World Journal of Gastroenterology Manuscript No: 73086 - Answering Reviewers

1. *Introduction I think it is important to mention that MINENs show separate patterns in which the NE and non-NE components are related to each other: Mosaic (two components separable), composite (closely intermingled) and amphicrine (in my opinion there are also Amphicrine MiNENs), with the latter being a special type of the composite tumors. I think Figure 1 should be changed regarding this in order to show the different spatial relations between NE and Non-NE components (at least composite versus Mosaic). Goblet cell adenocarcinomas: It is important to note that goblet cell adenocarcinomas are something really specific. They are not MINENS (genetically diverse from CRC and appendiceal adenocarcinoma: Jesinghaus et al., Modern Pathology, please CITE) and very often do not express endocrine markers or hormones (of course they can but this is not necessary for diagnosis). I would therefore not regard them as a perfect example for amphicrine tumours! Nevertheless I agree that the changed name is a real improvement as they have nothing in common with appendiceal*

The introduction was intended to outline general categories that could be considered "mixed neuroendocrine tumors" and orient the reader to the fact that MiNENs represent one specific subtype of these tumors. This general approach to classification of these tumors is based on Lewin (1987) and discussed by Uccella and La Rosa (2020). In this sense spatial separation is emphasized to distinguish mixed collision tumors (i.e. two separate clonal processes that collide but are not intimately intermingled) from MiNENs, as opposed to dividing MiNENs into mosaic and composite patterns.

The fact that goblet cell adenocarcinomas are a separate specific entity is noted and mention of it is deleted from the discussion of amphicrine tumors as well as being removed from Figure 1. It was originally included as an example of an amphicrine tumor because it is classified as such in the 2019 WHO classification, however the genetic differences mentioned are noted.

2. *Introduction I am glad that the authors mention that an abberant expression of NE markers does not qualify for the diagnosis of MiNEN if there is no NE morhology. This was recently shown by Konukiewitz et al in a study of more than 1000 CRCs, where they demonstrated that an expression of SYN in conventional adenocarcinomas does not influence prognosis (Konukiewitz et al. Cancers, 2021). This study should be cited there.*

This reference is appreciated and it has been added to the discussion of aberrant expression of NE markers.

3. *Section MiNENS The authors list commonly altered genes in MINENS. I think it should be mentioned, where exactly those alterations occur. Although the mentioned genes are of course often altered in MINENs, i think the authors should rephrase the molecular pathology section in a way that states that all MINENs (and also NECs) show a similar molecular profile as their pure adenocarcinoma counterparts. Then i would suggest to name specific examples where this occurs (e.g. colon). this is also a point that divides MINENS from goblet cell adenocarcinomas.*

This section has been rephrased in a way to emphasize that the molecular profiles of MiNENs mirror pure adenocarcinomas from the same anatomic location. Common mutations in the colon are provided as an example.

4. *CK7 In what kind of LC NECs was this studied (pulmonary?) Please state and CITE*

This was studied in the urinary bladder (Wang et al 2021), and this has now been explicitly stated.

5. *SC NEC This is not what I observed in the GI tract, especially not in the colon. Please provide evidence for this.*

This was orginally based on a statement made by Uccella S & La Rosa S (2020). Upon further review this is corrected: large cell neuroendocrine carcinomas are more common in MiNENs than small cell carcinomas (Watanabe et al 2016; Olevian et al 2016).

6. *Reporting I would mention that the suggested molecular testing of both components is often very difficult, as most MINENS are composite tumors with closely intermingled components. There it is very hard to extract e.g. DNA separately from the two components separately. This statement is also made at another section in the manuscript (prognosis and management), which is unnecessary.*

While molecular testing of both components would be ideal, the difficulty of this task in reality is noted. The redundant statement in Prognosis and Management has been removed.

7. *Prognosis and Management This section in general is a bit confusing, especially if the reader is not an expert on MINEN and NECs, as it is not clear after the first section on stomach cancer,*

if the second paragraph only talks about gastric MINEN/NEC or about GI-NEC in general. This should be clarified. Maybe also data about the colon should be included here. ....Treatment is tailored towards the most aggressive component of the tumor, usually an NEC or adenocarcinoma.... This is also confusing. I think it should be clarified that usually NECs are the more agressive component, MANETs with an indolent NET combined with an ADC is very rare. This should be rephrased.

The section has been edited to improve clarity. The second paragraph talks about GI-NEC in general, and this has now been explicitly stated. The paragraph describing treatment has been edited to clarify that indeed the most aggressive component of MiNENs is usually a NEC, and that adenocarcinomas with an indolent NET are rare.