June 20, 2014

Dear Editor,

Please find attached the edited manuscript in Word format (file name: 11490-review).

Title: Multimodality management of resectable gastric cancer: A review

Author: Helen Shum, Lakshmi Rajdev

Name of Journal: *World Journal of Gastrointestinal Oncology*

ESPS Manuscript: 11490

1. Format has been updated according to Editor's notes
2. References and typesetting were corrected.
3. The manuscript has been revised based on suggestions made by the reviewers. Our responses to the reviewer's comments are as below.

Review dated 2014-06-10 22:45

1. The abstract is confused and should summarize the contents of the manuscript.

   Response: The abstract on page 3 now states that this is a review article that summarizes key clinical trials that have defined optimal treatment options for non-metastatic non-cardia gastric cancer. (Tumors that arise beyond 5 cm of the EGJ or are within 5 cm of the EGJ but without extension to the esophagus or EGJ are still classified and treated as gastric cancers, this definition is now added to the manuscript on page 3, under "Introduction," paragraph 2). The most notable trials that have defined treatment approaches include INT-0116, MAGIC and the ARTIST, as stated in the abstract.

2. The conclusion is too simple and it should be more specific in multi-modality treatment and future directions.

   Response

   For patients with non-cardia gastric cancer, randomized trials and meta-analyses provide support for a number of approaches including adjuvant chemoradiotherapy (INT 0116 trial), perioperative (preoperative plus postoperative) chemotherapy, as was used in the MAGIC trial. Few studies have compared these approaches, and the optimal way to integrate combined modality therapy has not been definitively established. This is clearly indicated on page 15 of the manuscript, 2nd paragraph under "Conclusion." Decisions are often made based on institutional and/or patient preference. A major problem, at

least in the US, is that patients with gastric cancer are undergoing surgery prior to consultation by medical or radiation oncologists.

In Asia, different chemotherapeutic agents (such as S1) are used adjuvantly and adjuvant radiotherapy is often limited to patients with node positive gastric cancer. The conclusion section acknowledges these different management approaches and different treatment patterns in the East and West (page 15). The conclusion outlines evidence-based approaches to manage patients whether seen preoperatively or postoperatively. Pivotal trials such as the MAGIC and INT 0116 trials have been described in detail in earlier sections to guide the reader further.

A section on Future Directions exists on page 13-14 of manuscript.

3. The number of references of this review is not sufficient.

Response: This manuscript focuses on pivotal trials that have established an approach to the management of the resectable gastric patient. These references have been cited. As the manuscript has been revised, additional references have been cited.

Review dated 2014-06-07 20:12

1. ? Research method including the sources which the authors used and the period of time in databases. ? Not sufficient number of literature ? Lack definition in the method: neoadjuvant chemotherapy, perioperative chemotherapy, adjuvant chemotherapy and radiotherapy.

Response: The manuscript has been edited to state that this is a review article and a Pub Med search was conducted using "adjuvant", "neoadjuvant", "perioperative" therapy and "resectable gastric cancer". The abstract has been revised to state that this is a review article that summarizes key clinical trials that have defined optimal treatment options for non-metastatic non-cardia gastric cancer. These revisions appear on page 2 under the "Abstract" section and page 4 in the 3rd paragraph under "Introduction," respectively.

2. The abstract is clear for the reader. However, I do not quite agree with the sentence: "Surgical resection with at least a D1 lymphadenectomy and at least 15 regional nodes removed is the standard of care in the United States, while a D2 lymphadenectomy is the recommended procedure in Asia. " D2 lymphadenectomy is also a standard in Western and Central Europe.

Response: The manuscript has been revised on page 5 to reflect the NCCN guidelines. The guidelines recommend gastrectomy with DI or a modified D2

lymph node dissection, with a goal of examining 15 or if not more lymph nodes, for patients with localized resectable cancer. The guidelines emphasize that D2 dissection should be performed by experienced surgeons in high-volume centers. (National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines): Gastric Cancer. Version: Jan 2014.).

Additionally, the following changes are made on Page 5: "The depth of lymphadenectomy has been a topic of debate as well. A D1 dissection involves a gastrectomy and the removal of the greater and lesser omental lymph nodes. A D2 dissection involves the above plus the removal of all lymph nodes along the left gastric artery, common hepatic artery, celiac artery, splenic hilum and splenic artery. The D1 dissection was traditionally favored in the West, specifically in the United States, whereas D2 resection was preferred in the East and Europe."

3. References: 43 sources quoted by the authors seem not sufficient as for a review manuscript.

   Response: This manuscript focuses on pivotal trials that have established an approach to the management of the resectable gastric patient. The manuscript has also been revised and these references have been cited.

Review dated 2014-05-30 18:14

1. In Neoadjuvant chemotherapy, I feel the presentation of FAMTX trial is not suitable because this study is too old and the 5-year survival rate is too low.

   Response: The FAMTX trial discussion has been deleted on page 5.

2. Abstract, Introduction and Curative resection are very sharp and compact. However, subsequent paragraphs are slightly rambling talk. The author should change these paragraphs more compact and brief.

   Response: The FAMTX trial discussion has been removed. The discussion of trials in subsequent sections has been limited to pivotal Phase III trials conducted in the East and West.

Review dated 2014-05-28 23:16

1. The title is appropriate and reflects the major topic and content of the manuscript. However, the title is restrictive to resectable gastric cancer where as the review does also include some trials on advanced non-resectable gastric cancer. The title should also indicate that this is a review article. The abstract should indicate the nature of the manuscript as a limited review article and should summarize the

contents of the review and conclusions.

Response: The positive trials in advanced gastric cancer described in the manuscript have helped designed current trials in the curative setting. These advanced trials have been included in the manuscript to provide a reference to the reader. The abstract has been revised to indicate that this is a review article that summarizes key clinical trials that have defined optimal treatment options for non-metastatic non-cardia gastric cancer. See abstract on page 2.

2. The conclusion strays into points not covered in the review such as the utility of laparoscopic surgery and makes recommendations not supported by the review. There are a few points which the authors may consider revising: 1. The authors comment in their conclusion on the utility of laparoscopic surgery without having summarized the scientific basis under the surgical or curative resection section.

   Response: There was a comment on page 4, in paragraph 1 under "Curative resection" that stated a similar outcome between laparoscopic surgery compared to open surgery but with less complications. Additional data (see below) and references have been added in response as well (References 10-13).

   Page 4: "In 1999, Bozzetti et al found no difference in survival between total and subtotal gastrectomies but that subtotal gastrectomy was associated with improved nutritional status and quality of life[9]. With the advancement of laparoscopic techniques, laparoscopic gastrectomy was found to have similar outcomes but with fewer complications compared to open gastrectomy in meta-analyses and case-control studies[10-13]."

3. The authors repeatedly mention the inclusion of gastric cancer and cancer of EGJ in trials but at no point do they explain this inclusion in terms of biological behavior etc.

   Response: The classification and management of cancers arising at the EGJ have evolved over time. In the latest edition of the TNM staging manual, tumors arising at the EGJ, or in the cardia of the stomach within 5 cm of the EGJ that extend into the EGJ or esophagus (the so-called Siewert III EGJ tumors) are staged using the TNM system for esophageal rather than stomach cancer. However, tumors within 5 cm of the EGJ that do not extend into the esophagus are still staged (and treated) as gastric cancers. The manuscript has been revised to clarify the definition of gastric cancer on page 3, 2nd paragraph under "Introduction." Our review is focused on the multimodality management of non-metastatic non-cardia gastric cancer. The exact changes are as below:

   Page 3: "While gastric adenocarcinoma obviously includes tumors arising from the stomach, the classification of tumors of the gastroesophageal junction (GEJ)

has been a topic of debate. The most widely used classification was proposed by Siewert et al in 2000: type I tumors are tumors in the distal esophagus and may extend to the GEJ from above, type II tumors are adenocarcinomas of the cardia, arising at the GEJ, and type III tumors are cancers that originated from below the cardia and extend to the GEJ and distal esophagus from below[6] . It is also noted that the biologies of these distinct types of GEJ tumors are very different. Type I cancers are mostly associated with intestinal metaplasia and history of gastroesophageal reflux disease. On the other hand, types II and III cancers resemble proximal gastric cancer and have lymphatic spread preferentially to the celiac axis[6, 7]. The American Joint Committee on Cancer (AJCC) updated the staging of stomach adenocarcinoma in the 7th edition to include cancers of the GEJ arising more than 5 cm distally of the GEJ or within 5 cm of the GEJ but without extension to the esophagus or GEJ[8]. This distinction is important because many of the clinical trials included cancers of the GEJ in addition to cancers of the stomach. More importantly, cancers of the GEJ as described above behave similarly compared to gastric cancer and are treated as such."

4. The authors mention, patient heterogeneity in terms of Asian and Caucasian patients. However, they do not mention anything about disease heterogeneity.

   Response: We added data in the first paragraph of the "Introduction," page 3, regarding possible explanations for the differences seen between the two populations, mainly a difference in stage at diagnosis and use of second-line therapy. Corresponding references are 3-5.

   Page 3: "There is a significant disparity in the incidence and survival rates between the Asian and Western countries. For example, the overall 5-year survival worldwide was about 20% according to a report in 2008 but more than 70% in Japan for resectable disease. Such dramatic difference may be due to the implementation of screening programs in Japan where there is a higher incidence of gastric cancer resulting in detection of disease at earlier stages. In contrast, patients in the United States are usually diagnosed later in stage as routine screening for gastric cancer is not recommended owing to cost ineffectiveness[3]. The survival benefit may also be related to a more frequent use of second-line chemotherapy in Asian countries, most commonly irinotecans and taxanes, compared to the West[4, 5]."

5. The conclusion needs to be a little more specific in terms of what this literature review offers.

   Response: The conclusion outlines evidence-based approaches to manage resectable gastric cancer patients whether seen preoperatively or postoperatively."

For patients with non-cardia gastric cancer, randomized trials and meta-analyses provide support for a number of approaches including adjuvant chemoradiotherapy (INT 0116 trial), perioperative (preoperative plus postoperative) chemotherapy, as was used in the MAGIC trial. Few studies have compared these approaches, and the optimal way to integrate combined modality therapy has not been definitively established. Decisions are often made based on institutional and/or patient preference. A major problem, at least in the US, is that some patients with gastric cancer undergo surgery prior to consultation by medical or radiation oncologists.

In Asia, different chemotherapeutic agents (such as S1) are used adjuvantly and adjuvant radiotherapy is often limited to patients with node positive gastric cancer. The conclusion section acknowledges these different management approaches and different treatment patterns in the East and West.

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

Sincerely yours,

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