



**Hadassah Medical Organization
Hadassah University Hospital**

**Haggi Mazeh, MD
Surgery Department**

Oct 22nd, 2016

Jin-Xin Kong,
Science Editor, Editorial Office
World Journal of Gastrointestinal Endoscopy.
Dear Mr. Kong,

Thank you for the opportunity to revise our manuscript entitled "Non-Functioning Pancreatic Neuroendocrine Tumors - Surgery or Observation?"

We would like to thank the reviewers for their comments which have clearly improved the manuscript.

Please find the attached revised manuscript and our response to each comment below. All changes are highlighted in the text.

Reviewer num. 0007767:

This is nice review on an increasing important clinical question: small non-functioning PNETs.

Response:

We would like to thank the reviewer for the kind words.

Please add the 5th hereditary pancreatic neuroendocrine tumor syndrome (Mahvash disease). There are a few reviews on this condition (e.g. Mahvash disease: an autosomal recessive hereditary pancreatic neuroendocrine tumor syndrome. International Journal of Endocrine Oncology 2016).

Response:

Thank you for this comment. The additional information was added as suggested (page 6).

Please add that pancreatic polypeptide can be false positive due to eating and renal insufficiency.

Response:

Thank you for this comment. The additional information was added as suggested (page 10).

A recent paper on small pancreatic lesions is very illustrative for the etiology of small pancreatic masses (Differential diagnosis of small solid pancreatic lesions. Gastrointest Endosc 2016) and add perspective to clinicians. Please discuss this paper.

Response:

Thank you for this comment. A short discussion of the paper mentioned above was added (page 9, reference 31).

An algorithm (as a figure) starting with a small pancreatic mass will be very important to summarize the review's main points.

Response:

We appreciate this comment. An algorithm of the paper mentioned above was added as suggested (Figure 1, page 12, 23).

Currently the role of biopsy is not obvious in the workup of a small pancreatic mass.

Response:

We are in complete agreement with the reviewer's comment and we have added this controversy to the biopsy section (page 8-9). The clear added value of a biopsy is the opportunity to grade the tumor and thus tailor the treatment to the patient while

other clinicians argue that the theoretical risk of procedure complications outweigh the benefit. At our institutions we collaborate with outstanding gastroenterologists and we aim to obtain preoperative cytology whenever possible.

Reviewer num. 03334983:

The authors have reviewed in a pretty general fashion the issue of non-functioning pancreatic neuroendocrine tumors (pNET). Indeed the topic is interesting and the current discussion on that among the experts is hot enough at the moment, however it appears to me that unfortunately this review does not focus in a very specific way on the main topic as per the title while it rather covers the topic "non-functioning pNET" in a broadest way. I think that such cut affects the manuscript, which might gain value if focusing in a more targeted fashion on the title issue. For example, the sections on diagnosis and grading / staging are pretty long and may distract the reader from the focus on the operative vs observational approach to non-functioning pNET.

I suggest the authors to consider an exhaustive and careful revision of the manuscript with the primary goal of striking in a more compelling way the target as per the chosen title and avoiding spending too much space for a general and not particularly attractive overview on non-functioning pNET.

Response:

We appreciate the sincere comments and we have made considerable effort to revise and shorten the manuscript substantially. We believe the changes made contribute to a more focused and targeted review (main changes on pages 7-11).

There are a number of inaccuracies here and there along the manuscript which may give the impression of superficiality. For example, page 7, lines 11-12 reports an incorrect sentence since the WHO 2010 classification is actually considered carrying a prognostic value.

Response:

We agree with this comment. As per above, this is now revised as suggested according to the latest WHO 2010 classification, with updated reference (page 10, lines 19-21).

In Table 1, there is a mix up between staging and grading.

Response:

Thank you for raising our attention to this error. This is now revised correctly.

There are also some language and editorial inaccuracies which affect the manuscript. With that regard, for example, I suggest to avoid the use of abbreviations in Abstract and Core Tip and the authors should use always abbreviation already specified in the text, defining the acronym at the time of their first appearance.

There are a few typos and bibliographic inaccuracies as well (for example, page 7, line 9; page 12, line 15).

Response:

Thank you for this comment. All authors thoroughly re-read the manuscript several times and all grammar errors were corrected. Furthermore, specific changes pointed out by the reviewer were also addressed. (pages 3-4,16).

Reviewer num. 00699087:

This review manuscript describes the details of recent controversy in management of incidentally found small non-functioning neuroendocrine tumors. The authors described pros and cons on this issue, by referring many papers. Although they could not draw the definitive conclusion, this paper is well-written and introduces a lot of information regarding in this field. I believe this manuscript is worth for publication in World Journal of Gastrointestinal Endoscopy.

Response:

We would like to thank the reviewer for the kind words.

Introduction first paragraph As they described in the later text, neuroendocrine tumors are divided into two groups of functional and non-functional depending on the existence of symptoms caused by hormonal hypersecretion, not only by the ability of hormones and

peptides hypersecretion. The text of 4th line of Introduction should be changed. It should be good if they refer WHO classification (reference 37).

Response:

Thank you for this comment. The text was corrected in a more accurate and informative sentence, with reference to 2010 WHO classification (page 5, reference 2).

Imaging 2nd line: duo → due

Response:

This typo was corrected (page 7).

Grading and Staging in WHO classification 2010, several terms which used in WHO classification 2000 was disappeared, such as well differentiated neuroendocrine tumor and poorly differentiated neuroendocrine carcinoma. They should take out these words from line 4-5 of this paragraph. Also, the criteria of Grade 1 Ki-67 is $\leq 2\%$, not $< 2\%$.

Response:

The Grading and Staging section was revised and edited to be more accurate as suggested above (page 10, lines 12-15).

2nd paragraph of Grading and staging for readers better understanding, they should describe more details of the differences between AJCC and ENETS staging system, especially focusing on difference between T3 and T4.

Response:

We agree with the reviewer's comment. The major differences are now more clearly stated in the text (page 10).

Reference 37: Please confirm the author name.

Response:

The reference was confirmed (reference 2)

We hope that you find this revised manuscript suitable for publication in World Journal of Gastrointestinal Endoscopy.

Sincerely yours,

Haggi Mazeh, MD

Department of Surgery

Hadassah University Hospital Mount Scopus

POB 24035, Jerusalem 91240

Israel

Telephone: +972-2-5844550

Fax: + 972-2-5844584

Email: haggi.mazeh@gmail.com