

ANSWERING REVIEWERS



April 30, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: ReEdited_6832-review.doc).

Title: The imaging modalities in preoperative staging of gastric cancer

Author: Sung Wook Hwang and Dong Ho Lee

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6832

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

(1) Reviewer #1 (00004227)

(a) At introduction, authors comment an issue of EUS, regarding the limited depth of penetration. This is not really correct, since with most of the ultrasound devices, depth of penetration can be established up to 9 cm, for instance. Maybe the idea is that with EUS the field of view is not as big as with CT scan or MR, but sentence needs clarification

Answer: Thank you for the kind comment. Following the reviewer's comment, the description was modified more clearly.

(b) All over the manuscript, authors tries to establish metaanalysis as the key, providing the most important information, however I believe that that the best studies to provide the optimal information are the randomized controlled trials. Systematic reviews are important, also metaanalysis, but they are all based on controlled trials, so...I think this is a wrong message in the manuscript

Answer: We appreciate the valuable comment from the reviewer. We also considered this point very carefully. There are numerous studies regarding preoperative gastric cancer staging, and introducing all the studies was not considered as informative. Actually, there were several controversies even between the prospective studies, and RCTs directly comparing the accuracy between two modalities were very limited in this area: the meta-analysis and systematic reviews were based on retrospective and prospective studies, rather than RCTs. In addition, too many description of each study could make the readers confused and bored. Thus, the findings of meta-analyses and systematic reviews were considered as necessary in this article. In this regard, following the reviewer's comment, we tried to describe several well-conducted original studies at first and key findings of meta-analyses and systematic reviews such as publication bias and pooled accuracy were summarized later in each modality section. Together with comment (d), the manuscript was largely corrected especially in the section of EUS, MDCT and PET.

(c) there are some important papers missing in the review, for instance one published by Repiso et al at Spanish Journal of Gastroenterology, highlighting the importance of EUS, in terms of changing management of patients with gastric cancer. Please, include these studies, the deserve a comment in the review.

Answer: Thank you for the accurate comment. Following the reviewer's comment, the description about changing management of gastric cancer patients by EUS was added in the revised manuscript.

(d) All over the points, authors are repeating information, both in the text and in the tables. I would recommend to keep tables, and explain more the results in the text, for instance by explaining the ones with optimal methodology, best gold/standard and so on.

Answer: We appreciate the valuable comment from the reviewer. Mentioned above, together with comment (b), the manuscript was largely corrected especially in the section of EUS, MDCT and PET. Following reviewer's comment, we tried to keep the tables and explain more results in the manuscript.

(e) Review some english expression, that can be clearly improved

Answer: Following the reviewer's comment, we tried to polish English in the revised manuscript. Thank you.

(2) Reviewer #2 (00048205)

(a) Two types of EUS, miniature-probe and conventional EUS, are available in the clinical setting, so it is helpful for the authors to describe the type (probe/conventional) or mode (7.5-10/12/20 MHz) used in the previous studies.

Answer: Thank you for the accurate comment. Following the reviewer's comment, the description about EUS transducer types was added in the revised manuscript. In clinical practice, the mode of EUS was made on physician's decision, freely switching the EUS modes, and there were rare recent reports properly showing practical meaning of the EUS mode. Thus the description about EUS mode was not included in the revised manuscript.

(b) The ability of EUS to get specimens from cancerous lesions is the strength of EUS, compared with other modalities, such as MD-CT, MRI and PET-CT. It is better to discuss the usefulness of EUS-FNA for pre-operative diagnosis of gastric cancer with some data of EUS-FNA for gastric cancer.

Answer: Thank you for the accurate comment. Following the reviewer's comment, the description about EUS-FNA was added in the revised manuscript.

(c) The sensitivity and specificity of PET-CT can be affected by the cut-off value of SUV. So, it is better for authors to discuss the SUV value in the pre-operative diagnosis of gastric cancer.

Answer: Thank you for the kind comment. Following the reviewer's comment, the description about the cut-off value of SUV in PET was added in the revised manuscript.

(3) Reviewer #3 (00034167): No corrections were suggested

Reviewer #4

Major changes have been highlighted in RED color in the revised manuscript.

(1) Please clarify the study design of describing data in manuscript and Table. Meta-analysis using RCT or prospective studies is real meta-analysis with high evidence.

Answer: We appreciate the valuable comment from the reviewer. We also considered this point very carefully. Most of the meta-analyses included both prospective and retrospective studies. Thus, it was impossible to clarify the study design in each meta-analysis. Instead, we tried to comment about this point in the manuscript. Thank you.

(2) Data from prospective study are required for convincing data. Especially, prospective study is indispensable for diagnostic study to avoid many bias. Author should separately describe and discuss the data of prospective study and retrospective study. Moreover, author have to strength that the data from retrospective study is not convincing and conclusive in this manuscript. Please interpret and discuss based on evidence level of each study.

Answer: Thank you for the accurate comment. There are numerous studies regarding preoperative

gastric cancer staging, and introducing all the studies was not considered as informative. Actually, there were several controversies even between the prospective studies, and RCTs directly comparing the accuracy between two modalities were very limited in this area: the meta-analysis and systematic reviews were based on retrospective and prospective studies, rather than RCTs. In addition, too much description of each study could confuse and bore the readers. Thus, the findings of meta-analyses and systematic reviews were considered necessary in this article. In this regard, following the reviewer's comment, we tried to describe several well-conducted original studies at first and key findings of meta-analyses and systematic reviews such as publication bias and pooled accuracy were summarized later in each modality section

(3) Author should not conclude superiority and inferiority by comparison among meta-analyses of different background and different design. Changing of Title name may be better because the significance of EUS is still unclear in this article. Moreover, retrospective study of EUS for stage diagnosis would have many biases because most of patients must undergo CT and the result of CT give many information to diagnosis by EUS.

Answer: Thank you for the accurate comment. Following the reviewer's comment, the title was changed, and several comments were revised.

(4) Page 8: Evidence of neoadjuvant chemotherapy is limited to Western countries where D2 lymph node dissection is not standard. There is a lack of evidence for neoadjuvant chemotherapy in Asian countries with D2 dissection. Therefore, preoperative T staging for locally progressive cancer is not definitely necessary in Asian country. Preoperative assessment of invasion to adjacent organ such as pancreas (T4b) is important for indication of surgery, but CT would be superior to EUS about that. Hence, the importance of EUS is limited to diagnosis between T1a and T1b for indication of endoscopic resection, but this assessment is lacking in this review.

Answer: Thank you for your kind comment. We also considered this point very carefully. Differentiation of T1a and T1b is also an important issue in the preoperative staging of gastric cancer. However, in modalities other than EUS, the differentiation between T1a and T1b is considered as impossible. In addition, it needs many discussions confined to early gastric cancer. Thus, we thought that this would require a separate discussion in another review article. In the present article, we tried to mainly focus on TNM staging and other techniques such as EUS-FNA. Thank you.

(5) 19-20th line in page 12: The sentence "The high specificity might be helpful....." is incorrect and should be deleted. Because FDG-PET is very high false negative (low sensitivity).

Answer: Thank you for the accurate comment. Following the reviewer's comment, the sentence was deleted.

(6) Even if specificity of FDG-PET is so high, this modality is meaningless for pre-operative staging because of very low sensitivity. This description about high specificity of N-stage should be removed and author should discuss about that in the paragraph of FDG-PET.

Answer: Thank you for the accurate comment. Following the reviewer's comment, descriptions were revised in the manuscript.

3 References and typesetting were corrected

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

Sincerely yours,
Dong Ho Lee, M.D.
Department of Internal Medicine,
Seoul National University Bundang Hospital,

300 Gumi-dong, Bundang-gu, Seongnam, Gyeonggi-do,
463-707, South Korea

Telephone: + 82-31-787-7008

Fax: + 82-31-787-4051

E-mail: dhljohn@yahoo.co.kr

DH Lee