Author's response to reviews

Title: Biological Characteristics and Treatment Outcomes of Metastatic or Recurrent Neuroendocrine Tumors: Tumor Grade and Metastatic Site is Important for Treatment Strategy.

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Author's response to reviews: see over
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Dear Editor-in-chief,

Manuscript number: 1635118227333033

We wish to express our gratitude to you and the reviewers for the careful review of our manuscript entitled “Biological Characteristics and Treatment Outcomes of Metastatic or Recurrent Neuroendocrine Tumors: Tumor Grade and Metastatic Site is Important for Treatment Strategy”. We have tried to revise our manuscript based on the reviewers’ comments. Here we have addressed the concerns of the reviewers on separate pages, as well as our responses to specific comments. I hope that you and reviewers will find these alterations satisfactory. We look forward to having our manuscript published in *BMC cancer*.

Best wishes,

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Version 1 date 2010-06-01

We would like to thank the reviewers for their helpful comments and hope that we have now produced a more balanced and better account of our work. We revised the manuscript and yellow highlighted lines were marked in revised text. The followings are the comments of the reviewers and our responses to specific comments.
Reviewer #1:

**Reviewer:** Ursula Plöckinger

**Major considerations**

1. This is no homogenous enough tumour cohort for proper analysis

   ➤ The reviewer’s comment is definitely right. The reviewer pointed out appropriate and important weak point of our study.
   We also have concerned that the data pool was heterogeneous and the used regimens were too diverse to make a solid conclusion. We added a mention about it according to the reviewer’s concern in the text. (page 17, line 3-5: “And the data pool was heterogeneous and the used regimens were diverse, even though the relative rarity of NETs makes it difficult to collect sufficient numbers of homogenous groups.”)

   However, neuroendocrine tumor (NET) is very heterogeneous tumor which can derive from any parts of human body. And the relative rarity of NETs makes it difficult to collect sufficient numbers of homogenous groups. Furthermore, the used systemic regimens have not been satisfactory at all till now except recent some targeted agents. So the analysis of these patient pool is heterogenous in itself.

   Thank you for the concern raised by the reviewer for further improvement of our manuscript.

2. The grading should refer to the suggestions from the WHO on endocrine tumours which are still widely in use. Alternatively ENETS criteria could be used and compared

   ➤ The reviewer mentioned good point.
   Yes, there is a grading system for gastroenteropancreatic NET that was suggested by WHO. However, the grading system is not compatible with grading system in lung NET (typical carcinoid, atypical carcinoid, large cell neuroendocrine carcinoma, small cell lung cancer). For this reason and because our data dealt with NETs from all sites of body, we followed the analysis method used in the SEER report, which included NETs from most sites and classified NETs into 4 grade groups (Grade 1-4).

   The paragraph below is a part of text of the SEER report in US.
   “There is no accepted uniformed grading system for malignant NETs. Pathologists in the United States typically use the terms “carcinoid tumor” or “islet-cell tumor” to denote well-differentiated NETs (G1). The term “atypical carcinoid” is frequently used to describe a moderately differentiated
carcinoid and is classified as G2 tumor, poorly differentiated tumors are classified as G3 tumors, and anaplastic tumors are classified as G4 tumors. Tumors with mixed differentiation, such as adenocarcinoid and goblet-cell carcinoid tumors, are classified as having mixed histology.

So in our study population, the application of WHO or ENET criteria is somewhat difficult. But, we fully agree with the reviewer’s concern on grading system we used. So we added the sentence on the grading system and discussed on it in the text.

3. Ki67, regarded as the most important factor for prognosis and therapeutic efficacy is not even mentioned

Yes, the reviewer’s comment is right and important. Ki67 is regarded as the most important prognostic factor for long-term survival of patients with NET. We added the sentence on the importance of Ki67 and the limitation of our study which lacks the information of Ki67.

So we added the sentence on importance of Ki67. (page 17, line 6-9: Other limitation is that we did not analyze the prognosis and response to systemic treatment according to the Ki67 status of tumors. The Ki67 is being regarded as an important prognostic factor which demonstrates the proliferative capacity of tumors. In our patient pool, there was no available full data on Ki67.) And, one reference was added about role of Ki-67. (*Endocr Relat Cancer* 2007, 14(2):221-232.)

And we also added the sentence of stressing the necessity of Ki67 and Chromogranin A in future NET studies. (page 17, line 11-12: “Further study on NET should harbor the contents of Ki67 and chromogranin A.”)
4. No data on Chromogranin A are available

⇒ The reviewer’s comment is adequate and important.
We did not have any data about serum chromogranin A, because this was a retrospective research composed of patients from 1996, and the importance of serum chromogranin A is recently being highlighted.

We added the sentence about Chromogranin A according to reviewer’s comment.

(page 17, line 9-12: “Furthermore, we did not have data about serum chromogranin A, of which the clinical meaning and importance are being highlighted nowadays, because this study was a retrospective research composed of patients from 1996. Further study on NET should harbor the contents of Ki67 and chromogranin A.”)

5. In such a mixed cohort of tumours comparison of different treatment schemes given unrelated to the tumour treated is no sensitive way to analyse treatment effects

⇒ We fully agree with the concern of reviewer. This gives a limitation to the meanings from our study. If the homogenous cohort can be driven among all NETs with same treatment schemes, the derived information can be more solid.

However, considering the relative rarity of NETs (it is difficult to collect sufficient numbers of homogenous groups) and furthermore, rarity of unified treatment guidelines, our study can give an information on the treatment strategy to the physicians dealing with this heterogenous tumor.
Minor consideration

1. The text is too long

- We shorten the text in some degree according to the reviewer’s comment.(page 8, line 7, 10-11; page 9, line 4).

2. Results are reported in the text and in the tables

- We deleted several sentences that were too descriptive and the content of which were included in the tables or figures according to the reviewer’s comment. (page 8, line 7, 10-11; page 9, line 4).

3. In the figures the y axis should indicate overall survival instead of Probability of event-free

- We changed them according to the reviewer’s comment.

4. The English should be improved

- We received English proofreading service.
Reviewer #2:

**Reviewer's report**

**Version:** 1 **Date:** 11 February 2010  
**Reviewer:** Aaron R Sasson

**Reviewer's report:**

The manuscript by Kim et al is a retrospective review of 103 patients with neuroendocrine tumors of a wide variety of sites, but mostly from the gastrointestinal tract. They studied various prognostic factors as well as natural history and treatment of metastatic neuroendocrine tumors. They found, as did other studies, that grade is the most important factor for determining the biology of these tumors, as is the impact of having metastatic disease to the liver. In the treatment of metastatic disease, the authors’ utilized a wide variety of treatment options, making it difficult to obtain conclusions based on the optimal treatment modality. However, due to the nature of this disease, this is not uncommon in many publications. I thought the manuscript was well written and worthy of publication.

The only concern I had was on in the discussion session on page 16, line number 4. The authors incorrectly report the favorable use of somatostatin analogues in well-differentiated gastroenteropancreatic neuroendocrine tumors, that is incorrect. The study cited only used patients with mid gut neuroendocrine tumors and excluded pancreatic tumors. This was the only point that required a revision.

Response:

⇒ The comment of reviewer is absolutely right.

We have corrected “gastroenteropancreatic” to “midgut” according to reviewer’s comment.  
(page 16, line 6, “after use of somatostatin analogues in well-differentiated midgut NET”)
Reviewer #3:

**Reviewer's report**

**Version:** 1  **Date:** 24 April 2010  
**Reviewer:** Darryl Shibata

**Reviewer's report:**

The authors present a study of recurrent/metastatic of NETs in Korea. They primarily present the clinical characteristics associated with different outcomes. A weakness of the manuscript is the very heterogeneous groups of NETs from multiple different anatomical sites. Although this is a drawback, the relative rarity of NETs makes it difficult to collect sufficient numbers of homogenous groups. Overall the manuscript provides useful information on NETs, and documents the clinical characteristics for these rare tumors in Korea.

⇒ We thank the reviewer for favorable review and comments.