February 28th, 2022

Dear Editors and Reviewers,

Thank you for your kind comments and suggestions, according to which we have revised our manuscript.

Reviewer 1:
The review is focused on step-by-step surgical management of GEP-NET, especially for liver metastasis. The surgical treatment is important in metastatic GEP-NET, and many reviews focused on this topic. This article is emphasized liver transplantation of GEP-NET and its criterias. As a review, this article is not fully including latest view and studies of surgery for liver metastasis, especially surgery of GEP-NET in extrahepatic or high grade tumor. This article has high value but structure is need revise. The introduction of GEPNET is too much and not deep enough. The article need more work to be done before qualitied to be published.

Thank you for these comments. The manuscript has been rechecked and the necessary changes have been made in accordance with these suggestions.

Specific comments:
"NEUROENDOCRINE NEOPLASMS OF THE PANCREAS". Heterogeneity syndrome is different category, for exsample MEN1 related PanNET has better prognosis than sporadic PanNET, the surgical management and Watch/wait of MEN1 related PanNET is different, need to re-write.

In this review we focused on the sporadic NEN. As heterogeneity syndromes (MEN-1, VHL) are different category in diagnosis and management strategies, we decided not to elaborate on this topic. Detailed information on the principles of management can be found elsewhere.

The table 1 is not useful.

We believe that WHO classification for GEP-NEN and its division into NETs and NECs is of importance for better understanding of the presented subject.

The introduction defined NEN be divided into NET and NEC, based on its differentiation, the surgery strategy of NET and NEC is different, and the main content in the article is about surgery treatment of NET actually, but the article use NEN in most part of the content.

Thank you for these comment. We have distinguished the management of low-grade, and high-grade NEN, and NEC in the individual sections. Also separate section on high-grade GEP-NEN is added.

HIGH-GRADE GEP-NEN
Recent WHO classification of the NEN (Table 1) distinguished two groups of high-grade NEN[2]. Those are well-differentiated NET G3 with Ki67>20% and poorly-differentiated NEC. The term NEN G3 covers both types of those malignancies. The NEN G3 patients are heterogenous group concerning prognosis and treatment benefit. GEP NEC are usually highly aggressive, with a propensity for early metastases and dismal prognosis[52]. In the SEER database the median survival is 34 mo with localized disease, 14-16 mo with regional

disease, and 5 mo with distant disease[53]. Data on the NET G3 subgroup are extremely scarce, they are mainly located in the pancreas and have a better prognosis than NEC[52].
The treatment recommendations for NEN G3 patients are mostly expert consensus supported by heterogenous retrospective studies. The opinion is that surgery alone is rarely curative and that patients with limited disease should receive multimodality based treatment. The 5-year survival for localized disease depends on the primary site; the best is for colorectal, stomach, and pancreas primaries (40-50%)[53]. Metastatic surgery for GEP NEC is not recommended and the treatment is with systemic chemotherapy (etoposide and a platinum agent)[54].
A National Cancer Database Study summarized treatment and outcome of 1861 patients with high-grade NEN[55]. Over 64% of patients was in stage IV of the disease at the moment of diagnosis. The most common primary site was large bowel (26.6%). Only about 28% of the study population was amenable for surgery. The median survival was 9.3 mo. This study did not distinguish NET G3 and NEC due to disparity of study period and the novel WHO classification.

The surgery is not limited to liver metastasis or G1/2, the latest view and studies of surgery for liver metastasis, especially surgery of GEP-NET in extrahepatic or high grade tumor, need to be mentioned.

We have added a section on high-grade GEP-NEN (as seen above) and a section on extrahepatic metastases.

EXTRAHEPATIC METASTASES

The most common metastatic NEN sites are the liver, other intraperitoneal sites, bone, and the lung. Liver metastases occur in 40-95%[4] but peritoneal metastases can be a part of the metastatic tumour load in approximately 17-20% of cases[49]. The most common primary site for peritoneal metastases is small bowel[49-51]. Presence of the peritoneal metastases has an adverse impact on the patient survival, irrespective of the hepatic metastases[50, 51]. For patients with well-differentiated G1/G2 NET complete cytoreductive surgery can prolong overall and disease free survival. In the study from France, patients with peritoneal metastasis were treated with peritonectomy with or without partial hepatectomy[48]. 5-year and 10-year overall survival rates were 69% and 52%, respectively, and 5-year and 10-year disease free survival rates were 17% and 6%, respectively. The benefit from addition of hyperthermic intraperitoneal chemotherapy to complete cytoreductive surgery is questionable, according to authors of the study.
For high-grade NEN peritoneal metastases only medical treatment is advised[17].

Reviewer 2:

This article reviewed surgical management of GEP-NENs, including gastric, small intestine, pancreas, rectum and liver metastases. But the parts of gastric, small intestine, pancreas and rectum NENs were relative simple and repeat the points of NCCN and ENETs guideline. So I suggest that author put the emphases on liver metastases surgical management part.

Thank you for these comments. We provided more information on the suggested matter of surgical management of liver, and extrahepatic metastases by adding new section "EXTRAHEPATIC METASTASES".

Reviewer 3.

The abstract is consise and suggests the papir will go in detail in surgical management of NETs of small intestine, rectum and pancreas, but in the main text gastric NETs are also included. The background of the manuscript is well presented in the introduction and authors discuss current surgical options. The main contribution is in summarizing curative and citoreductive options, as well as the role of liver transplantation in NEN treatment. Authors give one table- WHO classification, which I think is important but maybe not best representing the topic of the Manuscript, so I would suggest maybe more schematic summary of surgical options as a more proper graphic. In the reference list, some references are duplicated.

Thank you for these comments. We have corrected the abstract – we have clarified inclusion of the stomach NEN in the article. Reference list was corrected – we apologize for our editorial mistake, the duplicated reference was changed to the proper one. Schematic summaries of surgical options in graphic form were added for SI-NEN (Figure 1) and PNEN (Figure 2);

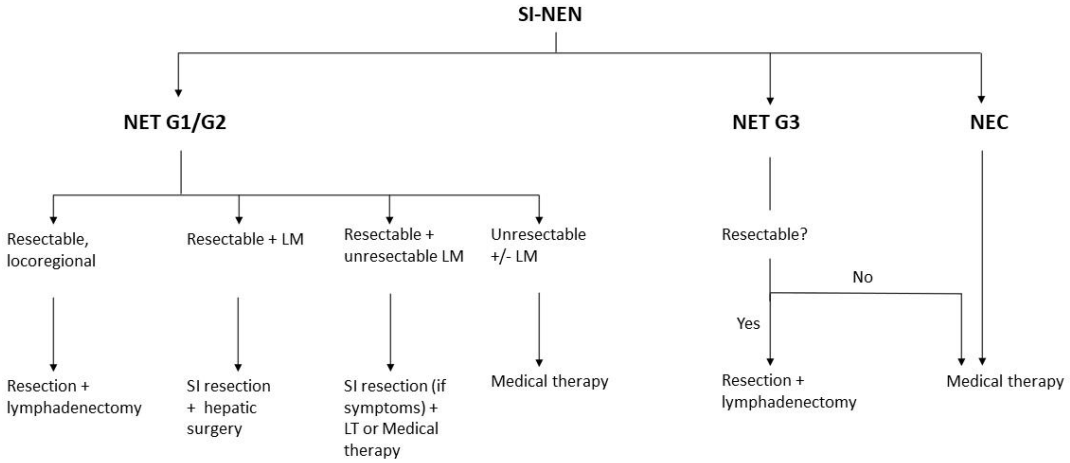

Figure 1. Therapeutic options for small intestine neuroendocrine neoplasm. SI-NEN, small intestine neuroendocrine neoplasm; NET, neuroendocrine tumour; G, grade; NEC, neuroendocrine cancer; LM, liver metastases; LT, liver transplantation.

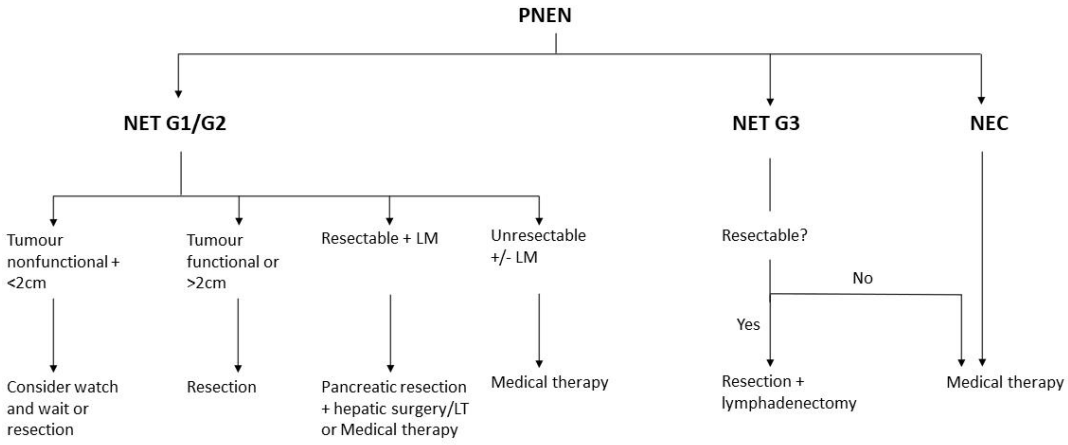

Figure 2. Therapeutic options for pancreatic neuroendocrine neoplasm. PNEN, pancreatic neuroendocrine neoplasm; NET, neuroendocrine tumour; G, grade; NEC, neuroendocrine cancer; LM, liver metastases; LT, liver transplantation.

Reviewer 4.

Specific comments:

English should be revised.

English was rechecked by the native speaker.

The manuscript lacks a discussion part, and current status and future perspectives about the surgical management of GEP-NENs should be fully discussed and concluded.

Thank you for these comment. This article has a form of a review therefore no discussion in the classic form is included. Each section is a discussion on the specific part of the topic and all are summarized in the "CONCLUSION".
We have added a section on future perspectives.

FUTURE PERSPECTIVES

Most of the ongoing or recently finished clinical trials examined medical therapies in advanced NEN demonstrating prolongation of the progression free survival[56]. NEN clinical trials pose logistical challenges due to the relative rarity of NEN and the necessity of multi-centric collaboration to ensure adequate recruitment. This is especially relevant to the concept of surgical trials in metastatic NEN, where only a quarter of patients may be amenable for surgery.
There are four ongoing, still recruiting, NEN clinical trials with surgical intervention (diagnostic or curative) (Table 2)[57]. Two are observational. One of those studies intent

medical or surgical treatment dependent of patients decision. Two studies are interventional and multicentric. None of those trials opens new surgical fields. For that to happen new diagnostic and predictive tools must be developed. Clift *et al* proposed 3 key areas:

The development of increasingly informative functional imaging,

The integration with imaging of real-time multianalyte genomic analysis of individual tumour,

The application of system biology strategies to a multidimensional assessment of the relationship of the metabolome, the microbiome and the proliferome to neuroendocrine neoplasia and the delineation of disease progression[56].

I recommend the authors to add a table to summarize some important clinical trials for the surgical management of GEP-NENs in this manuscript.

Thank you. We have added a table on clinical trials.

Table 2. Clinical trials for surgical intervention in NEN with open recruitment

Study title	Resection of metastatic PNETs after induction system treatment	Single-cell sequencing and establishment of models in NEN	Endoscopic ultrasound-guided radiofrequency ablation for the treatment	Prophylactic cholecystectomy in midgut NETs patients who require primary tumor surgery
Primary site	Pancreas	GEP NEN	Pancreas	Jejunum, ileum, proximal colon
Study type	Observational	Observational	Interventional	Interventional
Multicentric	No	No	Yes	Yes
Primary Purpose	N/A	N/A	Treatment	Treatment
Allocation	N/A	N/A	N/A	Randomized
Estimated Enrollment	180 participants	200 participants	70 participants	100 participants
Estimated Study Completion Date	July 25, 2025	December 2022	June 1, 2021	April 2025

NEN, neuroendocrine neoplasm; PNET, pancreatic neuroendocrine tumour; NET, neuroendocrine tumour; GEP NEN, gastroenteropancreatic neuroendocrine neoplasm; N/A, non-announced

Sincerely,

Rafał Stankiewicz
Department of General, Transplant and Liver Surgery
Medical University of Warsaw
1A Banacha Street, 02-097 Warsaw, Poland
Tel: +48 22 599 25 45
Fax: +48 22 599 15 45
e-mail: rstankiewicz0@gmail.com