Author's response to reviews

Title: Small bowel enteroclysis with magnetic resonance imaging and computed tomography in patients with obscure delivery of patency capsule

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Author's response to reviews: see over
Answer to the Reviewer BMC Medical Imaging

Dear Editor,

We are very grateful for the valuable criticism by the reviewers of our manuscript “5649953425556285 - Small bowel enteroclysis with magnetic resonance imaging and computed tomography in patients with obscure delivery of patency capsule”.

We have done our best to meet the suggestions by the reviewers and have given our well considered answers to their questions. The clarity of our manuscript has improved, as has the presentation of our message, i.e. MRI- and CT- enteroclysis examinations provide valuable diagnostic information in patients primarily considered for video capsule enteroscopy.

All changes made in the manuscript are highlighted in red. Our response to the reviewers’ remarks are given below one after the other as are our revised texts. By the adjustments made it is our sincere hope that the manuscript will meet your demands in standards and be accepted for publication in BMC Medical Imaging.

Page numbers are slightly different from those mentioned by the referees after our text revision.

First reviewer’s report
Title: Small bowel enteroclysis with magnetic resonance imaging and computed tomography in patients with obscure delivery of patency capsule
Version: 1 Date: 29 June 2011
Reviewer: Søren Rafaelsen

Reviewer’s report:
The question posed by the authors is well defined and relevant: the clinical value of subsequent MRI and CT examinations in patients in whom a test capsule did not present itself in due time. The study was approved by the Ethics committee and patients gave their informed consent. The methods are appropriate and well described.
The authors found the diagnostic value of MRI- and CT enteroclysis is sufficient for clinical management in this group of patients. Patients without alarm symptoms and pathological and pathological laboratory analyses did never show any erosions in the small bowel mucosa.
Comments:
Page 9 Methods: line 2:
Please specify the picture archiving system.

Reply: An added sentence: “Images were stored on Sectra PACS and evaluated on a Siemens work station”. ....All appropriate medical records etc.
Page 6, third section.

Page 14 Results:
"All patients without alarm symptoms and with normal laboratory analyses had also normal examinations." Please elaborate. The number of patients needs to be specified.
Reply. There were 17 patients who had normal laboratory parameters and no alarm symptoms. None of these had a pathological examination. This is added on page 14, line 5 from the bottom.

Page 18 Discussion:
Insert before conclusion:
Another limitation of this retrospective study is not all patients had a VCE. Endoscopy or clinical follow-up was used as “gold standard”.

Reply: The following sentence is now inserted on page 20, last paragraph in the discussion, and on page 19, second section.

A limitation of this retrospective study is that not all patients had a VCE. As only 29% of our patients had a final VCE we had to accept the clinical follow-up diagnoses as our “gold standard”.
One might comment that the absence of a final VCE proved our case, viz. gastroenterologists did not anticipate any further diagnostic information of importance for managing 71% of their patients besides the information obtained by the enteroclysis examinations.

At study begin we defined diagnostic results from upper and lower GI endoscopic studies during the follow-up period as our “gold standard”. Unfortunately only 20 VCEs were done, so we had to accept running clinical annotations as the truth.
The results apply to MR- and CT enteroclysis and not MR- or CT enterography.

Page 18 Conclusion:
"It is unknown to us to what extent any additional diagnostic information from the MRI- and CT examinations influenced clinical decision making." Move to limitations, in the discussion section.

Reply. This sentence is deleted and the last section is rephrased, see above in the discussion.
Second reviewer's report

Title: Small bowel enteroclysis with magnetic resonance imaging and computed tomography in patients with obscure delivery of patency capsule

Version: 1 Date: 29 July 2011

Reviewer: Johannes Heverhagen

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Abstract
The abstract of the manuscript must be understandable on its own without requiring the reader to access the complete manuscript. Please rephrase accordingly.

Background: The stated aim in the abstract is different from the aim stated in the main body of the text. Please check and rephrase accordingly.

Reply. We have now deleted “our primary” in the last section of background, so the aim is the same in both abstract and main body text.

Methods: Here, it should be explicitly stated that this is a retrospective study.

Reply. It is now clarified that the data was collected retrospectively. The cohort included all consecutive patients during the time-frame studied. The VCE method is only available at our hospital in the uptake area. So no patients are lost. To our knowledge, there is no other publication based on such a large patient cohort.

Results: The authors state that the 20 VCEs finally performed were mainly done in younger patients. However, only about 50% of patients were less than 30 years old. Please rephrase.

Reply. We have explained that younger in this sentence refer to younger than 50 years.

Results: Here, the authors mention alarm symptoms for the first time. It needs to be stated explicitly what these symptoms are.

Reply. The symptoms classified as alarm symptoms were weight loss, haematochezia, anemia, nocturnal diarrhoea, ileus, fistulas and abscesses. These are now added in the result section.

Conclusion: The provided conclusion does not match the stated aim of the study. Please rephrase.

Reply. The conclusion is now rephrased so it matches the aim.

Background
Page 5: As stated before the stated aim of the study in the main body of the text is different from the abstract. Please check and rephrase.
Reply. We have now deleted “our primary” in the last section of background, why the aim is the same in both abstract and main body text.

Methods
Page 6: The authors state that this is a partly retrospective review. This needs to be explained in more detail. Why is it only partly retrospective? For me, this is a completely retrospective study maybe with a re-analysis of some data.

Reply. The material was collected in a retrospective manner as was the reviewing of the medical records of the patients. However, the patients were clinically followed prospectively. Partly has been deleted on page 6.

Study Design
Page 6: The authors should provide the number of patients that underwent complete VCE during the inclusion period. This would help the reader to put the number of patients with late or unconfirmed delivery of the test capsule into perspective.

Reply. During the study period in total 714 VCE were performed. This has been added on page 16 in the discussion.

Page 6: The authors mention a further follow-up period stretching until mid 2010. What was done in this follow-up period?

Reply. At study begin we defined diagnostic results from upper and lower GI endoscopic studies during the follow-up period as our “gold standard”. Unfortunately only 20 VCEs were done and no upper or lower endoscopy, so we had to accept running clinical annotations as the truth.

MRI- and CT-Enteroclysis
Page 7: The authors used a true enteroclysis method to investigate the small bowel in MRI and CT. However, this is not the commonly used technique to evaluate the small bowel with MRI and CT. Usually, patients have to drink a certain amount of a distension medium immediately prior to the investigation. As we all know, this sometimes leads to incomplete distension but is a much more comfortable method and it is preferred by most patients. Therefore, I am not sure if the results of this study are transferrable to many clinical settings.

Reply. Personal communication with prof. Andrea Laghi, Rome, who has published series on MR-enterographies admits that the quality is less than with enteroclysis, a method advocated by the leading authority in the field, prof. Nick Gourtoyiannis, Crete. In our experience it is seldom problematic to use a naso-jejunal sonde. Without direct access to the small bowel it is hard to control filling of terminal ileum, the most afflicted part in inflammatory small bowel disease.

Page 7: The authors state that scanning commenced when caecal filling was established. How did the authors monitor caecal filling?

Evaluation of Enteroclysis
Reply. We would like to call the reviewers attention to the sentence: “The transit of the polyethylene solution was monitored with turbo spin-echo T2 weighted half Fourier acquired single-shot HASTE sequence.....”. We have rephrased the sentence so that it mirrors the original publication by Gourtsoyannis et al., page 8, line 17. An ordinary bolus tracking single slice technique is used at CT.

Page 9: The authors state that the exams were re-evaluated by two radiologists. How did they perform their evaluation? Was it done in consensus or separately?

Reply. This was done in consensus.

Page 9: The authors state that one of the radiologists was board certified. How about the other radiologist? Was he board certified too or still in training?

Reply. The second radiologist was in his final training. This is added in the text.

Page 9: The authors describe that radiological signs were summarized into three groups. One of these groups was an alleged bleeding source. Please provide their criteria for detecting such a bleeding source.

Reply. An alleged bleeding source was defined as a tumour protruding into the lumen or an ulcer. This is added in the text on page 10.

Results

Magnetic Resonance Imaging (MRI) and Computed Tomography (CT)

Page 11: Please state why the quality of the radiological examinations was rated suboptimal in two patients.

Reply: Typically breathing artefacts and in one case reflux of bowel fluid into stomach with less well distended small bowel as a consequence.

Page 12: Sensitivity for Crohn’s disease was extremely low in this series. Only six out of 47 patients were correctly diagnosed in CT and MRI. What is the reason for this very low sensitivity? Did the authors only look for active disease? The authors should provide the criteria they used for the detection of Crohn’s disease in CT and MRI.

Reply: We claim that all patients got a close to correct diagnosis. Although only six patients got the diagnosis Crohn’s disease, several differentials were a priori considered clinically. The disease panorama in our series mirrors the everyday clinical hardship correctly to differentiate GI-diseases with rather wage symptoms from each other, viz. IBS from early IBD. In fact the majority did not suffer from Crohn’s disease and showed no such signs during follow-up and were also classified accordingly at enteroclysis examinations. So in this light MRI and CT- enteroclysis examinations were on par with the clinical follow-up, i.e. diagnostically sensitive.
Page 12: The authors state that a miscellaneous finding was increased number of normal mesenteric lymph nodes. What is the clinical meaning of this finding?

Reply. No one actually knows. The sign was registered because we are contemporarily looking for signs of early Crohn’s disease and this might be an observation worth while!

Page 12: In another patient they stated increased contrast enhancement of normal sized mesenteric lymph nodes as a miscellaneous finding. Again, what is the clinical meaning of this finding?
Video Capsule Enteroscopy (VCE)

Reply. Again, no one knows. The sign of enhancement in a normal sized lymph node was registered because we are contemporarily looking for signs of early Crohn’s disease and this might be an observation worth while!

Page 12: The authors state that occult bleeding was an indication for VCE in five patients. However, CT and MRI detected 13 patients with occult bleeding. Why did not all 13 patients undergo VCE?

Reply. The text states that out of thirteen patients with clinically alleged occult bleeding, no case was confirmed by MRI or CT. However, in 5 patients the physician wanted confirmation of the absence of a bleeding source by referring these for VCE. As our series is a retrospective study without a standardazied protocol, physicians were free to manage their patients according to their choice.

Page 12: The authors state that VCE found Crohn’s disease in four patients. However, only one of them had signs of Crohn’s disease in MRI. As stated before, this provides a very low sensitivity for Crohn’s disease of MRI. Why is this the case?

Reply. The sensitivity of MRI for early Crohn’s disease or any other early SB disease with subtle sign is still unknown, although many scientists are working with the question (Lasocki et al 2011). In several studies, VCE has been shown to be the most sensitive examination to discover mucosal erosions (Saurin et al 2003, Albert et al 2005). The problem is that it may be too sensitive, discovering findings that could be present also in healthy persons. For more information see reply (page 12) above.

In this paragraph, the authors compare the results of MRI and VCE. However, I am missing such a comparison for CT and VCE.

Reply. We would very much like to perform the suggested comparison, but as we came across only one patient that had both examinations done, we were not able to.

At Study End
Page 14: The authors state that no correlation between alarm symptoms and
morphologic findings could be established. However, as stated before, the results of the imaging modalities seem to be rather poor. Therefore, it is expected that such a correlation cannot be found.

Reply. You are right. It is also surprising that some of these patients had normal laboratory tests indicating the enigmatous nature of Crohn’s disease. We need prospective studies based on a sufficiently large patient cohort and even more sensitive laboratory methods. This does not in any way mean that we should abstain from studying all our current methods scientifically. Our main aim was to find out whether or not the gastroenterologist had confidence in MRI- and CT enteroclysis and that seems to be the case.

Page 14: The authors state that in patients without alarm symptoms and with normal laboratory analysis the results of the imaging studies were negative. Why would patients without symptoms and with normal laboratory analysis undergo any imaging studies?

Reply. In the era before the introduction of the VCE, we did not have any such sensitive method to examine the small bowel mucosa. Today we are prone to use VCE as a first line diagnostic method in patients with symptoms of abdominal pain, changed bowel habits and so on, to ensure that they in fact do not suffer from any undiscovered organic disease explaining the symptoms, even if the symptoms are not alarming. Most patients with mild to moderate Crohn’s disease do not present alarm symptoms, but still need to be diagnosed and treated with anti-inflammatory drugs to prevent exacerbations. We have to learn more about which patient has to be admitted for imaging examinations and when.

Discussion
Page 16: The authors state that the results of MRI or CT together with clinical re-evaluation provided sufficient data not to undertake further enteroscopies. However, how do we know that the results provided by CT and MRI in this study were correct. As stated before, the outcome of CT and MRI in comparison with VCE and other clinical data were rather poor. Accuracy of imaging in this study was very low. Therefore, the results of CT and MRI might have provided a false sense of security for the clinician. This should be addressed in the discussion.

Reply. Again, we do not think that the diagnostic data from MRI and CT are that low. A normal study result in a patient that stays free from symptoms of IBD or IBS is a correct result. In order to verify absence of symptoms and signs of a significant disease, patients were followed prospectively. And looking at the results from this perspective it seems to be justified to state that a normal CT and MRI reassures the referring doctor and her/ his patient.

It is true that a VCE might have unveiled mucosal changes if performed. Because patients were admitted to PC and VCE even on mild to moderate clinical symptoms and signs, we think that the clinicians were prone to accept a normal CT and MRI diagnosis. This topic is now addressed in the discussion, page 19.
Page 17: The authors state that 23% of women and 20% of men showed pathological diagnoses. They conclude that this may indicate that men are less prone to seek health services. However, the percentages seem to be almost the same. Why would this allow such a conclusion?

Reply. You are right. As the fraction of sick patients is gender-independent, this sentence has been deleted in the manuscript. The reason that most patients admitted to VCE were women may depend on slower transit time in females.

Page 18: The authors state that their data could not disclose any correlation between clinical symptoms and finding at imaging examinations. While this is correct, this might be related to their imaging technique and analysis. This should be discussed further.

Reply. This is now discussed on page 20, last section. Many patients were admitted to PC and VCE on rather weak indications, with minor or no deranged laboratory tests. The normal findings at MRI and CT-enteroclysis examinations in these patients are explained by the fact that imaging signs of early mucosal disease is not well understood, maybe even not possible to unveil. So it might be concluded that in patients with mild symptoms and clinical findings, a gastroenterologist should not anticipate imaging findings beyond normality. If so there is good correlation between clinics and imaging.

Conclusion
The provided paragraph is not a conclusion but rather a summary of the results. Please completely rephrase the conclusion.

Reply. We have now rephrased the conclusion, see page 19

Abstract
Results: Here, the authors mention follow-up enteroclysis. It is not obvious for the reader that this enteroclysis is meant to be either MRI or CT enteroclysis. Please rephrase.

Reply: The text is rephrased so it now is stated in the heading, background and result section.

Study Design
Page 7: Please explain the term “bio-statistically”.

Reply: “Biostatistical parameters are: figures of diagnostic sensitivity, specificity and accuracy. The text is rephrased.

Magnetic Resonance Imaging (MRI)
Page 8: The authors need to provide a more detailed description of the used MRI
sequences.

Reply: The technique is briefly mentioned as we refer to the original work by prof. Gortsoyiannis and his group (ref. 6).

Page 8: The authors state that they used a coronal 2D gradient-echo sequence. Why did they choose to use a 2D and not a 3D sequence? A 3D sequence would have allowed to acquire thinner slices with a better spatial resolution.

Reply: see above. It is of interest to use the same sequences as the leading authority in the field in order to be able to compare imaging results and quality.

Results
Patient Characteristics
Page 11: This entire paragraph provides materials and methods and should be moved to the appropriate section.

Reply: We accept to move this paragraph to the Methods section if it complies with the journal.

At Study End
Page 13: The delay times between PC test and enteroclysis and between enteroclysis and final VCE examination seem very long to me. Especially for the case of chronic inflammatory disease the state of the disease might have changed in between examinations. Please comment.

Reply: Unfortunately this mirrors the clinical management of patients when not included in a prospective study. We had no influence on this.

Complications and Limitations
Page 14: Please state why the two enteroclyses were technically suboptimal. Please also state which criteria were used to assess technical adequacy.

Reply: The reasons for a suboptimal examinations were breathing artefacts and in one case reflux of bowel content into the stomach, thus reducing the amount needed to distend the SB in an optimal way.

Discussion
The second paragraph of this page should be part of the introduction and should therefore be moved to the appropriate section.

Reply: We have adjusted the text accordingly

Page 17: I would suggest to rephrase the last sentence of the first paragraph. This is hard to comprehend for the reader.
Page 17: Please remove the last sentence of the second paragraph. This has not been studied in this manuscript and is not really related to this study.
Reply: our pages are numbered differently so we have difficulties in meeting these requests. Please, give us more information.

References

