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REVIEW

Clinical prevention of gastric cancer by *Helicobacter pylori* eradication therapy: a systematic review

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Abstract *Helicobacter pylori* (*H. pylori)* infection plays an important role in gastric carcinogenesis. We conducted a systematic review concerning gastric cancer development after *H. pylori* eradication therapy. In total 15 papers matched our criteria, the results were reviewed. The *H. pylori* eradication therapy statistically diminished the prevalence of clinical gastric cancer by approximately one-third. The studies from Japan supported this conclusion; however, studies from overseas reported conflicting results. The differences in these conclusions lie in the diagnostic ability of endoscopic examination, since the clinical stage was quite different between these studies. Gastric cancer that developed after eradication revealed a mainly intestinal type histology and depressed-type appearance. The following are possible reasons for reduced gastric cancer: (1) eradication therapy inhibits the new occurrence of gastric cancer, (2) eradication regresses or inhibits the growth of gastric cancer, and (3) eradication interferes with the discovery of gastric cancer. Considering the biological nature of cancer cell proliferation, a sufficiently long-term follow-up may clarify the effect of eradication therapy on inhibition of the development (not discovery) of gastric cancer and reduction of gastric cancer-related mortality.

Keywords *H. pylori* · Eradication · Gastritis · Gastric cancer · Systematic review

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Introduction

Previous studies clarified the carcinogenic mechanism of human gastric cancer [1]. Two distinct pathways exist in gastric carcinogenesis: intestinal- and diffuse-type gastric cancer, and multi-step genetic and epigenetic alterations contribute to gastric carcinogenesis by the alteration of oncogenes, tumor-suppressor genes, cell-cycle regulators, cell adhesion molecules, DNA repair genes, and genetic instability and telomerase activation [1]. Further, recent genome-wide analysis revealed the specific genetic and epigenetic alteration contributing to gastric carcinogenesis [2, 3].

Clinically, gastric cancer is the second most common cancer in the world, and the number of newly diagnosed cases was calculated as 750,000 persons per year [4]. The discovery of *Helicobacter pylori (H. pylori)* in 1983 markedly changed the gastric carcinogenic theory, and it has been widely accepted that there is a strong association between *H. pylori* infection and gastric cancer [5]. Nomura et al. [6] and Parsonnet et al. [7] first reported the relationship between *H. pylori* infection and gastric cancer in 1991. In 1994, the International Center for Cancer Research officially recognized that *H. pylori* was a definite carcinogen for gastric cancer on the basis of several epidemiological reports [8]. *H. pylori* infection induces chronic inflammation of the gastric mucosa and, as previously demonstrated by Correa et al. [9], atrophic gastritis

and the subsequent intestinal metaplasia are regarded as essential for intestinal-type cancer development. In Japanese patients, *H. pylori* is known to be almost the sole factor inducing chronic gastritis, since autoimmune gastritis is very rare in Japan [10–12]. In addition, many investigations have shown a close relationship between *H. pylori* and not only intestinal-type cancer, but also diffuse-type cancer, especially in those of a younger age [13, 14]. In 2001, a prospective cohort study of 1,246 Japanese people conducted for 7.8 years demonstrated that gastric cancer developed only in patients with *H. pylori* infection [15]. In addition, advanced research has clarified the gastric carcinogenic mechanism after *H. pylori* infection [16]. The mechanism involving CagA protein, which is produced by *H. pylori* and injected into host cells, had the greatest impact on investigations in this field [17–19].

Now, we need to clarify whether we can control gastric carcinogenesis using eradication therapy for *H. pylori*. A recent report demonstrated that the incidence of *H. pylori*-negative gastric cancer is extremely low [20]. We also found that the incidence of gastric cancer patients without *H. pylori* infection was less than 1%. If we could completely control *H. pylori* infection, the incidence of gastric cancer would became less then 1/10 (or 1/100) and clinical practices regarding gastric cancer would markedly change. However, it is still unclear whether the eradication therapy for adults actually reduced the incidence of gastric cancer. In the present study, we conducted a systematic review concerning gastric cancer development after eradication therapy. The following were the main purposes of this review: (1) to clarify the incidence of gastric cancer development after eradication therapy, and discuss the clinical benefit of eradication therapy for gastric carcinogenesis, and (2) summarize the clinico-pathological feature of gastric cancer discovered after eradication therapy and clarify the character of these cancers.

Methods

Screening the papers for a systematic review

In the first stage, a search of the literature was conducted among articles registered up to November 2008 in PubMed using the following key words: "*Helicobacter pylori*", "gastric cancer", and eradication. The final aim was to collect papers providing clinical information on gastric cancer discovered after eradication therapy. After the addition of some related articles, 601 papers were finally acquired. In the second stage, these 601 papers were screened and further concentrated based on their titles and abstracts, using the following criteria: (1) papers describing gastric cancer after eradication therapy, (2) gastric cancer diagnosed by endoscopic/histological examination, and (3) a status of *H. pylori* infection was judged correctly. Omitted papers included the following: (1) review articles, (2) those not covering gastric cancer, (3) those concerning only in vitro or animal model studies, and (4) those not distinguishing gastric cancer from adenoma/dysplasia. As a result, 15 papers were chosen for this systematic review. If information on a subject was probably included in another paper, the duplicated data were omitted in the summarized table.

Results

Incidence of gastric cancer after eradication therapy

Out of the 15 papers collected, 12 (7 from Japan and 5 from overseas) described the effect of eradication therapy on the discovery of gastric cancer (Table 1). All five overseas studies were designed as randomized controlled trials [21–25]. Odds ratios in the five overseas papers were reported as 0.16–1.28, and all five studies concluded that the effect of eradication therapy was not significant.

On the other hand, seven studies (one randomized and six non-randomized trial) were reported from Japan [26–32]. Firstly, Uemura et al. [26] reported a reduced incidence of secondary gastric cancer development by eradication therapy in patients with endoscopic resection of primary gastric cancer. Another four non-randomized studies also demonstrated that eradication therapy significantly reduced the prevalence of gastric cancer discovery after eradication therapy. The odds ratios reported were quite similar with 0.21–0.36 [26–31]. Recently, Fukase et al. [32] (Japan Gast Study Group) conducted an open-label, randomized controlled trial and examined the rate of discovering of secondary cancer. They enrolled patients who previously received the endoscopic resection of primary cancer, and confirmed the same results (odds ratio: 0.34) [32]. These results completely agreed with conclusion by previous Japanese studies.

Clinicopathological feature of gastric cancer discovered after eradication therapy

Ten papers included in this review described clinicopathological data on gastric cancer discovered after eradication therapy (Table 2) [21, 22, 27, 29–35]. Focus should placed on the difference in the tumor stage between subjects from Japan and overseas. As demonstrated in Table 2, most gastric cancer patients (16/19; 84%) reported from overseas were diagnosed at an advanced stage, whereas only five of 81 (6%) Japanese cancer patients were diagnosed with advanced cancer. This difference was significant ($P < 0.01$).

Table 1 Effect of *Helicobacter pylori* eradication therapy on the discovery of gastric cancer

References	Year	Design	Period (years)	Number of cases		Discovered gastric cancer		OR (95% CI)	Tumor stage (I/II–IV)
				Eradicated	Control	Eradicated	Control		
Studies from overseas									
Wong et al. [21]	2004	RCT	7.5	817	813	7	11	0.63 (0.24–1.63)	ND[a]
Leung et al. [22]	2004	RCT	5	220	215	4	6	0.65 (0.18–2.32)	0/4
Mera et al. [23]	2005	RCT	12	394	401	5	4	1.28 (0.34–4.79)	ND
Zhou et al. [24]	2005	RCT	8	246	306	1	6	0.16 (0.02–1.37)	ND
You et al. [25]	2006	RCT	7.3	1,130	1,128	19	27	0.70 (0.39–1.26)	ND
Studies from Japan									
Uemura et al. [26]	1997	NR	4	65	67	0[c]	6[c]		0
Kato et al. [27]	2006	NR	5.9	1,788	1,233	23	44	0.36 (0.22–0.62)	22/0
Take et al. [28, 29]	2005, 2007	NR	3.9	953	178	9	4	0.26 (0.08–0.83)	8/1
Takenaka et al. [30]	2007	NR	3.3	1,519	288	6	5	0.21 (0.06–0.69)[b]	5/1
Ogura et al. [31]	2008	NR	3.1	404	304	6	13	0.34 (0.11–0.99)[b]	5/1
Fukase et al. [32]	2008	RCT	3	272	272	9[c]	24[c]	0.34 (0.16–0.73)	9/0

ND not described, *RCT* randomized controlled trial, *NR* non-radomized study

[a] Three patients died of gastric cancer

[b] Did not reach a significant difference regarding diffuse-type cancer

[c] Secondary cancer after endoscopic resection of primary cancer

Table 2 Characters of gastric cancer detected after eradication therapy

References	Year	Number	Tumor stage (I/II–IV)	Histology (intestinal/diffuse)	Macroscopic feature (elevated/depressed)
Studies from overseas					
Wong et al. [21]	2004	7	ND[a]	7/0	ND
Leung et al. [22]	2004	4	0/4	ND	ND
Kokkola et al. [33]	2008	35	3/12	4/11	ND
Total		46	3/16	11/11	
Studies from Japan					
Kamada et al. [34]	2005	20	19/1	15/5	2/18
Kato et al. [27]	2006	23	23/0	19/4	4/18
Take et al. [29]	2007	9	8/1	4/5	ND
Takenaka et al. [30]	2007	6	5/1	4/2	ND
Takata et al. [35]	2007	8	7/1	8/0	1/6
Ogura et al. [31]	2008	6	5/1	3/3	2/3
Fukase et al. [32]	2008	9[b]	9/0	9/0	ND
Total		81	76/5	62/19	9/45

ND not described

[a] Three patients died of gastric cancer

[b] Secondary cancer after endoscopic resection of primary cancer

In Japanese studies, in which most cancer lesions were detected in the early stage, the tumor histology was intestinal-type-dominant (62/81; 77%). Endoscopically, depressed-type features were characteristic in gastric cancer after eradication (45/54; 83%). Four papers commented on the risk factors of cancer development after eradication; these were the older age of patients[29, 30, 35] and advanced atrophic change in the gastric corpus [29, 34].

Discussion

Since *H. pylori* is the strongest known carcinogen, there is no doubt the eradication therapy is beneficial for gastric cancer prevention. Theoretically, eradication therapy will remove the direct carcinogenic effect of *H. pylori*. Recent studies have clarified two distinct carcinogenic mechanisms of *H. pylori* infection. One is a direct effect by *H. pylori*

itself on the surface epithelium, and the other is an indirect effect the chronic gastritis, including the characteristic inflammation associated with mononuclear cell/neutrophil infiltration. For the former pathway, one of the most important factors is CagA protein injected by *H. pylori*. The mechanism of CagA-related toxicity has been clearly demonstrated by Hatakeyama et al. [16]. The removal of CagA should be beneficial for the primary inhibition of gastric carcinogenesis. In addition, Matsumoto et al. [36] recently revealed the importance of aberrant expression of activation-induced cytidine deaminase after *H. pylori* infection. For the latter inflammation-related mechanism, it is supposed that superoxides produced by gastric inflammatory reactions plays an important role in this pathway [37, 38]. *H. pylori* eradication improves gastric inflammation by randomized controlled trials, suggesting the removal of inflammation-mediated carcinogenesis [23, 39].

Recovery from the pre-malignant status was also confirmed in several studies. Sung et al. [40] reported the results of a large-scale prospective randomized study, and concluded that eradication therapy prevents the progression of atrophy. Correa et al. [41] reported that eradication therapy could regress not only the degree of atrophy, but also intestinal metaplasia in a randomized controlled trial. Leung et al. [22] also demonstrated that eradication therapy could prevent the progression of intestinal metaplasia in a randomized controlled trial with a 5-year follow-up. In Japanese patients, several studies demonstrated the reversibility of atrophy after *H. pylori* eradication therapy [42–44]. Furthermore, we previously followed-up 22 patients in whom *H. pylori* was successfully eradicated for 5 years, and confirmed that glandular atrophy and intestinal metaplasia are reversible [45]. In addition, Gotoda et al. [46] was the first to report the endoscopic regression of gastric adenoma after successful eradication therapy.

What about gastric cancer? We demonstrated in this review that eradication therapy could not reduce the incidence of advanced gastric cancer (or gastric cancer in Western countries), but could lower the incidence of early gastric cancer in Japan. The odds ratio is quite similar in several non-randomized studies and one randomized controlled trial (0.21–0.36), suggesting the reliability of these results. How does eradication therapy influence gastric carcinogenesis? The following are the possibilities: (1) eradication therapy actually inhibits the new occurrence of gastric cancer, (2) eradications inhibit the growth of gastric cancer, and (3) eradication influences the endoscopic detection of gastric cancer.

It is difficult to discuss the first hypothesis based on only our review, because most cancer discovered after eradication was intestinal-type early cancer and was involved a relatively short-term follow up (less than 10 years). The focus should be placed on the natural time-course of gastric cancer. It takes a long time until a single cancer cell has grown sufficiently to be detectable on endoscopic examination. Although the growth rate of gastric cancer cells differs for each tumor, Haruma et al. [47] already reported that doubling time of early gastric cancer was approximately 16.6 months. From this fact, it is likely that when we detect a cancer lesion in the stomach by endoscopic examination, cancer cells have already been generated. Although the improvement of the pre-malignant status (atrophy or intestinal metaplasia) is linked to the regression of gastric carcinogenesis at an extremely early stage, a long-term (more than 10-year) follow-up may be necessary to confirm the effect of eradication therapy on gastric carcinogenesis.

Therefore, it is suggest that the second hypothesis may be likely to explain the results summarized in this review, that is, the eradication therapy had an anti-proliferative effect on gastric cancer cells in the early stage. Indeed, we previously reported that the Ki-67 labeling index in cancer cells was lower in cancer lesions without than in those with *H. pylori* infection [48]. However, we should confirm and recognize the biological meaning of "true cancer cells", which influence clinical cancer mortality. Fundamentally, cancer cells show autonomous and invasive growth. Actually, the eradication therapy markedly alters the environment around cancer cells, reducing some important chemokines, cytokines, and growth factors [49, 50]. Of course, these greatly modify the growth of gastric cancer cells, but it means the simple inhibition of reactive growth and not autonomous growth.

In addition, we should pay attention to the third hypothesis. Researchers can evaluate the degree of carcinogenesis only based on the discovery rate of gastric cancer by endoscopic examination. Due emphasis must be placed on the differences in the diagnostic ability of each examination. Actually, as demonstrated in Table 2, the difference in the tumor stage discovered after eradication was quite marked between studies from Japan and overseas, resulting in a completely opposite conclusion.

If the eradication therapy truly exhibits an anti-proliferative effect against early cancer cells as described, the therapy should also have same effect on "detectable" early gastric cancer. In addition, if the eradication itself influences the tumor morphology, this may affect the tumor discovery rate. We previously investigated the morphological changes in gastric cancer after *H. pylori* eradication. After a one-month follow-up, one-third of the gastric tumors (not only adenoma but also cancer) became indistinct, and some tumors were difficult to discern through ordinary endoscopic observation, especially in cancer with an intestinal histology and elevated appearance [51]. Even if the true incidence of cancer is not affected, the clinical incidence of cancer discovery would be influenced by successful eradication therapy. Furthermore, we detected a

unique histological change in cancer tissue, that is, normal columnar epithelium over the neoplasm [51]. These must make it more difficult to detect gastric cancer by endoscopic observation. Recently we found that the gastrin–gastrin receptor system may play a role in the regression of early gastric cancer tissue [52].

It is interesting that most cancer discovered after eradication revealed depressed features. Comparing to the ordinary cancer discovered, this morphological feature is characteristic [53]. There are two ways in which gastric tumors may grow: one is invasive downward growth, and the other is expansive growth in the upward (luminal) direction. The latter may include a reactive factor, which may be regulated by the gastric inflammation induced by *H. pylori* infection. From our summarized data, the endoscopic appearance of cancer discovered after eradication was depressed-type-dominant, supporting this hypothesis. If the eradication therapy mainly influences the expansive growth, the true biological behavior of gastric cancer may not be improved simply by eradication therapy.

The final goal of gastric cancer prevention is decreased mortality from gastric cancer. Until now, studies revealed the effect of eradication only for the prevention of intestinal-type cancer, and no study clarified the effect against diffuse-type cancer. As is well known, the progress in cancer mass screening and endoscopic treatment plays an important role in the control the gastric cancer mortality, especially in intestinal-type cancer [54]. The next target in this field must be the diffuse-type gastric cancer which has a biologically malignant character, especially in younger patients. Recent studies revealed a high odds ratio for diffuse-type gastric cancer discovery in patients with nodular gastritis, which may be an important background [55, 56]. This type of gastritis should be an important target for earlier eradication therapy to reduce cancer death. Finally, in this systematic review, it should be emphasized that five (6%) tumors was discovered at an advanced stage even in Japanese studies. These tumors included both intestinal- and diffuse-type cancer, and notably two studies showed advanced cancer with an intestinal histology [29, 35]. Especially, our case revealed a submucosal tumor-like feature, which may be an new clinical problem within this field [35]. We have to pay attention to the delayed discovery of early gastric cancer, based on changes in morphology.

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