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Toulouse, January 10th, 2014

Dear Editor

Please find enclosed the edited manuscript in Word Format (file name: Bournet Review 01467723.docx).

Title: ROLE OF ENDOSCOPIC ULTRASOUND IN THE MOLECULAR DIAGNOSIS OF PANCREATIC CANCER

Authors: Barbara Bournet, Marion Gayral, Jérôme Torrisani, Janick Selves MD, Pierre Cordelier PhD, Louis Buscail

Name of the Journal: *World Journal of Gastroenterology*

ESPS manuscript No: 6776

The manuscript has been improved and revised according the suggestions of the editor and the reviewers:

- 1) The format has been updated according to the instruction for authors and the correction requested by Editor throughout the text: Address of authors, Authorship, place of table 1 within the text, format of references (including PMID and doi when available), format of references within the tables 1 and 2, format of figure 1 that has been included as a power point format with independent lines and arrows, typesetting.

- 2) Revision has been made according to the suggestions of the reviewers: A special chapter has been added page 7 indicating that in near all of the cases of pseudotumorous chronic pancreatitis and autoimmune pancreatitis tissues, molecular analysis revealed a wild type *Kras* in EUS-FNA materials. In other term, when facing to a clinical and radiological presentation of pancreatitis or pancreatic inflammatory mass, a wild type *Kras* is highly evocative of benignity. In this chapter (and also in Table 1) we have added a summary of a prospective recent study that is in press on this topic. This study (new reference 39) strengthens these conclusions and demonstrates that *kras* assay improves the diagnosis of pancreatic cancer when EUS-FNA cytopathology is doubtful or inconclusive.

Thank you for your time and consideration of our manuscript for a possible publication in *World Journal of Gastroenterology*.

Best regards

Prof. Louis Buscail, MD, PhD

A handwritten signature in black ink, consisting of a large, stylized 'L' followed by a series of loops and a final flourish.

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RESPONSES TO REVIEWERS AND EDITOR - Ms JCG13216 Revised

Reviewer #1 Comments:

1. *I am not sure how this study is different than the previous study published by the same group, reference 14. Can they clarify are these the same patients? Are these a new set of patients?*

- RESPONSE : In the discussion section (page 13 first paragraph) we have precised that our previous study (reference 14) was performed on a group of patients (inclusions from January 2005 to April 2007) that is different from that of the present study (inclusions from January 2010 to February 2013).

2. *One major weakness of the study is that it is a heterogeneous group of patients, not everyone went to surgery for a true gold standard. A better design would be for patients who were surgical candidates, who underwent EUS FNA, who had the diagnosis by EUS -FNA cytology versus EUS-FNA cytology + KRAS? It seems a mixed bag of patient with benign disease, adenocarcinoma and other diagnoses.*

- RESPONSE : We have stated in the discussion section (page 12, second paragraph): One limitation of our study is the fact that the final diagnosis was not obtained systematically during surgery. However, when facing to PDAC patients, more than 75% of patients have an unresectable tumor and it is difficult to include surgical resection as the gold standard.

3. *The yield of EUS FNA cytology is in the rather low end of the spectrum, which may enhance the performance characteristic of the KRAS mutational analysis. Do we have the size of these lesions? It is suggested that cytology yield is much lower is the lesions are smaller than 1 cm and better as the lesions increase in size (Dig Dis Sci. 2011 Nov;56(11):3370-5. doi: 10.1007/s10620-011-1782-z. Epub 2011 Jun 19. Relationship of pancreatic mass size and diagnostic yield of endoscopic ultrasound-guided fine needle aspiration. Siddiqui AA, Brown LJ, Hong SK, Draganova-Tacheva RA, Korenblit J, Loren DE, Kowalski TE, Solomides C.)*

- RESPONSE : In the discussion section, we have added two sentence and the above reference from Siddiqui et al. as follow (page 11, fourth paragraph, new reference 21): In the present study, the size of the solid mass was greater than 1 cm in size. The parameter of tumor size could not alter the yield of cytopathology (21). However the amount of desmoplastic reaction, differentiation, vascularization or inflammation is difficult to appreciate.

4. *Is there a reason why they used the Cook's proCore needle? Why not using the regular FNA needle? Another study suggested no difference between regular 22G needle and 22G proCore needle (Gastrointest Endosc. 2012 Aug;76(2):321-7. doi:10.1016/j.gie. 2012 .03 .1392. Epub 2012 May 31. Randomized trial comparing the 22-gauge aspiration and 22-gauge biopsy needles for EUS-guided sampling of solid pancreatic mass lesions Bang JY, Hebert-Magee S, Trevino J, Ramesh J, Varadarajulu S.)*

- RESPONSE : In the Patients and methods section we have now precised that : when first FNA was judged insufficient the second FNA was performed using EUS-Procore 22-gauge needle (page 5, first paragraph).

5. *Can they clarify the EUSN1 needle by Wilson-Cook? Was this a regular 22G? What percentage of the time they use this needle instead of the proCore and why?*

- RESPONSE : In the Patients and methods section (page 5, first paragraph) we have also precised that :

- EUS-FNA was performed with the « regular 22-gauge EUSN1 needle »
- EUS-Procore 22-gauge needle was used in 20% of patients.

Responses to the Editor comments:

- The Title Page has been corrected as requested
- Tables are submitted as separate Word files