Correspondence

Long journey to prevent metachronous gastric cancer after endoscopic resection

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The "Perspective" by Drs. Cho *et al.* (1) is a very interesting and informative article for the readers. They have summarized the recent issues regarding the effects of *Helicobacter pylori* (*H. pylori*) on the prevention of metachronous gastric cancer (MGC) after endoscopic resection (ER), including our study (2). We thank them for their kind comments and interest in our article.

Does *H. pylori* eradication actually prevent MGC from the perspective of basic and clinical evidence?

As Cho *et al.* (1) mention in their paper, there has been great debate about whether *H. pylori* eradication actually prevents MGC. Our recent open-label, randomized, controlled trial (RCT) demonstrated that *H. pylori* eradication did not produce significant changes in the molecular alterations related to carcinogenesis in patients once gastric cancer had occurred in the stomach (2). To date, only a few studies investigated the effects of eradication on molecular alterations in the background mucosa with gastric cancer (3,4). Shin *et al.* (4) reported that a decrease in the *MOS* methylation level was not observed among patients with intestinal metaplasia (IM) or those with gastric cancer, and the methylation level in *MOS* was persistently increased in patients with gastric cancer even after *H. pylori* eradication (mean follow-up duration, 26.0 months). Choi *et al.* (5) postulated that a long-term investigation (over 5 years) could clarify the exact role of *H. pylori* eradication. One of the limitations in our study was that the intervention period of the RCT was short (1 year), and thus it may be necessary to conduct follow-up for a long time. In Japan, it has been only 3 years since the government approved health insurance coverage for the treatment of *H. pylori* in chronic gastritis in 2013. Therefore, future studies of molecular events with a long-term investigation following eradication are expected to resolve this matter in Japan.

Cancer risk is generally higher in patients who underwent ER than in those with chronic gastritis, because the patients who develop gastric cancer enter the state of "field cancerization". To date, there have been a few meta-analyses regarding the effects of *H. pylori* eradication on MGC after ER (6,7). These studies concluded that *H. pylori* eradication is associated with a reduction of the incidence of gastric cancer. A recent meta-analysis by Chen *et al.* (8) showed that, for patients without IM at baseline diagnosis, *H. pylori* eradication may halt the progression to a precancerous lesion including IM and reduce the risk of gastric cancer, whereas when IM presents, no preventive effect was observed after eradication, neither in the risk of gastric cancer nor in the progression to a precancerous lesion. This result supports the study by Wong *et al.* (9).

H. pylori infection may be a promoter for gastric carcinogenesis

In the animal model, *H. pylori* infection alone never causes gastric tumorigenesis, and other factors including methyl N-nitrosourea or salt are needed to develop stomach cancer (10). In addition, the lesions that developed in *H. pylori*-infected models are heterotopic proliferative glands, similar to mucinous adenocarcinoma, different from gastric adenocarcinoma. Therefore, the results from animal models highlight that *H. pylori* is not an initiator, but it might be a promoter of gastric carcinogenesis (11). Taken together, it makes sense to us that *H. pylori* eradication alone cannot prevent the development of gastric cancer, including MGC. Additionally, it may be true that the elimination of the bacteria delays the development of gastric cancer if *H. pylori* infection plays a role as a promoter of gastric carcinogenesis. In any case, it will be best to provide eradication for the chronic gastritis patients who did not pass the "point of no return".

Beyond *H. pylori* eradication for MGC prevention

The number of molecular alterations related to gastric carcinogenesis may be approximately 20 at most. However, we still cannot identify the indisputable biomarkers heralding the "point of no return" in *H. pylori*-associated carcinogenesis despite the efforts of many investigators worldwide. Thus, additional efforts are needed for a secondary prevention study of MGC for patients whose *H. pylori* has been eradicated. Actually, a combination of anti-oxidative or anti-inflammatory agents, dietary or nutritional intervention activating molecular mechanisms for cancer prevention, reversion of premalignant lesions, and even ablation of cancer stem cells rather than *H. pylori* treatment is needed, as Cho *et al*. state, as short-term interventions to revert premalignant lesions (siTRP) (1).

In conclusion, patients with IM may not benefit from *H. pylori* eradication with respect to the risk of MGC. Additionally, in view of the present situation, in which we cannot identify a definite biomarker for gastric cancer development, it is appropriate that surrounding break-up should be considered, such as siTRP, rather than *H. pylori* treatment to prevent MGC.

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Footnote

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References

1. Cho NG, Kim HS, Song GW, et al. Surrounding break up after Helicobacter pylori eradication to prevent metachronous gastric cancer after endoscopic submucosal resection. Transl Cancer Res 2016;5:S71-5.
2. Kawanaka M, Watari J, Kamiya N, et al. Effects of Helicobacter pylori eradication on the development of metachronous gastric cancer after endoscopic treatment: analysis of molecular alterations by a randomised controlled trial. Br J Cancer 2016;114:21-9.
3. Nakajima T, Enomoto S, Yamashita S, et al. Persistence of a component of DNA methylation in gastric mucosae after Helicobacter pylori eradication. J Gastroenterol 2010;45:37-44.
4. Shin CM, Kim N, Lee HS, et al. Changes in aberrant DNA methylation after Helicobacter pylori eradication: a long-term follow-up study. Int J Cancer 2013;133:2034-42.
5. Choi J, Kim SG, Yoon H, et al. Eradication of Helicobacter pylori after endoscopic resection of gastric tumors does not

reduce incidence of metachronous gastric carcinoma. Clin Gastroenterol Hepatol 2014;12:793-800.e1.
6. Yoon SB, Park JM, Lim CH, et al. Effect of Helicobacter pylori eradication on metachronous gastric cancer after endoscopic resection of gastric tumors: a meta-analysis. Helicobacter 2014;19:243-8.
7. Lee YC, Chiang TH, Chou CK, et al. Association Between Helicobacter pylori Eradication and Gastric Cancer Incidence: A Systematic Review and Meta-analysis. Gastroenterology 2016;150:1113-1124.e5.
8. Chen HN, Wang Z, Li X, et al. Helicobacter pylori eradication cannot reduce the risk of gastric cancer in patients with intestinal metaplasia and dysplasia: evidence from a meta-analysis. Gastric Cancer 2016;19:166-75.
9. Wong BC, Lam SK, Wong WM, et al. Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. JAMA 2004;291:187-94.
10. Han SU, Kim YB, Joo HJ, et al. Helicobacter pylori infection promotes gastric carcinogenesis in a mice model. J Gastroenterol Hepatol 2002;17:253-61.
11. Tatematsu M, Tsukamoto T, Mizoshita T. Role of Helicobacter pylori in gastric carcinogenesis: the origin of gastric cancers and heterotopic proliferative glands in Mongolian gerbils. Helicobacter 2005;10:97-106.

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