Reviewer’s report

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

Version: 2 Date: 27 Aug 2018

Reviewer: Labrini Papanastasiou

Reviewer's report:

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 e.g. 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 (e.g. tumor properties, positive rates based on localization examination, treatment and curative outcomes). They are advised to redraft the section in order to shorten it.

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

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.

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.

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 hypoglycemria 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.

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

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

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.

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

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

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.

12. 'Ct generated a positive rate of 33-64% (11)': The reference that the authors mentioned concerns the sensitivity of EUS and not of 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.

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.

14. In the manuscript, corrections should be made on the expressions, terminology used, and the grammar in order to have a good language flow.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

Quality of written English
Please indicate the quality of language in the manuscript:

Not suitable for publication unless extensively edited

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?
If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal