obstruction. This may well be due to the size of the cohort in this study".

- Reviewers comment
8/ The outcomes of patients with stent as a bridge to surgery and with stent in a palliative aim should be separated.

- Response
The complications as well as the survival of patients who had surgery or those who had palliative therapy are delineated in the results section. Also it is shown in figure 2 and thus we do not think that adding an additional able describing the outcome of each would add any information to the data already presented. If the reviewer feels strong about this matter we would be happy to add an additional table but we believe that it would only add unnecessary length to the manuscript.

- Reviewers comment
1/ In the sentence: "the duration between the initial symptoms of the patient and the SEMS insertion, and the duration between of the SEMS insertion and last date of follow up" the word of should be removed.

- Response
We have removed it as instructed by the reviewer.

- Reviewers comment
Remarque: your study confirmed long term deleterious effect of stent even as bridge to

surgery as illustrated Fig 3 with no 5 years survival in stent group and less than 5% 4 years survival in the same group.

- Response

We believe that the difference in the survival curves in the figure 2 are not a function of the stents rather than that patents with advanced unresectable disease, i.e. stage IV, had a worst prognosis as shown in figure 3.

(3) Reviewer No. 3

- Reviewers comment

The authors tried to find predictors of complications and survival in patients undergoing colon stenting for malignant colorectal obstruction. However, there was no interesting issues in this manuscript. The number of cases is too small to reach any conclusions, and definition of complication and variables were poorly defined. Analysing all kinds of complication in one analysis is not appropriate because the characteristics of complications (migration, obstruction...) having different related factors can be mixed and confounding factor.

- Response

We respect the opinion of the reviewer.

However we would like to point out a few issues

-This management strategy is still of debate in the literature as delineated in the discussion.

-Although the number of cases in this study is not huge, the majority of the studies in the literature remain in the same range.

-The variables were clearly defined in the methods section and if the reviewer would be able to point out where the ambiguity resides we would be happy to clarify it for him.

-Although such a combined endpoint of complications might have some heterogeneity within it but owing to the small number of individual complications it would be very unlikely to find any predictors for any individual complication. Furthermore, such a combined endpoint is well accepted and used in the cardiology literature.

($) Reviewer No. 4

- Reviewers comment

Good paper accept it please cite WSES guidelines on colonic obstruction

- Response

We thank the reviewer for his comment. We have cited the WSES guidelines and expanded on it in the discussion as suggested by the first reviewer.

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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