

April 25, 2015



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 17699-review.doc).

Title: CT and MRI Features of Lipid-rich Neuroendocrine Tumors of the Pancreas

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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, and changes are listed point-by-point on the next page.

3 References and typesetting were corrected

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

Sincerely yours,

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To the comments of reviewers:

Reviewed by 02348457

(1) In the introduction part, the author describe the the importance for differentiating PanNETs from other pancreatic lesions, however, the importance for differentiating lipid-rich PanNETs from non-lipid rich PanNETs is not mentioned. The significance of this research will be stressed if the author emphasize its importance for differentiating lipid-rich PanNETs from non-lipid rich PanNETs.

We fully agree to reviewer's comment. Then, we inserted the following sentence in Introduction.

New sentence: However, the clinicopathological characteristics of lipid-rich PanNET and difference from the usual PanNET remain unclear.

(2) It is better to replace MRI with chemical shift MRI as key word.

We replaced MRI with chemical shift MRI as key word, according to reviewer's suggestion.

(3) In the first paragraph of the discussion part, the author mention that different results are found in tumors with clear cells and ADRP-positive lipid-rich cells. But it makes me confuse that whether the results come from the tumors only with one kind of the cells mentioned above respectively or maybe some of them contain both kinds of cells. Therefore, the author is better to explain it more clearly here.

As mentioned in Discussion, some lipid-rich PanNETs have clear vacuolated cytoplasm, depending on the amount of lipid, under light microscopy. Thus, lipid-rich PanNETs have occasionally been classified as clear cell PanNETs. We performed immunohistochemical ADRP staining to check for lipid-rich cells in PanNETs. In our study, ADRP-positive lipid-rich cells were observed in 15 of 34 tumors (44.1%), and clear cells were observed in 8 (23.5%). All of the clear cells were observed in ADRP-positive lipid-rich PanNETs and there were no clear cells associated with ADRP-negative tumors ($P < 0.001$). We believe that our result can be explained by the fact that ADRP immunohistochemistry offers a more sensitive technique to demonstrate lipid droplets compared with hematoxylin-eosin staining.

Therefore, we inserted the following sentence in Discussion.

New sentence: The results can be explained by the fact that ADRP immunohistochemistry offers a more sensitive technique to demonstrate lipid droplets compared with hematoxylin-eosin staining. [24]

(4) I am also confused with the sentences "In our study, all of the four PanNETs in a patient withbut two of four PanNETs contained ADRP-positive lipid-rich cells" in the second paragraph of the discussion part, I can not understand very well with its findings. The expression should be well organized in order to make it more easily for readers to understand. In general, this paper is good and carefully-writing. But there are still a few problems with sentence structure, verb tenses

and clause construction.

We changed the following sentences.

Previous sentences: Lipid-rich PanNETs are strongly associated with von Hippel-Lindau disease^[4] or MEN 1^[6]. It is reported that 60% of von Hippel-Lindau disease-associated PanNETs will exhibit at least focal clear-cell cytology^[4], and Fryer et al.^[6] have reported that PanNETs contained lipid-rich cells either focally or entirely in six of 16 patients (37.5%) with MEN 1. In our study, all of four PanNETs in a patient with von Hippel-Lindau disease contained ADRP-positive lipid-rich cells and clear cells. No clear cells were identified in any PanNETs of two patients with MEN 1, but two of four PanNETs contained ADRP-positive lipid-rich cells.

New sentences: Lipid-rich PanNETs are strongly associated with von Hippel-Lindau disease^[4] or MEN 1^[6]. It is reported that 60% of von Hippel-Lindau disease-associated PanNETs will exhibit at least focal clear-cell cytology^[4]. In our study, all of four PanNETs in a patient with von Hippel-Lindau disease contained ADRP-positive lipid-rich cells and clear cells. Fryer et al.^[6] have reported that PanNETs contained lipid-rich cells either focally or entirely in six of 16 patients (37.5%) with MEN 1. In our two patients with MEN 1, two of four PanNETs contained ADRP-positive lipid-rich cells.

Reviewed by 00713469

(1) The authors present a paper on CT and MRI features of lipid-rich neuroendocrine tumors of the Pancreas. The paper is well written and sustained by appropriate iconography. Even if the general message is not new, it could be interesting for improving the radiological assessment of these lesions. Unfortunately, the number of patients studied is low and, if possible, the authors should increase the cohort to strengthen their efforts. Although the article is essential in its structure, the purpose is well defined and it transmits properly the message becoming of potential interest for the readers.

We fully agree to reviewer's comment. Pancreatic neuroendocrine tumors are uncommon pancreas tumors with a incidence of less than 1 / 100,000 persons per year. We found only 30 patients with pancreatic neuroendocrine tumors who underwent enhanced CT and chemical shift MRI April 2001 and June 2013. Therefore, we have mentioned the following sentence as a study limitation in Discussion: This study included a relatively small number of patients. A larger study would be required to definitively establish the characteristic features of lipid-rich PanNETs.