

Dear Editor,

we submit our revised paper n° 21664 "Endoscopic Ultrasonography: Transition towards the future of gastro-intestinal diseases".

Here are our point-by-point answers to the Reviewers' comments:

Reviewer n.00068723

COMMENTS TO AUTHORS

This review discussed the whole aspects of EUS, and was well-organized. EUS-guided confocal laser endomicroscopy was informative and interesting. It was reasonable that successful drainage rate was the same between ERCP and EUS-BD, while complication rate was higher in EUS-BD than ERCP. It was reasonable but interesting that rate of pancreatitis was lower in EUS-BD. EUS-BD requires advanced skills, and its complication is severe. More detailed description of complications would be desirable. The readers should know the adverse events.

Response: we described in detail the adverse event of EUS-BD (page 7 from line 3 to line 6, page 7 line 15, page 7 from line 18 to line 24), according to the reviewer's advice.

How was the outcome of EUS-guided pancreatic fiducial placement for pancreatic cancer? Did the cancer volume reduce? How was the survival of the patients?

Response: the aim of the study reported (Davila Fajardo et al.) was to describe safety and feasibility of EUS-guided fiducial placement by using a 22 gauge needle, no data about the patients follow-up and treatment outcomes were reported. We added these considerations in the manuscript together with the only data available about the short term outcome of two patients (page 9 from line 20 to line 22), as the reviewer suggested.

Sampling of portal blood with EUS-FNA. How was the circulation tumor cells detected? Were they observed under a microscope? Was the sampled blood subjected to laboratory tests, such as carcinoembryonic antigen (CEA)? Was the sampled blood subjected to real-time quantitative PCR of tumor specific genes? As the authors mentioned, this technique was novel. Readers would know this technique in more detail.

Response: when we wrote the manuscript the study was published as an abstract. Now the study is in press on Gastroenterology, so we can better describe the technique and the methods in more details, as the reviewer suggested (page 11 from line 7 to line 21); accordingly to this change we also modify the reference details (n. 42).

Reviewer n. 02897448

COMMENTS TO AUTHORS

I congratulate the authors with a well done study to introduce the most up-to-date advances and cutting-edge technologies in the field of interventional EUS and EUS-guided confocal laser endomicroscopy. The paper is well written in good English and is easy to understand. To improve the quality of the EUS-FNA of solid lesions, Alizadeh AHM compared two techniques of EUS-FNA. The study should be included for up to date references.

Alizadeh AHM, Hadizadeh M, Padashi M, et al. Comparison of two techniques for endoscopic ultrasonography fine-needle aspiration in solid pancreatic mass. Endoscopic Ultrasound 2014;3:174-178.

Response: the study of Alizadeh et al, has been included in the manuscript (see page 6 from line 16 to line 21) and in the reference (at n. 25) according to the reviewer's advice.

Reviewer n. 02445450

COMMENTS TO AUTHORS

This is a well-written review, especially on future possibilities of EUS-guided confocal laser endomicroscopy. 1. Because EUS-guided CLE is mainly emphasized in the abstract/introduction and most recently appeared in the clinical field, how about writing about CLE first?

Response 1. We wrote about EUS-guided confocal laser endomicroscopy first in the paper (from page 3 to page 5), as suggested by the reviewer. References' order was changed.

2. Figure 1. Are there any other images to give us diagnosis of intraductal papillary mucinous neoplasm? If added, it might be of help for readers' understanding.

Response 2. Figure 1 shows finger-like projections, typical of intraductal papillary mucinous neoplasm in a sagittal view (A); and dark rings with a central core, typical of intraductal papillary mucinous neoplasm when imaged in cross section (B); no other images are available for this neoplasm.

3. Figure 2. Are there any pathological figures corresponding this place?

3. Response 3. Figure 2 shows the vascular network of a serous cystadenoma by needle-based confocal laser endomicroscopy. It corresponds to subepithelial capillary

vascularization on the pathological specimen, as reported in the figures of the article recently published by Napoleon et al. (n. 12 in the reference section of our paper), but we can not provide pathological figures in this setting because of in our series no patients with serous cystadenoma underwent to surgery.

4. Figure 3. How could you get the same surface when you made the histological specimen?

Response 4. The surface of the histological figure, was the same of figure 3A, because it was imaged in cross section.

5. Figure 4/5. Are there any histological figures? In Figure 4, please put the size bar. Even without additional histological figures, this manuscript is considered to be fully worth publication.

Response 5. We put the size bar in Figure 4, as requested by the reviewer.

About Figure 4 we can not provide the correlative histological figure because we do not perform FNA or surgery of normal pancreatic tissue; regarding figure 5 we can not provide the histologic correlative because the malignancy of the lymph node was confirmed by a tomography positron emission (PET) and the patient underwent to radiotherapy and not to surgery.

Please find enclosed the revised manuscript containing the changes in BOLD.