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TOPIC HIGHLIGHT

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Metachronous gastric cancer after successful *Helicobacter pylori* eradication

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Abstract

The high incidence of gastric cancer in Japan initially resulted in establishment of a country-wide gastric cancer screening program to detect early and treatable cancers. In 2013 countrywide *Helicobacter pylori* (*H. pylori*) eradication was approved coupled with endoscopy to assess for the presence of chronic gastritis. Current data support the notion that cure of the infection in those with non-atrophic gastritis will prevent development of gastric cancer. However, while progression to more severe damage is halted in those who have already developed, atrophic gastritis/gastric atrophy remain at risk for subsequent development of gastric cancer. That risk is directly related to the extent and severity of atrophic gastritis. Methods to stratify cancer risk include those based on endoscopic assessment of the atrophic border, histologic grading, and non-invasive methods based on serologic testing of pepsinogen levels. Continued surveillance is required because those with atrophic gastritis/gastric atrophy retain considerable gastric cancer risk even after *H. pylori* eradication. Those who have already experienced a resectable early gastric cancer are among those at highest risk as metachronous lesions are frequent even after *H. pylori* eradication. We review the role of *H. pylori* and effect of *H. pylori* eradication indicating the incidence and the predictive factors on development of metachronous cancer after endoscopic therapy of early gastric cancer. Studies to refine risk markers to stratify for risk, surveillance methods, intervals, and duration after successful *H. pylori* eradication, and whether adjuvant therapy would change risk are needed.

Key words: Atrophic gastritis; Pepsinogen; miRNA; Intestinal metaplasia; Cancer prevention

Core tip: For the patients with a history of endoscopic resection of early gastric cancer, *Helicobacter pylori* (*H. pylori*) eradication followed by continued surveillance for gastric cancer is generally required because those with severe gastric atrophy retain considerable gastric cancer risk even after *H. pylori* eradication. We review the role of *H. pylori* and effect of *H. pylori* eradication indicating the incidence and the predictive factors on development of metachronous cancer after endoscopic therapy of early gastric cancer.

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INTRODUCTION

Gastric cancer is the fourth most common cancer and second leading cause of cancer deaths worldwide with more than 700000 deaths annually[1]. There are marked geographic differences in gastric cancer incidence both within and between countries and regions with the high-

est incidence occurring in Japan, Korea, China, Eastern Europe and parts of Central and South America[2]. An attempt to reduce gastric cancer mortality led Japan in the 1950's to establish secondary cancer prevention programs to detect malignant lesions in an early and potentially treatable stage. Improved detection of early lesions using double contrast roentgenography of the stomach, gastrocamera and most recently endoscopic examination with biopsy of suspected lesions has resulted in improved survival of patients receiving operative therapy[3].

Endoscopic methods to remove premalignant as well as superficial malignant gastric lesions such as endoscopic mucosal resection and endoscopic submucosal dissection have now become the standard of care in Japan and Korea for management of early gastric cancers with no evidence of lymph node metastasis. This program has been highly successful and currently more than half of Japanese gastric cancer cases are diagnosed at an early stage[4]. Because endoscopic submucosal dissection involves removal of both the mucosa and submucosa, large lesions can be resected *en bloc* yielding an improved histopathological diagnosis compared to endoscopic mucosal resection. However, both methods result in greater post-interventional quality of life compared to surgical resection[5].

While endoscopic removal of an early gastric cancer only solves the problem of that particular lesion it does not affect the overall cancer risk. The stomach in patients with early gastric cancer typically exhibits extensive chronic atrophic changes with multiple areas with preneoplastic changes and often contains microscopic foci of intramucosal cancer[6,7]. Prior studies that examined stomachs of patients with early gastric cancer reported that detailed histologic examination will reveal foci of intramucosal cancer in up to 15%[8-10]. The presence of these lesion is likely at least partially responsible for the fact that the risk of developing a metachronous lesion following endoscopic removal of an early gastric cancer has ranged between 1% and 4% per year[8,11-13]. Because of the high risk of metachronous lesions it is recommended that these patients are enrolled in a life-long endoscopic surveillance program.

The factors that influence the rate of appearance of metachronous lesions remain unclear, however some studies have shown that *Helicobacter pylori* (*H. pylori*) eradication results in a lower risk of developing a metachronous lesion[14]. Based on prior studies and the cancer field effect, it should not be surprising that either metachronous lesion remains a risk. For example, *H. pylori* eradication in patients with *H. pylori* infection and atrophic gastritis but no evidence of cancer has been shown to reduce but not eliminate that risk suggesting a role for the organism itself, for continuing *H. pylori*-induced inflammation, or both in relation of cancer risk.

H. pylori and gastric cancer

In 1994, the International Agency for Research on Cancer (IARC) of the World Health Organization classified *H. pylori* as a definite carcinogen[15]. Two decades then passed before this knowledge was translated into the decision to approve population-wide *H. pylori* eradication for any population[7]. During this interval a number of misconceptions regarding the attributable risk of *H. pylori* infection in gastric cancer were corrected and the role of atrophic gastritis as a surrogate for cancer risk was confirmed[16]. It is now accepted that *H. pylori* infection is responsible for more than 95% of gastric cancers (*e.g.*, one study in Japan demonstrated that *H. pylori*-negative gastric cancer accounted for less than 3% among all gastric cancers)[17]. *H. pylori* infection causes progressive damage to the stomach that may eventually result in atrophic gastritis/gastric atrophy with a rapidly increasing risk of gastric cancer. It is this progressive nature of the process that makes it so dangerous and many have been lulled into compliancy when deciding what to do with a patient with mild or non-atrophic gastritis without recognizing that the current histology is actually an early stage of a progressive process and the subsequent changes are largely irreversible. However, progression can be prevented or halted by *H. pylori* eradication but the cancer risk associated with atrophic damage can at best be only partially reversed. As such, *H. pylori* infection has been likened to infestation with termites which also cause typically silent put progressive damage. As with termites, the best results are obtained when the problem is discovered before permanent and extensive damage has occurred. The failure to recognize the progressive nature of the process can result in compliancy during which an individual cancer risk progressively increases[18].

H. pylori induced gastritis is typically acquired in childhood. Initially the inflammation and damage is most severe in the non-acid secreting gastric antrum. Over time the damage progresses into the gastric corpus as an advancing atrophic border which can be recognized endoscopically, and the damage clinically progresses more rapidly along the lesser curve than the greater curve[19,20]. Chronic inflammation related with *H. pylori* affects differentiation and promotes metaplasia[21-23]. As the damage advances into the corpus along the atrophic border it leaves behind a lawn of pyloric metaplasia (also known as pseudopyloric or mucus metaplasia) now recognized to be similar or identical to spasmolytic polypeptide/trefoil factor family 2 (TFF2)-expressing metaplasia (SPEM) described in animal models of gastric cancer[24,25]. The recognition that pyloric metaplasia could be easily recognized by immunostaining as SPEM rather than the previous cumbersome process of identifying it on the basis of corpus location and pepsinogen I staining allowed many older observations to be rapidly confirmed and extended[16]. It is now believed that intestinal metaplasia arises from SPEM and SPEM may also provide the cell of origin of gastric cancer[25,26]. Intestinal metaplasia is no longer thought to be the precursor of gastric cancer but rather is an easy recognized surrogate for the presence and extent of gastric mucosal atrophy[27-29]. The concept of multifocal atrophic gastritis actually represents scat-

tered areas of intestinal metaplasia arising within a lawn of SPEM-type atrophy damage[30-32]. The ease of diagnosing pyloric metaplasia has allowed development of a new gastric cancer risk stratification system, the corpus-predominant gastritis index, to join the Operative Link for Gastritis Assessment (OLGA) and OLGA-M histology systems of stratifying gastric cancer risk[33].

SERUM MARKERS FOR GASTRIC CANCER RISK ASSESSMENT

Pepsinogen

For population wide testing it is important have efficient and cost effective practical mass screening methods that correlate with the risk of developing gastric cancer (*i.e.*, non-invasive risk stratification). Since *H. pylori* infection is the necessary but insufficient cause of gastric cancer, identification and eradication of *H. pylori* is the most important step; eradication *H. pylori* infections which will ultimately eliminate gastric cancer. There are a number of validated non-invasive methods to identify *H. pylori* infection ranging from serologic methods, through the urea breath test and stool *H. pylori* antigen testing[34]. However in populations where gastric cancer is common, *H. pylori* eradication alone is often insufficient as many individuals will have already have experienced irreversible gastric damage and thus carry an ongoing risk for development of gastric cancer despite *H. pylori* eradication. In the past when the emphasis was on identifying incidence cases of gastric cancer in high prevalence countries such as Japan, a number of approaches (secondary cancer prevention) were tested. Measurement of serum pepsinogens proved to be a useful non-invasive method of identification of patients at risk and also proved cost effective for enriching the population with gastric cancer in screening studies[35-37]. The concept is based on the fact that pepsinogen Ⅰ is produced by the chief and mucous neck cells in the fundic glands whereas and pepsinogen Ⅱ is produced throughout the stomach as well as by Brunner's glands[38,39]. Damage to the gastric corpus results in a progressive decline in both pepsinogen Ⅰ levels and the ratio of pepsinogen Ⅰ to pepsinogen Ⅱ (pepsinogen Ⅰ / Ⅱ). Pepsinogen testing thus allows a non-invasive assessment of the presence and extent of atrophic gastritis and can be used to risk identify patients endoscopic cancer screening programs or for possibly needing endoscopic surveillance after *H. pylori* eradication[6,29,35,37,40-42]. While this approach has been shown to be useful, the cumulative data have shown some limitations. Probably the most important limitation is that *H. pylori* eradication can significantly change pepsinogen levels with a decrease of pepsinogen Ⅰ and pepsinogen Ⅱ and an increase of pepsinogen Ⅰ / Ⅱ even among those at high risk for gastric cancer[43,44]. Thus, at least as currently used, serum pepsinogen testing cannot be used as a reliable marker of atrophy for patients who already have been treated by eradication therapy.

Japan has a large cadre of endoscopists experienced in detection of atrophic gastritis and early gastric cancer and the decision was made that *H. pylori* eradication therapy should be accompanied by endoscopy to examine the extent and severity of gastritis. In countries where gastric cancer risk is lower and a large number of experienced endoscopists is lacking, it would probably be more prudent and cost effective to use pre-therapy pepsinogen testing to risk stratify patients into those possibly at higher risk for subsequent gastric cancer and those with little or risk post *H. pylori* eradication. Those in the higher risk category could then undergo endoscopy using a validated risk stratification system to identify those with indications for continued surveillance.

Micro-RNA

Micro-RNAs (miRNAs) are 18-25 nucleotide noncoding RNA sequences that are transcribed but not translated into proteins. Some miRNAs have been shown to possess oncogenic or tumor suppressor activity and relate to apoptosis, proliferation, differentiation, metastasis, angiogenesis, and immune response, which are all potentially involved in cancer initiation, progression and treatment response[45,46]. MiRNAs can also be detected circulating in a cell-free form in blood, most probably in exosomes which protect them against degradation by ribonuclease, and their signatures in blood are similar in men and women, as well as individuals of different age[47,48]. Furthermore, miRNA levels are similar in plasma and serum, and freeze/thaw as well as prolonged storage at room temperature does not affect their levels[48]. Thus, serum miRNAs have the potential of a novel biomarker for many cancers. Lawrie *et al*[49] first discovered tumor-specific deregulation of circulating miRNAs and subsequently, circulating miRNAs have been suggested great potential as biomarkers for many cancers including gastric cancer[48,50,51]. Moreover, accumulating reports suggest the potential of miRNAs in the early detection of gastric cancer.

We investigated serum miRNAs as markers to individuals at high risk for gastric cancer not only before *H. pylori* eradication but also after eradication. The serum levels of miR-106b and let-7d before and after *H. pylori* eradication; miR-21 after eradication were significantly higher in the high-risk group than in controls. *H. pylori* eradication significantly changed serum pepsinogen levels even in the high-risk group, whereas eradication did not significantly alter miR-106b and let-7 levels in the high-risk group. These results suggest that serum miRNAs may be equivalent or even superior to serum pepsinogen as a biomarker to detect those at high risk for gastric cancer before and after *H. pylori* eradication[52].

EFFECT OF *H. PYLORI* ERADICATION ON CANCER INCIDENCE

In the first half of the 20th century it was recognized that gastric cancer risk was related to atrophic gastritis[7,53]. The late 20th century brought new information

and identified that gastric cancer was an inflammation-related cancer caused by chronic infection with *H. pylori*. It was initially unclear whether *H. pylori* eradication alone would suffice to eliminate or greatly reduce gastric cancer risk or whether some form of surveillance would be still required. The fact that those with atrophic gastritis whose *H. pylori* had disappeared spontaneously following destruction of the normal gastric niche for their growth still retained a high risk of gastric cancer suggested that *H. pylori* eradication alone was likely to prove insufficient[6]. Many clinical studies have subsequently examined the effect of *H. pylori* eradication on the subsequent incidence of gastric cancer. For example, Take *et al*[54] in a prospective non-randomized eradication study among more than1100 Japanese patients with peptic ulcers showed that *H. pylori* eradication reduced the risk of subsequently developing gastric cancer. A follow-up for a mean of 3.9 years of these patients found that gastric cancer developed in less frequently among those who had had successful *H. pylori* eradication compared to those with persistent infection (0.23% *vs* 0.70% at 1 year, $P = 0.04$, log-rank test)[54]. While eradication did not completely eliminate the risk, and the risk was related to the extent of atrophic gastritis at the time of eradication therapy[54]. The remained risk of developing gastric cancer was reported to be 0.30% per year[55]. The Shangdong intervention trial failed to find a difference in gastric cancer incidence after 7.3 years but did find a significant fall 14.7 years post *H. pylori* eradication therapy[7,56]. The latest meta-analysis has confirmed that successful eradication reduced the risk for gastric cancer and included 6 randomized controlled trials including four from China, one from Japan, and one from Colombia. The median follow-up period was 6 years. The pooled analysis yielded a relative risk for gastric cancer of 0.65 (95%CI: 0.43-0.89) following successful eradication therapy[57].

One effect of *H. pylori* eradication therapy is to stop the progression of damage and thus lock in or reduce the gastric cancer risk present at the time of *H. pylori* eradication[6]. Thus, those with non-atrophic gastritis would be expected to have negligible risk of subsequently developing gastric cancer whereas those with atrophic gastritis would be expected to have a risk equal to or somewhat lower than others with the same pattern of gastritis but definitely lower than an untreated cohort whose risk would increase yearly as the disease progressed[6]. The available data confirm these expectations[6,41]. However, there are few studies that have followed patients who were matched based on risk stratification. A longitudinal cohort study of 9.3 years in Japan reported significant reduction in cancer incidence after eradication in *H. pylori* positive patients with mild atrophic gastritis as evaluated by serum pepsinogen testing. The incidence per 100000 person-year in those with persistent infection was 111 compared to 69 among those the infection was eradiated. However the cancer incidence was not significantly different (237 *vs* 223) among the patients with more severe atrophy[58].

Eradication of the infection stops the inflammatory process, promotes healing of gastritis and resolution of inflammation. Nonetheless, the link between *H. pylori* and cancer runs through atrophic gastritis and intestinal metaplasia, and eradication cannot reverse the severe atrophic damage and intestinal metaplasia, especially incomplete type or SPEM that has already occurred. For examples, *H. pylori* eradication prior to development of intestinal metaplasia improves corpus gastritis enhancing sonic hedgehog (SHH) and its downstream regulators and diminishing SHH methylation and aberrant CDX2 expression, which inhibit intestinal development and differentiation and reverse gastric phenotype. However, eradication in patients with high risk such as atrophy with intestinal metaplasia, especially incomplete type or a history of endoscopic treatment for gastric cancer does not result in much if any improvement[22,59,60]. The ability to predict the point of no return for the development of the malignancy is of particular interest and whether the presence of severe atrophy, SPEM, or some intestinal metaplasia subtypes alone or together correspond to this point, still need to be investigated[61].

CUMULATIVE INCIDENCE OF METACHRONOUS CANCER AFTER ERADICATION

The group with the highest risk of gastric cancer includes those who have already had one cancer cured by upper gastrointestinal endoscopy. Several studies have reported incidence of metachronous cancer after successful *H. pylori* eradication (Table 1).

Uemura *et al*[62] were the first to show that *H. pylori* eradication could reduce the risk of development of gastric cancer in this group of patients when, in a retrospective study, 132 patients with early gastric cancer were followed after endoscopic resection; metachronous gastric cancer developed only in 6 of 67 (9%) patients without eradication over a follow up of 3 years. A later multicenter prospective randomized study in Japanese patients followed for 3 years after endoscopic removal of an early gastric cancer found metachronous gastric cancer in 9 of 272 (3.3%) patients with *H. pylori* eradication *vs* 24 of 272 (8.8%) controls[14]. The incidence of metachronous gastric cancer was reduced significantly (OR = 0.35, 95%CI: 0.16-0.78; $P = 0.009$) consistent with *H. pylori* eradication having a benefit in delaying the onset of new cancers in the same stomach.

In contrast, a Japanese retrospective study reported that *H. pylori* eradication did not reduce the incidence of metachronous gastric cancer. Baseline severe mucosal atrophy and a follow-up of more than 5 years were found to be independent risk factors for the development of metachronous gastric cancer[63]. Moreover, a recent Japanese multicenter retrospective cohort study from 12 hospitals detected metachronous multiple cancers in 65 of 1258 (5.2%) during a mean of 26.8 mo. The cumulative

Table 1 Incidence of metachronous cancer after successful *Helicobacter pylori* eradication

Ref.	Country	Subject No.	Study design	Mean follow-up periods	Incidence (%)	Eradication effect (95%CI)
Uemura *et al*[62], 1997	Japan	65/67	NR	3 yr	0 *vs* 9	effective $P = 0.011$
Fukase *et al*[14], 2008	Japan	272/272	Multicenter open-label RCT	3 yr	3.3 *vs* 8.8	effective 0.35 (0.16-0.78) $P = 0.009$
Shiotani *et al*[12], 2008	Japan	80	single arm	33 mo	11.3	
Hanaoka *et al*[66], 2010	Japan	82		55 mo	14.6	
Maehata *et al*[63], 2012	Japan	177/91	retro NR	3 yr 1.1-11.1 yr	8.5 *vs* 14.3	OR = 1.71 (0.72-4.03)
Kato *et al*[64], 2013	Japan	263/105	Multicenter retro cohort	26.8 mo 2-5 yr	3.5/Y	NS
Seo *et al*[65], 2013	South Korea	61/13	retro cohort	27.2 mo	9.8 *vs* 23.1	OR = 0.36 (0.08-1.70),
Chon *et al*[69], 2013	South Korea	129 85/44	Retro NR	26 mo 16.5-30 mo	4.7 *vs* 11.4	effective HR = 0.143 $P = 0.008$

Subject No.: Number of subjects with eradication/without eradication and with failure of eradication; RCT: Randomized controlled trial; NR: Non-randomized; Retro: retrospective; NS: Not significant.

incidence of metachronous cancers increased linearly and the mean annual incidence rate was 3.5%. The incidence rate did not differ between patients with or without *H. pylori* eradication[64]. A recent study from Korea also reported that metachronous gastric cancer showed a decrease in the eradicated group, but this did not reach statistical significance (OR = 0.36, 95%CI: 0.08-1.70, $P = 0.189$), although metachronous gastric cancer was significantly decreased in the eradicated group (OR = 0.108, 95%CI: 0.016-0.726, $P = 0.035$) among the subgroup who were followed-up for more than 18 mo[65].

These recent studies have all confirmed that the presence of one early gastric cancer identifies a group of patient at extremely high risk of metachronous cancer consistent with the histologic analysis of the remaining gastric mucosa in patients with early gastric cancer undergoing gastric resection. The risk of a metachronous cancer among those not having *H. pylori* eradication appears to be in the range of 3%-4% per year (*e.g.*, 3000 to 4000/100000 per year) (Table 1). Overall *H. pylori* eradication appears to reduce that risk but this is not seen in all studies and studies are needed to identify risk factors that correlate with subsequent risk such as pattern and extent of atrophy as well as better characterization of the mucosa in terms of inflammation, presence and extent of SPEM, different types of intestinal metaplasia, gastric microbiota, *etc.*.

PREDICTIVE FACTORS FOR METACHRONOUS GASTRIC CANCER AFTER *H. PYLORI* ERADICATION

Previous studies have looked at factors that helped predict development of gastric cancer after *H. pylori* eradication and those data might provide clues to risk stratification after endoscopic removal of an early gastric cancer and *H. pylori* eradication. *H. pylori* eradication will thus produce two populations: those with minimal to no risk and those with some residual risk for cancer. Those with residual risk can likely be assured that their risk will not increase as they age and although it will probably decrease somewhat, some risk remains[7]. Our previous study showed that atrophy in biopsy specimens from the lesser curvature of the corpus was strongly associated with gastric cancer risk[12]. The frequency of severe atrophy assessed by histology (100% *vs* 53.2%, $P = 0.03$) was higher and the serum pepsinogen I / II ratio before *H. pylori* eradication was significantly lower in the group that developed metachronous cancer compared to the group that did not. A pepsinogen I of < 25 ng/mL before eradication was significantly associated with development of a new lesion[12]. Moreover, extensive atrophic gastritis diagnosed by autofluorescence imaging (AFI), which is new endoscopic imaging technology using illumination of different wavelength light through a filter in a light source[21], was a significant predictor for metachronous cancer developed after successful eradication and could possibly be useful to identify patients undergoing endoscopic submucosal dissection who still required intensive surveillance after eradication[66].

For many individuals *H. pylori* eradication equates with cancer prevention whereas for others it only produces a reduction in risk. This difference in outcome depends on the level of risk when the eradication is performed. For those with history of endoscopic resection of one cancer, *H. pylori* eradication followed by surveillance for gastric cancer is generally indicated (*i.e.*, a combination of primary and secondary prevention), because the risk of gastric cancer remains high even after *H. pylori* eradication[6,53]. The previous study indicated that levels of hMLH1 promoter hypermethylation, which is a frequent cause of the microsatellite instability (MSI) -H phenotype, are similar in the surrounding non-cancerous tissue compared to cancer tissue[67]. In addition, another study indicated that MSI and hypermethylation of hMLH1 in cancer lesions were detected more frequently in the patients with multiple gastric cancers than those with

solitary gastric cancer[68]. These results indicate that inactivation of hMLH1 through promoter hypermethylation seems to be involved in the development of multiple gastric cancers following the MSI pathway. MSI or hypermethylation of hMLH1 as well as serum miRNA might be potential predictive markers for metachronous cancer. Studies are required to establish appropriate markers irrespective *H. pylori* eradication for gastric cancer screening.

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