Peer Review File

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Reviewer A

Thank you for an interesting and well-written manuscript.

You describe P-NET, but the new WHO classification divides neuroendocrine neoplasms into NET or NEC based on Ki-67, histology, differentiation and tumor biology. Please describe that in the Introduction.

Reply: Thank you for your comments. We have updated the introduction to emphasize the significance of grading and histopathologic characteristics in pNETs.

Changes in text: See Page 3, line 83-89.

There are many abbreviations, BR, PDAC, NT. Could you reduce the number of abbreviations with 40%?

Reply: We removed the abbreviations for neoadjuvant therapy (NT) and non-functional (NF), while retaining BR (borderline resectable) and PDAC (pancreatic ductal adenocarcinoma).

Changes in text: Throughout the manuscript NT was expanded to neoadjuvant therapy and NF was expanded to non-functional to reduce the number of abbreviations.

I do not know if it is possible, but could you describe medical treatment with SSA, targeted therapy and PRRT more thoroughly?

Reply: We have added additional information in these sections.

Changes in text: See Page 7, line 293-295; Page 8, line 320-326; Page 8, line 334-336; Page 9, line 343-345.

Reviewer B

The review is written very systematically and comprehensive. Unfortunately it still lacks definite recommendations except of upfront surgery whenever feasible. Although data is missing, I recommend to give a more detailed conclusion for the readers' every day practice.

Would you recommend a revised definition of borderline resectability for pNET? Which criteria do you regard as appropriate?

Reply: Thank you for your important question. Suggested criteria for defining BR-pNET was previously discussed in the “Definition of Borderline Resectable pNET” but has now been added to the conclusion section as well.

Changes in text: Page 12, line 485-491.

As you state in line 454 that experienced institutions should consider a more

aggressive surgical approach. How do you define an experienced institution, which prerequisites should they have?
Reply: Little literature has evaluated optimal volume thresholds for managing neuroendocrine tumors. We have included some additional references on this topic, but a comprehensive discussion is outside of the scope of this review.
Changes in text: See Page 12, line 494.

in line 216 a survival benefit is mentioned. Can you quantify it?
Reply: We added data that extended resection results in a 5-year OS rate of around 80%, compared to the 5-year OS rate of around 45% in unresected patients.
Changes in text: See Page 6, line 224-226.

Please explain the role of liver transplantation and of bevacicumab.
Reply: Liver transplantation: We added a brief paragraph discussing liver transplantation specifically in the context of liver metastasis.
Bevacizumab: We added the possible role of different molecular targets in treating pNET as combination therapies, such as bevacizumab with everolimus.
Changes in text: Liver transplantation: See Page 7, line 263-267.
Bevacizumab: See Page 8, line 320-326.

Is there data on an overall survival benefit of SSA? line 277.
Reply: We included information stating that there was no significant difference in overall survival between lanreotide and placebo.
Changes in text: See Page 7, line 293-295.

For targeted therapies (line 294) it might be of use to remember the readers, that sunitinib targets the VEGF receptor, hence a PRRT therapy often is not feasible after this treatment due to markedly lowered SUV.
Reply: Thank you for this comment. We did a literature search but had difficulty finding a reference to support this statement.
Changes in text: N/A

line 311: Can you quantify the risk for renal failure or myelodysplastic syndroms, and compare the risk to the risk of pancreatic surgery?
Reply: We have added the risk estimates for PRRT. Risks of pancreatic surgery are discussed elsewhere in the manuscript.
Changes in text: See Page 8, line 334-336.

line 319. 79% relative or absolute risk reduction? If relative, please add the absolute risk.
Reply: The NETTER-1 trial demonstrated a 79% improvement in the hazard ratio for progression free survival (PFS). We revised this section to make it more clear for the reader.
Changes in text: See Page 9, line 343-345.

line 427: can you quantify the risk of recurrence? I feel in localized pNET the risk is quite low.
Is there a role for tumor markers like chromogranin A in decision making (in my opinion there is no)?
Reply: We added the risk of recurrence following resection. It varies widely depending on the risk factors. We also added findings that show chromogranin A as a predictive factor to determine risk of recurrence.
Changes in text: See Page 11, line 456-458 and 460-463.

in references please remove (in eng) in all references.
Some references are cited as "T. Author et al" some with all authors. Please standardize.
Ref 18 and 47: "). United States" seems dispensable.
Reply: We have modified our manuscript as advised. We removed all (in eng) from the references and changed to the Vancouver reference style. Removed “United States” in References.
Changes in text: Reference section. See Page 13-20, line 513-829.

Reviewer C
The authors propose a literature review on the treatment of pancreatic neuroendocrine tumours.
The topic is very interesting as the authors focus on the concept of resectability, which in pdac is yet present in the guidelines while in pnet it is not considered.
The article is well written. the introduction could be slightly extended.
PMID: 35794053.
PMID: 30140036
The division into paragraphs increases the order of the study and enhances comprehension. Missing is a reference to the importance of grading and histopathological differentiation of pnet, a parameter that has become fundamental in decision making in this pathology. In this regard, some authors have proposed decision-making algorithms that could be useful in the discussion and to discern patients in whom 'complex' resections are appropriate and patients in whom it is better to avoid. I recommend this review and the WHO guidelines on tumour differentiation
Reply: Thank you for your feedback. We have revised the text to describe the significance of grading and histopathologic characteristics in pNETs and added these references. We have emphasized the ongoing lack of consensus regarding the resectability of pNETs, a key focus of this review.
Changes in text: See Page 3, line 83-89 and Page 12, line 485-491.