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Dr. Lian-Sheng Ma, Founder and Chief Executive Officer

Baishideng Publishing Group, Inc.

Dear Editor:

Thank you for your preliminary decision regarding our invited paper entitled "Molecular factors, diagnosis and management of gastrointestinal tract neuroendocrine tumors: An update" (Manuscript NO: 78469), which was sent to the *World Journal of Clinical Cases* for consideration for publication as a *Review*.

Additionally, I thank the reviewers indeed for their earnest efforts in reviewing the manuscript. Especially, a lot of thanks to Reviewer 1 for his meticulous and arduous efforts spending much time to make extended valuable comments. I accepted and responded step by step to all considerations improving enough the manuscript.

All the suggestions were addressed in the document and three new recent references (81,82,83) have been added. The changes are highlighted by yellow.

Reviewer 1

1. This manuscript is a narrative review and not a systematic review aiming in updating the current knowledge on GI NETs. It has been accepted by the Company Editor-in Chief (Dr. Ma LS) in such form and he invited me officially to write on this topic. However, this study focuses only in GI NETs and is extended. Pancreatic NETs is another interesting issue. Maybe, the suggested systematic review on both GI and pancreatic NETs would be a matter of another most extended trial.
2. I agree that GI and pancreatic NETs are quite different in molecular pathology and treatment requiring distinct approach. It has been added the following text:
''*GI and pancreatic NETs are quite different in molecular pathology and treatment requiring distinct approach. In this extended narrative review focusing in GI NETs*'' *(page 5, last two lines: 30,31).*
3. Key words have been improved (page 2, lines 22-23).
4. NETest utility in NETs and other novel biomarkers. It has been clarified further by adding the following text:
''*Novel biomarkers include circulating tumor cells, circulating tumor DNA, circulating microRNAs, and NETest. Liquid biopsy based on mRNA analysis in the serum is a useful novel biomarker. In particular, the NETest index is a new biomarker in peripheral blood that is based on the simultaneous assay of 51 neuroendocrine-specific marker genes by PCR (polymerase chain reaction). This test expresses the percentage of positivity of the genes involved. The results show a scale from 0 to 100% as an activity index. The cutoff point is 20%. An index between 20 and 40% indicates stable disease, while an index above 40% indicates progressive disease. Its diagnostic accuracy is high (99%) compared to that of CgA (21 to 36%). Additionally, it is very useful for follow-up after therapeutic excision or determining the response to drug therapy. It can reveal recurrence and may predict prognosis. A new immunohistochemical marker is the transcription factor*

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insulinoma-associated protein 1 (INSM1), which is more specific for the differentiation of NETs of the pancreas and rectum'' (page 10, lines 22-31; page 11, line 1).

5. Imagistic section has been improved (updated) by adding the missed modalities. Actually the main new diagnostic modalities were included in Introduction section (page 5, lines 18-26) to emphasize their great importance.

''Positron emission tomography-computerized tomography (PET-CT) combining functional metabolic and anatomical imaging as well as octreotide scintigraphy (Octreoscan), which is also called somatostatin receptor (SSTR) scintigraphy [16-18], are the preferred imaging diagnostic tools, although no modality alone offers the best results [19]. FDG-PET (fluorine-18-labeled deoxyglucose), gallium PET/CT, ^{18}F-FDOPA PET/CT (^{18}F-fluorodihydroxyphenylalanine) and SPECT (single photon emission computerized tomography) scans are several new imaging tools. ^{18}F-FDOPA PET/CT is the most accurate novel tool for detecting metastasis from small bowel NETs [20].''

Also added, *''Diffusion weighted MRI and contrast enhanced MRI aid in the detection of small hepatic metastases.High resolution MDCT''* (page 13, lines 20-22). *''As mentioned in Introduction section the novel diagnostic imaging includes PET-CT, FDG-PET, gallium PET-CT, FDOPA PET-CT (the most accurate) and SPECT [16-20]. Contrast enhanced ultrasound is used for follow-up''* (page 13, lines 26-28).

6. ''Long acting release of somatostatin analogs'' has been corrected to *''Long acting release somatostatin analogs''*(page 20, lines 30-31) as suggested.

7. ''Progress in PET-CT and scintigraphy with new radioactive agents (^{64}Cu-DOTATATE or ^{68}Ga-DOTATATE) replacing octreotid have improved the current diagnostic imaging.'' has been corrected to *''Progress in PET-CT and scintigraphy with new radioactive agents (^{64}Cu-DOTATATE or ^{68}Ga-DOTATATE) replacing enough octreoscan has improved further the current diagnostic imaging.''* (page2, lines 13-15).

8. GI-NETs and GIS-NETs because of their similarity the former term replaced the latter term throughout the text as suggested.

9. As suggested the following text has been clarified: *''The vast majority of them are sporadic. However, at a rate less than 5%, they are found in genetic syndromes, mainly MEN 1 (multiple endocrine neoplasia), in the form of pancreatic islet cell neoplasms (gastrinoma, insulinoma, glucagonoma, in order) which carry a high rate of malignancy''* page 4, lines 6-9).

10. *'' Positron emission tomography-computerized tomography and (PET-CT) SPECT (single photon emission computerized tomography)''* have been corrected as suggested page 5, lines 18,23; page 13, line 24)

11. *''malignant neoplasia''* replaced *''cancer''* and it has been explained *''Small intestine NET is the most common malignant neoplasia of the small bowel''* (page 6, line 16)

12. It has been clarified enough by adding new text *''The correct identification of cell origin and understanding the mechanisms of the tumorigenesis could open new horizons in prophylaxis and treatment. It is now considered that the origination of cancers is from stem cells. Each cell division implies a bit risk of mutation; thus any stimulation of proliferation has an increased risk of mutation. Some hormones (gastrin, estrogen, testosterone) and growth factors, by acting as signal molecules, play an important role in tumorigenesis; e.g. increased gastrin may cause growth of enterochromaffin-like (ECL) cells and sequence of hyperplasia, dysplasia, gastric NETs type 4, and possibly NECs or diffuse adenocarcinomas [27].''* (page 6, three last lines and page 7, lines 1-6)

13. The section ''Molecular factors-Genomic profile'' has been improved enough as suggested by adding the following texts:

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a. ''*The variants in these genes are associated with inherited susceptibility for malignancies. However, it is not yet known whether there is an association with NET development.*'' (page 6, lines 8-10)
b. ''*A familial existence of small intestinal NETs has been reported. In a family with 16 affected individuals, a heterozygous deletion at 7q31.2 (cystic fibrosis locus) was found.*'' (page 6, lines 18-20)
c. ''*Cancer cells develop mechanisms that increase nutrient uptake, since they require a vast amount of nutrients for their survival. Metabolic players could have a potential role in NETs.*'' (page 6, lines 25-26)
d. ''*The correct identification of cell origin and an understanding of the mechanisms of tumorigenesis could open new horizons in prophylaxis and treatment. Currently, cancers are considered to originate from stem cells. Each cell division carries a slight risk of mutation; thus, any stimulation of proliferation has an increased risk of mutation. Some hormones (gastrin, estrogen, testosterone) and growth factors play a pivotal role in tumorigenesis by acting as signaling molecules. For example, increased gastrin levels may promote the growth of enterochromaffin-like (ECL) cells and induce a sequence of hyperplasia, dysplasia, type 4 gastric NETs, and possibly NECs or diffuse adenocarcinomas [27].*
Gene expression profiling can be used to classify small intestine NET subtypes and accurately predict metastasis. This might lead to individualized treatment.'' (page 7, lines 3-13)
e. '' *GI-NECs are genetically different from GI-NETs.*'' (page 7, line 23)
f. ''*TP53, RB1, KRAS mutations have been detected in gastric and colorectal NECs, although BRAF mutations have only been reported in colorectal NECs [31]. KRAS or BRAF pathway-related signal transduction is very important in carcinogenesis. Activation of these oncogenes contributes to carcinogenesis. The most common mutation involves the KRAS oncogene on chromosome 12p, which exists in an inactive form. It activates the p21 protein, which causes cell transformation, proliferation, and invasion. Inactivation of tumor suppressor genes, such as the TP53 (tumor protein) gene that promotes apoptosis (programmed cell death) and prevents cancer, leads to uncontrolled cell growth, proliferation and carcinogenesis. Additionally, the inactivation of maintenance genes, which regulate DNA damage repair, predisposes patients to cancer. The Notch signaling pathway maintains the required physiological balance among cell proliferation, differentiation and apoptosis. The mammalian target of rapamycin (mTOR) pathway is another cellular signaling pathway that is essential for physiological functions, such as cell growth and proliferation, but its hyperactivation may lead to carcinogenesis. Therefore, it is a target of novel therapeutic biological agents. [4,31-33].*'' (page 7, lines 28-31; page 8, lines 1-13)
14. As suggested the following text has been clarified: ''*The clinical presentation is influenced by hormone secretion or not, therefore defining them as functional or nonfunctional.*'' (page 8, lines 24-25).
15. NET carcinoma has been replaced by the correct *NEC (neuroendocrine carcinoma)* (page 5, lines 9-10) and also in key words.
16. The abbreviation is explained: *PPIs (proton pump inhibitors) receiving* (page 10, line 21-22).
17. The inexact information has been deleted as suggested: *"The modalities of somatostatin receptor scintigraphy used in clinical practice include radiolabeled metaiodobenzylguanidine, 11indium pentetreotide (octreoscan), radiolabeled vasointestinal peptide, radiolabeled monoclonal antibodies and the abovementioned positron emission radionuclides''* (page 13, lines 11-15). A modified text has been added ''*The role of nuclear medicine in diagnostic imaging is essential but has changed sufficiently in recent years. The somatostatin receptor scintigraphy by ^{111}indium pentetreotide (octreoscan) was the most used method for many years in clinical practice [67], but it is no longer the preferred imaging investigation method. However, despite important novel advances, its value may still be useful in some cases [18].*'' (page 14, lines 11-15).

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18. For type 4 ECL- Cell gastric NET, it has been added the following text: '*Type 4 enterochromaffin-like (ECL) cell NETs have similar characteristics to type 3. However, they are more aggressive and have a worse prognosis. These constitute either poorly differentiated NECs or variably MiNEN. [35].''* (page 9, lines 16-19).
19. As suggested, it has been developed the idea by adding the text: *''A new immunohistochemical marker is the transcription factor, insulinoma-associated protein 1 (INSM1), which is more specific of differentiation for NETs of pancreas and rectum.''* (page 11, lines 1-4)
20. The biomarker 5-HIAA has developed further as suggested in the modified text:
*''5-HIAA (*5-hydroxyindoleacetic acid**)** *is the main metabolic product of serotonin. Its assessment in 24-hour urine determines serotonin levels in NETs originating from enterochromaffin cells mainly in the small bowel, secrete serotonin. It is associated with tumor burden. However, it may have false-positive results in some cases (foods, drugs or various diseases)''(*page 11, lines 5-9).
21. I agree that APUDomas is rather an outdated terminology. After all, there is the statement *''The neoplasms of the neuroendocrine cells or APUD cells were previously called APUDomas, but the term NETs now prevails''* page 4, lines 19-20).
22. As suggested pathology and prognostic factors were split (page 15, lines 19-20).
23. The treatment section has been updated, focusing on IFN, telotristat and somatostatin receptor antagonists therapy, as suggested. Three new recent references (84,85,86) have been added, thus the total number is 105 and the references number has been changed by plus 3 (87-105). Added text is as follow:
a. *''Telotristat is an inhibitor of tryptophan hydroxylases (TPH 1 and TPH2) that limits serotonin biosynthesis and relieves manifestations of carcinoid syndrome. Telotristat together with a long-acting somatostatin analog is currently recommended for uncontrolled carcinoid syndrome diarrhea by the USA NCCN (National Comprehensive Cancer Network) [84]''.* (page 18, lines 29-31; page 19, lines 1-2).
b. *''PRRT has superiority over somatostatin analogs (SSAs) and is the first choice of treatment for patients with advanced well-differentiated NETs (effectiveness 96%). PRRT is followed by SSA plus bevacizumab (effectiveness 86%) and SSA plus IFN-a (interferon alpha) (effectiveness 78%); all three have similar serious side effects [85].*
There have been five somatostatin receptor (SSTR) subtypes, i.e., SSTR1, 2A and 2B, 3, 4, and 5. Somatostatin receptor antagonist therapy targets these subtypes by exerting antineoplastic activity. Peptide receptor radionuclide therapy (PRRT) uses radiolabeled SSA radionucleotides (Y90 or Lu177), which are firmly connected with a transport vehicle that binds directly to tumor cells, similar to a Trojan horse. It may be the most important anti-SSTR2 (most frequently expressed in lung and gastroenteropancreatic NETs) treatment for NETs in recent years [86].
The vast majority of target treatments include the above mentioned agents against somatostatin receptors and also against paramycin pathways (mTOR) such as everolimus [87]. New drugs (ganitumab or cixutumumab) that increase the efficacy of everolimus have been reported [86]. (page 19, lines 13-28).
c. *''somatostatin receptor antagonists''* in ''core tip'' section (page 3, lines 3-4).
24. Conclusions section has been improved by more appropriate data summarize as suggested. Added text is as follow:
a. *''Liquid biopsy and the NETest gene index is a useful novel biomarker in peripheral blood. The somatostatin receptor scintigraphy is no longer the preferred imaging investigation. ^{68}Ga-DOTATATE PET/CT or the newest ^{64}Cu-DOTATATE PET/CT are the preferred imaging.''* (page 23, lines 5-8).
b. *''(surgery is necessary for tumors 2 cm or more in size)'', '' as well as debulking surgery in secreting NETs''* (page 23, line 9-11)

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c. *''Somatostatin receptor antagonist therapy exerts antineoplastic activity. Radiolabeled peptide receptor radionuclide therapy and somatostatin analogs plus bevacizumab or IFN-a are novel therapeutic options. Telotristat treatment is indicated for persistent diarrhea in carcinoid syndrome.''* (page 23, lines 14-18)
d. ''Future assessments should be focused on targeted biological agents of the implicated molecular factors, new effective chemotherapy drugs, gene therapy and the use of artificial intelligence in the diagnosis and management of these diseases to open new horizons for therapeutic strategies.'' (page 23, lines 20-23)

Reviewer 2: Many thanks for his considerable comments.
a. The three minor linguistic amendments have been done as suggested (page 4, lines 6-9; page 8, line 23; page 9, line 20).
b. The intussusception with 3 new references (39,40,41) has been added in section ''Clinical presentation'' as suggested *''Small and large bowel NETs or even stomach NETs may rarely manifest as acute intussusception."* (page 9, lines 30-31).
c. The artificial intelligence in the diagnosis and management of GI-NETS with its reference (105) has been added as suggested. ''The role of artificial intelligence and machine learning and a deep understanding of the diagnosis and management of NENs of the gastrointestinal system have been recently evaluated. A standard of practice has not yet been established; however, it may serve as a useful adjunct in current practices *[105]''* (page 22, lines 25-28). Also, *''and artificial intelligence in the diagnosis and management''* in Conclusions (page 23, lines 22-23).

I am sending the revised manuscript and hope to receive a favorable final decision.

We look forward to hearing from you at your earliest convenience.

Sincerely,

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