

University of Saskatchewan and Saskatoon Health Region  
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To:  
Lian-Sheng Ma, Company Editor-in-Chief, Editorial Office  
**Baishideng Publishing Group Inc**  
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Date 17th June 2020

Dear Company Editor-in Chief

Thank-you for your email dated June 12<sup>th</sup> and we are delighted to note its contents.  
Please find below a detailed response to all the queries listed including those of the peer reviewer in relation to our submitted manuscript as detailed below:

**Journal title:** World Journal of Gastroenterology

**Manuscript NO:** 56996

**Title:** *MIXED EPITHELIAL ENDOCRINE NEOPLASMS [MEEN] OF THE COLON AND RECTUM – An evolution over time – A targeted review*

**Authors:** Rani Kanthan, Suresh Tharmaradinam, Tehmina Asif, Shahid Ahmed and Selliah C Kanthan

**Received Date:** 2020-05-22

**Date sent for review:** 2020-05-22

**Date reviewed:** 2020-06-09

**Reviewer ID:** 00070021

**Review time:** 18 Days

**Correspondence To:** Suresh Tharmaradinam, MD, Doctor, Resident Physician, Pathology and Laboratory medicine, University of Saskatchewan, Royal University Hospital 2839 - 103 Hospital Dr, Saskatoon S7N 0W8, Saskatchewan, Canada. [sut358@usask.ca](mailto:sut358@usask.ca)

#### Peer-review report

**Reviewer #1:**

**Scientific Quality:** Grade A (Excellent) Thank-you

**Language Quality:** Grade A (Priority publishing) Thank-you

**Conclusion:** Accept (General priority) Thank-you

#### Specific Comments to Authors:

Kanthan and colleagues conducted an excellent, comprehensive and broad review of the rare entity: "Mixed epithelial endocrine neoplasms of the colon and rectum" where they explained in depth, the history of the nomenclature, clinical and pathologic aspect of the tumor, treatment and prognosis of this rare disease. They also added a schema proposing a new classification for this rare type of tumor that is really clear concise and very helpful for clinician in order to guide their treatment strategies. The language is excellent and highly pedagogic providing newcomers to the field and students with a great opportunity to have an overview of this rare tumor. However, below some minor comments for further clarifications:

- 1- Page11: Add reference to the following phrase: "Ca15.3 and Ca19.9 can be used clinically to identify and follow disease progression and remission:"
- 2- Page 43: in the proposed classification diagram: there is some contradiction in the intermediate and low grade categories as they both have adenoma and NET low grade. Please clarify

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Improving health through excellence in education, research and clinical care.

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### **Reply to Peer Reviewer Report**

*Many thanks for your kind comments as a reviewer of our manuscript. We are pleased that you enjoyed reviewing our manuscript that provides, as identified by yourself, a broad comprehensive review of the history of the nomenclature, clinical and pathologic aspect of the tumor, treatment and prognosis of this rare disease with the proposition for a new classification with simplified, clinically relevant and meaningful terminology.*

*We have addressed your specific comments below:*

**#1- Page 11:** Add reference to the following phrase: "Ca15.3 and Ca19.9 can be used clinically to identify and follow disease progression and remission:"

*We have revised this statement to be more inclusive and explicit and have added the relevant references as seen below Page 11-Tumoral markers such as carcinoembryonic antigen (CEA), carbohydrate antigen 15-3 and 19.9 (CA15-3, CA19.9) can be used clinically to identify and follow up for disease progression and remission <sup>(81, 85)</sup>.*

**#2- Page 43:** in the proposed classification diagram: there is some contradiction in the intermediate and low grade categories as they both have adenoma and NET low grade. Please clarify

*We are grateful for this pick up of the typographical error in the diagram for the intermediate grade category of **Mixed Epithelial Endocrine Neoplasms-MEEN**.*

*The **ENDOCRINE** component in both intermediate grade and low grade MEEN are similar - either Neuroendocrine Tumor Grade 1 /or Grade2 i.e. NET1 or NET2.*

*The difference lies in the **EPITHELIAL** component.*

*The epithelial component in the Low grade MEEN is an Adenoma [Tubular, Villous and/or Tubulovillous], whereas the epithelial component in the Intermediate Grade MEEN can be adenocarcinoma, signet ring cell adenocarcinoma or amphicrine carcinoma.*

*These corrections are reflected in the revised Table 2B which has been uploaded as a power point image.*

*We sincerely thank the reviewer for this opportunity to correct and provide clarification of this unforeseen error.*

### **Science Editor:**

**Scientific quality: This is a review of the colorectal mixed epithelial endocrine neoplasms. The topic is within the scope of the WJG. Thank-you**

**(1) Classification: Grade A; Thank-you**

**(2) Summary of the Peer-Review Report: The authors conducted an excellent, comprehensive and broad review of the rare entity. They also added a schema proposing a new classification for this rare type of tumor that is really clear concise and very helpful for clinician in order to guide their treatment strategies. The language is excellent and highly pedagogic providing newcomers to the field and students with a great opportunity to have an overview of this rare tumor. However, below some minor comments for further clarifications. Page 43: In the proposed classification diagram: there is some contradiction in the intermediate and low-grade categories as they both have adenoma and NET low grade. Please clarify. The questions raised by the reviewers should be answered- This has been completed as discussed above**

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**3) Format:** There are 2 figures. A total of 139 references are cited, including 40 references published in the last 3 years. There are no self-citations. Thank-you, please note there is one citation of Kanthan R included [Ref #2].

**4) Language evaluation: Classification: Grade A.** Thank-you

**5) Academic norms and rules:** The authors provided the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement. No academic misconduct was found in the Cross Check detection and Bing search. Thankyou

**6) Supplementary comments:** This is an invited manuscript. The study is without financial support. The topic has not previously been published in the WJG. The corresponding author has not published articles in the BPG. Thank-you for these comments.

#### **5 Issues raised:**

**(1) I found no "Author contribution" section. Please provide the author contributions; Provided below**

*"All authors made a substantial contribution to the concept, design, acquisition of data and manuscript writing. Each author has participated sufficiently in the work to take public responsibility for the appropriate portions of the content. Preliminary drafts and revisions were undertaken for review of intellectual content and the final version is approved by all authors prior to submission for publication."*

**(2) I have changed the manuscript type "review" to "systematic review". The authors need to provide the Biostatistics Review Certificate and fill out PRISMA checklist form with page numbers. Please revise the manuscript according to the Guidelines and Requirements for "systematic review"**

This review is **not** a **systematic** review.

Systematic reviews are governed by very stringent criteria as defined below:

*"A systematic review attempts to collate **all empirical evidence** that fits **pre-specified eligibility criteria** in order to **answer a specific research question**. It uses explicit, systematic methods that are selected with a view to **minimizing bias**, thus providing more reliable findings from which conclusions can be drawn and decisions made (Antman 1992, Oxman 1993)"*

**As per Cochrane Handbook, 1.2.2 guidelines The key characteristics of a systematic review are:**

- a clearly stated set of objectives with pre-defined eligibility criteria for studies;
- an explicit, reproducible methodology;
- a systematic search that attempts to identify all studies that would meet the eligibility criteria;
- an assessment of the validity of the findings of the included studies, for example through the assessment of risk of bias; and
- a systematic presentation, and synthesis, of the characteristics and findings of the included studies)

The differences between a systematic review and a comprehensive literature review are elucidated in the table format below as Available at: <http://dx.doi.org/10.6084/m9.figshare.766364>

Kysh, Lynn (2013): Difference between a systematic review and a literature review. [fig. share].

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	Systematic Review	Literature Review
<b>Definition</b>	High-level overview of primary research on a focused question that identifies, selects, synthesizes, and appraises all high quality research evidence relevant to that question.	Qualitatively summarizes evidence on a topic using informal or subjective methods to collect and interpret studies.
<b>Goals</b>	Answer a focused clinical question Eliminate bias	Provide summary or overview of topic
<b>Question</b>	Clearly defined and answerable clinical question Recommend using PICO as a guide	Can be a general topic or a specific question
<b>Components</b>	Pre-specified eligibility criteria Systematic search strategy Assessment of the validity of findings Interpretation and presentation of results Reference list	Introduction Methods Discussion Conclusion Reference list
<b>Number of Authors</b>	Three or more	One or more
<b>Timeline</b>	Months to years Average eighteen months	Weeks to months
<b>Requirements</b>	Thorough knowledge of topic Perform searches of all relevant databases Statistical analysis resources (for meta-analysis)	Understanding of topic Perform searches of one or more databases
<b>Value</b>	Connects practicing clinicians to high quality evidence Supports evidence-based practice	Provides summary of literature on a topic

*Our manuscript is a **targeted comprehensive literature review with summarization** of mixed epithelial endocrine tumors of the colon and rectum as they have evolved over the years with a) no attempt to answer any predefined question b) no attempt to eliminate bias, c) no statistical analysis undertaken and d) no search undertaken of every relevant database or every published and unpublished data on this topic. Infact, such review is fraught with difficulty due to the varying terminologies in the literature reports and in this context, the main thrust of this review is the proposal for a new simple encompassing non ambiguous clinically relevant terminology for these lesions to be referred to as **Mixed Epithelial Endocrine Neoplasms [MEENS]** of low, intermediate and high grade potential.*

*In summary, this manuscript represents a "broad and comprehensive review" (as noted by our peer reviewer) that provides an explicit upto date evidence based knowledge of this topic.*

*We take entire responsibility for this error as we used the word systematic instead of systemic and now have eliminated this word completely to avoid any ambiguity or confusion. Furthermore, the methodology section now outlines the steps utilized to procure this body of evidence for the summarized report and these have been adapted based on the principles outlined in the PRISMA report which is referenced as #22.*

*These changes are also reflected in the updated revised format of Table 1 which has been uploaded independently as requested.*

*We trust the companion editor will agree with our interpretation on this issue and find the changes appropriate and in support of the same.*

- (3) **I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor-all original revised updated drawing for Table 1 and the power point images for table 2A and Table 2B have been uploaded independently. As requested [in accommodation for color blindness], red and green colors have been avoided in the submitted tables/figures. At the initial submission, we just followed the online instructions of embedding all figures and tables within the manuscript.**
- (4) **I found the authors did not add the PMID and DOI in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout.**

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*The reference list has been revised as requested with track comments on references in which such information were not found, as many of them are excerpts from books and meeting abstracts.*

- (5) **I found the authors did not write the “article highlight” section. Please write the “article highlights” section at the end of the main text; and - This is only required for a systematic review - this is not applicable for our comprehensive targeted literature review as there is no research question being answered nor a hypothesis that is being tested.**
- (6) **The authors need to provide an editable manuscript (format: .doc or .docx).** *This manuscript comprised of the text and references only have been uploaded in a Microsoft Word format for ease of editing as requested. The accompanying Tables/figures are uploaded independently as indicated earlier for reprocessing as needed.*
- (7) **Re-Review: Required.** *Revised manuscript with revised tables/power point images are uploaded for re-review.*
- (8) **Recommendation: Conditionally accepted.** *-Thankyou kindly.*

**Step 8: Submit the revised manuscript and all related documents-CHECKLIST**

- (1) 56996-Manuscript File - **REVISED manuscript file as word document is uploaded**
- (2) 56996-Answering Reviewers- **Detailed signed letter with response to all reviewers queries is uploaded**
- (3) 56996-Audio Core Tip- **Core Tip section is uploaded**
- (4) 56996-Biostatistics Review Certificate-**Not Applicable**
- (5) 56996-Conflict-of-Interest Disclosure Form-**Uploaded**
- (6) 56996-Copyright License Agreement-**Uploaded**
- (7) 56996-Approved Grant Application Form(s) or Funding Agency Copy of any Approval Document(s)-**Not Applicable**
- (8) 56996-Non-Native Speakers of English Editing Certificate- **Not Applicable - Language -Excellent**
- (9) 56996-Video-**Not Applicable- no video or supplementary material for submission**
- (10) 56996-Image File- Uploaded - **Revised Table 1, Table 2A and Table 2B are uploaded individually.**
- (11) 56996-PRISMA 2009 Checklist-**Not applicable**
- (12) 56996-Supplementary Material- **Not applicable**

We trust this revised manuscript and their accompanying revised tables/figures that is being re submitted within the specified time frame of 14 days (we are resubmitting within a week) is now acceptable for publication.

We look forward to your continued support in this regard.

Thank-you,

Dr. Suresh Tharmaradinam

Dr Rani Kanthan