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Andrzej S Tarnawski, DSc, MD, PhD, Professor

Editor-in-Chief

*World Journal of Gastroenterology*

Dear Editor,

I wish to resubmit our revised manuscript for publication in the *World Journal of Gastroenterology* special issue *Novel cancerous mechanism of gastric tumors to cancers*, titled “Confusion and prospects for carcinogenesis of gastric adenoma and dysplasia—What is the correct answer currently?” The manuscript ID is 80043.

We thank the editors and reviewers for their thoughtful suggestions and insights. The manuscript has benefited from these insightful suggestions. I look forward to working with you and the reviewers to move this manuscript closer to publication in *World Journal of Gastroenterology*.

The manuscript has been rechecked and the necessary changes have been made in accordance with the reviewers’ suggestions. The responses to all comments have been prepared and attached herewith. In addition, we also revised minor errors, though they did not influence the scientific content. The revised portions of the manuscript are indicated in red font.

Thank you for your consideration. I look forward to hearing from you.

Sincerely,

Shinichi Kinami, MD, PhD

Department of Surgical Oncology, Kanazawa Medical University

1-1 Daigaku, Uchinada-machi, Kahoku-gun, Ishikawa 920-0293, Japan

Tel: +81-76-286-2211

Fax: +81-76-286-4626

Email: kinami@kanazawa-med.ac.jp

## Reviewer 1

**Response:** I would like to thank you for reviewing our article and for your kind comments.

This review article has the author's deep experience. It is positioned to answer an important question: What is the Gastric adenoma-carcinoma sequence different from colon adenoma-carcinoma sequences, and do we need to perform endoscopic resection in all low-grade gastric adenoma? This review article provided helpful information on the carcinogenesis of early gastric neoplasm for therapeutic endoscopists. Also, I hope this article will significantly help beginners and endoscopists active in ESD. There were discrepancies between endoscopic forceps biopsy before resection and final ESD pathology. As the author mentioned, about 10% of the low-grade gastric adenoma, which was confirmed at the forceps biopsy, could change cancer or high-grade adenoma in the final pathology. Many endoscopists may be considering whether ESD should be an appropriate method for Low-Grade Adenoma. I think the quality of almost all parts of the article is excellent and well organized so that readers can understand the contents without confusion. I only have the following minor points, but I hope some of my comments help improve the manuscript's quality. I hope the part about stomach cancer in the Introduction Section is in front of this section because CRC is comparable to explaining Gastric Neoplasm Carcinogenesis.

**Response:** We are grateful for your thorough evaluation. It is very encouraging. Based on your suggestion, I have rewritten the 'Introduction' section as follows.

**Revised text:** "Gastric cancer is one of the most common cancers worldwide. However, the incidence of gastric cancer declined in many Western countries during the 20th century. Japan was one of the countries with a high incidence of gastric cancer, but the incidence is also decreasing. This fact proves that *Helicobacter pylori* (*HP*) infection is deeply involved in the development of gastric cancer<sup>[1]</sup>. In Japan, the water supply and sewerage systems were completed in the 1960s, and the *HP* infection rate has decreased among the generations born subsequently<sup>[2,3]</sup>. Most patients with gastric cancer in Japan are elderly, and the incidence of gastric cancer among age groups with low *HP* infection rates is low. Besides *HP*, many factors are known to be involved in gastric carcinogenesis. These include salt intake, smoking, exposure to N-nitroso compounds, and Epstein-Barr virus infection<sup>[4-7]</sup>. However, the molecular mechanisms leading to gastric carcinogenesis are not well understood. In contrast, the molecular mechanism leading to colorectal cancer has been clarified to some extent. Colorectal cancer is one of the most common cancers worldwide. Many

colorectal cancers are thought to develop from adenomas and serrated polyps through the adenoma-carcinoma sequence. The molecular mechanism of colorectal carcinogenesis has long been a subject of interest and has been well-studied, with genetic and epigenetic changes in oncogenes and tumor suppressor genes identified in considerable detail.

There are various reasons for this difference in the understanding of the molecular mechanisms between gastric carcinogenesis and colorectal carcinogenesis. The most important is that gastric carcinogenesis is often of the *de novo* type and does not necessarily follow the adenoma-carcinoma sequence, making it difficult to examine the genetic changes from benign lesions to carcinoma in a sequential manner. Another reason is that the diagnostic criteria for gastric adenomas are vague and differ between countries in the East and West.

In this article, we describe the issues surrounding gastric adenomas, the molecular mechanisms of carcinogenesis that have been identified to date, and future perspectives.”

## Reviewer 2

**Response:** I would like to thank you for reviewing our article and for your kind comments.

Manuscripts about gastric carcinogenesis are heavily needed! With decreasing number of Hp+ individuals, we see more and more gastric neoplasm cases with no Hp infection (some for sure never had any!) Comparing colorectal cancer with gastric cancer is fine in my eyes... so much interest and time has been put into the carcinogenesis of colorectal cancer but not yet gastric cancer.... out attempts slowed down a lot after the Correa Hypothesis which is not optimal as we all know from our daily routines.

**Response:** Thank you for your invaluable comments. I agree with all your opinions. I also feel that it is challenging to elucidate the mechanism of gastric carcinogenesis because, unlike colorectal cancer, gastric cancer is greatly affected by various external factors.

Minor: diagnostic criteria However, intramucosal carcinoma is also considered a cancer, which is different from the classification in Western countries This is just not true! It is lousy, sometimes very loud Western pathologists who consider mucosal carcinoma in the stomach as carcinoma in situ or non invasive or what ever. Lousy

pathologists also experience problems with gastric biopsies and rarely make a carcinoma diagnosis on biopsies unless it is a clear signet ring cell cancer. But this is not a “Western concept”! It is the sequele of some (loud) lousy Western pathologists. Sorry, but I have to make this very clear! The situation is different in the colon since there Western pathologists are indeed forced by some influential people to stick to a WHO classification that doesn't accept mucosal carcinomas in the colon. But that is a total different topic and even more lousy. So, after making this clear I would suggest to change that specific sentence into: However, intramucosal carcinoma is also considered a cancer, which is not accepted by some pathologists in Western countries. References ... please consider to cite this manuscript with adenoma diagnoses also in healthy stomachs: It should be at least cited together with ref 4 ! Helicobacter Infection and Gastric Adenoma. Bertz S, Angeloni M, Drgac J, Falkeis C, Lang-Schwarz C, Sterlacci W, Veits L, Hartmann A, Vieth M. Microorganisms. 2021 Jan 5;9(1):108. doi: 10.3390/microorganisms9010108

**Response:** Thank you for your kind and valuable comments. My primary profession is as a surgeon, and I also specialize in endoscopic treatment, but unfortunately, I have attended only a few international pathology conferences. My descriptions are based on what I heard from several pathologists in Japan, which resulted in this expression. I want to express my deepest apologies to my overseas comrades for the inaccurate expression. Based on your comment, I changed the text as follows and added the suggested reference. The reference numbers were adjusted accordingly.

**Revised text:** Page 7, Lines 15–16. “However, intramucosal carcinoma is also considered a cancer, although this [is not accepted by some pathologists](#) in Western countries.”

#### **Comment to Science editor**

I forgot to write CONCLUSION. I added CONCLUSION as follows.

**Revised text:** Page 12, Line 23 – Page 13, Line 4.

#### **CONCLUSION**

Gastric carcinogenesis occurs mostly *de novo*, and the adenoma-carcinoma sequence does not appear to be the main pathway of carcinogenesis. Superficial gastric tumors can be roughly divided into the *APC* mutation type and the *TP53* mutation type, which are mutually exclusive. For lesions diagnosed as category 3 or 4 in the Vienna classification, it is desirable to perform endoscopic submucosal dissection for accurate diagnosis and staging. If there is lymphovascular or submucosal invasion,

additional surgical treatment of gastrectomy with lymph node dissection is required.