

Dear Editor,

Thank you for informing us of the results of the peer-review process for our submitted invited review article.

We would like to extend our gratitude to the members of the reviewer board who spent their time reviewing our work – we are impressed by the number of reviewers who contributed to this process.

Please find below our responses to each of the reviewers' comments.

Furthermore, please find the requisite emendations to the article in the attached revised manuscript.

We hope that this second iteration of the review article is acceptable for publication.

On behalf of both authors,

Yours sincerely,

Dr Ashley K. Clift

Reviewer #01559615

This is an excellent review paper coming from England. Current knowledge on the topic is well collected and presented. The selection criteria of liver transplantation treatment for patient with NET metastasis (especially to the liver) are clearly answered in the text. In addition, all areas of conflict in the field are briefly discussed.

We thank the reviewer for their kind comments regarding our work – we are pleased to receive this positive feedback, and hope that future readers will think similarly regarding this revised manuscript.

Reviewer #00054120

Thank you for submitting this outstanding review, I enjoyed reading it and I am sure the health care providers who take care of these cases will find it valuable for their practice and will enrich their knowledge.

We humbly thank this reviewer for their positive appraisal of our work.

Reviewer #00071178

Authors described a review on liver transplantation for NETs metastasised to the liver. I would like to learn about the authors' views on postoperative immunosuppressive treatment protocols. In other words, will there be a difference between the immunosuppressive treatment protocols of these patients and the immunosuppressive treatment protocols of HCC patients? The manuscript should be prepared according to the format of the WJG

We thank this reviewer for their comments, and for raising the issue of post-transplant immunosuppression. However, we are slightly bemused at the grading of language quality as needing 'a great deal of polishing' (in the online scoring data) – we cannot identify such issues.

In our initial manuscript, we briefly discussed the possible roles of adjuvant therapy, but did not discuss post-transplant immunosuppression in as much detail. We have added some data to the manuscript stating that immunosuppression strategies post-OLT for NET are not dissimilar to those for HCC. However, there is evidence to suggest that modifications to this, such as addition of NET targeting agents, i.e. mTOR inhibitors may be useful additions to this armoury on the basis of their anti-proliferative effects shown in advanced NET (Yao JC, et al. NEJM 2011). We hope that the

reviewer and editorial board are in agreement with these changes. Lastly, we have followed the advice of the editors with regards to the formatting of our article.

Reviewer #01221925

This is an interesting paper reviewing the role of liver transplantation in the management of neuroendocrine tumors. The authors very correctly point out the significant challenges involved in the assessment of the different studies given the significant variability both in the type of disease as well as in the management. 1) The authors may wish to offer a clear comparison between liver transplantation used for neuroendocrine tumors vs for other indications, in the sense that if the outcomes are not as good with neuroendocrine tumors as with the other indications, then it is hard to justify the use of a limited resource. Additionally, the authors may wish to comment on the possible use of extended criteria donors. 2) Could the authors elaborate more on their suggestion of the use of the Milan criteria for these patients?

We thank this reviewer for raising a number of points, which we are happy to address. Regarding the indications for transplantation in NET vs. HCC, we felt that the comparison of selection criteria in Table 2 served this end. However, to make our intentions clearer, we have added a brief additional section to this on the relevant part of the revised manuscript. As we discussed in the first manuscript, studies have found OLT in NET to have comparable outcomes to that for HCC (Fan ST, et al. HPB 2015). Regarding the use of Milan criteria – there are two separate sets of criteria, which again are detailed in Table 2 – one is only applicable for HCC, and one that applicable only in NET.

Reviewer #00504591

Clift and Frilling described a review on liver transplantation for neuroendocrine tumors. I have some comments. 1. What is suggested the paragraph with italic letters? Is it a summary? It is not necessary. 2. The section “Orthotopic liver transplantation” is long which should be divided with subsections. 3. Is there some role of chemotherapy before liver transplantation?

We thank the reviewer for their comments. In view of some sections of the review being long and discussing many studies (as this reviewer alludes to in their second point), we wished to provide readers with a small, digestible summary to reinforce the key messages of each section. We would like to leave it to the editor’s discretion to consider whether or not to omit these short paragraphs from the manuscript.

According to their critique, we have inserted some sub-sections in the “orthotopic liver transplantation” component.

Lastly, whilst we discussed neoadjuvant concepts (i.e. therapy prior to liver transplantation) in the initial manuscript, we did not detail specific roles of specific chemotherapy agents. There are at present no cytotoxic chemotherapy-based neoadjuvant concepts for transplantation in NET. Of note, the response of NET to chemotherapy is limited, except in some cases of pancreatic NET. For small bowel NET, neoadjuvant ¹⁷⁷Lu-PRRT may be an option, as this has been shown to be useful in downstaging tumours prior to liver resection, and also in a case report of multivisceral transplantation (Frilling A, et al. Transpl Proc 2013). We have partially rephrased the relevant section of the revised manuscript to make this clearer.