

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: Interesting well presented manuscript; however, the authors should also underline the need to evaluate the response to the different types of treatment and the relative criteria; for this purpose the authors should discuss this topic and use as reference the following paper: Current imaging evaluation of tumor response to advanced medical treatment in metastatic renal-cell carcinoma: Clinical implications; Caruso M, Romeo V., Stanzione A, Buonerba C, Di Lorenzo G, Maurea, S. Applied Sciences (Switzerland), 2021, 11(15), 6930. Furthermore, the possibility that with pancreatic neuroendocrine tumors may also occur other type of tumors should be underlined with treatment implications; for this topic, the authors may cite the following paper: Maurea S, Corvino A, Imbriaco M, Avitabile G, Mainenti P, Camera L, Galizia G, Salvatore M. Simultaneous non-functioning neuroendocrine carcinoma of the pancreas and extra-hepatic cholangiocarcinoma. A case of early diagnosis and favorable post-surgical outcome. JOP. 2011 May 6;12(3):255-8. PMID: 21546703.

Question 1: however, the authors should also underline the need to evaluate the response to the different types of treatment and the relative criteria; for this purpose the authors should discuss this topic and use as reference the following paper: Current imaging evaluation of tumor response to advanced medical treatment in metastatic renal-cell carcinoma: Clinical implications; Caruso M, Romeo V., Stanzione A, Buonerba C, Di Lorenzo G, Maurea, S. Applied Sciences (Switzerland), 2021, 11(15), 6930.

Answer: Thanks the first reviewer for his comments. The reviewer suggested that we should emphasize the methods and criteria for evaluating the efficacy of different treatments, and suggested a reference to an article on kidney cancer, but the main content of our manuscript is a review of the latest clinical and basic advances in the medical treatment of pancreatic neuroendocrine tumors. The imaging criteria and radiomic and efficacy assessment methods mentioned by the reviewer are not the scope of our review. The reviewers' suggestions will inform our future research directions, but are not particularly appropriate for the revision of this article.

Question 2: Furthermore, the possibility that with pancreatic neuroendocrine tumors may also occur other type of tumors should be underlined with treatment implications; for this topic, the authors may cite the following paper: Maurea S, Corvino A, Imbriaco M, Avitabile G, Mainenti P, Camera L, Galizia G, Salvatore M. Simultaneous non-functioning neuroendocrine carcinoma of the pancreas and extra-hepatic cholangiocarcinoma. A case of early diagnosis and favorable post-surgical outcome. JOP. 2011 May 6;12(3):255-8. PMID:

21546703.

Answer: The reviewer also suggested that the article we should refer to is a case report of hepatobiliary duct carcinoma combined with non-functional pancreatic neuroendocrine carcinoma, and suggested that we emphasize the therapeutic implications of pancreatic neuroendocrine tumors occurring in other types of tumors. We carefully read the article mentioned by the reviewer, but the case report concluded that the occurrence of pancreatic neuroendocrine carcinoma was not associated with hepatobiliary duct carcinoma and recommended the use of MRI for early and accurate diagnosis. We also searched for articles on pancreatic endocrine tumors combined with other types of tumors (except MEN-1 syndrome), and most of them were case reports, and basically no association between tumorigenesis and treatment was suggested, so we thought we could leave this part out of the manuscript for now.

Reviewer #2:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: Thank you for giving me the opportunity to review this interesting article. The authors summarized the recent findings and future perspectives regarding medical treatment for pancreatic neuroendocrine neoplasms (PanNENs). Overall, this review is well-written and presented in a timely fashion. I think the different aspects discussed in the review should be informative for readership of the journal because treatment for PanNENs is evolving rapidly. I would like to point out some minor issues and attach the Reviewer's comments as below.

1. The authors should use the term 'PanNEN' or 'PanNET' based on WHO 2019 classification, not 'pNEN' or 'pNET'.
2. There are some minor mistakes in the figure of molecular mechanisms of treatment for PanNENs. The number of this figure is 'Figure 2', not 'Figure 1'. 'Metfoemin' should be corrected to 'Metformin'.
3. The clinical practice guidelines for GEP-NENs in Japan as well as in China have recently been revised. Therefore, I recommend adding the following papers to the references to better reflect the real-world situation in Asia: Ito T, et al. *J Gastroenterol* 2021, 56, 1033-1044, doi: 10.1007/s00535-021-01827-7. Hijioka S, et al. *Jpn J Clin Oncol* 2021, 51, 1185-1196, doi: 10.1093/jjco/hyab076.

Question 1: The authors should use the term 'PanNEN' or 'PanNET' based on WHO 2019 classification, not 'pNEN' or 'pNET'.

Answer: We have changed 'pNEN' or 'pNET' to 'PanNEN' or 'PanNET' in manuscript .

Question 2: There are some minor mistakes in the figure of molecular mechanisms of treatment for PanNENs. The number of this figure is 'Figure 2', not 'Figure 1'. 'Metfoemin' should be corrected to 'Metformin'.

Answer: We have corrected the 'Metfoemin' to 'Metformin' in the 'Figure 2'.

Question 3: The clinical practice guidelines for GEP-NENs in Japan as well as in China have recently been revised. Therefore, I recommend adding the following papers to the references to better reflect the real-world situation in Asia: Ito T, et al. J Gastroenterol 2021, 56, 1033-1044, doi: 10.1007/s00535-021-01827-7. Hijioka S, et al. Jpn J Clin Oncol 2021, 51, 1185-1196, doi: 10.1093/jjco/hyab076.

Answer: Related description was added :#1 The Japan Clinical Oncology Group (JCOG) is also conducting a multicenter, randomized, controlled, phase III trial (jRCT1031200023) to confirm the superiority of combined everolimus plus lanreotide therapy over everolimus monotherapy for advanced GEP-NETs. #2 Peptide receptor radionuclide therapy (PRRT) has been widely used in the treatment of NETs in Europe, the USA and Asia. And I added the papers mentioned by reviewer to the references 50 and 76.