Reviewed by 03545890

Congratulations for your very interesting manuscript. In my opinion the manuscript offers a new insight in the management of meuroendocrine carcinomas of the pancreas. Some grammatical errors should be revised.

RESPONSE: we thank the Reviewer for his/her nice comments. We have edited the entire paper in order to revise possible grammatical errors.

Reviewed by 02276089

The review "Management of neuroendocrine carcinomas of the pancreas (WHO G3): A tailored approach between proliferation and morphology" by Stefano Crippa, et al. succinctly summarizes current understanding of the pancreatic NEC (PNEC) with regard to their clinical and pathological characteristics as well as diagnosis and treatment. This review is well written, helpful for the clinicians to grasp the current knowledge of the disease management for PNEC. A major criticism is that this review fails to clarify the criteria for classifying the well- and poorly-differentiated PNEC as well as the positivity for 68Ga PET and 18FDG PET, thus the diagnosis of different subclass of PNEC remains an individual clinical decision.

RESPONSE: we thank the Reviewer for his/her nice comments. We agree with the Reviewer that at the moment is difficult to fully re-classify well- and poorly-differentiated PNEC, but the aim of this review was "to analyze the current knowledge on pancreatic NEC (PNEC) analyzing their clinical and pathological characteristics, review their treatment and prognosis, and evaluate potential pitfalls in their current classification." We have showed that there are some pitfalls in the current WHO classification, and the main problem is the inclusion in the same category (NEC – WHO G3 PNET) of both well- and poorly-differentiated tumors. However, we agree with the reviewer that histological diagnostic criteria for well- and poorly-differentiated PNEC are not defined and accepted. Moreover, the positivity/negativity for 68Ga PET and 18FDG PET are useful and important for the diagnosis of NEC but, again, we cannot trust only on PET studies and data from PET imaging should be carefully integrated with other clinico-pathologic data. As pointed out in the manuscript (please read the beginning of page 8 of the revised version of the manuscript), tissue biopsy is of paramount importance.

We have changed the text as follows:

-page 7: "Although PET imaging can be of help in differentiating poorly- and well-differentiated NEC, there are still many situations of uncertainty or of mild positivity of both 68Ga PET and 18FDG-PET; therefore all data from PET imaging should be always carefully integrated with clinical and pathological features."

-page 10: "Unfortunately definitive histological diagnostic criteria are not clearly defined and accepted. Therefore further and larger studies are needed in order to better define and clarify histological diagnostic criteria and classification of both PD NEC and WD NEC."

-page 11: "although PET cannot fully discriminate between the two forms and data from PET imaging should be carefully integrated with other clinico-pathologic data."

-page 14: "Specific and definite diagnostic criteria for histological diagnosis of PD NEC and WD NEC are also required."

In addition, typos and grammatical errors need to be corrected. For example, page 2 "which represents the goal standard" should be "which represents the gold standard"; page 4 "More than 70% of patients present with metastatic or…., only 20 to 30% of patients…". This sentence is confusing in that it is not clear these patients are all patients or PNEC patients.

RESPONSE: we thank the Reviewer for his/her comments. An English speaker has edited the entire manuscript. We have changed "goal standard" with "gold standard" in the Abstract of the paper. The sentence "More than 70% of patients present with metastatic or…., only 20 to 30% of patients…" has been revised as follow (please read page 6 of the revised version of the paper): "More than 70% of patients with pancreatic NEC present with metastatic disease or with locally-advanced tumors, and only 20 to 30% of patients are amenable of surgical resection".

Algorithm is used at various places throughout the text, as it is not strictly an algorithm, a flowchart or decision chart is preferred.

RESPONSE: we have changed the word algorithm with flowchart along the manuscript.

Fig. 5, Rb should be RB.
RESPONSE: *we have changed Figure 5 as requested.*