Author’s response to reviews

Title: Clinical Management of Malignant Insulinoma: A Single Institution’s Experience over Three Decades

Authors:

Jie Yu (bailubailing@163.com)
Fan Ping (pingfan6779@163.com)
Huabing Zhang (huabingzhang@sina.com)
Wei Li (WeiLi43@163.com)
Tao Yuan (yuan3750057@163.com)
Yong Fu (YongFu057@163.com)
Kai Feng (KaiFeng0695@163.com)
Weibo Xia (WeiboXia357@126.com)
Lingling Xu (llxuwsh@163.com)
Yuxiu Li (liyuxiu@medmail.com.cn)

Version: 3 Date: 25 Oct 2018

Author’s response to reviews:

POINT-BY-POINT RESPONSES TO REFEREE COMMENTS

Manuscript: BEND-D-18-00164R2

Manuscript title: Clinical analysis of 15 cases of malignant insulinoma

We are very grateful for the opportunity to address the editor and reviewers’ comments and submit a revised manuscript. Point-by-point responses are presented below.
Delphine Vezzosi (Reviewer 1): The authors described in this monocentric retrospective study the clinical characteristics, the treatment and the follow up of 15 malignant insulinomas.

Major remarks

Malignant insulinomas are rare and monocentric study is difficult to conduct. By consequence, duration of inclusion is very long in this work (1984-2017). Because of this long time many important data are missing. For example, tumor staging and Ki67 measurement is today mandatory to manage malignant insulinomas. Unfortunately these parameters are missing for most of the patients described in this study. The benefit of this study is narrowed.

Moreover it is difficult to compare patients along a period of 30 years. For example, treatment of malignant insulinomas is not the same in 1984 and in 2017. As a consequence, survival of these patients cannot be compared.

Response: Thank you for this comment. These are indeed limitations of the study, which have been added in the study limitations section (Line 23-26 Page 14 and Line 1-5 Page 15).

Minor remarks

Assays kits for insulin and C-peptide should be mentioned.

Response: Thank you for pointing out this, which is now added (Line 2-4 Page 6).

The ratio of Insulin/glucose is no more a criteria for the diagnosis of insulinoma.

Response: Thank you for pointing out this, and we have deleted the related content.

Table 2: range of blood glucose should be mentioned.

Response: Thank you for this observation, and we have added the range of blood glucose in Table 2 (Line 4 Page 8).

Surgery should be more accurately described, page 10: what does "resection of pancreatic lesions" mean? Enucleation, distal pancreatectomy…

Response: Thank you for pointing out this, and we have added accurate surgery description (Line 11-14 Page 10 and all the document).

Page 10, line 24 and in all the document: could you present results as a percentage rather than a ratio?
Response: Thank you for pointing out this, and we have changed all ratios to percentages (Line 5 Page 10 and all the document).

Labrini Papanastasiou (Reviewer 2): In this retrospective study, Yu et al analysed data from a series (15 cases) of malignant insulinoma presented at their institution between 1984-2018. The subject matter of the manuscript is interesting. Several modifications should be made and the following points should be addressed:

1. Results and Discussion are too extensive and should be shortened. In particular, the results' subsections concerning qualitative diagnosis and lesion localization, tumor properties, are very detailed and should be summarised in a comprehensive way. Repetitions should be avoided eg some of the results given in tables are not needed to be repeated in the manuscript. Discussion is too long with many repetitions concerning the results (eg tumor properties, positive rates based on localization examination, treatment and curative outcomes). They are advised to redraft the section in order to shorten it.

Response: Thank you for this comment, and we have redrafted the Results and Discussion sections to make them short and concise (from Line 14 Page 6 to Line 22 Page 14).

2. It is not obvious in the result section, the total number of patients that had histological confirmation. Please clarify in the relative section.

Response: Thank you for this comment. A total of 10 patients had histological confirmation of a pancreatic primary lesion or liver metastatic lesion through surgical or puncture biopsy pathology (Line 2-3 Page 8).

3. It is also confusing, in the same section, the number of patients without metastases upon diagnosis that did not undergo surgery and received medical therapy (5 patients underwent surgery and 3 patients received only interventional therapy= 8 patients in total, as stated in 2nd paragraph of treatment and efficacy in the results). However, the authors previously mentioned that these patients were 7. Thus, the authors should check and correct appropriately discrepancies in the text.

Response: Thank you for this comment, and we have figure out the correct number (Line 11-19 Page 10 and Line 1-2 Page 11).
4. In the clinical manifestation subsection of the results, the following sentence is unclear: 'Seven patients developed metastases...to have multiple liver metastases.' Please rephrase, correct the expressions and/or syntax.

Response: Thank you for this comment, and we have rewrite the sentence to make them more clearly (Line 6-9 Page 7).

5. The authors, in order to explain the symptoms of hypoglycaemia used the expressions 'central nervous depression symptoms' and 'autonomic nervous system excitement' that are not appropriate. It is known that hypoglycemia causes neurogenic (autonomic) and neuroglycopenic symptoms. The neurogenic symptoms include tremor, palpitations, anxiety sweating and hunger; the neuroglycopenic symptoms include cognitive impairment, behavioural changes, seizure and coma. Thus, the authors should change the terms with widely used ones throughout the manuscript. They should also state whether their patients exhibit neurogenic symptoms as well.

Response: Thank you for this comment. We have changed the terms with widely used ones throughout the manuscript, and stated neurogenic symptoms in the patients (Line 1-6 Page 7 and all over the manuscript).

6. Was the tumor size of the insulinoma of their patients correlated with the insulin levels?

Response: Thank you for this comment. Spearman analysis was performed to test the associations between the tumor size and insulin, C-peptide, and glucose levels (Table 3). As shown, a positive correlation was found between tumor size and insulin and C-peptide levels, but a negative correlation was identified between tumor size and glucose levels, although none of the differences reached significance due to the small sample size (Line 15-17 Page 8 and Line 1-7 Page 9).

7. Apart from antitumoral treatment, had the authors also administrated medical anti-secretion treatment with diazoxide for symptomatic control of these patients?

Response: Thank you for this comment. Because the availability of diazoxide was limited in hospitals and pharmacies in mainland China, only one patient (Patient No. 10) received diazoxide in a short period of time, but the drug was discontinued due to poor performance (Line 3-5 Page 11).
8. 'Selective celiac arteriography produced a 100% positive rate for primary pancreatic lesion':
The authors analysed the positive detection rates of various imaging procedures in their study. Does this refer to the sensitivity of the methods? The authors should use the same terminology throughout the text.

Response: Thank you for this comment. We have changed the “positive detection rate” to “sensitivity” throughout the text (Line 8-14 Page 9 and throughout the text).

9. References should be added in the statements 'Insulinoma is the most common pNET with a prevalence...million people', 'Malignant insulinoma is extremely rare and accounts for...cases in the background section

Response: Thank you for this comment, and we have added related reference (Line 19-10 and Line 23-24 Page 3).

10. In discussion section, Reference 5 concerns Baudin et al and not Hirshberg et al. Please correct.

Response: Thank you for catching this error, which is now corrected (Line 20-21 Page 12).

11. In discussion section, the paragraph concerning the metastatic sites of insulinomas 'Liver metastasis...previous studies' is better to be moved in the subsequent tumor properties subsection.

Response: Thank you for this comment, and we have redrafted this section (Line 19-25 Page 12 and Line 1-2 Page 13).

12. 'Ct generated a positive rate of 33-64% (11)': The reference that the authors mentioned concerns the sensitivity of EUS and not CT for the detection of insulinoma. The authors should correct it and cite the appropriate reference. Moreover, they should give a reference for MRI sensitivity. The reference of Jin et al is lacking as well.

Response: Thank you for catching this error, and we have cited the right reference and added the reference of Jin et al. Moreover, we have added the discussion of the sensitivity of MRI (Line 4-5 and Line 13-15 Page 13).
13. Because of the lack of histological information the authors could not perform tumor staging and grading. In addition, because of the small number of patients (6) that were followed-up, they could not analyse the survival rate. The limitations of the study could be added in the last part of the discussion.

Response: Thank you for this comment, and we have added them in Strengths and Limitations section in the last part of the discussion (Line 23-26 Page 14 and Line 1-5 Page 15).

14. In the manuscript, corrections should be made on the expressions, terminology used, and the grammar in order to have a good language flow.

Response: Thank you for this comment. We have submitted our manuscript to the language editing institution American Journal Experts (AJE) and have gained the Editorial Certificate (see attached the Editorial Certificate of AJE).

Punit Sharma, MD, FEBNM, FANMB (Reviewer 3): In this study the authors have presented the clinical analysis of 15 cases of malignant insulinomas managed at their Institution. They have retrospectively analysed their data and presented the diagnostic and therapeutic approaches, while highlighting the natural history of the disease. The presentation is good and to the point. While the number of patients is low, even accounting for the rarity of tumor, the patient analysis is comprehensive. Because the patient enrollment spans over decades the diagnostic and therapeutic approaches are a bit heterogeneous. These points to be added under the study limitations. Also, it would be recommended that the authors change the title of the study to "Clinical Management of Malignant Insulinoma: A single Institutional experience of three decades" or something similar. The current title is too bland. Also, Insulinomas are most common FUNCTIONAL neuroendocrine tumors and not the most common pancreatic neuroendocrine tumors (nonfunctioning are commonest). This needs to be corrected in the manuscript.

Response: Thank you for this comment. Firstly, we have added Limitation section (Line 23-26 Page 14 and Line 1-5 Page 15); Then, we have changed the title to "Clinical Management of Malignant Insulinoma: A Single Institution’s Experience over Three Decades" (Line 2-3 Page 1). Lastly, we have corrected the “most common neuroendocrine tumors” to “most common functional neuroendocrine tumors” (line 19-20 Page 3 and Line 22-23 Page 11).