

September 22, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 13045-review.doc).

**Title:** Mixed adenoneuroendocrine carcinoma of the ampulla: Two Case Reports

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**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 13045

The manuscript has been improved according to the suggestions of reviewers:  
1 Format has been updated.

2 Revision has been made according to the suggestions of the reviewer.

(1) I have gotten a copyediting service provided by Jing-Yun Ma Expert Group, and now the paper has reached grade A in language evaluation.

(2) According to the editor's suggestions, the abbreviations and acronyms and comments were added. According to the suggestion offered by 00722213, all corrections have been made.

(3) The responses to the reviewer's comments (02541992) are as follows:

1). Response to comment: (Why a pancreaticoduodenectomy? Why somatostatin? Is the neuroendocrine component the most aggressive?)

Response: As in our cases, the preoperative biopsy showed poorly differentiated adenocarcinoma and imaging showed no distant metastasis. We chose pancreaticoduodenectomy as the preferred treatment based on the results of biopsy and imaging examination. Pancreaticoduodenectomy is an optimal surgical approach for ampulla cancer. MANEC of the ampulla, which is considered as a malignant tumor, is a subtype of ampulla tumor. We proposed that pancreaticoduodenectomy may be an optimal surgery approach for MANEC of the ampulla without surgical contraindication.

MANEC including two components: adenocarcinoma and neuroendocrine carcinoma, most neuroendocrine tumors overexpress receptors like SSTR2 for somatostatins, somatostatin analogues could be a therapeutic option for functional neuroendocrine tumors because they reduce hormone-related symptoms and also have antitumor effects. But in our cases the tumors did not cause hormone hypersecretion and associated symptoms.

As for MANEC, Lee proposed that when MANECs with well-differentiated neuroendocrine components of benign or low grade malignant behavior, chemotherapy would be focused on exocrine component. In contrast, in those with small cell neuroendocrine carcinoma or large cell neuroendocrine carcinoma (LCNEC), endocrine component would be the main target of the therapy.

2). Response to comment: (the lesion is rare, symptoms are not specific, How should we pay more attention on the early diagnosis? Why would it improve the prognosis?)

Response: It is really true as Reviewer suggested that the MANEC of ampulla is rare, and symptoms are not specific, so the early diagnosis was very difficult. Clinicians should pay attention to the clinical features of MANEC of ampulla. For patients with symptoms such as abdominal pain, nausea, vomiting, epigastric discomfort, jaundice, endoscopy and MRCP examination is helpful to the diagnosis. The prognosis of malignant tumor is usually related to its stage, the same is true of MANEC, so effective

treatment in early stage could improve the prognosis.

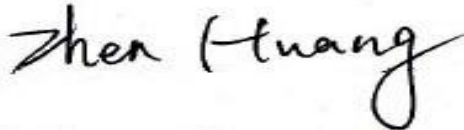
Considering the Reviewer's suggestion, we have re-written the last paragraph according to the suggestion offered by 02541992. Special thanks to you for your good comments.

(4) All the revisions I made have been highlighted in red in the updated vision.

3. References and typesetting were corrected.

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

Sincerely yours,

A handwritten signature in black ink that reads "Zhen Huang". The signature is written in a cursive, flowing style.

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