Peer Review File

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Reviewer A

This is a well-written and comprehensive review of a topic that warrants attention with an appropriate balance between what it strongly supported by evidence (very little) and what is speculative but promising (mostly).
I have only minor comments:

Comment 1: Line 176- radionucleotide should read radionuclide
Reply 1: We have changed the word radionucleotide to radionuclide.
Changes in text: We have changed the word radionucleotide to radionuclide.

Comment 2: In the PRRT section you might also cite papers published prior to the Carlsen series. These are:
1. Zhang, J. et al. Peptide Receptor Radionuclide Therapy in Grade 3 Neuroendocrine Neoplasms: Safety and Survival Analysis in 69 Patients. J. Nucl. Med. 60, 377–385 (2018).
2. Thang, S. P. et al. Peptide receptor radionuclide therapy (PRRT) in European Neuroendocrine Tumour Society (ENETS) grade 3 (G3) neuroendocrine neoplasia (NEN) - a single-institution retrospective analysis. Eur J Nucl Med Mol I 45, 262–277 (2018).

Reply 2: We have cited both the above papers in the PRRT section.
Changes to text: Lutetium-177 (177Lu)-DOTATATE is FDA-approved for SSTR-positive NET. A survival analysis among 69 patients with HG NEN (predominant PAN-NEN) showed that PRRT is effective in patients with Ki-67 index less than 55% who failed chemotherapy. Another retrospective analysis among 28 patients with Grade 3 NEN treated with PRRT has shown better median PFS among patients with a Ki-67 index less than 55% compared to the patients with Ki-67 index greater

Reviewer B

The present paper is a review on management on high-grade pancreatic neuroendocrine neoplasms. The topic is very relevant and covers most aspects. However it has several aspects that needs modification.

Major comments
Comment 1. The nomenclature is not correctly used. High-grade (HG) neuroendocrine neoplasms (NEN) should be used when addressing both NET G3 and NEC. NET should only be used when addressing well-differentiated tumours. Neuroendocrine carcinoma (NEC) are always poorly differentiated, and according to WHO should only be mentioned as NEC, it is not necessary to specify they are poorly differentiated. When referring to studies, the study cohort NEN, NET or NEC must be correctly mentioned.
a. The title should be changed to HG pancreatic NEN- as it covers both NET G3 and NEC.
b. Line 24: delete poorly differentiated

c. Line 43 Neuroendocrine neoplasms
d. Line 44 NEN- not NET
e. Line 45 classified HG digestive NEN
f. Line 48: NEN not NETS
g. Line 63 delete High grade and PD, NEC is sufficient
h. Line 127: NEN- not NETs
i. Line 132: pan NEN
j. Line: 142: NEN- check study population
k. Line 160: NEN
l. Line 163: HG NEN
m. Line 165: HG NEN
n. Line 175: NEN
o. Line 179: NEN
p. Table 2 is not only for NEC.

Reply 1 and changes in text:
A: the title is changed
B: Line 24: Removed poorly differentiated and changed to HG pancreatic NENs
C: Line 43: Deleted NETs and changed to NENs
D: Line 44: Deleted NET and changed to NEN
E: Line 45: Added HG digestive NENs
F: Line 48: Changed NETs to NENs
G: Line 63: Deleted High grade and PD and changed to NEC
H: Line 127: NET changed to NEC.
I: Line 132: Changed to NEN
J: Line 142: NET changed to NEN
k. Line 160: NET changed to NEN
l. Line 163: NET changed to HG NEN
m. Line 165: NET changed to HG NEN
n. Line 175: NET changed to NEN
o. Line 179: NET changed to NEN
p. We have updated table 2 to studies on NEC only

Comment 2: The review is stated comprehensive. I miss a section on adjuvant treatment after radical surgery (surgery of localized NET G3 and NEC is standard outside US).
Reply 2: We have now included a section on adjuvant therapy.
Changes in text: Most Digestive NEC studies didn't elucidate whether chemotherapy was adjuvant or neo-adjuvant. Adjuvant chemotherapy after curative resection showed improved outcomes in a cohort study among 1861 patients with localized digestive NEC. In this study, 519 patients underwent curative resection and 224 patients received post-operative chemotherapy. In a similar fashion, chemotherapy showed a better prognosis post-operatively in a retrospective analysis in localized digestive NEC patients. In contrast, post-operative chemotherapy did not improve prognosis in a national database analysis done among 759 patients with localized digestive NEC

Comment 3: Furthermore there is no chapter on 2-line treatment- only a statement in the conclusion. Recently 2 prospective studies have used FOLFIRI as a second-line treatment (BEVANEC from Walter and NALIRI from McNamara).
Reply 2: We have included both BEVANEC and NALIRI.

Changes to text: A randomized trial compared FOLFIRI plus Bevacizumab (n=65) with FOLFIRI alone (n=68) in patients with GEP NEC. There was no difference in OS between the two groups. Another randomized study compared Nanoliposomal-Irinotecan (nal-IRI) plus 5-FU with Docetaxel in GEP NEC patients. Only nal-IRI/5-FU reached the threshold efficacy to be tested into phase-III trial. There is an unmet need in establishing a second line chemotherapy regimen in treating patients with NEC.

Comment 4. The authors state that surgery is reserved for NET G1-2. This is not correct and MUST be modified. All guidelines even NCCN, UpToDate and NANETS recommend surgery of resectable NET G3. For NEC all guidelines outside US recommend consideration of surgery if localized NEC- eg ENETS digestive NEC guidance paper (J Neuroend 2023). This is based on US data (A Dasari- in Cancer 2018 and Oncologist 2023) showing a 25-40% 5 y survival of patients with localized disease. Updated NANETS recommendations (ERC 2023) are also more open for considering surgery in NEC.

Reply 4: We have extensively modified the section on surgery.

Changes to text: Surgical resection has been well described in Grade 1 and Grade 2 PAN-NETs. Palliative debulking surgery in NECs remain controversial and in a systematic review conclusion on overall survival couldn't be drawn. A multicenter study among 60 patients with localized HG digestive NEN (72% NEC) showed an overall survival of 58.5% two years after radical surgery among the NEC sub-group. 5-year OS was better in surgical group compared to non-surgical group in a study (39% vs 10%) among 2245 patients with localized G3 digestive NEN.[33]. Radical surgery was associated with better overall survival compared to no surgery in localized NEC in a propensity analysis.

Comment 5. There are no data to support using SSA in NEC, not even in NET G3. This should be mentioned.

Reply 5: We modified the somatostatin section.

Changes to text: In contrast, NECs do not typically express SSTR, and use of SST analogues is questionable, and no data is available.

Minor comments:

1. NANETS 2010 guidance paper (4) could be replaced with NANATS 2023 recommendation (J Eds J: ERC 2023) and ENETS 2023 guidance (Sorbye H: J Neuroendo 2023).

Reply 1 and changes to text : NANETS 2010 is replaced by ENETS 2023.

2. Reference 18 is old and relevant for NET G1-2. There are several new publications of molecular characteristics of HG digestive NEN (se ENETS and NANETS papers from 2023).

Reply 2 and changes to text: We deleted the paragraph Scarpa et al.

3. The study of P Kunz (32) is for NET G1-2 and not G3- so not that relevant.

Reply 3 and changes in text: Deleted this reference.

4. Further studies on NET G3 that could be mentioned : Chan DL: Oncologist 2021, 26, 950-955 De Mestier L: ERC 2021, 28, 549-561

Reply 4: Added Chan DL study
Changes in text: A retrospective analysis showed an ORR of 41% in G3 NEN patients treated with CAPTEM. Additionally, another retrospective analysis among G3 NET patients showed a better OS and PFS with an alkylating-based regimen compared to platinum-etoposide

5. References 23 and 24 are old and not reliable.
Reply 5 and changes in text: Deleted both references.

6. Table 2 needs an update and should be restricted to NET G3 and NEC studies. NALIRI study (no 5 on list) has been published. Basket studies are not that relevant, as few NEC are included in such studies.
Reply 6 and changes in text: We have now restricted table 2 top only studies involving NEC, removed NALIRI, Deleted basket studies.

Reviewer C

I am adding some suggestions to improve content of this manuscript:

Comment 1: Line 50 of the introduction mentions rapid evolution of understanding and treatment for high grade NETs. In the conclusion, the authors state that there is a deficit of innovative treatment strategies. I would agree on the latter. I would advise to alter the initial statement, as while the understanding may have improved, there is still a lot of work to be done in relation to better treatment options.
Reply 1: Line 50 has been modified.
Changes in text: Over the past decade, there has been a rapid evolution in our understanding of high-grade NENs but we lack innovative treatment strategies

Comment 2: In describing the molecular landscape, please reference Yachida S et al Cancer Discovery 2022, 12: 692-711 which describes the genomic alterations during tumour progression and speaks about pancreatic NEC and NET. Please also include some text summarising these findings.
Reply 2: Added Yachida et al
Changes in text: Also, PAN-NECs could be classified into ductal and acinar types based on the genomic profiling. CDKN2A silencing and alteration of WNT signaling are the commonly seen genomic alterations in acinar type in contrast to ductal type that involves KRAS mutation.

Comment 3: In section relating to surgery, the authors state that surgery is reserved for grade 1 and grade 2 PAN NENs. I don't agree. There are select situations where surgery may be considered for those with grade 3 disease. Please discuss and reference Dasari A et al 2022, Oncologist, 27: 299-306 - paper about role of surgery in these patients.
Reply 3: Added dasari et al

Changes in text: Finally, a survival analysis showed a trend toward improvement in overall survival in patients with GEP-NEC treated with local resection.

Comment 4: In relation to reference 27, are the authors sure that there were only 11 patients in this study? Or was it 11 with pancreatic primaries specifically? Please check and alter as necessary.
Reply 4: Modified the sentence
Changes in text: 11 patients with pancreatic primary.

Comment 5: In the chemotherapy section, please add some details about the phase 3 randomised trial of Irinotecan/Cis vs platinum/etoposide - Morizane C et al 2022, JAMA Oncol 8: 1447-1455.
Reply 5: Added the suggested reference.

Changes in text: TOPIC-NEC randomized 170 digestive NEC patients into irinotecan and cisplatin regimen vs etoposide and cisplatin regimen. OS was similar in both groups however G3 and G4 adverse effects were more common in etoposide group

Comment 6: What about second line chemotherapy options - FOLFIRI/FOLFOX, nal-IRI/5-FU. Please discuss and reference McNamara MG et al 2023, eClinical Medicine (NET-02 second-line trial) and Walter T et al 2023 BEVANEC study (Lancet Oncology) FOLFIRI vs FOLFIRI/Bev.
Reply 6: Added both references
Changes in text: A randomized trial compared FOLFIRI plus Bevacizumab (n=65) with FOLFIRI alone (n=68) in patients with GEP NEC. There was no difference in OS between the two groups. Another randomized study compared Nanoliposomal-Irinotecan (nal-IRI) plus 5-FU with Docetaxel in GEP NEC patients. Only nal-IRI/5-FU reached the threshold efficacy to be tested in phase-III trial. There is an unmet need to establish a second-line chemotherapy regimen in treating patients with NEC

Comment 7: In section on immunotherapy, please also discuss Patel SP et al 2021 Cancer, 127: 3194-3201.
Reply 7: Added the reference
Changes in text: In addition, A prospective trial showed an ORR of 26% in HG NEN patients who were treated with ipilimumab plus nivolumab. A total of 19 patients were included in the HG NEN cohort among which 11% were pancreatic primary.

Comment 8: In section on sunitinib, please add line of therapy for studies mentioned.
Reply 8: Added line of therapy details
Changes in text: Among these 35 patients, 9 patients did not receive prior chemotherapy, 18 patients had 1 to 2 lines of chemotherapy and 8 patients received 3 to 4 lines of chemotherapy before initiating somatostatin analogues. In this study, a total of 19 patients received somatostatin analogues among which it was first-line treatment in 16 patients and second-line in the remaining

Comment 9: In relation to PRRT, please add that use of PRRT in the grade 3 setting is not approved in many countries and trial enrolment is recommended.
Reply 9: Mentioned the above detail
Changes in text: It is important to note that PRRT for G3 NET is not approved in many countries and trial enrollment is recommended.

Comment 10: For table 2, can you also add a column to describe line of therapy for each study. First-line, second-line, many previous lines?
Reply 10 and changes in text: A separate column with line of therapy is now included.

Comment 11:Please include a treatment algorithm figure, including potential treatment options and recommendations at various lines of therapy.
Please also review ESMO guidelines on treatment of these patients by Pavel M et al.
Reply 11 and changes in text: We have included a treatment algorithm figure,

Comment 12: You have included very little, if anything, on molecular profiling in this disease and the potential utility of this in the future. Please reference Frizziero M et al, Clinical Cancer Research 2022, 28: 1999-2019, at least, and summarise the data available in this field of study.
Reply 12: Frizziero et al is added
Changes in text: Genomic aberrations in TP53 and RB1 genes are frequently observed in extrapulmonary NEN (EP-NEN)