Reviewer 1:

This is an interesting trial about comparing plastic to SEMS for the palliation of lower malignant biliary abstraction. M&M: The authors should state the total number of stents placed in all centers through the total time of 37 months and argue why such a low number of inclusions were performed.

-We thank reviewer 1 for the comments.

- The study was conducted to include only one stent per patient; stent failure was considered if an additional ERCP was performed for stent replacement or suspicion of obstruction, the patient was excluded afterwards. We therefore did not track the number of stents placed per patients past the initial one up to death, stent change or loss of follow-up.

The authors should state the total numbers of pts. for each center.

-No screening log was done as it did not reflect local practices. However, included below contains the table of patients enrolled per center;

	# of patients
Center #1	28
Center #2	17
Center #3	3
Center #4	30
Center #5	4
Center #6	3

The economical impact of this approach should be integrated into this paper to compare both groups. The authors planned enrollment of 120 pts. and state that due to "trial fatigue" only 85 pts. could be included.

- We agree with the reviewer and the extensive direct and indirect cost data were collected; these have been submitted as a separate manuscript for thematic reasons and length considerations; the data were presented at DDW 2013; Barkun AN, Adam V, Martel M, Cost Effectiveness Analysis of Partially Covered Self Expandable Metal Versus Polyethylene Stent for Patients With Malignant Biliary Obstruction, Gastrointestinal Endoscopy, Volume 77, Issue 5, Supplement, May 2013, Page AB241

The authors planned enrollment of 120 pts. and state that due to "trial fatigue" only 85 pts. could be included. In the statistical part this should be included may be as an interim analysis calculation with 80 ptd.

- We reviewed this request with our statistical consultant and were advised that we cannot validly perform an unplanned interim analysis retrospectively.

Results: The authors should state their standard approach to management secundary biliary obstruction after stenting (restenting or stent in stent) and should make a work up in detail to theses pts. which are commonly the problematic group.

- The reviewer brings up indeed a good clinical question but this was not an aim nor addressed in this trial – we refer the reviewer to the response to his/her first comment.

Discussion: The cost-effectiveness should be included to value this paper.

- We have addressed this question above

Table: Table on can be deleted

- We have deleted the requested table and renumbered the manuscript accordingly .

Table 2: The carracter of the stenosis (length an diameter should be added) and the type and length of the used stent

- The SEMS stent used was the partially covered Wallstent® Endoscopic Biliary Endoprosthesis with Permalume™ covering comprised that is of two components: the implantable metallic stent and the Unistep™ Plus Delivery System, (Boston Scientific, Natick, MA) (SEMS). The plastic stent used was a 10 French (Fr) Amsterdam-type Polyethylene (PS) biliary stent, as detailed in the study design and randomization section.

The following has been added to the result section:

"The mean length of Wallstents used was 61.4±11.2 mm (median: 60mm, min: 40mm, max: 80mm),; 95,1% patients received a 10Fr diameter and 4.9% an 8F diameter.

In the Traditional (plastic stent) group, the stent length was 76.0±18.2mm (median: 70, min: 50, max:120); all these stents had a 10Fr diameter; this had been added in the results section"

Lab values prior procedure without fu can be deleted.

- It is not current practice to delete information at baseline as it provides a better trend of our population and is required by methodological publishing guidelines. However, for the reviewer's perusal, we have indicated the values below

Characteristic		Partially covered SEMS	10-French polyethylene plastic stent
Laboratory data	Alkaline phosphatase (IU/L)	659.5 ± 356.9	518.2± 316.0
	Bilirubin (mg/dL)	10.56 ± 7.47	11.10 ± 7.74
	Hematocrit (%)	45.50 ± 58.10	37.02 ± 6.19
	Hemoglobin (g/dL)	12.04 ± 1.65	12.36 ± 2.17
	INR	1.18 ± 0.21	1.25 ± 0.37
	AST (IU/L)	155.83 ± 90.27	184.69± 149.02
	ALT (IU/L)	233.63 ± 164.60	256.26 ± 248.84

Table 3: The complications should be stated to early (1 week) and late during follow-ip. Ref.:

-All complications where observed after 7 days. This information has been added as a foot note under table3.

There are to many references they should be reduced to maximum 15-20

- We thought the references would be difficult to be reduced to 15-20 as requested by the reviewer unless specific suggestions are made. If not, we are happy to let the editor comment on the numbers of references acceptable for the journal format and article type, in keeping with the authors instructions of the journal.

Reviewer2:

Although the manuscript extension is large, it could be interesting to provide certain missing data: SEMS diameter and length, plastic stent type (Cotton-Leung...) and length.

We thank reviewer 2 for the comment; this point was addressed and appropriate information integrated in the manuscript as per our response to reviewer #1 (see above).

Reviewer 3:

GENERAL COMMENTS MAY CONSIST OF FOUR MAJOR POINTS

(1) The importance of the research and the significance of the research contents; **The authors try to answer a clinical question regarding the efficacy - primary outcome - of the placement of two different types of sent in patients with infra-hilar biliary obstruction due to malignancy, as palliative care. Also, main secondary outcomes are the adverse events and the quality of life measurements that are attributed to each type of stent. These are fundamental questions of a clinician that tries to deliver the best palliative care to this patient population.**

(2) The novelty and innovation of the research; **There is neither novelty nor innovation in this research.**

(3) Presentation and readability of the manuscript; and (4) Ethics of the research. **The presentation of the manuscript, as well as, its readability is excellent.**

SPECIFIC COMMENTS MAY CONSIST OF THE FOLLOWING POINTS

Title: Whether it accurately reflects the major topic and contents of the study.

Regarding Title:

Minor Comments:

1. The title refers to "covered metal stents", however, the metallic stents are "partially covered".

- We thank the reviewer for the suggestion. The title has been changed to: A Randomized Multicenter Trial Comparing 10-French Plastic to Partially Covered Metal Stents for the Palliation of Lower Malignant Biliary Obstruction.

Abstract: Whether it gives a clear delineation of the research background, objectives, materials and methods, results (including important data) and conclusions. Whether the innovative and significant points conform to the background, objectives, materials and methods, results (including important data) and conclusions.

Regarding Abstract:

Minor Comments:

1. The abstract does not mention that the trial refers to palliative care of malignancy patients.

- The patient population section in the abstract has been modified as requested and now reads as follow:

Patient population: Palliative patients aged >18 , for infrahilar malignant biliary obstruction and a Karnofsky Performance Scale Index >60%, from 6 participating North American university centers.

Materials and methods: Whether its materials are characterized by the following features, such as large sample size, multi-center case analysis, samples from special cases, cells or tissues. Whether the methods used are innovative and advanced. Whether a detailed description is provided for any modified or novel methods to allow other investigators to reproduce or validate. Whether the design of the controls is rational and reliable, and whether the statistical methods used are appropriate.

Regarding Materials and Methods:

Minor Comments:

1. **(study design and randomization) and (Interventions and follow-up management) The technical characteristics of the Wallstend® , the sizes that were used, as well as, the n of each type should be mentioned.**

   We thank reviewer 3 for the comment; this point was addressed and appropriate information integrated in the manuscript as per our response to reviewer #1 (see above).

2. **(Interventions and follow-up management) The total hospital stay should be measured in outcomes.**

   The following data have been added in the results:

   "29.8% were inpatients; amongst these, the mean hospital stays related to the procedure were 2.5±1.6 days in the SEMS group, and 4.9±4.7 days in the PS group."

   Durations of hospital stay in follow-up were not recorded.

3. **(Interventions and follow-up management) The follow-up is "quarterly scheduled" in this section of the manuscript, however, the follow-up in data collection section of the manuscript is at 1 month, then after 2 months, and after that in a quarterly basis (i.e. every three months).**

   We thank the reviewer and have accordingly made the following modification:

   "Each patient had a one- and three-month follow-up, followed by quarterly scheduled follow-up sessions up to 2 years following stent insertion."

Major comments:

1. **(study design and randomization)The authors should mention if the materials and devices used were FDA - or other, site specific respective polices - during the study period.**

   A sentence has been added in the method section:

   " (...)both stents are FDA approved".

2. **(study design and randomization) The study initiated before 2004, and 85 patients enrolled over 37 months. The authors should mention the total follow-up time, and the end of the study. However, even if the maximum time periods should be considered, the end of this study was likely to take place during 2009. The authors should comment regarding this gap of publication time till 2013.**

The last patient was included in 2005 and the study was terminated in 2008. after an initial analysis and abstract submission, due to lack of funding, the final analyses and were only reviewed and performed in 2010-2011.

3. **(outcomes measures) Repeat ERCP for stent replacement was considered to represent a stent failure. Does repeat ERCP for the management of the metal stents failure was considered as failure? This should be clearly stated.**

   Any stent failure and stent dysfunction, regardless of the failure, was considered as a stent failure.

   We specified in the method section the following sentence:

   "Repeat ERCP for stent replacement or suspected obstruction using a stent of any type was considered to represent a stent failure."

METHODS:

Results: Whether the results provide sufficient experimental evidence or data to draw firm scientific conclusions. Whether the sample size and the statistical data, especially graphic data that reflect the results, are adequate for a clinical study.

Regarding Results:

Major comments:

1. **Even if mentioned by authors, n=85 patients remains not to be the appropriate sample size needed to draw valid conclusions.**

   We strongly disagree with the reviewer as we did show a significant difference for stent failure when comparing SEMS to PE. Although we did not obtain the sample size initially calculated, we can reject the null hypothesis. The reviewer's comment would be correct if no statistically signifiifcant difference had been noted, as a type II error could then have occurred due to lacking of statistical power. But such consideration is irrelevant to this trial. We did however state in our discussion that 85 patients were included instead of the planned 120.

2. **Baseline characteristics for both groups should be compared and p values should be mentioned in table 2**

   As requested by the review, we have included p-values in table 2.

3. **The stent patency period is not clearly defined. Was it calculated as the interval between stent insertion and its obstruction? Or, was it calculated as the interval between stent insertion and patient death with a patent stent? It would be better if the results were presented as cumulative stent patency. In figure 2, the "y" axis should correspond to % of patients with patent stent. This interpretation will make more understood according to the results, that the time to stent failure might be bigger than time to death for the SEMS group. However, in the way data and analysis are presented, it might be considered as clinically incompatible, and one should re-evaluate statistical methods used in accordance with the follow-up loss. This is a major issue for this study as it changes the result of the primary outcome. I strongly recommend for the authors to re-evaluate the results, and if still valid to address the rational.**

   Better yet than cumulative stent patency is the presentation and analysis of data in a survival analysis. The advantage of this approach as is well recognized in statistical textbooks is that not only are patients included up to the time of failure, but the data of those who die with a patent stent are included inn the form of censored information at the time of death. This is a standard and recommended approach, and one which we has often been used in the literature (we refer, as supporting evidence the reviewer to the data analysis and discussion we provided in a recently published meta-analysis comparing fully covered to partially covered stent by Almadi et al. in Clinical Gastroenterology and Hepatology).

4. **In the QoL – SF 36 measurements, authors should state the number of patients that completed a second OR a third questionnaire.**
   We thank the reviewer, we have added the following sentence:
   "31 patients answered only once to the SF36 questionnaire, 17 answered to two questionnaire and 13 responded to 3 questionnaires"

Minor Comments:

1. **CONSORT diagram is not visible for review.**
   We are sorry, and have uploaded a higher resolution version of the diagram.

Discussion: Whether it is well organized, and whether systematic theoretical analyses and valuable conclusions are provided.

Regarding discussion: It is well organized. However, it should present the strengths of the study as equally of its limitations. In "conclusions", authors should reconsider if this trial really confirms an answer to the primary study question.

We believe that this trial clearly provides an answer to the study question as stated in the conclusion. A lack of power was not an issue. We refer the reviewer to our responses to the methodological issues raised above with regards to sample size and data presentation.

We have thus correctly concluded that: "The present study confirms that insertion of a partially covered SEMS for patients with infrahilar biliary obstructing tumors results in a longer duration until stent failure as compared to a commonly used plastic stent (in this case, an Amsterdam-type Polyethylene stent) without increased complication rates".

References: Whether the references are appropriate, relevant, and updated.

Regarding References: Appropriate and relevant.

Tables and figures: Whether tables and/or figures reflect the major findings of the study, and whether they are appropriately presented.

Regarding Tables and Figures: as above mentioned.

CLASSIFICATION OF THE MANUSCRIPT

Reviewers must classify the manuscript into grades A, B, C, D and E, where grades A and B are excellent or very good, grades C and D are good or fair and grade E is poor. If the reviewer cannot decide the grade, then mark it as unsure.

CLASSIFICATION OF THE MANUSCRIPT: D

LANGUAGE EVALUATION

(1) Grade A: priority publishing; (2) Grade B: minor language polishing; (3) Grade C: a great deal of language polishing; and (4) Grade D: rejected. The revised articles should be in grade B or grade A.

LANGUAGE EVALUATION: A

THE REASONS FOR REJECTION OF AN ARTICLE INCLUDE

(1) scientific contents do not accord with the World Journal of Gastroenterology scopes; (2) data are inadequate to support proper explanations or conclusions; (3) the related work has been published and only a few new points are added; (4) the article contains accumulated information that has been previously published with only a few technical improvements; (5) the article is expected to attract only a

very small number of readers; and (6) the article has been rejected previously and resubmitted without adding any new valuable contents.

THE REASONS FOR REJECTION: **(2) data are inadequate to support proper explanations or conclusions; (3) the related work has been published and only a few new points are added;**

We respectfully again submit that reviewer 3 is in error and refer to the response to major comment #1.

Reviewer 4:

This is an interesting study. Unfortunately the enrollment goal of 120 patients was never realized. Despite this significant shortcoming, I still believe that there is clinically useful data in this study which can be of help to clinicians. However, prior to possible publication, the following concerns should be addressed. 1. From 85 patients that were enrolled, 3 were excluded from further analysis. The results shown are therefore from 82 patients. In the abstract of the paper please change the number of patients to 82 (41 in each arm).

We thank reviewer #4 for the comment; the abstract was modified as follows:

85 patients were accrued over 37 months, 42 were randomized to the SEMS group and 83 patients were available for analysis.

Please also change the numbers in table 2. 2. Based on the sample size calculations, 120 patients needed to be enrolled in the study. However, due to “trial fatigue”, only 85 patients were enrolled and only 82 appropriately entered into the study. This is an important piece of information that has to be included in the abstract of the paper. 3.

This suggestion has been added to the abstract:

"From an initially planned 120 patients, only 85 patients were recruited "

Please report data as median and 25th-75th percentiles rather than mean ±SD. Reporting median (25th-75th percentiles) gives a clearer picture of the dataset and is not influenced by outliers.

In the data clean-up process, all outliers have been assessed and verified with original data, furthermore, if n>30, we assume the values are normally distributed yielding our choice to present the values as mean ±SD. We will however submit to the format of the journal.

Furthermore, at times it simply makes no sense to report data as mean ±SD (for instance stent lengths of 5.56 ±2.54 cm). 4.

We agree with the reviewer that in this case the most meaningful presentation of the data is by showing median , min and max. This point was addressed and appropriate information integrated in the manuscript as per our response to reviewer #1 (see above).

Please report how many ERCP procedures were performed in patients in each group during the 2 years of follow up or prior to death.

An ERCP was performed in each group but when the patient achieved the outcome they were excluded from the study, we did not get any additional data after patient exclusion. We refer the reviewer to the response to the first comment by reviewer #1.

Reviewer 5:

Some form of straight forward economic analysis should be considered. For example what is the relative cost of both stents and how many of each were used.

We thank the reviewer for this comment and agree that this is an important issue. We refer the reviewer to reviewer #1 who had a similar comment to which we responded.