Dear Editor-in-Chief, World Journal of Hepatology

Name of journal: *World Journal of Hepatology*

ESPS Manuscript NO: 10772

Columns: Minireviews

Member ID: 01560498 WJH

(Peer Reviewer of World Journal of Hepatology)

Manuscript title: Pancreatic neuroendocrine tumor accompanied with multiple liver metastases

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Thank you for your valuable suggestions.

According to your suggestions, we carefully revised our initial manuscritpt. Revised points were shown in red (Marked revised manuscript). We also prepared clear version (Clear revised manuscript).
Also, we made point-by-point responses, separately.

Please review our revised manuscript.

If something is wrong, please do not hesitate to contact me by e-mail.

Sincerely yours,

Tomohide Hori, PhD., MD.
Peer Reviewer of World Journal of Hepatology

To reviewer 1

Thank you for your valuable suggestions.
According to your suggestion, we revised our initial manuscript.

1. In the chapter on management of unresectable liver metastases

Thank you for your valuable suggestion that two important therapeutic options are missing for unresectable liver metastases.

Reviewer# 2 also suggested that therapeutic options for unresectable liver metastasis, especially peptide receptor radionuclide therapy (PRRT) and transarterial radioembolisation (i.e., selective internal radiotherapy [SIRT]).

According to your suggestion, we added the chapter for therapeutic option for unresectable liver metastasis, and innovative therapies (PRRT and SIRT) were mentioned in the revised manuscript. New references are listed in the revised manuscript.

2. Histological details in our regretful case

Thank you for your valuable suggestion.

The tumor was histopathologically well-differentiated and the Ki-67 index was < 10%.

According to yours suggestion, we added the histological details in this paper.

To reviewer 2

Thank you for your valuable suggestions.

According to your suggestions, we revised our initial manuscript.

1. A better characterization of the neuroendocrine tumor

Thank you for your valuable suggestion.

According to yours suggestion, we added the mentions as ‘In particular, Ki67 expression has been considered as a prognostic factor of risk of recurrence[21,24,28]. A Ki67 proliferation index of <10% is a characteristic of well-differentiated tumor, which we have adopted as a cut-off value to consider GEP-NET patients for LT candidates[21,24].’. In our case, the tumor

was histopathologically well-differentiated and the Ki-67 index was < 10%. According to yours suggestion, we added the histological details in this paper.

2. LT for uresectable liver metastases

Thank you for your valuable suggestions.

According to yours suggestion, we added the mentions as 'The Milan Criteria is maybe a better definition of selection criteria for LT[21]. In the last decade, selection criteria based on clinical presentation have been integrated with a proper histopathologic classification and diagnostic techniques[21]. In particular, Ki67 expression has been considered as a prognostic factor of risk of recurrence[21,24,28]. A Ki67 proliferation index of <10% is a characteristic of well-differentiated tumor, which we have adopted as a cut-off value to consider GEP-NET patients for LT candidates[21,24].'.

In Discussion section, we added the mentions about the LT for P-NET with important references, as 'In LT for P-NET patients, previous excellent reports focused on a prognostic factors for overall survival, a post-transplant risk of recurrence, a better selection criteria, a difference between P-NET and others, and an importance of the post-transplant surveillance[21,24,28]. There is a difference in behaviors between P-NET and the other tumors, the indication for LT for unresectable liver metastases is

unique for P-NET[21,24]. Also, an importance of careful surveillance after LT due to the risk of recurrence was documented[21,24]. Tumor re-staging should be scheduled at least 4 times per year for the first two years and continued thereafter with progressively longer follow-up intervals[21].

3. Resection of primary tumor before LT

Thank you for your valuable suggestions.

According to yours suggestion, we added the mentions as 'As described above, primary tumor should be removed before LT. However, optimal timing for LT in patients with stable versus progressive disease remains unclear[20]. In previous report, 83% of patients had undergone surgical treatment for primary tumor, and a 5-year overall survival has increased to 59% in relation with fewer patients presenting poor prognostic factors[20]. Favorable outcomes in cases of unknown primary tumor might suggest that a failure to detect the primary tumor before LT should not be considered as an absolute contraindication[20].'

4. Discussion section

Thank you for your valuable suggestion.

According to yours suggestion, we added mentions and new references as

‘novel managements (i.e., PRRT and SIRT) are currently available for unresectable liver metastases, with acceptable side effects[29-34]. Effective and beneficial treatment options for P-NET patients with liver metastases should be carefully considered.’.

Also, we added the mentions about the LT for P-NET with important references, as ‘In LT for P-NET patients, previous excellent reports focused on a prognostic factors for overall survival, a post-transplant risk of recurrence, a better selection criteria, a difference between P-NET and others, and an importance of the post-transplant surveillance[21,24,28]. There is a difference in behaviors between P-NET and the other tumors, the indication for LT for unresectable liver metastases is unique for P-NET[21,24]. Also, an importance of careful surveillance after LT due to the risk of recurrence was documented[21,24]. Tumor re-staging should be scheduled at least 4 times per year for the first two years and continued thereafter with progressively longer follow-up intervals[21].’

We understand that our case is just a personal experience. Then, we added a mention as ‘Though we understand that any decisions cannot be made based on a single patient experience, ・・・’

5. Important optional therapies (PRRT and SIRT)

Thank you for your suggestion.

Reviewer# 1 also suggested that therapeutic options for unresectable liver

metastasis, especially peptide receptor radionuclide therapy (PRRT) and transarterial radioembolisation (i.e., selective internal radiotherapy [SIRT]).

According to your suggestion, we added the chapter for therapeutic option for unresectable liver metastasis, and an innovative therapies (PRRT and SIRT) were mentioned in the revised manuscript. New references are listed in the revised manuscript.