Response to the Editor

We are most grateful to you and the reviewers for the helpful comments on the original version of our manuscript. We have accommodated all comments and suggestions in the revised version of our paper.

There was no Running title in the original manuscript.

A. We added Running title in the revised manuscript as follows.

"Contrast-enhanced harmonic EUS for lymph node"

Q1. Please provide the postal code. And check throughout, thank you!

A1. We added the postal code "589-8511" in the revised manuscript.

Q2. Please provide these files, which are necessary for final acceptance, each in a separate PDF file, signed by the Correspondence author or a copy of Institution approval document(s)/letter(s) or waiver of confirmation. For sample wording and detailed information, please see the Revision policy in the attachment or Instruction to authors on our website. Thank you!

A2. We uploaded PDF files signed by the corresponding author.

Q3. A list of 5–10 keywords should be given.

A3. We appreciate your helpful comment. As suggested, we added the key words "pancreatobiliary carcinoma" and "EUS-FNA" in the revised manuscript.

There was no Core tip statement in the original manuscript.

A. We added Core tip statement in the revised manuscript as follows.

Diagnosis of malignant intra-abdominal lymph nodes is often challenging for endoscopists and radiologists. In the present study, the diagnostic accuracy for differentiating malignant from benign lymph nodes of standard EUS, color Doppler EUS, and CH-EUS relative to EUS-FNA was assessed.

A secondary objective of the present study was to assess the N-stage diagnostic accuracy of CH-EUS and EUS-FNA in patients who underwent surgical resection. In conclusion, CH-EUS was more accurate than standard and color Doppler EUS, except the short axis cut-off. Notably, three patients excluded because of EUS-FNA failure were correctly N-staged by CH-EUS.

Q4. Please reformat all the reference numbers (superscript with square brackets). Please check throughout. Normal line space is required. Please check throughout. Thank you!

A4. As suggested, we reformated all the reference numbers to superscript with square brackets.

There was no COMMENTS statement in the original manuscript.

A. We added COMMENTS statement in the revised manuscript as follows.

Q5. The graphs supplied should be decomposable (each part of your figure could be moved so as to easily edited). You can send it as word or PPT format so that I can edit them easily. Thank you!

A5. As suggested, we edited the Fig.1 to the PPT format, and added it to the supplementary materials in the website.

Q6. Please add PubMed citation numbers and DOI citation to the reference list and list all authors. Please revise throughout. For those references that have not been indexed by PubMed, a printed copy of the first page of the full reference should be submitted.

A6. As suggested, we added PubMed citation numbers and DOI citation to the reference list and list all authors in the revised manuscript.

COMMENTS TO AUTHORS

The authors demonstrated the clinical utility of contrast-enhanced harmonic EUS (CH-EUS) as a diagnostic tool for detecting lymph node metastasis in patients with pancreatobiliary carcinoma. Although this paper is informative and interesting for the further developments of imaging approaches, some revisions are needed.

Comment

1. Scale bars for the magnification should be indicated in **Figure 2-A, 2-B, 4, and 5**.

A1. As suggested, we added scale bars in Figure 2-A, 2-B, 4, and 5.

2. The authors should discuss about the future perspectives of CH-EUS in the clinical management.

A2. As suggested, we added about the future perspectives of CH-EUS in the clinical management in the Discussion section as follows.

In view of the high accuracy described in this study, in the future, CH-EUS may help to detect the in-operable stage better and thereby helps to avoid unnecessary surgery. Hence, CH-EUS will play an important role in determining the optimal treatment of pancreatobiliary carcinomas.

3. In the present study, the authors demonstrated the high accuracy rate of CH-EUS for predicting lymph node metastasis. How about the combined analysis based on CH-EUS and other modalities, such as short axis 13 mm or longer and CIV absent, for gaining the further high accuracy?

A3. We appreciate your important comments. In the current study, we demonstrated the higher diagnostic accuracy of CH-EUS than other modalities. According to your suggestion, we evaluated the combined analysis based on CH-EUS and other modalities. However, all combined analysis based on CH-EUS and other modalities did not gain higher diagnostic accuracy in comparison to CH-EUS alone (See the table below). Therefore, we regrettably gave up adding this analysis in the revised manuscript.

	Sensitivity	Specificity	Accuracy
Heterogeneous (CH-EUS)	**83% (39/47)**	**91% (79/87)**	**88% (118/134)**
Heterogeneous and/or Short axis 13 mm or longer	98% (46/47)	78% (68/87)	85% (114/134)
Heterogeneous and/or Long axis 20 mm or longer	98% (46/47)	55% (48/87)	71% (94/134)
Heterogeneous and/or Round shape	94% (44/47)	69% (60/87)	78% (104/134)
Heterogeneous and/or Sharp edge	94% (44/47)	23% (20/87)	48% (64/134)
Heterogeneous and/or Hypoechogenicity	98% (46/47)	53% (46/87)	69% (92/134)
Heterogeneous and/or CIV absent	92% (43/47)	68% (59/87)	76% (102/134)

COMMENTS TO AUTHORS

The authors compared the CH-EUS with standard EUS and color Doppler EUS for evaluating the accuracy of lymph nodes metastasis. The manuscript is well prepared and has an explicit explanation in each section. Though the EUS-FNA used as a gold standard in primary analysis is not good enough as you mentioned in the limitation, it is reflected with good sensitivity for EUS-FNA and CH-EUS in secondary analysis. There is one minor question in "Equipment" section that 10-15 fps represent for frame per second or other else?

A. We appreciate your helpful comments. As you suggested, "fps" means frame per second. We exchanged the term "fps" to "frame per second" in the Equipment section.

COMMENTS TO AUTHORS

A very well performed, interesting study, thank you.

A. We appreciate your interest to our manuscript.

COMMENTS TO AUTHORS

This paper compared the diagnostic accuracy of standard EUS, color Doppler EUS and CH-EUS in terms of the ability to differentiate malignant nodes from benign nodes and compared the accuracy of CH-EUS and EUS-FNA in terms of N-stage diagnosis in patients who underwent surgical resection. the author found that CH-EUS depicted the microvasculature of intra-abdominal lymph node very clearly. Thus, it may be a useful modality for differentiating malignant from benign lymph nodes in patients with pancreatobiliary carcinomas and may complement standard EUS, color Doppler EUS and EUS-FNA, all of which have limitations. This is a wonderful paper.

A. We appreciate your interest to our manuscript.