**Helicobacter pylori** eradication may influence timing of endoscopic surveillance for gastric cancer in patients with gastric precancerous lesions

**A retrospective study**

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**Abstract**

Chronic atrophic gastritis and intestinal metaplasia related to *Helicobacter pylori* infection, are major risk factors for gastric adenocarcinoma. Eradication of *H pylori* and endoscopy surveillance of precancerous lesions may reduce the risk and/or lead to early detection of gastric cancer improving survival. In this study, the progression of precancerous lesions after *H pylori* treatment was evaluated.

Patients with incomplete or complete intestinal metaplasia and/or gastric atrophy at the index endoscopy, were examined for the extension/ histological worsening of precancerous lesions at the endoscopy surveillance for gastric cancer. Progression of lesions was evaluated according to *H pylori* status, age, and sex. Cox proportional hazard regression model and Kaplan–Meier curves were used to evaluate the strength of predictors for lesions progression.

Among 105 patients (61 women) *H pylori* negative patients showed a milder worsening of gastric lesions between index and surveillance endoscopy compared with patients positive for the infection (log-rank test: \( P < .0001 \), \( P = .012 \), and \( P = .032 \) for antrum, angulus, and corpus, respectively). The Cox regression model showed persistence of *H pylori* infection (hazard ratio = 4.436; \( P < .0001 \)) as the only relevant factor for lesion progression, whereas age >65 years and sex were not significant predictors.

According to literature our results demonstrate that *H pylori* eradication is the major factor able to delay gastric precancerous lesions progression. Time interval for endoscopic surveillance in patients negative for *H pylori* infection and with gastric precancerous lesions may be extended.

**Abbreviations:** EGD = esophagogastro-duodenoscopy, GI = gastrointestinal, HR = hazard ratio, UBT = \(^{13}\)C-urea breath test.

**Keywords:** endoscopic surveillance, gastric atrophy, gastric intestinal metaplasia, *H pylori* infection

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1. Introduction

*Helicobacter pylori* is a definite pathogen and infection is always and universally associated with mucosal inflammation.\(^{[1-3]}\) The infection is usually acquired in childhood, although clinical manifestations may occur in adult life.\(^{[4-7]}\) Normal gastric mucosa is essentially devoid of inflammatory cells. After colonization, *H pylori* leads to an active chronic inflammation due to infiltration of the gastric mucosa by polymorphonuclear and mononuclear inflammatory cells resulting in an active-chronic gastritis. Histopathological features may vary in the different parts of the stomach, being more severe in areas were acid production is lower.\(^{[1-3]}\) Over time the inflamed area tends to invade the corpus from the antrum. The natural history is a loss of parietal cells, reduction in acid secretion, and development of gastric atrophy.\(^{[1,8]}\) Failure to replace the loss of gastric epithelial cells by an appropriate cell proliferation may result in the replacement of an intestinal-type epithelium.\(^{[9]}\)

The rate of progression to atrophy and the risk of gastric cancer vary within different geographic regions in relation to other environmental factors such as diet, especially rich in salt and poor in fresh fruits and vegetables, smoking habits, virulence of the organism, and the genetic background of the host.\(^{[10]}\)

There are 2 main histologic variants of gastric adenocarcinoma. The most frequent is the so called “intestinal type,” because its similarity to adenocarcinomas of the intestinal tract and strongly related to *H pylori* infection. Gastric cancer of “diffuse type” is less common, is characterized by a lack of intercellular adhesions caused by a germline mutation in the protein E-cadherin and the association with *H pylori* infection is weaker.\(^{[9]}\)

The sequence of events leading to gastric cancer from gastritis related to *H pylori* infection is a long process characterized by...
development of increasingly severe types of intestinal metaplasia in areas with multifocal and total atrophy, dysplasia, and eventually invasive carcinoma.[16,17] The extent of intestinal metaplasia is a crucial predictor of cancer. Antral predominant gastritis is usually associated with duodenal ulcer and inflammation confined to the antrum. Corpus predominant gastritis may evolve into atrophic gastritis and progress to gastric atrophy with replacement of gastric glands with intestinal metaplasia. This pattern of gastritis is more often associated with gastric ulcer and gastric carcinoma.[12] In several studies, intestinal metaplasia was observed as a precursor lesion for intestinal type gastric cancer.[13-15] For example, in Japanese patients positive for *H pylori* infection, the presence of intestinal metaplasia was the only condition associated with the occurrence of intestinal-type gastric cancer.[16] In China, in a high prevalence area of gastric cancer, a considerable proportion (33%) of the population harbored intestinal metaplasia and 20% dysplasia, more common in the lesser curvature and in the incisura.[17] For these reasons surveillance for gastric cancer with standard upper endoscopy and gastric biopsy mapping would be appropriate in individuals with intestinal metaplasia. However, experience is limited and guidelines issued by the American Society for Gastrointestinal Endoscopy recommend endoscopic surveil- lance for gastric intestinal metaplasia only in patients at increased risk for gastric cancer.[18] On the other hand, evidence-based guidelines on the management of patients with precancerous conditions developed by the European Society of Gastrointestinal Endoscopy, the European Helicobacter Study Group, the European Society of Pathology, and the Sociadade Portuguesa de Endoscopia Digestiva, recommend endoscopic surveillance every 3 years in all patients with extensive mucosal atrophy and/or intestinal metaplasia in the antrum and corpus.[19] Instead, there is no evidence to recommend surveillance in patients with mild to moderate atrophy and/or intestinal metaplasia restricted to the antrum.[17]

The aim of this study was to evaluate the progression of gastric precancerous lesions in patients positive and negative for *H pylori* infection.

2. Methods

2.1. Patient selection

This was a retrospective single-center study. Patients with histological features of gastric precancerous lesions such as atrophy, incomplete or complete intestinal metaplasia on gastric biopsies obtained during upper endoscopy, and undergoing follow up esophago-gastro-duodenoscopy (EGD) for surveillance of gastric cancer were evaluated for the study.

Patients were referred to the Digestive Endoscopy Service, Department of Internal Medicine, University of Sassari, Italy, by family physicians or specialists for any reason including dyspeptic symptoms, gastro-esophageal reflux disease, surveillance programs, and other.

2.2. Diagnostic methods

At the time of EGD each patient was interviewed by a gastroenterologist and diagnostic symptoms in addition to demographic information and all relevant clinical data were recorded. The endoscopist carefully evaluated the entire stomach, using a white light endoscope. At least 5 nontargeted biopsy specimens including 2 from the antrum, 1 from the angulus, and 2 from the corpus of the stomach were obtained. In addition, targeted biopsies of irregular areas of the mucosa, if present, were taken and specimens from each region stored in separate vials.

Biopsy specimens were stained with hematoxylin-eosin and Giemsa stains, and morphology was assessed by an expert GI-pathologist. According to a previous study[7] the simultaneous infiltration of gastric mucosa with polymorphonuclear and mononuclear inflammatory cells was defined active-chronic gastritis. The presence of several lymphoid follicles was defined follicular gastritis. Normal gastric mucosa replaced by intestinal epithelium was classified as intestinal metaplasia and loss of glands as atrophy. After the procedure, endoscopy findings and histology examinations were entered in a computerized database. The surveillance endoscopy was repeated 3 years later from the index endoscopy according to the interval recommended by the major GI Societies.[16,17]

2.3. *H pylori* status

*H pylori* infection was defined by detection of a positive rapid urease test and/or the presence of *H pylori* on histological examination of gastric biopsies. When the infection was suspected, for example, in the case of active chronic gastritis and/or atrophy and/or intestinal metaplasia, but the bacteria were not found in the gastric specimens, the presence of *H pylori* was confirmed by 13C-Urea Breath Test (UBT). All patients, positive for the infection, were treated for *H pylori* eradication. Posttreatment success was defined by a negative 13C-UBT or antigen fecal test 30 to 40 days after completing therapy.

An Institutional Review Board approval was obtained from Comitato di Bioetica, Azienda Ospedaliero-Universitaria di Sassari (Prot N° 2477/2; CE 2017). Since only pre-existing charts were used, all patient records were de-identified before the analysis.

2.4. Statistical analysis

Based on the results of biopsies, patients were stratified into 3 categories related to the localization within the gastric mucosa (antrum, angulus, and corpus). For each category, the histologically identified lesions at the index endoscopy and at the surveillance upper endoscopy, were coded as an ordinal variable: no lesions; gastric atrophy; and metaplasia, for both. In addition, precancerous lesion progression was coded as dichotomous variables. More specifically, “zero/one” for absence/presence of extension (e.g., from antrum to the angulus and/or to the corpus) respectively, and for absence/presence of histological worsening (e.g., from atrophy to intestinal metaplasia). Kaplan–Meier curves were constructed by using the time interval between index and follow-up endoscopy, and the above dichotomous variables as outcome. The log-rank test was run to detect statistically significant differences. Patients were subdivided according to the *H pylori* status into negative and positive, and in each category the possible progression of lesions from one segment of the stomach to another one was evaluated. A Cox proportional hazard regression model was used to evaluate the strength of predictors of lesion worsening and extension in the stomach. A final binary variable was constructed combining the 2 variables expressing the lesion worsening at antrum, angulus, and corpus, and the 2 variables expressing lesion extension.

3. Results

A total number of 105 patients (44 men, 61 women) with endoscopic finding of gastric precancerous lesions participated in
the study. Women were slightly older than men (60.6 ± 11.0 vs 58.1 ± 11.8 years) (Table 1). The prevalence of *H pylori* infection was 72.4% (76 patients out of 105) and was successfully treated in 57 patients. Nineteen patients, for different reasons (they did not take the treatment, did not check for the eradication after therapy, etc.), were still positive at the first surveillance endoscopy for the infection.

The frequency of subtype lesions at the baseline endoscopy, among 525 gastric specimens analyzed, is reported in the Table 2 according to the segment of the stomach involved. At baseline, all patients showed lesions at least in the antrum. Patients with atrophy and/or intestinal metaplasia, but negative for *H pylori* infection were 29. The presence of gastric lesions was considered as a proxy of a previous *H pylori* infection. Patients with dysplasia underwent a different management.

The Kaplan–Meier curves expressing the histological worsening of lesions (from atrophy to metaplasia) subdivided according to *H pylori* status (negative or positive) for each gastric segment (antrum, angulus, and corpus) are represented in the upper panel of Fig. 1. Patients in whom *H pylori* infection was successfully eradicated showed a milder worsening of gastric lesions between baseline and the first surveillance upper endoscopy compared with patients positive for the infection (log-rank test: *P* < .0001, *P* = .012, and *P* = .032 for antrum, angulus, and corpus, respectively).

The lower panel of Fig. 1 shows Kaplan–Meier curves expressing segmental extension of gastric lesions (from antrum to angulus and from angulus to corpus) for patients subdivided by *H pylori* status. Although a trend for a faster lesion extension was observed in patients *H pylori* positive, this difference was not statistically significant (log-rank test: *P* = .182, *P* = .302 for the

### Table 1

| Variable                                      | Values             |
|-----------------------------------------------|--------------------|
| Age (median and range, y)                    | 63 (30–80)        |
| Gender (male: female)                        | 44:61             |
| *H pylori* status                            |                    |
| *H pylori* negative                          | 29 (27.6%)        |
| *H pylori* eradicated                        | 57 (54.3%)        |
| *H pylori* positive                          | 19 (18.1%)        |
| Average time spanned between baseline endoscopy and first follow-up (median and range, mo) | 35 (0–151) |

### Table 2

| Distribution of precancerous lesions in the different segments of the stomach. |
|------------------------------------------|------------------|
| Precancerous lesions                     | Antrum No | Angulus No | Corpus No |
| No lesions                               | 0          | 48         | 65        |
| Atrophy                                  | 35         | 35         | 29        |
| Atrophy and IM*                          | 44         | 15         | 9         |
| Atrophy and dysplasia                    | 2          | 2          | 2         |
| IM                                       | 13         | 5          | 0         |
| IM and dysplasia                         | 2          | 0          | 0         |
| Atrophy and IM and dysplasia             | 9          | 0          | 0         |

*IM = intestinal metaplasia.*

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Figure 1. In the upper panel; KM curves show the local worsening of lesions (from atrophy to metaplasia/displasia), subdivided according to *H pylori* status for each gastric segment (antrum, angulus, and corpus). Lower panel; KM curves expressing local extension of lesions (from antrum to angulus and from angulus to corpus) for patients subdivided by *H pylori* status. KM = Kaplan–Meier.
Table 3

Predictors of lesion worsening and extension in the stomach evaluated by Cox proportional hazard regression model.

| Variable       | HR     | 95% confidence interval | P-value |
|----------------|--------|-------------------------|---------|
| Age            |        |                         |         |
| <65            | 1.00   |                         |         |
| ≥65            | 1.011 (0.457–2.233) | 0.979 |
| Gender         |        |                         |         |
| Female         | 1.000  |                         |         |
| Male           | 0.636 (0.315–1.287) | 0.209 |
| H. pylori status |        |                         |         |
| Negative or eradicated | 1.000 |                         |         |
| Not eradicated  | 4.392 (2.196–8.779) | <0.0001 |

HR = hazard ratio

therapy delays the progression of intestinal metaplasia. It has been demonstrated that the frequency of precancerous lesions and gastric cancer risk increases by infection with more virulent strains of *H. pylori* that express the cag-pathogenicity island (CagA-positive strains), able to amplify the inflammatory response. The risk of malignancy may be related to specific amino acid EPIYA segments, able to increase the phosphorylation-dependent CagA activity. However, differences in cancer risk between virulent and non-virulent *H. pylori* strains are approximately doubled. Up to date, no one specific virulence factor identified showed a disease-specific association. The extent and severity of inflammation in response to *H. pylori* colonization, associated with environmental and host characteristics, seem to be the most important factors involved in the risk of gastric cancer. In fact, gastric cancer risk is modulated by host genetic factors and any *H. pylori* bacterium is capable to promote mutagenesis and to induce carcinogenesis. According to these observations, in our study, the only condition able to modify the evolution of premalignant lesions, was the eradication of *H. pylori*.

In a large cohort of 11,202 patients from Sardinia, undergoing upper endoscopy, we observed a dramatic decrease in the prevalence of *H. pylori* infection over the 19-year studied period (from 1995 to 2013). The studied patients between the years 2010 and 2013 had consistently lower prevalence of *H. pylori* infection than those between 1995 and 1999 (26% vs 64%, respectively, P < 0.0001). A similar falling pattern was observed for intestinal metaplasia, follicular gastritis, dysplasia, and atrophy among the same studied cohort, although the prevalence was highest in the oldest cohorts. In line with a robust body of research, these results confirm the tight relationship between *H. pylori* infection and development of gastric precancerous lesions. In general, surveillance for gastric cancer in patients with incomplete or extensive intestinal metaplasia is indicated every 3 years. In patients with environmental (not autoimmune) focal or confined to antrum intestinal metaplasia, the risk of developing gastric adenocarcinomas appears to be low even in geographic areas at high incidence of gastric cancer. Our results confirm these observations, since gastric cancers did not occur in any patient, although in our followed-up cohort there were index endoscopies dating back to 1993. Our study encompasses several limitations: for example, the small size of the studied cohort did not allow to stratify for additional analyses. Moreover, other known factors implicated in the gastric carcinogenesis including smoking habit, consumption of salted food and alcohol, and obesity, given the retrospective nature of the study were not collected. Nonetheless our findings clearly indicated that atrophic gastritis and/or intestinal metaplasia do not represent a risk of gastric cancer, especially in those patients *H. pylori* negative. Relying on a homogenous genetic background of our populations, the only important variable able to influence the worsening appears to be *H. pylori* infection, making the analysis of additional risk factors for gastric cancer worthless.

For example, in countries with a high prevalence of gastric cancer, such as Japan, the government on 2013 approved insurance coverage to test and treat *H. pylori* as primary prevention for gastric cancer. This program encompasses also secondary prevention in patients with gastric precancerous lesions by posttreatment surveillance. In addition, recommendations of the Kyoto Global Consensus Conference on *H. pylori* gastritis reported that “*H. pylori* gastritis should be defined as an infectious disease, even when patients have no symptoms and...
irrespective of complications such as peptic ulcers and gastric cancer,” and “...infected individuals should be offered eradication therapy, unless there are competing considerations.” The same was also strongly recommended by the Maastricht V/Florence Consensus Report on the Management of *Helicobacter pylori* infection—from the European Helicobacter and Microbiota Study Group. Moreover, “*H pylori* Eradication as a Strategy for Preventing Gastric Cancer” was published by the World Health Organization as a report of the International Agency for Research on Cancer.

It appears evident, on the behalf of most representative society guidelines, for primary prevention of gastric cancer the best strategy is *H pylori* eradication. For secondary prevention surveillance is necessary. However, surveillance needs standard upper endoscopy, an invasive, unpleasant, expensive, and demanding procedure. The major International Societies suggest endoscopic surveillance for gastric cancer in patients with extensive mucosal atrophy and/or intestinal metaplasia or additional risk factors.

In conclusion, according to our findings, timing of endoscopy surveillance for gastric cancer may be extended in patients with chronic atrophic gastritis and intestinal metaplasia after *H pylori* eradication. Additional studies are needed to define the most appropriate schedule time for surveillance in this subgroup of patients. This strategy will avoid useless patients concern and additional expenditure for the health system.

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