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**Management of *Helicobacter pylori* infection after gastric surgery**

Lin YS *et al*. Manage *H. pylori* after gastrectomy

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**Abstract**

The Maastricht IV/Florence Consensus Report and the Second Asia-Pacific Consensus Guidelines strongly recommend eradication of *Helicobacter pylori* (*H. pylori*) for patients with previous gastric neoplasia already treated with gastric surgery. However, the guidelines do not mention optimal timing, eradication regimens, diagnostic tools, and follow-up strategies for patients undergoing gastrectomy and do not indicate if eradication of *H. pylori* reduces the risk of marginal ulcer or stump cancer in the residual stomach after gastrectomy. The purpose of this review is to provide an update that may help physicians properly manage *H. pylori* infection in patients after gastric surgery. This review focuses on (1) the microenvironment change in the stomach after gastrectomy; (2) the phenomenon of spontaneous clearance of *H. pylori* after gastrectomy; (3) the effects of *H. pylori* on gastric atrophy and intestinal metaplasia after gastrectomy; (4) incidence and clinical features of ulcers developing after gastrectomy; (5) does eradication of *H. pylori* reduce the risk of gastric stump cancer in the residual stomach? (6) does eradication of *H. pylori* reduce the risk of secondary metachronous gastric cancer in the residual stomach? and (7) optimal timing and regimens for *H. pylori* eradication, and diagnostic tools and follow-up strategies for patients undergoing gastrectomy.

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**Key words:** *Helicobacter pylori*; Gastrectomy; Gastric stump; Treatment outcome; Stomach neoplasms; Stomach ulcer; Atrophic gastritis; Metaplasia

**Core tip:** For patients undergoing gastric surgery due to acute complications of peptic ulcers diseases or gastric cancer, this operative procedure might increase the occurrence of biliary enterogastric reflux and potentially inhibit the growth of *Helicobacter pylori* (*H. pylori*) in the stomach. Bile reflux and *H. pylori* infection appear to have a synergistic effect on cell proliferation in the gastric remnant and may explain the increased risk of cancer after gastrectomy. The first-line triple therapy regimen is effective for the eradication of *H. pylori* in gastrectomized patients. Serology is the only test that is not affected by local changes in the stomach, and could be used to avoid false-negative results from other tests.

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**INTRODUCTION**

*Helicobacter pylori* (*H. pylori*)is a human pathogen that has infected half of the global population, and its discovery has revolutionized the concept of gastroduodenal diseases. *H. pylori* infection is an important etiologic factor for gastritis, peptic ulcer, and gastric malignancy. In 2012, the Maastricht IV/Florence Consensus Report reinforced the finding that *H. pylori* infection is the most commonly proven risk factor for gastric cancer in humans[1]. Eradication of *H. pylori* has been shown to prevent gastric cancer in patients with this infection; a pooled analysis of 6 studies with mostly Asian participants followed up for 4-10 years showed that the relative risk for gastric cancer after eradication of *H. pylori* was 0.65 (95%CI: 0.43-0.98), and a significant reduction in cases of gastric cancer was seen in subjects with eradication before the development of atrophic gastritis or intestinal metaplasia[2]. The authors suggest that *H. pylori* eradication treatment reduces the risk of gastric cancer, but the risk is not abolished.

Nowadays, eradication of *H. pylori* is strongly recommended in (1) patients with gastroduodenal diseases such as peptic ulcer disease and low-grade gastric mucosa-associated lymphoid tissue lymphoma; (2) patients with atrophic gastritis; (3) first-degree relatives of patients with gastric cancer; (4) patients with unexplained iron deficiency anemia; and (5) patients with chronic idiopathic thrombocytopenic purpura[3]. Prophylactic eradication of *H. pylori* after endoscopic resection of early gastric cancer should be used to prevent the development of metachronous gastric carcinoma[4]. However, the effect of *H. pylori* eradication on the gastric remnant after surgical resection has not been clearly determined[5]. There is some new evidence regarding this, and the Maastricht IV/Florence Consensus Report and the Second Asia-Pacific Consensus Guidelines strongly recommend eradication of *H. pylori* for patients with previous gastric neoplasia already treated with subtotal gastric resection[1,6]. However, the guidelines do not mention optimal timing, eradication regimens, diagnostic tools, and follow-up strategies for patients undergoing gastrectomy and do not indicate if eradication of *H. pylori* reduces the risk of ulcer or stump cancer in the residual stomach after gastrectomy.

The purpose of this review is to provide an update that may help physicians properly manage *H. pylori* infection in patients after gastric surgery. A literature search was mainly conducted in PubMed (1948-), supplementary search in Embase (1974-) and Google Scholar. Search keywords used controlled vocabulary (MeSH or Emtree) and text words, including: *helicobacter pylori*[mesh], *helicobacter* infections[mesh], *helicobacter*, *campylobacter*, *h. pylori*, *c. pylori*; gastrectomy[mesh], gastrectom\*, hemigastrectom\*, gastric surger\*, stomach surger\*; gastric stump[mesh], stump\*, residual, remnant\*; eradicat\*; spontaneous remissions[mesh], spontaneous clearance, spontaneous regression\*, spontaneous eradicat\*; atrophic gastritis[mesh], atrophy[mesh], atroph\*, dysplas\*; metaplasia[mesh], metaplas\*; peptic ulcer[mesh], ulcer\*; stomach neoplasms[mesh], local neoplasm recurrence[mesh], second primary neoplasms[mesh], cancer\*, maliganc\*, carcinoma\*, cancerogen\*, carcinogen\*, neoplasmogen\*, oncogen\*, tumorigen\*. The keywords based on PubMed syntax were revised adequately for the remaining databases. The complex search strategies for the individual sub-topics were properly established, including the combinations of the keywords and the filter of the articles (principally according to the Oxford level of evidence).

**MICROENVIRONMENT CHANGE IN THE STOMACH AFTER GASTRECTOMY**

Food retention and bile reflux have frequently been observed in patients with gastric cancer following subtotal gastrectomy[7]. After gastric surgery, the biochemical profile, microbiological profile, or pH of the gastric juice is dramatically altered. A previous study assessed the presence of N-nitrosamine compounds and bacteria in the gastric juice after gastric surgery[8] and showed that patients who underwent gastric resection with both Billroth (B)-II and B-I gastrectomies had higher mean pH, N-nitrosamine concentrations, nitrate reductase-positive bacterial counts, and anaerobic bacterial counts. In a higher pH microenvironment, the stomach will subsequently reduce concentrations of ascorbic acid, which is an antioxidant that scavenges carcinogenic N-nitrosamines and reactive oxygen species. Oxygen radicals induced by inflammation could contribute to the risk of development of gastric cancer, and the variation of the biochemical and microbiological microenvironment in the gastric juice may play a certain role.

Residual mucosa in the stomach after gastrectomy is considered a risk factor for the development of cancer of the gastric remnant. Chronic inflammation from biliary enterogastric reflux results in hyperplastic changes in the gastric epithelium of the remnant. Bechi *et al*. found that the hyperplastic changes gradually decreased with increasing distance from the anastomosis, which means that the gastric histological findings after partial gastrectomy were affected by reflux[9].

Fukuhara *et al*[10] evaluated 62 patients who underwent curative gastrectomy for gastric cancer for the association between bile reflux and gastritis. The period of bile reflux into the gastric remnant was measured with the Bilitec 2000, and the remnant gastritis was semiquantified using the neutrophil infiltration score based on the updated Sydney System 12 wk after surgery. The results showed that the correlation was independent for *H. pylori* infection, and the investigators concluded that biliary enterogastric reflux after distal gastrectomy can cause remnant gastritis.

**PHENOMENON OF SPONTANEOUS CLEARANCE OF *H. PYLORI* AFTER GASTRECTOMY**

Whether *H. pylori* could persistently survive in the altered environment after gastrectomy remains an interesting issue. Suh et al. reported an overall spontaneous clearance rate of *H. pylori* infection of 38.6% (27/70 patients) during a mean period (from surgery to follow-up tests) of 1.02 ± 0.5 years[11]. The activity and chronic inflammation scores were significantly decreased in the spontaneous clearance group.

The influence of different procedures and duration after surgery on spontaneous clearance of *H. pylori* has been addressed. Generally, with B-I anastomosis, the gastrointestinal tract has normal continuity and the remaining duodenum offers more resistance to recurrent ulceration than the jejunum. The prevalence of *H. pylori* infection was significantly higher in patients who had a partial wedge resection compared with subtotal gastrectomy, because wedge resection results in less biliary enterogastric reflux due to preservation of the pylorus[12]. The lower rate of *H. pylori* infection found in patients who underwent B-II may reflect the role of bile reflux, which may interfere with colonization of *H. pylori*[13].

There was a trend toward a decreasing prevalence of *H. pylori* colonization as the length of time after surgery increased. In our previous study, the prevalence of *H. pylori* 1 to 15 years after surgery was 29.5%, after 16 to 30 years was 13.6%, and after more than 30 years was 10%[13]. The overall spontaneous clearance rate of *H. pylori* after partial gastrectomy was 43%. We also confirmed that B-II was associated with a higher rate of bile reflux and lower prevalence of *H. pylori* infection than the B-I procedure.

It was assumed that the microenvironment for *H. pylori* colonization after surgical interventions changes dramatically and thus influences their survival. First, the hypochlorhydric environment due to antrectomy is an unfavorable factor for the growth of *H. pylori*[14]. Second, biliary enterogastric reflux emerges because of the loss of the pyloric ring, which might inhibit *H. pylori* growth. Third, the substitution of intestinal-type epithelium for gastric parietal cells makes the mucosa more resistant to *H. pylori* infection[15]. Finally, loss of the usual site of infection plays a major role because the prevalence of *H. pylori* remains high after vagotomy, which carries only the hypochlorhydric environment[16]. All of these factors may make the microenvironment unfavorable for *H. pylori*.

**EFFECTS OF *H. PYLORI* ON GASTRIC ATROPHY AND INTESTINAL METAPLASIA AFTER GASTRECTOMY**

After gastrectomy, a potential cause of remnant gastritis is *H. pylori* infection accompanied by biliary enterogastric reflux[17]. Iferadication of *H. pylori* in patients after gastrectomy is beneficial, what would be the effect of *H. pylori* eradication on gastric atrophy and intestinal metaplasia at the gastric remnant? Fukuhara et al. investigated concentrations of interleukin (IL)-8, a sensitive marker of inflammation in the gastric mucosa, 3 months after surgery. In the absence of *H. pylori* infection, IL-8 concentrations were 13, 56, and 87 pg/mg in groups A (Roux-en-Y), B (B-I), and C (B-II), respectively (*P* < 0.05). In the presence of *H. pylori* infection, IL-8 concentrations were 61, 161, and 234 pg/mg protein in groups A, B, and C, respectively (*P* < 0.01)[18]. Both bile reflux and *H. pylori* infection are independent risk factors for the development of gastritis and intestinal metaplasia in the remnant stomach after distal gastrectomy. Cho *et al*. found that in the absence of *H. pylori*, regardless of eradication, treatment or spontaneous clearance may lead to regression of gastric atrophy and intestinal metaplasia in the remnant stomach with time[19]. It is difficult to separate causally relevant factors of bile reflux and *H. pylori* infection from co-incidences or collateral changes. Abe et al. examined the severity of remnant gastritis in 184 patients who had had distal gastrectomy performed using the B-I (*n* = 106), B-II (*n* = 36) and jejunal interposition (*n* = 42). *H. pylori* infection was confirmed in 55.6% of the B-I patients and 76.1% of the jejunal interposition patients. The rate of *H. pylori* infection was higher for jejunal interposition patients than for B-I (*P* < 0.05)[20]. The severity of chronic and active inflammatory cellular infiltration tended to be inverse proportional relation with the endoscopic severity of the remnant gastritis. We still do not know the bile reflux with its subsequently decreased *H. pylori* incidence may neutralize the effect on cancer development?

Ando *et al*[10] found that chronic inflammation and atrophy scores were improved after eradication and no secondary stomach cancers were found on endoscopy[5]. In a study by Kato *et al*[21]the pH of gastric juice was measured in 112 *H. pylori*-positive patients who underwent distal gastrectomy and *H. pylori* eradication therapy. The pH of the gastric juice showed a reverse correlation with the serum pepsinogen I/II ratio, which could be a suitable surrogate marker of gastric mucosal atrophy. The investigators concluded that eradication therapy for the remnant stomach contributes to the possible improvement of stomach conditions by normalizing the pH of the gastric juice.

**INCIDENCE AND CLINICAL FEATURES OF ULCERS DEVELOPING AFTER GASTRECTOMY**

The need to perform gastrectomy on patients with peptic ulcer disease has decreased since the discovery of *H. pylori* and the development of proton pump inhibitors. The sequelae of gastrectomy are recurrent ulcers, especially marginal ulcers, or cancer of the gastric remnant.

It has been reported that the incidence of marginal ulcers varies from 0.6% to 16%[22,23]. Development of a marginal ulcer after gastrectomy for a bleeding ulcer is a serious threat to the patient. *H. pylori* infection is the primary risk factor for gastric ulcers. However, its role in marginal ulcers after surgery is unclear. A study by Chung *et al*., which included a consecutive series of 78 patients with endoscopic ulcers and 759 patients without ulcers after gastrectomy[24], showed that the incidence of ulcers after gastrectomy was 9.3% and the majority (92%) were marginal ulcers. Ulcers were more common in patients with B-II anastomosis and pre-existing peptic ulcer disease. Infection rates of *H. pylori* did not differ significantly between the 2 groups and suggested that *H. pylori* is not an important factor in ulcerogenesis after gastrectomy.

In a study by Leivonen *et al*[25] 41 of 155 patients had an ulcer at the site of anastomosis or in the gastric stump after a median interval between surgeries of 4 years. The recurrence rate was higher after B-II (34%) than after Roux-en-Y (14%) or B-I reconstruction (24%). Interestingly, recurrent ulcer was less often found in those with *H. pylori*–positive gastritis (18%) than *H. pylori*–negative gastritis (26%). It seems that *H. pylori* infection plays a minor role in the pathogenesis of ulcer recurrence after partial gastrectomy. Eradication of *H. pylori* of the remnant stomach is therefore presumably not effective in preventing ulcer recurrence. A randomized controlled study on a larger scale to assess the clinical relevance is therefore still necessary.

**DOES ERADICATION OF *H. PYLORI* REDUCE THE RISK OF GASTRIC STUMP CANCER IN THE RESIDUAL STOMACH?**

Gastric stump cancer (GSC) is defined as a carcinoma developing in the gastric remnant more than 5 years after surgery for benign disease[26]. It is recommended that patients with previous gastric neoplasia already treated by subtotal gastric resection undergo eradication therapy[1,6], but the recommendations do not mention the need for eradication of *H. pylori* to prevent GSC in patients who have undergone gastrectomy for benign lesions such as ulcer with bleeding, perforation, or obstruction.

In a study by Chung, GSC was found in 6 (0.7%) of 837 patients who underwent gastrectomy[24]. The overall risk increased over time, and the median interval between the initial gastrectomy and diagnosis of GSC was 25 years[24]. The occurrence of GSC is higher in patients with an initial diagnosis of gastric rather than duodenal ulcer and after B-II reconstruction[27], and GSC is predominantly found in men[24]. A meta-analysis of 22 studies showed that the overall relative risk for GSC was 1.66 (95% CI: 1.54-1.79)[27]. Patients who underwent surgery 15 or more years previously had a weighted mean relative risk of 1.48 (95%CI: 1.31-1.67). Spontaneous clearance of *H. pylori* after partial gastrectomy was noted with time after surgery[13,19] and had a reverse association with the occurrence of GSC. Biliary enterogastric reflux may impair the growth of *H. pylori*.

The cause of cancer in the gastric stump is multifactorial, and the increased mucosal cell proliferation caused by bile reflux has been claimed to increase the risk of GSC[28]. Leivonen conducted a retrospective study of 130 patients who underwent partial gastrectomy for peptic ulcer. Cell proliferation was determined using immunohistochemical staining of Ki-67 antibodies from gastric remnants, and there was no clear association between proliferation and *H. pylori*. However, a significant difference was seen between reconstruction types, which is known to be associated with bile reflux[29]. One large population-based study from Sweden revealed an increased risk of cancer in the gastric remnant only 30 years or more after gastric resection for benign disease, whereas other factors did not influence this risk[30]. Roux-en-Y reconstruction has been shown to eliminate the symptomsof bilereflux gastritis. Twenty-nine patients partially gastrectomized for peptic ulcer were reoperated 4-13 years later with a Roux-en-Y reconstruction because of reflux gastritis in 12 patients and gastric severe dysplasia/early gastric cancer in 17 patients[31]. The prevalence of *H. pylori* infection was not statistically different between the patients with reflux gastritis (6/12) and those with severe dysplasia or gastric neoplasms (12/17). It meant *H. pylori* plays less role on GSC after gastric surgery for peptic ulcer.The subsequent biopsies from the new anastomotic region were taken 5-17 years after Roux-en-Y reconstruction and were evaluated for active chronic gastritis, atrophy, intestinal metaplasia and dysplasia. A progression of active chronic gastritis, atrophy, intestinal metaplasia and dysplasia was seen even the reflux was tried to be diverted after Roux-en-Y reconstruction but was independent of *H. pylori* infection.

In the intact stomach, *H. pylori*–associated gastritis is considered a major risk factor for cancer and as for other cancers; removing one factor does not prevent all gastric cancer cases. Based on these clinical observations, it is difficult to determine a certain role of *H. pylori* eradication for prevention of GSC[32]. A cohort study to assess the clinical relevance of *H. pylori* eradication in this circumstance is therefore necessary.

**DOES ERADICATION OF *H. PYLORI* REDUCE THE RISK OF SECONDARY METACHRONOUS GASTRIC CANCER IN THE RESIDUAL STOMACH?**

***In patients with endoscopic resection of early gastric cancer***

EGC Gastric cancer is considered to develop from precursor lesions such as chronic atrophic gastritis, intestinal metaplasia, and dysplasia. Uemura et al. first provided evidence that eradication of *H. pylori* had a direct effect on decreasing the occurrence of secondary metachronous gastric cancer[4] in patients undergoing endoscopic resection. However, the results were limited by non-randomized study.

The effect of *H. pylori* eradication to prevent metachronous gastric cancer remains a controversial issue. We reviewed the recent randomized controlled trials to highlight the controversy (table1). Fukase *et al*[34] confirmed that eradication of *H. pylori* after endoscopic resection of early gastric cancer is beneficial after 3 years of follow-up in a randomized controlled trial. But the results were limited by open-labeled study and non-blindly follow-up endoscopy. Many synchronous cancers, which were detected within 1 year were included in the study. A recent retrospective study conducted by Maehata *et al*[35] about metachronous gastric cancer after endoscopic resection of early gastric cancer showed that the rates of metachronous cancer were 14.3% in the persistent infection group and 8.5% in the eradicated group (*P* = 0.262). Because the median follow-up period in a retrospective study was 3.0 years, it seems to be existing uncertainty based on a small sample size and not long-term following up. When the follow-up period was censored at 5 years, the incidence rate in the eradicated group was lower than that observed in the persistent group (*P* = 0.007).

There was controversial result showing that there were no significant differences in the development of metachronous carcers from a prospective, randomized, open-label trial conducted by Choi *et al*[36] In this study, the incidence of metachronous carcinoma between the 2 groups did not differ significantly at 1, 2, 3, and 4 years after *H. pylori* eradication. To determine the long-term effect of *H. pylori* eradication on the development of gastric cancer, the long-term follow-up is necessary. In the mean 5 years follow-up period, metachronous gastric carcinoma had developed in 22 patients in the eradication group and 43 in the control group (HR = 0.497; *P* = 0.008), which was presentation in DDW2012 by Kato *et al*[37]. These results suggested that *H. pylori* eradication could prevent the development of metachronous gastric cancers during a long-term follow-up.

***In patients with subtotal gastrectomy***

A well-designed prospective study revealed that *H. pylori*–positive patients undergoing gastrectomy for cancer had a higher risk of precursor malignant lesions compared with *H. pylori*–negative patients in the cancer group (OR = 4.20; 95%CI: 1.10-15.96), and the odds ratio was less significant when compared with that of *H. pylori*-positive and *H. pylori*–negative patients undergoing gastrectomy for duodenal ulcer (OR = 1.59; 95%CI: 0.44-5.73)[33]. This might be indirect evidence that *H. pylori* eradication therapy prevents the development of metachronous gastric cancer after previous gastrectomy[33].

In contrast, a recent randomized clinical trial from Korea showed that 4 of 190 patients had metachronous gastric cancer in the remnant stomach after gastrectomy during a median of 5 years of follow-up[19]. There was no difference in the development of metachronous gastric cancer according to eradication of *H. pylori* (3 patients) or not (1 patient). A possible limitation is that the small number of target patients, short observation period, and mucosal baseline conditions differ in many aspects. A meta-analysis showed a favorable overall survival in gastric cancer patients with *H. pylori* infection (HR = 0.71; *P* = 0.001)[38]. *H. pylori* might contribute to an improved anti-tumor immune response and microsatellite instability[38]. But the study was limited by heterogeneity and it included non-randomized and retrospective data. In addition, *H. pylori* negative status had poor prognosis in advanced gastric cancer might be related to post-operative bile reflux which eradicated *H. pylori* and destroyed parietal cells.

Taking together, the incidence of metachronous gastric cancer after endoscopic resection will not decrease unless there is early eradication before the progression of gastric mucosal atrophy[35]. To determine the long-term effect of *H. pylori* eradication on the development of metachronous gastric cancer after endoscopic resection of early gastric cancer, the long-term follow-up seems to be necessary. This approach also prevented development of metachronous gastric cancer in the remnant stomach after subtotal gastrectomy[39,40]. The Maastricht IV/Florence Consensus Report recommended eradication of *H. pylori* in patients with previous gastric neoplasia already treated with endoscopic or subtotal gastric resection, which seems to broaden the indication to include adenoma or dysplasia under the terminology of neoplasia[1]. Eradication of *H. pylori* was suggested, and the risk of gastric cancer may be more effective if eradication occurs before the development of preneoplastic conditions[1, 41]. Recent studies showed that eradication of *H. pylori* in the remnant stomach significantly decreased inflammation and activity scores[42, 43]. IL-1β was confirmed to be a potent inhibitor of gastric juice secretion, and Kato *et al*[44] proved that IL-1β messenger RNA levels, which lead to gastric dysplasia, correlated with the pH in the remnant stomach after eradication of *H. pylori*. However, a meta-analysis of the role of IL-1β and IL-1 receptor antagonist gene polymorphisms in the risk of gastric cancer showed only an association in white patients, not in Asian patients[45]. The effects of *H. pylori* eradication to prevent metachronous gastric cancer should be carefully and continually evaluated in well-designed, long-term follow-up studies.

**OPTIMAL TIMING AND REGIMENS FOR *H. PYLORI* ERADICATION, AND DIAGNOSTIC TOOLS AND FOLLOW-UP STRATEGIES FOR PATIENTS UNDERGOING GASTRECTOMY**

The optimal timing for eradication of *H. pylori* in gastrectomized patients is not clear. The efficacy of *H. pylori* eradication depends on the gastric pH, bacterial loads, the level of drug in the gastric mucosa, and acquired resistance. Liou *et al*[46] showed that antibiotic resistance, rather than host CYP2C19 polymorphisms or bacterial virulence, was the most important factor for successful eradication of *H. pylori*. Bacteria may produce β-lactamase in the gastric juice of patients with a remnant stomach, leading to transfer of drug resistance genes and interference with the efficacy of eradication[47].

The eradication rate in the remnant stomach was 90% after first-line triple therapy, which was comparable to the rates of 85%-88% in nonsurgical patients[42,48]. After gastrectomy, alkaline duodenopancreatic juice neutralized gastric acid that inhibited growth of *H. pylori*. The bacterial loads of *H. pylori* infection would be considered smaller for patients with gastrectomy, so a short triple therapy regimen might be effective. In addition, there was no difference in the eradiation rates between the 3-day and 7-day treatment groups (90.9 *vs* 93.8%)[49]. Temporal minor side effects were noted in 3 of 20 cases[42,48]. The effect of *H. pylori* eradication was not different whether it occurred postoperatively or preoperatively[50].

For a good diagnostic tool with a sensitivity of more than 80%, a histological test is better than either the urea breath test (UBT) or rapid urease test (RUT) after gastrectomy[51]. The reduced size of the stomach and bile reflux decreases the chance of *H. pylori* survival after gastrectomy. In addition, because the test urea passed through the residual stomach faster, UBT is not recommended for patients who have undergone gastrectomy[52]. A modified UBT with change of body position and using a film-coated 13C-urea table[53] or endoscopic sprayed UBT[54] has been suggested, but these procedures are complicated. Although the RUT is superior to UBT, the pooled sensitivity was 79%, which is still less than 80%[51]. When RUT is considered, the preferred site for biopsy would be the fundus[55, 56] or corpus[57]. Bile reflux disturbs the environment for *H. pylori* colonization in the distal gastric remnant and leads to a lower density of *H. pylori*. It is also recommended that more than one diagnostic method be used to decrease the false-negative rate in such circumstances.

According to the present Maastricht IV/Florence Consensus Report, serology is the only test that is not affected by local changes in the stomach, which may avoid false-negative results[1]. This is attributable to the fact that antibodies against *H. pylori* and especially against its most specific antigen, CagA, remain elevated despite transient decreases of the bacterial load and for long periods (months, even years) after the disappearance of *H. pylori* from the stomach[58]. By selecting a suitable cutoff value of 0.14, the *H. pylori* stool antigen test is also an reliable noninvasive diagnostic tool with a sensitivity of 93% and specificity of 100%[49].

**CONCLUSION**

It has been suggested that the biochemical and microbiological profiles of the gastric juice dramatically change after gastric surgery. We believe that this operative procedure might increase the occurrence of biliary enterogastric reflux and potentially inhibit the growth of *H. pylori* in the stomach. Compared to the B-I procedure, the B-II procedure had a higher bile reflux rate and was associated with a lower prevalence of *H. pylori* infection. There was a trend toward decreasing prevalence of *H. pylori* colonization with time after operation. Bile reflux and *H. pylori* infection appear to have a synergistic effect on cell proliferation in the gastric remnant and may explain the increased risk of cancer after gastrectomy. *H. pylori* is not an important factor in ulcerogenesis after gastrectomy. Eradication of *H. pylori* of the remnant stomach is presumably not effective in preventing ulcer recurrence. *H. pylori* does not appear to be an important risk factor for GSC; therefore, a cohort study to assess the clinical relevance of *H. pylori* eradication is necessary. The Maastricht IV/Florence Consensus Report recommends eradication of *H. pylori* in patients with previous gastric neoplasia already treated with endoscopic or subtotal gastric resection, which seems to broaden the indication to include adenoma or dysplasia. The first-line triple therapy regimen is effective for the eradication of *H. pylori* in gastrectomized patients. Serology is the only test that is not affected by local changes in the stomach, a combination of serology with histological test or *H. pylori* stool antigen test could be used to avoid false-negative results.

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**Table 1 Effect of *Helicobacter pylori* eradication to prevent metachronous gastric cancer after in a prospective of randomized controlled trials**

| **Author** | **Year** | **Treatment method** | **Case number** | **metachronous cancer**  **Eradication** | **metachronous cancer**  **No eradication** | **Definition of new cancers** | ***P* value**  **(95% CI)** | **Follow-up, yr** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Choi *et al*[36] | 2013  RCT | Endoscopic submucosal dissection | 901 | 10/444 | 17/457 | new carcinoma in areas of other than the site of primary gastric cancer | *P* = 0.15 | 3 |
| Maehata  *et al*[35] | 2012  Restropective | Endoscopic submucosal dissection | 268 | 15/177 | 13/91 | new carcinoma in areas other than the site of primary gastric cancer; at least 1 year after the endoscopic resection | *P* = 0.262  *P* = 0.007 | 3  5 |
| Fukase  *et al*[34] | 2008  RCT | Endoscopic submucosal dissection | 544 | 9/272 | 24/272 | new carcinoma in areas of other than the site of primary gastric cancer | *P* = 0.009 | 3 |