Peer Review File

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Review Comments

Comment 1: In the present manuscript, Liu and colleagues retrospectively analyzed 73 patients with non-functioning (NF) neuroendocrine neoplasms of the pancreas (pNEN) who underwent resection between 2012 and 2017 and mainly compared 28 T1 pNEN (<2cm) with 45 pNEN larger than 2 cm (T2-T4). They found that "3 patients with small NF-PNETs had malignant behaviors". The "clinically significant pancreatic fistula rate" was 25%. Additionally, grade and lymphovascular invasion were shown to be a significant risk factor in multivariate analysis, while in univariate analysis male gender, perineural invasion as well as size >2cm were associated with worst survival. The authors concluded that "the cut off tumor size of 2 cm was not effective in predicting the malignancy of NF-PNETs." The paper is carefully compiled. Unfortunately, the patient population is too small (n=28 according to the title) and the follow-up to short (less than 5 years) in order to draw any clinical relevant conclusions (Conclusion is not supported by the data). Recent (not cited!) studies have shown on 3243 pNEN patients, that resection of pNEN <2cm was associated with better survival compared to watch-and-wait (Chivukula et al, Surgery, 2020, PMID 31537303) and that resection of 1-2 cm pNEN lead to significant better survival compared to surveillance while tumors below 1 cm did not benefit from resection (Assi et al, The oncologist, 2020, PMID: 32043766).

Reply 1. We would like to thank the reviewer for evaluating our manuscript and providing useful comments. We have modified the inappropriate conclusion according to your advice. However, we have to admit that small sample size and short follow-up were the limitations of the present study, probably due to the low incidence of this tumor entity. We also look forward to further prospective, randomized controlled trials or retrospective studies with large sample sizes in the future. (see Page 13, line 8-14).

Changes in the text: Despite its limitations, the current study showed that small NF-PNETs are not immune from potential malignancy compared to NF-PNETs >2 cm, and surgical resection may be considered and can present favorable postoperative and long-term outcomes for small tumors. Parenchyma-sparing pancreatectomy may be an alternative for selected small local NF-PNETs. Further research is needed to confirm whether surgery is beneficial for small NF-PNETs of different tumor size groups than nonsurgical management.

Comment 2: The paper needs native English editing and needs to be shortened significantly, particularly the discussion and the results also.

Reply 2: Thank you for the suggestion. According to your suggestion, we have substantially simplified the manuscript, and it has been polished by two professional English editors before resubmission.

Comment 3: The reference list needs to be updated.

Reply 3: Thanks for this precious comment. We have updated our reference list to include more relevant literature and added the related result of the reference study in the Discussion (see Page

10, line 14-17, and Page 16, line 18-23).
Changes in the text: Recently, published studies with large sample size have indicated that the resection of PNETs ≤2 cm is associated with better survival than observation, and surgery result in significantly better survival in patients with PNETs 1-2 cm but not those with PNETS <1 cm (29,30).

Comment 4: All pNEN are potentially malignant! The word "malignancy" should be replaced by metastasized or defined with recurrence free survival.
Reply 4: We completely agree with you that all PNETs are potentially malignant. According to the previous studies, the malignancy of NF-PNETs was defined based on the presence of tumor recurrence, nodal or distant metastases (synchronous or metachronous) in our study (see Page 9, Line 3-5).
Changes in the text: For this reason, malignancy in NF-PNETs was defined as the existence of tumor recurrence or nodal/distant metastasis (synchronous or metachronous) in the present study.

Comment 5: Significant differences in outcome comparing T-stage has been already shown in many papers (ENETS/AJCC TNM classification).
Reply 5: We appreciate your kind suggestion and comment. We must apologize for this stupid mistake and we have modified the error description in the article (see Page 9, Line 6-10).
Changes in the text: Primary tumor size is associated with clinical T-stages criteria according to the ENETs/ American Joint Committee on Cancer (AJCC) TNM classification staging system. Significant differences in outcome comparing T-stage has been shown in many previously published papers and 2 cm has been widely adopted as the cutoff point in determining the biologic features of NF-PNETS (22).

Comment 6: Introduction, line 20: ENETS guidelines (2017) should be cited.
Reply 6: Thanks for this necessary suggestion. We have cited ENETS guidelines (2017) in the introduction and discussion section (see Page 10, Line 7-11).
Changes in the text: Controversy exists regarding the choice between active resection and conservative observation for patients with small NF-PNETs. ENETS guidelines recommend surgical resection for patients with small NF-PNETs, and observation for young patients who have small NF-PNETs <2 cm affected by MEN1 syndrome or those who have a severe comorbidity and are ineligible for surgery (11).

Comment 7: Results: Ki67% should be provided.
Reply 7: Thanks for this kind suggestion. We have added the data of Ki-67 index in table 1 and results (see Page 7, Line 6-7).
Changes in the text: The Ki-67 index was apparently lower in small NF-PNETs than in large NF-PNETs (P<0.001).

Comment 8: Tables: In table 1 G3 NET and G3 NEC were separated while all G3 were combined in table 4, in which pNEN of all sizes are put together but also needs to be seperated.
Reply 8: Thank you for bringing them to our attention. We are so sorry for the confusion. We

have separated G3 NET and G3 NEC and divided all tumors into small and large group in Table 4 (see Table 4).