Author's response to reviews

Title: Endoscopic ultrasound-guided sampling of solid pancreatic masses: 22-gauge aspiration versus 25-gauge biopsy needles

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Dear Editor,

RE: Endoscopic ultrasound-guided sampling of solid pancreatic masses: 22-gauge aspiration versus 25-gauge biopsy needles

We thank the editors and reviewers of ‘BMC Gastroenterology’ for taking the time to review our article. The comments from the reviewers were most helpful, and we have included our responses to the comments below. We also revised the manuscript as suggested by the reviewers. We hope this revised manuscript will be suitable for publication in ‘BMC Gastroenterology’.

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COMMENTS FROM REVIEWER #1

Major compulsory revisions:

1. The measured outcomes reported in tables 4 and 5 are unclear without referring to the methods and so I suggest that the data is either presented in another format or the legend includes a brief description of how the data is presented so that it can be more easily interpreted.

We added a brief description of how the data were presented for easy interpretation of the data in Tables 4 and 5.

2. These data are retrospective review of data but this is not immediately clear reading the abstract and methods to make it clear it is not an RCT. Also, I
imagine from reading the methods that the 2 groups were separated over time with the older group sampled using the 22G needle and the newer group with the 25G needle. These groups therefore may have introduced other bias such as improved operator techniques so this requires clarification.

We revised the abstract and methods to clarify that this study is not a prospective randomized comparative study. We divided the patients chronologically, according to the time period during which the needles were used, into two groups. Therefore, we agree that the bias-related improvements in the techniques of the operator may have been introduced. A discussion of this viewpoint was added in the manuscript.

Minor discretionary reviews:
1. The authors report other similar data from alternative published studies with reported sensitivities of 64%-95% but report their own sensitivity as 60% and 32%. The published series may overestimate the sensitivity of FNA sampling for diagnosis of pancreatic cancer but this observation should be discussed further.

In our study, the 25G FNB group showed a better histological diagnostic yield in terms of specific tumor discrimination compared with the 22G FNA group (60.6% vs. 32.4%, P = 0.018). However, these results were unsatisfactory compared with those of previous studies, which used larger-gauge FNB needles [1, 2]. In the present study, samples for histological analysis were collected after tissue acquisition for cytological analysis, which was somewhat biased against histology. Moreover, we restricted the number of needle passes for obtaining histological specimens to 2 to prevent procedure-related complications. These factors may be related to the relatively low histological diagnostic yield compared with those of previous studies, which used larger-gauge FNB needles [1, 2]. We discuss this viewpoint in the manuscript.

Other comments
1. Generally well written
2. The numbers included are small and so of limited value compared to already published series.

We describe this viewpoint as a limitation of our study in the manuscript.
3. The 2 groups, although not randomized and likely involve different time frames, do appear sufficiently similar to make a comparison.
4. Grouping of definite and suspicious for malignancy is debatable in terms of suitability for clinical confirmation of cancer although in my view is acceptable. This issue may need clarification and discussion.

In daily clinical practice, physicians are often unable to consider results that are suspicious for malignancy as benign. Additionally, based on our experience with EUS-FNA for solid pancreatic masses, false-positive cases were not encountered. Therefore, as the reviewer’s view for this issue was acceptable, our
opinion is that it is reasonable to consider suspicious cases as malignancies.

5. Presenting the data on other parameters such as quantity of blood staining is some clinical interest to those in the area and is therefore suitable for inclusion but probably adds little to the ‘bottom line’ of the final diagnosis of cancer v no cancer.

The quantity of blood staining likely adds little to the ‘bottom line’ for the final diagnosis of malignancy. However, contamination with blood can prevent accurate cytological interpretation. In the study of Nakai et al., the diagnostic yields of the suction and slow-pull techniques were retrospectively studied for patients who underwent EUS-FNA for pancreatic solid lesions [3]. In this study, use of the slow-pull technique employing regular FNA needles was associated with less blood contamination and better diagnostic yield with a 25-gauge needle.

COMMENTS FROM REVIEWER #2
Reviewer’s report:
No recommendations for change

COMMENTS FROM REVIEWER #3
Major compulsory revisions:
1. This is a retrospective comparative study of the usefulness of 22G needle and 25G needle in the EUS-FNA of the pancreatic masses. A previous metaanalysis showed that there is a non-significant difference in sensitivity (78% vs 91%), and 100% specificity, with no difference in the number of passes or complications (Affolter et al. Dig Dis Sci 2013), which is consistent with the presented results.

The reported diagnostic accuracy of core histology specimens is 45% for the 25G needles (Sakamoto et al 2009) and 60 to 87% for the 22G needles (Sakamoto 2009, Ramesh 2015, Bang 2012). In the present study, the diagnostic accuracy by using the 22G needle was only 34%. Please explain.

In Bang et al.’s prospective comparative study, 56 patients were randomized to undergo EUS-guided sampling of the pancreatic mass lesion with either the 22G FNA or the 22G FNB device [2]. The specimens obtained with the needles only underwent cell block processing for histological assessment. The histological diagnostic yield of the 22G FNA needle in our study (34.2%) was lower than that reported by this previous study (66.7%). There is one explanation that may contribute to this difference. In the study of Bang et al., the specimens obtained with the 22G FNA needle underwent cell block analysis for histological assessment, and some studies have shown that cell block is a valid technique for performing histologic assessments and can improve the diagnostic accuracy of smears [4-6]. In our study, the specimens for histological examination were placed in formalin solution, and the cell block technique was not used for histological assessment. A discussion of this viewpoint was added in the manuscript.

In Sakamoto et al.’s prospective comparative study, the authors performed
EUS-FNA using 25G and 22G FNA needles and 19G Trucut needles in each patient [7]. Puncture by 25G and 22G FNA needles and 19G Trucut needles was performed two times in each patient. The overall rate of histological diagnosis using the 22G FNA needle was 62.5%. The histological diagnostic accuracy of the 22G FNA needle in our study (34.2%) was lower than that reported by this previous study (62.5%). The difference in the tissue preparation technique for histological analysis may explain the difference in the results between the two studies. However, we could not find any explanation for the tissue preparation technique utilized for histological analysis in the study of Sakamoto et al..

Ramesh et al.’s prospective comparative study compared flexible 19G and 25G needles for EUS-FNA of solid pancreatic masses [8].

2. Methodology problems. “The number of needle passes for obtaining histological specimen was limited to 2 to prevent procedure-related complications” Please give details on the presumed complications or explain why there were 5 passes for cytology and only 2 for histology. This could conduct to unreliable conclusions.

In our study, the materials obtained on the first pass of EUS-guided sampling were mounted onto slides for conventional smear (CS) with alcohol fixation, and the materials obtained from the following pass of EUS-guided sampling were placed into an ethanol-based preservative (CytoRichRed™; Becton-Dickinson Diagnostics, Burlington, NC, USA) for SurePath™ (Becton-Dickinson Diagnostics, Burlington, NC, USA), a liquid-based preparation (LBP). If the materials for CS or LBP that were assessed macroscopically by the endosonographer were insufficient, more passes of EUS-guided sampling for CS or LBP were performed. After we obtained the material for CS and LBP, additional two passes were performed to obtain a histological specimen. There was no significant difference in the mean number of needle passes between the groups (22G FNA: 5.05 vs. 25G FNB: 5.55, P = 0.132), and no early or late complications were identified in either group. We performed EUS-guided sampling in inoperable solid pancreatic lesions and solid pancreatic lesions, in which it was difficult to differentiate between malignant and benign lesions in other diagnostic tests. Because cytology is more sensitive than histology alone in the diagnosis of pancreatic malignancies [9], we first obtained specimens for cytological examination. After the material for cytological examination was obtained, we restricted the number of needle passes for obtaining histological specimens to 2 to prevent procedure-related complications such as pancreatitis, bleeding, bile peritonitis or malignant seeding [10]. A discussion of this viewpoint was added in the manuscript.

Minor essential revision
1. Please define “macroscopically sufficient material” for histological evaluation.

In our study, macroscopically sufficient material for histological evaluation was defined as one or more small-core biopsy cylinders obtained by EUS-guided sampling. A discussion of this viewpoint was added in the manuscript.
Discretionary revision
1. Please insert 22G group and 25G group in the Table 2.

We used FNA devices in the 22G group and FNB devices in the 25G group. Therefore, we inserted '22-gauge FNA' and '25-gauge FNB' into Table 2.

References