Author’s response to reviews

Title: Is MRCP necessary to diagnose pancreas divisum?

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Author’s response to reviews:

Point by point comments
Changes that were made in the manuscript during revision are underlined.

Reviewer 1:

Comment 1-1:
The entitled manuscript "Is MRCP necessary to diagnose pancreas divisum? " in an interesting study, with a clear hypothesis and established objectives. However, needs some improvements and clarification of the clinical importance context and benefits. Furthermore, it is a single center retrospective study. So, it will be necessary an clinical validation of the present study with a multicenter study to increase the relevance and confirm or not these findings. And other important point is about the costs? It will be able to performe worldwide?
Response 1-1:
Concerning the clarification of the clinical importance and benefits we added a sentence into the “conclusion” paragraph emphasizing that omitting the 3D-MRCP in MRI exams performed for diagnosis or exclusion of PD may improve cost effectiveness and patient compliance. Concerning the validation of the results we added a sentence into the “limitations” paragraph stating that the results of our study are limited by the low number of PD cases and should be confirmed in a larger prospective trial.
Reviewer 2:

Comment 2-1:
Response 2-1:
The statement has been clarified.

Comment 2-2:
P. 7, line 29-39: the objectives of the study are not supposed to be described in this section. The last paragraph of introduction/background is usually a more appropriate place.
Response 2-2:
The last paragraph of the “introduction” has been modified to clarify the study objectives. Accepting possible redundancies, we kept the paragraph stating the objectives in the “method” section with some modifications as well, because we believe that the primary and secondary endpoints of a trial should be presented to the reader there.

Comment 2-3:
p. 7, line 39: Standard of reference is named here and further down in the image analysis section (redundancy)
Response 2-3:
After revision, details on the MRI protocol are now given only in the “imaging” section.

Comment 2-4:
p.8, line 50: "PD was deemed to be present when a dominant dorsal pancreatic duct was visualized to enter the duodenum superior to the common bile duct". Is this definition of PD sufficient? What about the cases when a prominent Santorini duct communicates with the Wirsung? Better to use the description given in the discussion section (p.12, line 18-26)
Response 2-4:
After revision, the PD definition given in the “methods” section matches the one given in the “discussion” section and was somewhat clarified. We did not differentiate between complete and incomplete PD, because data indicate that both variants may be associated with increased risk of pancreatitis. This already has been discussed in the “discussion” section before revision. In single cases it may be difficult to distinguish between incomplete PD and patent Santorini duct (which is considered to be a normal finding). However, we used the caliber of the duct opening to the minor papilla as the discriminating feature. Only if the duct draining via the minor papilla was considered the dominant duct in regards of caliber, the case was diagnosed PD.

Comment 2-5:
p. 8, line 45-50: Standard of reference: the choice of using all the available sequences - included those tested - as standard of reference may cause the so-called "incorporation bias", that is when the results of the test under study (i.e., non-MRCP and 3D-MRCP sequences) are part of the information available to the consensus panel making the consensus diagnosis. That poses the results at risk of overestimating the accuracy of the test. Suggestion: instead of performing a single-reader analysis compared to a probably biased standard of reference, the authors may consider evaluating the interrater agreement among two or three readers in the identification of PD on non-MRCP sequences versus 3D-MRCP.
Response 2-5:
This again is a relevant aspect. We improved our discussion of study limitations in the “limitations” section. We added a statement concerning the incorporation bias. The lack of an interrater agreement analysis was included in the text prior to revision.
Comment 2-6: Are the two radiologists constituting the consensus panel and the one who evaluated the images, three different radiologists? Please describe the field of expertise as well as years of expertise of the two radiologists used for the consensus diagnosis. Were the two radiologists of the consensus panel blinded to clinical information? How was disagreement managed? Additional expert? Discussion? Other? Please describe.
Response 2-6:
The paragraph in the “image analysis” section was clarified accordingly.

Comment 2-7
p.8, line 55: "Inability of pancreatic duct orifice assessment". It is unclear. What do the Authors mean?
Response 2-7:
The sentence was revised in a way that greater clarity should be present now.

Comment 2-8:
p.8 line 60: please clearly define that the analysis of "the general magnitude of motion artifacts" corresponds to the parameter "image quality" (as it appears later in the results)
Response 2-8:
The sentence was revised accordingly.

Comment 2-9:
p.9, line 10-11 (Statistical analysis): please define "performance". Sensitivity? Specificity? (these parameters are described in the results section, but not in the materials and methods).
Response 2-9:
The sentence was revised accordingly.

Comment 2-10:
p. 9, line 23: "active control method": maybe "comparator"/"standard of reference" might be a more appropriate term
Response 2-10:
The sentence was revised accordingly.

Comment 2-11
p.10, line 45-48: it would be nice to have some numerical details about the non-inferiority of non-MRCP sequences. Figure 1 is a bit difficult to perceive.
Response 2-11:
We added the lower bounds of 95% confidence intervals, which are the basis stating nonferiority or not, to this paragraph.

Comment 2-12:
"ERCP - Endoscopic retrograde cholangiopancreaTICOgraphy": has to be corrected in cholangiopancreatography
Response 2-12:
The sentence was revised accordingly.
Reviewer 3:

Comment 3-1:
One of the major limitations of the study is the lack of endoscopic retrograde cholangiopancreatography (ERCP) as the gold standard for the diagnosis of PD. The second limitation is absence of any 2D single shot breath-hold MRCP sequences, usually employed in a standard acquisition (being fast and sensitive in most of cases). These issues should be extensively commented in discussion sections. Moreover I think that the acquisition time and time sparing in the MRCP study should be highlighted to increase the strenght of manuscript. Further comment are specified below.

Response 3-1:
For sure, ERCP is the historical gold standard for PD diagnosis. However, because of ERCP invasiveness, nowadays an ERCP procedure would rarely be performed to diagnose or exclude PD if the patient is eligible for MRI. In the age of MRI, ERCP is frequently reduced to ERC to reduce complication rates, but ERC is not sufficient to assess pancreatic duct anatomy. Thus, the de facto gold standard in PD diagnosis is 3D-MRCP. The lack of ERCP has been discussed already but we refined the corresponding statement in the “limitations” section.

We agree that 2D single shot MRCP sequences certainly have a role in assessing pancreatic duct anatomy. However, in our opinion, the overall value of 2D MRCP sequences is debatable, and our institution decided to omit these sequences from our standard MRCP protocol in favor of other investigational sequences. The images from thick slab 2D MRCP sequences, e.g., contain a large volume comparable to a conventional x-ray summation image, so that spatial mapping of findings is not possible and superimposition of anatomic structures may suggest relationships that are not present, e.g. duct connection of pancreatic cysts). However, to acknowledge the value of 2D MRCP for visualization of the pancreatic anatomy we revised the “discussion” section considerably (see also comment 3-11).

Comment 3-3
Abstract, methods: I suggest to modify the word "fashion" with "manner"
Response 3-3:
The abstract was revised accordingly.

Comment 3-4
Abstract, conclusions: Please modify "have" with "offer".
Response 3-4:
The abstract was revised accordingly.

Comment 3-5:
Keyword #3) please remove
It would be better to add as keywords "TIRM" and "HASTE" sequences.
Response 3-5:
The keywords were revised accordingly.

Comment 3-8:
Please spell out "ERCP".
Response 3-8:
Revised accordingly.

Comment 3-9:
Since your results focused on TIRM and HASTE sequence, it would be reasonable to add some
information on these sequences justifying your choice.
Response 3-9:
We revised the “background” section accordingly.

Comment 3-10:
Imaging: please add the acquisition time of each sequence employed. Why the authors did not use also the 2D single-shot breath-hold MRCP sequences? It is well known that they are faster than 3D and in most of cases offer an higher sensitivity value in assessment of MPD. Please discuss it, also in Discussion section.
Response 3-10:
Acquisition times were added to the “methods” section.
Concerning the use of single shot MRCP sequences see responses 3-1.

Comment 3-11:
Why the authors did not use any oral contrast agent? Can this approach inficiate the final results? And in how many cases the negative contrast agent could improve the visual assessment of MPD?
Response 3-11:
At our institution negative oral contrast agents such as pineapple juice are not routinely used. These contrast agents reduce background signal from the stomach and duodenum and, thus, might be considered beneficial for single shot thick slab MRCP or for 3D-MRCP-MIPs for the above mentioned reasons. We added a paragraph concerning oral contrast agents to the “discussion” section.

Comment 3-12:
Page 9 Line 15. Please better describe which sequences were used as standard of reference. Did the authors used a combination of T2 weighted sequences, or T1weighted sequences. The written sentence create a sohort of confusion.
Response 3-12:
We revised the sections “imaging” and “image analysis” accordingly to clarify the definition of the standard of references.

Comment 3-13:
Why the authors did not use two independent readers in a blind manner, but used one reader in the first part of analysis and two in the second part. I think that the randomized analysis from two independent readers can improve the value of manuscript.
Response 3-13:
This is an important limitation of our study that has been addressed in the “limitations” sections

Comment 3-14:
the diagnostic performance of each sequence (expressed as sensitivity and specificity) should be statistically compared with the more appropriate test.
Response 3-14:
Primary objective of our study was to demonstrate noninferiority of non-MRCP T2-weighted sequences compared with 3D-MRCP. Thus, we decided for dedicated statistical non-inferiority tests as reviewed by Ahn et al (Radiology. 2013;267:328–38).

Comment 3-15:
Please spell out the name and city of the software you used to perform the statistical analysis.
Response 3-15:
We revised the sections “statistical analysis” accordingly.
Comment 3-16:
Please compare the results regarding the acquisition time of each sequence.
Response 3-16:
The mean acquisition time of 3D-MRCP and the acquisition times per protocol of TIRM and HASTE have been added to the “results” section and are discussed in the “discussion” section (first paragraph, conclusion).

Comment 3-17:
Please add the number of pathological findings on pancreatic parenchyma (i.e. cystic lesions; adenocarcinoma; pancreatitis, etc)
Response 3-17:
A table (table 3) was added that summarizes the pancreatic imaging findings.

Comment 3-18:
Page 11 Line 33 please add "alone" after TIRM N
Page 11 Line 35 please add "alone" after HASTE.
Response 3-18:
Cleared accordingly.

Comment 3-21:
The authors should add comment and compare the results of previous published study using the same sequences.
Response 3-21:
We added a paragraph to the “discussion” commenting on the value of HASTE and TIRM for pancreatic imaging.

Comment 3-22:
Page 13, lines 37-47: since the author did not mention on these sequences, the sentence should be deleted or, alternatively, add a comment specifying why the author did not use theme.
Response 3-22:
Our intention was to discuss new developments in the field of MRCP that may help to overcome the susceptibility of conventional respiration-navigated 3D-MRCP to artifacts. However, according to the reviewer’s suggestion, we decided to delete the paragraph.

Comment 3-23:
A comment about the lack of 2D single-shot MRCP sequences should added.
Response 3-23:
A paragraph on other MRCP techniques has been added to the “discussion” (see also comments 3-1 and 3-10).

Comment 3-24:
A comment about the lack of negative oral contrast agent administration should be added.
Response 3-24:
A paragraph on oral contrast agents has been added to the “discussion” (see also comment 3-11).

Comment 3-25:
Moreover to increase the value of manuscript I think that a mention about the time sparing in acquisition protocol should be added. Response 3-25:
We revised the “conclusion” section accordingly.

Comment 3-26:
please rewrite in "Non-MRCP T2-weighted MR sequences, usually included on standard abdominal MR protocol, are non-inferior to 3D-MRCP alone in assessment of correct diagnosis of PD.
Response 3-26:
We revised the “conclusion” section accordingly.