Perspective

Surrounding break up after *Helicobacter pylori* eradication to prevent metachronous gastric cancer after endoscopic submucosal resection

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Comment on: 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.

Abstract: Still debates exist whether *Helicobacter pylori* (*H. pylori*) eradication can impose the chance of gastric cancer prevention since the effects of *H. pylori* eradication on the development of metachronous gastric cancer (MGC) after endoscopic treatment. Supported with other evidences that eradication can prevent gastric cancer as well as rejuvenation of atrophic gastritis and some improvements of dyspeptic symptoms, in February 21, 2013, Japanese government decided to eradicate *H. pylori* in patients with chronic gastritis. This is largely due to sincere hope either to lessen gastric cancer incidence as well as mortality or improve the quality of life of Japanese people. Though *H. pylori* had been defined as class 1 carcinogen by IARC at 1994, several evidences confirmed that *H. pylori* played promoting actions gastric carcinogenesis rather than as initiator. With the findings that field cancerization is one of core pathways of *H. pylori*-associated gastric carcinogenesis, the answer to debates that eradication alone was insufficient to prevent MGC includes either the discovery of biomarkers to eradicate earlier before stepping into irreversible stage of gastric carcinogenesis or adoption of strategy to perform siTRP (short-term intervention to revert premalignant lesion). Therefore, surrounding break up should be considered as siTRP after the successful eradication to prevent *H. pylori*-associated gastric cancers.

Keywords: *Helicobacter pylori* (*H. pylori*); metachronous gastric cancer (MGC); surrounding break up; eradication; gastric cancer prevention

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Effects of *Helicobacter pylori* (*H. pylori*) eradication on the development of MGC after endoscopic resection of early gastric cancer; never ending story should be finished

H. pylori infection, gastric inflammation, and subsequent changes in genetic or epigenetic mutations eventually can develop gastric cancer (1). Though the anticipation for preventing gastric cancer through eradication had been raised, following clinical studies have revealed its limited effects in these purposes. Practically, the number of metachronous gastric cancer (MGC) that emerges after successful endoscopic treatment of early gastric cancer has decreased with successful eradication in some studies, but not in all, leaving the curiosity about the real effects of eradication in preventing MGC development after endoscopic mucosal resection. Recently, in order to make clear whether *H. pylori* eradication actually suppresses the development of MGC after endoscopic resection, Kawanaka *et al.* (2) studied to clarify either the molecular markers related to carcinogenesis in intestinal metaplasia (IM) by a

cross-sectional study or the changes of those markers by an open labeled randomized controlled trial (RCT) of *H. pylori* treatment. In their studies, they found that microsatellite instability and immunohistochemical staining to Das-1 (7E12H12, IgM isotype) antibody showed significantly higher incidences in both the *H. pylori*-positive and -negative patients compared with the control group, but *H. pylori* eradication did not provide significant reversals of any molecular alterations. Stimulated with the result by Uemura *et al*. (3) that *H. pylori* infection significantly led to gastric carcinogenesis in large Cohort study, the meta-analysis by Fuccio *et al*. (4) showed *H. pylori* eradication seems to reduce the risk of gastric cancer, whereas the analysis by Take *et al*. (5) showed the risk of gastric cancer remains even after *H. pylori* eradication. In a similar way, with respect to the effects of *H. pylori* eradication on the prevention of MGC after endoscopic resection, studies conducted by several Japanese and Korean doctors reported that *H. pylori* eradication significantly reduced the risk of the development of new gastric cancer in patients who underwent ESD (6-8), whereas there are retrospective and prospective open-label trial showing that *H. pylori* eradication did not reduce the incidence of MGC in patients who underwent ESR (9-12).

There were several speculations to explain this discrepancy about the necessity of *H. pylori* eradication in patients who underwent ESD and whether patients presenting with chronic atrophic gastritis (CAG) whether eradication can impose the chance of rejuvenation through eradication. One of the answers come from very recent publication by Jung *et al*. (13) that CAG with intestinal metaplasia, open type CAG and moderate to severe degree of intestinal metaplasia was significantly associated with MGC development in case of eradication failure, signifying that *H. pylori* eradication may be essential in preventing metachronous lesions after ESD for precancerous lesions before carcinomatous transformation. According to Sugimoto *et al*. (14), MGCs were found in 23 of 155 patients following ESD, 3.5% per year, among which the cumulative incidence of MGC was significantly high in patients with intestinal metaplasia and neutrophil infiltrations, especially in the corpus, concluding that the presence of intestinal metaplasia before ESD is closely associated with the development of MGC after ESD. The other explanation is that the gastritis-like lesion emerging after eradication might determine the chance of MGC development. According to report by Moribata *et al*. (15), the emergence of map-like redness after *H. pylori* eradication, even though in the absence of intestinal metaplasia, was useful endoscopic findings in predicting the development of MGC after ESD. Map-like redness on endoscopic findings denotes "gastritis-like appearance" better seen under narrow band imaging of magnifying endoscopy (16). Lastly, the timing of eradication and the age of patients might affect the outcome of MGC development. According to Watari *et al*. (17) and Jang *et al*. (18), since patients with precancerous lesions with molecular alterations that do not reverse after *H. pylori* treatment, represent the lesion passing "point of no return" and may be at high risk condition, by which earlier *H. pylori* eradication should be considered for preventing gastric cancer prior to the appearance of precancerous lesions. Generally, old age more than 60 years old is also independent risk factor MGC (19).

H. pylori infection eradication alone is not sufficient to prevent cancer; *H. pylori* as promoter for gastric carcinogenesis

Debate that *H. pylori* might play a causative role in gastric carcinogenesis still exists in spite of IARC's definition of *H. pylori* as a class I carcinogen. In order to define the exact role of *H. pylori* infection in gastric carcinogenesis, our group (20) established a mice model of *H. pylori* infection. As results, the incidence of gastric cancer at the 50th week was 80% in mice treated with both methyl N-nitrosourea (MNU) 240 mg/L and *H. pylori* infection, whereas only 27% in mice treated with only MNU 240 mg/L, concluding *H. pylori* infection promoted gastric carcinogenesis rather than direct carcinogens. Similarly, in order to evaluate the difference in susceptibility to stomach carcinogenesis in relation to age of acquisition of *H. pylori* infection, Cao *et al*. (21) designed an experiment involving inoculation of *H. pylori* ATCC43504 followed by MNU treatment at different ages. As results, the earlier acquisition of *H. pylori* significantly increased gastric chemical carcinogenesis with MNU, as compared to the case with later infection. In Mongolian gerbil models, *H. pylori* infection significantly caused gastric carcinogenesis, whereas the eradication resulted in curtailment of enhancing effects. However, in mice or rats, *H. pylori* infection alone never caused gastric tumorigenesis until 20 months later, suggesting *H. pylori* is not an initiator, but might be a strong promoter for gastric carcinogenesis (22). A high-salt diet has been revealed to synergistically enhance development of stomach cancer with *H. pylori* infection; the latter exerts stronger promoting effects than the former (23). On serial investigation of *H. pylori*-infected models,

long-term *H. pylori* infection developed highly proliferative and dilated glands containing a large amount of mucin, called heterotopic proliferative glands, simulating mucinous adenocarcinoma, but not gastric adenocarcinoma, leading to conclusion that *H. pylori* infection thus appears to have a strong promotional influence but not to initiate gastric carcinogenesis (22). Therefore, translating these findings into the debates that *H. pylori* eradication does not warrant the prevention of MGC development in patients receiving ESD, either the discovery of biomarker or consideration of other strategy such as dietary or nutritional intervention to mitigate promoting contribution should be considered.

Still there is no biomarker significantly telling "the point of no return" in *H. pylori*-associated carcinogenesis

Gastric atrophy and intestinal metaplasia are defined as preneoplastic conditions of gastric cancer, whereas *H. pylori*-associated CAG by itself potentiates a risk for gastric cancer development. Though *H. pylori* eradication in some, overall reduction of GC incidence has been shown. However, this effect is not noted in all (24). Therefore, enormous effects had been thrown to discover biomarkers telling "the point of no return" and right person who can be benefited from successful eradication. Furthermore, MGC after ESD still occurs to some degree even after eradication, Watari *et al.* (25) studied to discover biomarkers related to carcinogenesis expressed in intestinal metaplasia through a hospital-based, case-control study of 75 patients, 50 gastric cancer patients who had undergone ESD, and 25 age- and sex-matched chronic gastritis patients for whom *H. pylori* had been successfully eradicated. As results, microsatellite instability and Das-1 reactivity in intestinal metaplasia strongly predicts the development of MGC. Enomoto *et al.* (26) found serum pepsinogen test and DNA methylation in CpG islands significantly reflected the progression of CAG showing a high likelihood of future cancer development, so called epigenetic "field cancerization" (27). Though global DNA hypomethylation is an early molecular event in *H. pylori*-related gastric carcinogenesis (28), aberrant methylation of CpG islands in promoter regions can permanently inactivate tumor-suppressor genes, as mutations and chromosomal abnormalities do. For instances, cyclin-dependent kinase inhibitor 2A (CDKN2A), cadherin-1 (CDH1), and mutL homolog 1 (MLH1) are inactivated more frequently by aberrant methylation than by mutations in gastric cancer, of which the amount of methylated DNA molecules in the gastric mucosa significantly fluctuated in active *H. pylori* infection (29), showing the presence of an epigenetic field for cancerization in *H. pylori* infection. Taken together of all these facts, in order to prevent MGC after ESD, eradication of *H. pylori* seems to be supplemented with strategies such as surrounding break up. Combination with anti-oxidative or anti-inflammatory agents, dietary or nutritional intervention to cope with filed cancerization, and earlier and effective eradication. In our institute, we have extended our efforts under the siTRP (short-term intervention to revert premalignant lesion).

siTRP (short-term intervention to revert premalignant lesion) strategy to prevent gastric cancer

The conclusion that "prevention might be better than treatment in cancer treatment" is reached after 30 years "war on cancer" initiated by National Cancer Act by President Richard Nixon in 1971. Besides of PhytoCeuticals, life-style modification including non-smoking, non-alcohol, weight reduction, and some natural agents, molecular targeted therapeutics achieved high goal of effectiveness under the concept of therapeutic or preventive "synthetic lethality" of which extended application can be included within the scope of chemoprevention (30). In clinic, siTRP strategy has been applied in patients with *H. pylori*-associated CAG, patients after ESD, and persons who are the first relatives of gastric cancer (31). Fortunately, in contrary to cancer chemotherapeutics, natural agents activating molecular mechanisms for cancer prevention, reversion of premalignant tumors, and even ablation of cancer stem cells, are actively developed, armed with mechanisms such as selective induction of apoptosis, suppression of growth factors, suppression of cell proliferation inhibiting angiogenesis, stimulating mesenchymal-epithelial transition, and hardening the tumor microenvironment.

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