November 19, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5342-review.doc).

Title: Predictors for failure of stent treatment for benign esophageal perforations – a single center 10-year experience

Author: Saga Persson, Peter Elbe, Ioannis Rouvelas, Mats Lindblad, Koshi Kumagai, Lars Lundell, Magnus Nilsson, Jon A Tsai

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 5342

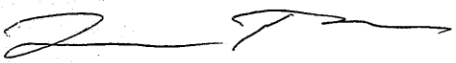
The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer
(1) 00057695
(2) 00058455
(3) 00003940
(4) 00008985

3 References and typesetting were corrected

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

Sincerely yours,



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Response to referee 00003940

Would they recommend now that those with delayed presentation and with pleural sepsis had esophageal resection?

Our main message is that treatment with stents should be considered for most patients with EPR. In case of delayed treatment, where the perforation is not sealed promptly with a stent and sepsis continues despite maximal drainage procedures, esophagectomy should be considered at an earlier stage, probably earlier than the median 12 days among the patients presented here where esophagectomy was performed after failed stenting. We now discuss this further.

Further would they recommend a conservative management with no stent for patients with a minimal perforation?

We agree that the indication for stent therapy should be individualized and tailored for the patient. However, there are no strict criteria for when for instance only drainage is sufficient. Therefore, we may have "over treated" with stents in some cases. Since the clinical course of this condition is very unpredictable, we think that this is a reasonable financial price to pay. Moreover, the stent treatment *per se* for this condition has no complications according to our experience. This is now discussed in the manuscript

Was it possible to predict treatment failure in a timely fashion that an esophagestomy is still feasible?

The mortality after esophagectomy was substantial (3/6). The number of cases is too small for drawing any conclusions regarding at what time point esophagectomy still would be feasible. One can of course speculate that the mortality after esophagectomy would have been lower if performed at an earlier time point. This is now discussed in the manuscript.

I think the language is a little verbose. I do not think they need to repeat all the results in the tables in the description of the results but to highlight the important findings.

The results section has been shortened.

Response to referee 00008985

1. Is there any patient treated with SEMS insertion under LA or intravenous sedation instead of GA? Because in the reviewer's institution, we never insert SEMS in GA.

All patients received stent during general anesthesia.

2. The selection of patient for SEMS probably is safer to base on patient's clinical condition rather than just "intention to treat". Not sure if the last patient of "cardiovascular comorbidity" could have different outcome if operated promptly.

Please see point 4. The patient with “cardiovascular comorbidity” differed from all others who received stent as a primary treatment with an intention to heal the perforation. In the records it was clearly stated that a stent would never heal the perforation and that the intervention was purely palliative to postpone death a few days. The intention to heal the perforation among the other cases is clearly demonstrated by frequent re-interventions and among the cases where the stents failed, the long time frame (median 12 days) until the management strategy was changed.

3. The authors did not mention when and how to retrieve the SEMS after insertion. The retrieval of SEMS could be extremely challenging especially in older days when only metallic stents were available. If the stent left in situ for too long, it might not be possible to retrieve it. In the benign condition, if the stent is left too long period may cause long-term problem.

The SEMS were generally changed/extracted after a maximum of 4 weeks in order to minimize difficulties retrieving it. If the leakage persisted at that time, another stent was applied. In our material, we had no major complications associated with stent extraction. One patient initially treated at our unit was scheduled for stent extraction at a county hospital. Due to difficulties with the procedure, the patient was referred back to us where the extraction was uncomplicated. No stent-related complications occurred. Re-interventions were common because of stent dislocations or insufficient sealing, which however not should be regarded as complications. This is now explained in the text.

4. I would be very cautious to give a comment / conclusion that SEMS is indicated for all/most EPR patients since I still believe clinical condition is probably the most important consideration factor in choosing the most appropriate treatment strategy for these patients.

We agree that the indication for stent therapy should be individualized and tailored for the patient. However, there are no strict criteria for when for instance only drainage is sufficient. Therefore, we may have “over treated” with stents in some cases. Since the clinical course of this condition is very unpredictable, we think that this is a reasonable financial price to pay. Moreover, the stent treatment *per se* for this condition has no complications according to our experience. This is now discussed in the manuscript

5. It would be better if the authors could provide which type of SEMS they used in these patients.

Indeed, it would be preferable to also demonstrate which types of stents were used for every case. There have been no uniform reporting criteria in the medical charts regarding this and the

information has unfortunately been missing in several cases. What we can say though, is that in almost all cases fully covered metallic stent were used.

6. There are some obvious grammatical mistakes.

The grammar mistakes have been corrected.

Response to referee 00057695

I have the following comments: 1. In the narrative there are many words that are not spaced. This may be due to the way the article format was downloaded in my computer, or this was actually the case in the submitted draft. If it is the latter, this needs to be clarified and corrected.

This might have been due to changed format when downloading the document.

2. Abstract: I felt the abstract was a little bit long and hence can be made shorter by trimming unnecessary details. Also correct the time range for the successful SEMS.

The abstract has been revised according author instructions provided by the journal for brief articles.

3. In the management strategy: give the name antibiotics used and their dosages and frequency. Also how were the feeding jejunostomy inserted?

All patients received broad-spectrum antibiotics, usually Imipenem 500 mgX3, which thereafter was changed depending on culture results, resistance patterns and need for fungus prophylactics. We have added this information in the manuscript.

4. Results, line 9: change the word (acute) in (acute esophagectomy) to (emergency).

This has been changed in the manuscript.

5. In the Clinicopathological findings, paragraph 2 , line 7: the number of recovered patients was 33 and not 30. Also after the remaining patients add the number of patients between brackets (n=3).

This has been changed in the manuscript.

6. Discussion: the first paragraph contained some repeated sentences. Second paragraph, it was mentioned that "SEMS placement can be completed in any hospital where endoscopic service is available". I disagree with this statement as stent placement is hardly available in many endoscopic units around the world despite the widespread availability of diagnostic endoscopic services. This is specifically true in the developing and under-developed countries. Covered stents are very expensive and cannot be afforded by many. I suggest the authors highlight the cost of endoscopic stenting in their discussion.

This is indeed a relevant concern. The costs of stents are now mentioned in the manuscript. Compared to the very high overall cost for these patients, the costs for stents is a relatively small expense in our setting. Three stents are roughly equivalent to the cost of one day at the ICU, excluding addditional expenses for medications etc there. This is now mentioned in the paper.

7. How many attempts at redo stenting is tried before failure is declared and surgery is contemplated? I believe under this setting, the prognosis is poor and surgery carries high mortality rate. Further clarification is needed here.

There is no algorithm available for this question and we do not have a pre-defined maximum number of re-interventions. In this study, the highest number of endoscopic re-interventions was 3, which is similar to other studies and maybe could serve as some kind of ”guidline”. It should be emphasized that 3 re-interventions were done in some cases where the stent strategy eventually was successful.

8. Regarding referred patients, inevitable delay is expected especially in countries where referral to tertiary centers is hampered by bureaucracy. This will adversely affect the outcome of endoscopic stenting. Unless a fast-tack referral system is available, delays are expected with subsequent higher morbidity and mortality. This needs to be alluded to in the discussion.

This is a valid point that we now further emphasize in the text.

9. When is the appropriate time for stents removal, if they are not biodegradable? This should be mentioned in the Methods and should be supported by references.

To our knowledge, there are no available guidelines regarding optimal time for stent extraction when treating benign esophageal diseases. In our unit, leakages have been frequently re-evaluated and the decision of adjustment/change/extraction of stent has been made on an individual basis. In general, the stent has been extracted or – in case of persistent leakage -changed within 4-6 weeks. This has been done in order to minimize ingrowth of granulation tissue, which could yield difficulties during extraction. This is now described in the methods section and we have added a reference about this.

10. Were there any stent-related complications, or complications during or after removal of the stents?

In our material, we had no major complications associated with stent extraction. One patient initially treated at our unit was scheduled for stent extraction at a county hospital. Due to difficulties with the extraction the patient was referred back to us, where the extraction was eventful. No stent-related complications occurred. Re-interventions were common due to stent dislocations or insufficient sealing, which however not should be regarded as complications. This is now explained in the text.

Response to referee 00058455

1. For a patient of EPR, is the response of treatment depended on stent itself or feeding jejunostomy or percutaneous thoracic drains?

The response of treatment is not depended on stent itself. The stents are part of a multimodal management strategy, which includes resuscitation, broad spectrum antibiotics and source control of infection with drainage procedures based on the clinical and anatomical conditions. The outcome is obviously dependent on an optimal application of all these treatments combined. This is clearly stated in the manuscript. In the literature, there is however no substantial consecutive series of patients with perforations of the upper GI tract, treated with only drainage where the mortality is as low as presented here.

2. Is the timing of percutaneous thoracic drains or stent, which one provided real value for a patient of EPR?

The drainage procedures are performed at the same time or very near the time point for insertion of stent. Again, both stents and drainage are part of a multimodal management strategy, which makes it hard to distinguish the effect of each intervention.

3. The authors should clarify if only stent providing the good outcome of treatment for EPR.

See above.

4. A reference as below might give other answer about the stent for EPR. Endoscopic stent insertion versus primary operative management for spontaneous rupture of the esophagus (Boerhaave syndrome): an international study comparing the outcome. Schweigert M, Beattie R, Solymosi N, Booth K, Dubecz A, Muir A, Moskorz K, Stadlhuber RJ, Ofner D, McGuigan J, Stein HJ. Am Surg. 2013 Jun;79(6):634-40.

The article that is referred to is a comparison of two centers in two different countries where one mainly used stents as primary treatment whereas at the other, surgery was the treatment of choice. This study only consisted of spontaneous ruptures. In our series also iatrogenic cases were included and failure of stenting was more frequent in this group, even if the difference was not statistically significant. There were also several differences in the management at the center that used stents compared to our treatment strategy. Most notably, acute esophagectomy was not performed in any of the patients where stents failed.