



PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 73086

Title: Mixed neuroendocrine-non-neuroendocrine neoplasms of the digestive system: A mini-review

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06209563

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Germany

Author's Country/Territory: Canada

Manuscript submission date: 2021-11-09

Reviewer chosen by: AI Technique

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Reviewer performed review: 2021-11-09 17:04

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No



Peer-reviewer statements	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No
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SPECIFIC COMMENTS TO AUTHORS

Thank you very much for giving me the opportunity to review this nice review by Toor et al. on MiNENs of Digestive system. The review is well written and the authors clearly show that they have expertise in this field. Nevertheless, I have some minor critique points.

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 NETs.

2. Introduction I am glad that the authors mention that an aberrant expression of NE markers does not qualify for the diagnosis of MiNEN if there is no NE morphology. This was recently shown by Konukiewicz 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 (Konukiewicz et al. *Cancers*, 2021). This study should be cited there.

3. Section MiNENS The authors list commonly altered genes in MINENS. I think it



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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. 4. CK7 In what kind of LC NECs was this studied (pulmonary?) Please state and CITE 5. SC NEC This is not what I observed in the GI tract, especially not in the colon. Please provide evidence for this. 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. 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 aggressive component, MANETs with an indolent NET combined with an ADC is very rare. This should be rephrased.



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Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
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Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

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