Manuscript NO: 48757
Title: Gastric Neuroendocrine Neoplasms Type 1: a Systematic Review and Meta-analysis

Dear Dr Yan,

We would like to thank you for considering our manuscript for publication and giving us the opportunity to revise and resubmit it. We appreciate the time and detail provided by you and each reviewer and welcome essentially all proposals for changes. We have now incorporated the suggested changes into the manuscript to the best of our abilities. We hope that the revised manuscript fulfills the high standards of World Journal of Gastroenterology.

We have responded specifically to each suggestion below. To make the changes easier to identify where necessary, we have numbered them. All the changes in the manuscript are highlighted in yellow using Word Editor and they are indicated point by point in the reply to you and the referees.

Kind Regards,
On behalf of the authors,
Apostolos V. Tsolakis MD, PhD

Referees' comments:

Reviewer #1:

Comments to the Author.

1) This is a systematic review and meta-analysis attempting to elucidate some aspects of the prognosis and therapy of gastric NEN type 1. Specifically, authors explore the size, grade and depth of invasion of the primary neoplasm as prognostic factors for lymph node metastases and the type of surgical intervention (endoscopic versus surgical) for local recurrence. As authors mention, the correlation of LN metastatic disease to survival outcomes is uncertain, and thus the characteristics of the primary tumors examined are not prognostic for survival. However, the review and meta-analysis remains useful as an overview of the field.

Reply:

We thank the Reviewer for the positive feedback and address the additional comments below.

2) It is unclear from the methods if only studies with localized disease (assumingly this would be the aim?) would be included and how staging was done to exclude metastases in the included studies. This should be clarified.

Reply:

We thank the Reviewer for this point, as this is indeed a matter of clarification. Patients with distant stage disease were not included in the present meta-analysis. The staging methods applied in the included studies and according to the TNM classification varied greatly and was primarily based on available histopathology in all patients subjected to resective surgery. However, in patients subjected to endoscopic resection staging criteria were applied to data extracted from endoscopy and corresponding histopathology regarding T stage and endoscopic ultrasonography as well as cross-sectional imaging regarding the presence of locoregional LN metastases (N stage), as reported in these studies. This is now clarified in the Methods Section (page 9, line 219-224) as well as in the limitations of our study in the Discussion Section (pages 16-17, line 429-432), as there is indeed a discrepancy in the sensitivities of the different staging methods applied.

3) It is also unclear how the type of NEN (type 1 versus other types) has been ascertained. Have the authors attempted to verify the type from any data provided in the original reports or relied exclusively on the evaluations of the original authors? This is quite important given the lack of clarity of diagnostic criteria and becomes more important for reports from centers with less of an expertise on these tumors.

Reply:

We thank the reviewer for this important remark. GNEN1 diagnosis was based on histopathological and biochemical criteria reported in the Methods section of all the included studies. Registry and institutional studies reporting data without specifying the diagnostic criteria of GNEN1 (histopathologic confirmation and hypergastrinaemia), as well as data on all types of GNEN and GNECs together with GNEN1 were excluded from our study. This is now clarified in the Methods Section (page 8, line 190-193).

4) In the search strategy, terms used do not include outcomes such as lymph node metastases or infiltration and various survivals. Have these included in the search. Articles may have been missed if those terms not included for example in combination with "gastric neuroendocrine tumor" or "neoplasm".

Reply:

We thank the Reviewer for this remark. The design of the search strategy applied and the systematic search of the present meta-analysis were meticulously discussed with and conducted by the university librarian. We used general mesh terms as well as other terms in the abstract of the potentially eligible studies, but we refrained from using specific outcome terms to avoid a more narrow study selection. The search strategy applied resulted in 2933 titles (Figure 1). We also now provide the detailed search strategy applied in our study in the Supplement (Supplementary Table 1), as indicated in the PRISMA checklist.

5) The size cut -off of 1 cm used is clinically relevant but larger sizes could be also of interest as prognostic factors for LN metastatic disease as larger tumors are often present. It would be clinically relevant to identify larger size tumors with still good prognosis. It would be very interesting and would enhance the report if authors performed such analysis.

Reply:

This is an important point raised by the Reviewer. Larger sizes and the cut-off of 20mm are indeed of interest as prognostic factors for LN metastatic disease. Therefore, we looked for this information in the included studies but there was a lack of data on larger sizes with double zero cells in the tables of the extracted data in most studies, i.e. meta-analysis at 20 cm size cut-off was not feasible. This is now addressed in the discussion section (page 14, line 364-369).

6) Similarly distant metastases as an outcome in addition to LN metastases would be a clinically relevant point, possibly even more relevant than LN metastases. Were distant metastases searched for as an outcome? Authors should comment.

Reply:

We thank the Reviewer for this comment. GNEN1 is a generally benign disease with very few metastatic cases reported in contemporary literature, thus not sufficient material for a meta-analysis. Additionally, the primary outcome investigated in the present study was the rate of LN metastases stratified by clinico-pathological parameters in order to identify the patients in higher risk for regional metastases and guide the selection of treatment in a patient-tailored manner, i.e. surgical *vs.* endoscopic resection. This is now elaborated in the Discussion section (page 14, line 367-369).

7) In the local recurrence analysis, the number of patients included should be mentioned.

Reply:

We apologize for the inconsistency and have now added this information in the Results section (page 12, line 297-299).

8) In table 1 the meaning of initials and * should be explained.

Reply:

We thank the Reviewer and have now defined the abbreviations in Table 1.

9) In table 2 the scale used according to NOS should be explained.

Reply:

NOS scale is now explained in the legend of Table 2.

10) In the discussion, authors mention a few relevant points regarding the quality of the included studies that may constitute limitations of the meta-analysis. Additionally, heterogeneity of the studies makes CIs of ORs of different summary estimates quite broad to a degree that one wonders about clinical usefulness. Authors should further comment.

Reply:

We thank the Reviewer for these remarks and we have now elaborated further on this in the limitations of our study in the Discussion section (pages 16-17, line 429-432).

Reviewer #2:

11) Overall, this is a need for meta-analysis for GNEN1s due to limited data with lot of heterogeneity. Hence, this manuscript, in my view provide valuable information to clinicians managing such patients. Strengths: 1. There is limited literature on GNEN1. The authors included only those studies with at least ten patients with GNEN1. They excluded case reports and small case series. 2. Only the latest eligible study from any institute was included.

Reply:

We thank the Reviewer for the positive comments on the need for the present meta-analysis and the strengths of our study. We address the weaknesses highlighted by the Reviewer point by point, as specified below.

12) Weaknesses: (a). The confidence interval for LN metastases is very broad and ranges from 1.5 to 80. It is difficult to conclude from these results if a cut-off of 10 mm is accurate versus not. (b). This study does not provide an independent risk assessment. I suppose none of the studies included a multivariate analysis to evaluate which among - size vs. depth of invasion had a higher risk. However, this is a limitation of the study. So also, the study doesn't provide information when both size and depth (propria involvement) are present.

Reply:

a. The broad confidence interval for LN metastases is indeed broad and constitutes a limitation of the study depicting the study heterogeneity. This is also in accordance with the Reviewer#1 point nr 10, and we have now elaborated on this in the Discussion section (pages 16-17, line 429-432).

b. We agree with the Reviewer that our study does not provide an independent risk assessment. The design itself of the present meta-analysis is based on pooled estimates on events per number of patients in the included studies, i.e. we could not assess data at the individual level for each patient in order to provide a multivariable analysis or address additive effects when two or more of the investigated clinico-pathological parameters are present. Hence, these are indeed limitations of the study and are addressed as indicated by the Reviewer in the Discussion section (pages 16-17, line 429-432).

13) Considerations: In study methods, they mention that the study hypothesis was formulated prior to data collection. What was the study hypothesis? It is not clear from the text preceding this statement in the methods.

Reply:

This is of course a pertinent point raised by the Reviewer. We have now clarified the study hypothesis in the Introduction section (page 7, line 169-173).

14) Some spelling errors; such as - greater (in methods/ bias assessment).

Reply:

We apologize for this and have now corrected the spelling errors, as indicated by the Reviewer.

15) The rate of LN metastases for a cut-off size of 10 mm was 15.3% vs. 0.8% for lesions >10 mm and <10 mm. The authors need to specify the cut-off size accurately. What did they consider 10 mm as? so they need to use "≥" symbol for either >10 mm or < 10 mm.

Reply:

We thank the Reviewer for this comment. We have now used the symbols ≥10 mm and <10 mm, as appropriate.

16) Why is there a number 12 next to title heading 'Discussion'

Reply:

This was due to the line numbers.

Reviewer #3:

17) These main research findings of this paper will be important for the understanding of prognosis and selectin of therapy for GNEN1. Therefore, this paper is quite a fascinating manuscript, and I believe the paper will be of interest to the readership of WJG. However, the authors should also clarify and correct the points listed below.

Reply:

We thank the Reviewer for the generous comments and the positive feedback. We clarify the Reviewer's comments as specified bellow.

18) In this paper, authors did not deal with endoscopic ultrasonography and laparoscopic surgical resection at all, therefore, it is uncomfortable to discuss these modalities. The paragraph documented about endoscopic ultrasonography and laparoscopic surgical resection should be deleted, therefore, the description about these modalities should be deleted in the core tip.

Reply:

Following the Reviewer's comment we have now omitted part of this paragraph regarding the application of minimally invasive laparoscopic surgical techniques. However, we feel that endoscopic ultrasonography is an important adjunct and has a place in the work-up of GNEN1; particularly, with the aims to evaluate the depth of invasion in larger lesions, but also to identify locoregional LN metastases.

19) Supplementary figures “2A-4A, 2B-4B cannot be found.

Reply:

We apologize for the inconsistency and have now uploaded these figures separately in the Supplement.