Eradication of *Helicobacter pylori* After Endoscopic Resection of Gastric Tumors Does Not Reduce Incidence of Metachronous Gastric Carcinoma

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BACKGROUND & AIMS: **It is not clear whether eradication of *Helicobacter pylori* infection reduces the risk for metachronous gastric carcinoma. We performed a prospective, randomized, open-label trial of the effects of *H pylori* eradication on the incidence of metachronous carcinoma after endoscopic resection of gastric tumors.**

METHODS: **From April 2005 through February 2011 there were 901 consecutive patients with *H pylori* infection who had been treated with endoscopic resection for gastric dysplasia or cancer and who were assigned randomly to groups given therapy to eradicate the infection (n = 444) or no therapy (controls, n = 457). The eradication group received 20 mg omeprazole, 1 g amoxicillin, and 500 mg clarithromycin twice daily for 1 week. Patients underwent endoscopic examination 3, 6, and 12 months after treatment, and then yearly thereafter. The primary outcome was development of metachronous gastric carcinoma.**

RESULTS: **During a median follow-up period of 3 years, 10 patients who received *H pylori* eradication and 17 controls developed metachronous carcinoma; this difference was not significant ($P = .15$). The incidence of metachronous carcinoma between the 2 groups did not differ significantly at 1, 2, 3, and 4 years after administration of the therapy. There were no significant differences in the development of metachronous carcinoma among patients who were positive (n = 16) or negative (n = 11) for *H pylori* infection ($P = .32$).**

CONCLUSIONS: **In this prospective trial, eradication of *H pylori* after endoscopic resection of gastric tumors did not significantly reduce the incidence of metachronous gastric carcinoma. ClinicalTrials.gov Number: NCT01510730.**

Keywords: Clinical Trial; Stomach Neoplasm; Therapy; *Helicobacter pylori*.

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Helicobacter pylori infection results in gastric atrophy, intestinal metaplasia, and a partial progression to dysplasia or cancer. The association between *H pylori* infection and the development of gastric cancer has been established by epidemiologic studies.[1–3] However, in a large randomized controlled trial, eradication of *H pylori* did not show a significant reduction of the incidence of gastric cancer and was effective only in the subgroup without precancerous lesions (ie, dysplasia, intestinal metaplasia, or atrophy).[4] In contrast, a randomized study conducted in Japan showed that *H pylori* eradication after endoscopic resection of early gastric cancer (EGC) significantly reduced metachronous gastric cancer.[5]

Endoscopic resection has been accepted in Korea and Japan as the first-line treatment for indicated cases of EGC because it has been proven both minimally invasive and effective.[6,7] Gastric dysplasia also can be a candidate for endoscopic resection because it has some potential for malignancy and is regarded as a precursor of gastric cancer.

It has not yet been clarified whether *H pylori* eradication can reduce the incidence of metachronous cancer after endoscopic resection in patients with gastric dysplasia or cancer. We performed a prospective,

Abbreviations used in this paper: EGC, early gastric cancer; ESD, endoscopic submucosal dissection.

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randomized, open-label trial of the effect of *H pylori* eradication on the incidence of metachronous carcinoma after endoscopic resection of gastric dysplasia or EGC.

Patients and Methods

Patients and Endoscopic Resection

From April 2005 through February 2011, consecutive patients with EGC or gastric dysplasia who were candidates for endoscopic resection were enrolled prospectively at Seoul National University Hospital. Patients infected with *H pylori* who had undergone endoscopic resection therapy were eligible for the study. Indications for endoscopic resection for EGC were as follows: differentiated adenocarcinoma, tumor confined to the mucosa, gross tumor size no more than 2 cm in diameter, and no evidence of distant metastasis. Some patients who did not meet any of these criteria were treated with endoscopic resection because of severe comorbidity, old age, or reluctance to undergo surgery. Endoscopic resection also was performed for gastric high-grade dysplasia irrespective of tumor size and morphology. The patients with low-grade dysplasia were recommended to choose any of several treatment options (endoscopic ablation with argon plasma coagulation, endoscopic resection, or periodic follow-up evaluation) on the basis of patient preference, size of the lesion, and physician recommendation. For EGC patients, the pretreatment tumor-staging method was contrast-enhanced abdominal computerized tomography and endoscopic ultrasonography. Endoscopic resection was performed by the endoscopic submucosal dissection (ESD) technique in almost all cases. Conventional endoscopic mucosal resection technique also was performed for lesions smaller than 5 mm in diameter. ESDs were conducted by a single skillful endoscopist (S.G.K.). The procedure was described previously[8]: demarcation using chromoendoscopy with indigocarmine solution, marking around the lesion, and circumferential incision and submucosal dissection with an insulation-tipped knife. Pathologic mapping was evaluated with slices prepared at 2-mm–thick intervals. Histologic evaluation of gastric tumor was based on the Vienna classification: low-grade dysplasia, high-grade dysplasia, carcinoma in situ, and invasive cancer (intramucosal or submucosal carcinoma).[9] If massive submucosal or lymphovascular tumor invasion or positive tumor margin in vertical or lateral resection were found in pathologic mapping, the patient was urged to undergo an additional gastrectomy with lymph node dissection. During endoscopic resection, biopsy samples were taken from 2 sites in the lesser curvature of the antrum and 2 sites in the lesser curvature of the corpus for histologic detection of *H pylori* and rapid urease test (CLO test; Delta West, Bently, Australia). *H pylori* status was considered positive if the result of 1 or both tests (rapid urease test or histology) was positive.

Inclusion criteria for the study were as follows: (1) *H pylori* infection with gastric low-grade dysplasia, high-grade dysplasia, or EGC; and (2) complete resection of gastric tumor by endoscopic resection. Patients were excluded for the following reasons: (1) prior gastrectomy, (2) prior endoscopic resection, (3) prior *H pylori* eradication, (4) pregnancy, (5) age younger than 20 years or older than 75 years, (6) severe comorbidity, (7) incomplete endoscopic resection (massive submucosal invasion or positive vertical or lateral resection margin), or (8) history of allergic reaction to antibiotics. All patients provided written informed consent, and the institutional review board of Seoul National University Hospital approved this study (H-0903-016-273). This trial was registered at ClinicalTrials.gov, NCT01510730. All investigators had access to the study data and had reviewed and approved the final manuscript.

Randomization

Patients were advised to visit the clinic 2 weeks after endoscopic resection, at which time they were registered for the study if they met the entry criteria. By using a random-number chart, we randomly assigned patients to either the *H pylori* eradication group or the control group. Patients in the eradication group received 20 mg omeprazole, 1 g amoxicillin, and 500 mg clarithromycin twice daily for 1 week. Patients in the control group received no antibiotics for eradication of *H pylori*.

Follow-up Endoscopic Examination

Follow-up endoscopic examination was performed by a single endoscopist (S.G.K.) to detect any mucosal abnormalities and to take biopsy specimens if necessary. The patients with endoscopic resection for EGC were followed up at 3, 6, and 12 months, and annually thereafter. The patients with endoscopic resection for gastric dysplasia were followed up at 3 and 12 months and annually thereafter. *H pylori* status (determined by rapid urease test and histology) was evaluated by the same manner at all endoscopic follow-up evaluations.

Outcome Measurement

The primary outcome was the development of metachronous gastric carcinoma (new carcinoma occurring at another site in the stomach) during follow-up evaluation. If the tumor developed at the site of previous endoscopic resection, the lesion was considered a remnant tumor rather than metachronous carcinoma. Because high-grade dysplasia has been considered a precursor of gastric cancer, the development of high-grade dysplasia also was assessed in both groups. With regard to final *H pylori* status, the development of metachronous carcinoma was compared between patients with positive and negative *H pylori* status on their last follow-up