Author’s response to reviews

Title: Combination of CEUS and MRI for the diagnosis of periampullary space-occupying lesions: a retrospective analysis

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Author’s response to reviews:

Dear Dr. Krüger,

Thank you very much for your decision letter and advice on our manuscript (Manuscript #BMIM-D-19-00140) entitled, “Combination of CEUS and MRI for the diagnosis of periampullary space-occupying lesions: a retrospective analysis.” We also thank the reviewers for their constructive and positive comments and suggestions. Accordingly, we have revised the manuscript. All amendments are highlighted in red in the revised manuscript. In addition, point-by-point responses to the comments are listed below this letter.

This revised manuscript has been edited and proofread by Medjaden Bioscience Limited.

We hope that the revision is acceptable for the publication in your journal.

Look forward to hearing from you soon.
With best wishes,
Yours sincerely,

Song Su

First of all, we would like to express our sincere gratitude to the reviewers for their constructive and positive comments.

Replies to Reviewer 1

Specific Comments
1. fine study, of good clinical use

Response: Thank you for your recognition of our research. Pancreatectoduodenectomy (PD) is the most challenging operation in general surgery. The accurate preoperative diagnosis is crucial to PSOLs, reducing unnecessary PD for patients with benign PSOLs and diagnosing and treating patients with malignant PSOL in a timely manner.

Replies to Reviewer 2

Specific Comments
1. Please explain why the number of patients with disease and patient without disease is different between the different techniques.

Response: Thank you for your thoughtful suggestion. We take pathological examination results as the gold standard. Different examination methods have different diagnostic efficacies, so different methods often yield different results. We have added this information in the Discussion (Page 13-14, Lines 253-261, 271-279 and 283-285).

2. Please describe the patient spectrum and why they were referred to CEUS/MRI (symptoms, laboratory findings,...).

Response: Thank you for your insightful suggestion. Accordingly, the patient spectrum and why they were referred to CEUS/MRI (symptoms and laboratory findings) have been added and
shown clearly in a Table. We have added the description in the revised manuscript as “As shown in Table 1, 102 patients (50 males, 52 females; age range, 25-75 years; BMI, 20.84 ± 2.54 Kg/m2) who had undergone both MRI and CEUS in our hospital between June 1, 2015 and May 1, 2018 were enrolled. The patients were admitted due to jaundice (81/102), abdominal pain (67/102), diarrhea (12/102), abdominal distension (35/102), and vomiting (9/102).” (Page 10, Lines 199-203 and Table 1).

3. Methods for pathological examination, including whether pathologist were blinded to the results of the index tests, should be accurately described in a dedicated subparagraph.

Response: Thank you for raising this concern to our attention. The pathologists were blinded to the results of the index tests. We have added this information in the manuscript. “The pathological data from all of the cases were analyzed by two pathologists with more than 15 years of experience. The pathologists were blinded to the clinical and imaging findings.” Please see the Methods of the revised manuscript (Page 8, Lines 159-161).

4. Authors should address more extensively the potential clinical implication of their findings in the discussion.

Response: Thank you for your kind reminder. We have added information about the potential clinical implication of our findings in the Discussion. As one of the most difficult surgical procedures in general surgery, pancreaticoduodenectomy (PD) is the standard treatment for patients with resectable malignant PSOLs. The operation time is long, and many organs are removed during the operation. A previous study reported that the incidence of PD postoperative complications may be as high as 30%-65% [1]. Patients with benign PSOLS may suffer from unnecessary PD due to the misdiagnosis of benign lesions as malignant PSOLs. Meanwhile, if malignant PSOLs are misdiagnosed as benign PSOLs and treated with medication or without treatment, the misdiagnosis will lead to aggravation of the patient's condition and delay the treatment. In view of the respective characteristics of CEUS and MRI, we explored the multimodality imaging to improve the accuracy of PSOL diagnosis. We found that CCWM improved the ability to identify benign and malignant PSOL, reduced the occurrence of unnecessary PD caused by benign lesions, and allowed for the timely and effective treatment for those malignant diseases (Page 12 and Page 14, Lines 231-232 and Lines 288-292). The paper by Hill et al. has been cited as Ref. 28 in the revised manuscript.”
Replies to Reviewer 3

Minor considerations:

1. The authors applied magnetic resonance imaging (MRI), contrast-enhanced ultrasound (CEUS), and the combination of CEUS and MRI (CCWM) for a periampullary space-occupying lesion (PSOL), which they also described as a periampullary cancer (PAC).

Response: Thank you for your insightful suggestion. PSOL includes malignant lesions which are called PAC, and benign lesions. PAC includes ampullary carcinoma, distal bile duct cancer, pancreatic head and uncinate process carcinoma, and duodenal carcinoma. Accordingly, several sentences have been added in the Background (Page 4, Lines 60-64) of the revised manuscript to address this issue.

2. They tried to categorize the image findings on MRI as described in page 9. However, there were no descriptions of scoring.

Response: On page 9, we described the typical PAC imaging manifestations on MRI according to previous studies. Two experienced radiologists made the diagnosis based on these manifestations, yet there was no scoring system used in this study.

3. However, this study included various types of diseases in both benign and malignant lesions. The range of disease was too wide to show the difference among lesions statistically.

Response: Thank you for bringing this concern to our attention. Indeed, the range of diseases enrolled in this study was wide. The purpose of this study was to discover a new multi-modality diagnostic technology to improve the diagnostic accuracy of PSOL. The results showed that the specificity, PPV, and accuracy of CCWM were more significantly effective than MRI or CEUS individually (all p<0.05). These findings have potential clinical implication for the diagnosis of PSOLs. In future research, we will perform a more in-depth study of PSOL by including a smaller range of diseases.
References: