

ANSWERING REVIEWERS



April 23, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 10316-review.doc).

Title: Role of surgery and transplantation in the treatment of hepatic metastases from neuroendocrine tumor

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 10316

The manuscript has been improved according to the suggestions of reviewers:

Reviewer 1:

1) The title does not reflect the content of the manuscript in that other local-regional therapies are reviewed along with resection and transplantation. For accuracy and to avoid bias, the title should be changed to more accurately reflect the content.

The recently published literature with reviews of the ELTR and UNOS database on liver transplantation for hepatic metastases of neuro-endocrine tumors suggest that transplantation could also be offered as a line of management in these group of patients. The title aims to emphasize that transplantation should also be considered as a treatment option in these patients and the management of such patients should be considered in centers where the entire array of management is available under one roof. The purpose of reviewing loco-regional therapies is that they are used as adjunct to the surgical therapies and are used to treat recurrences post surgery. Also the emphasis on systemic therapies to stabilise the disease when the patient is being considered for transplant.

2) The issue of patient selection and inherent limitations in evaluating contemporary practice must be acknowledged. Survival rates are compared based upon retrospective/experiential studies which are inherently limited by alterations in patient selection. This is known to result in selection of patients with varying tumor burdens, grade/stage, tumor types, and center experience or preference.

The need for standardized prospective trials and the alterations in patient selection have been mentioned. The wide variety of treatment algorithms and the inherent inadequacy of retrospective studies have also been mentioned.

3) Further detail must be provided when reviewing some of the experiences in the literature. It is very clear for example, that neuroendocrine tumors can vary widely with respect to risk of overall progression. This is particularly notable for cases of carcinoid vs. other NETs. This is briefly eluded in the last section on systemic therapy, but is

entirely disregarded in the earlier sections on other local-regional therapies (ablation, surgery, transplant, TACE). Mention is made of grade being important with respect to transplant, however no information is provided about influence of these factors on expected outcomes with surgery, RFA, and other modalities. Recommendations for surgery in the discussion and conclusion must therefore be tempered by the underlying biology and tumor type. Other reviews and experiences certainly recommend a more circumspect approach for example to patients with metastatic carcinoid or disease not able to undergo an R0 resection for low grade who can otherwise experience a very long, symptom-free long term survival.

The manuscript has been revised to incorporate the changes in management of these tumors with respect to the underlying tumor grade and biology. The conclusion has also been tempered to include the biology and type of tumor.

4) The tables need to be clarified in that some data cells contain units with “months” whereas others do not. The cells should be consistent or if no room, then footnote should be provided as to what units the data reflect.

The tables have been checked, and the corresponding units have been edited. Footnote has also been provided for certain cells where the data cannot be presented within the cell.

5) While the manuscript is generally very readable, there are some grammar and word choice errors that should be corrected.

The grammar and word choice errors have been corrected.

Reviewer 2:

1. This is a clear and well-written review article and will have significant impact on this specific and rare condition of neoplasm.

2. There is a need to give an abstract of this review.

Abstract has been written.

3. Although English is well written, there are still some typo mistakes that need to be addressed. For examples, on page 1 in the introduction section, line 8 from the bottom, “NEC” should be “NET”. On page 5 line 2, “NE” should be “NET”. One page 8 line 6, “multi-centric” may be “multi-centre” etc.

The mistakes have been corrected and the entire article has been checked for errors.

4. There is no page number.

Pages have been numbered.

5. Tables 2.1, Table 3.1 and Table 4.1 should label as Table 2, Table 3 and Table 4. In addition, there are no indications of where these tables should be placed in the text, although it is clear each table belongs to each chapter of the article.

The tables have been relabeled, and the specific references have been made in the text.

References and typesetting have been corrected and the format has been updated.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,