Observational Study

Medicine®

OPEN

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

A retrospective study

Maria Pina Dore, MD, PhD[a,d,*], Alice Cipolli, MD[a], Matteo Walter Ruggiu, MD[b], Alessandra Manca, MD[b], Gabrio Bassotti, MD[c], Giovanni Mario Pes, MD[a]

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 = esophago-gastro-duodenoscopy, GI = gastrointestinal, HR = hazard ratio, UBT = ^{13}C-urea breath test.

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

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 with 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

Editor: Eva Zapata.

The authors declare that they have no competing interests.

[a] Dipartimento di Medicina Clinica e Sperimentale, [b] Dipartimento di Scienze Chirurgiche e Microchirurgiche, University of Sassari, Sassari, [c] Dipartimento di Medicina Clinica e Sperimentale, University of Perugia, Perugia, Italy, [d] Baylor College of Medicine, Houston, Texas.

[*] Correspondence: Maria Pina Dore, Clinica Medica, Universita' di Sassari, Viale San Pietro, 8, 07100 Sassari, Italy (e-mail: mpdore@uniss.it).

Medicine (2018) 97:4(e9734)

Received: 19 September 2017 / Received in final form: 5 January 2018 / Accepted: 9 January 2018

http://dx.doi.org/10.1097/MD.0000000000009734

development of increasingly severe types of intestinal metaplasia in areas with multifocal and total atrophy, dysplasia, and eventually invasive carcinoma.[11] 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.[14] 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.[15] 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 surveillance for gastric intestinal metaplasia only in patients at increased risk for gastric cancer.[16] 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 Sociedade 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.[17] 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 digestive 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 ^{13}C-Urea Breath Test (UBT). All patients, positive for the infection, were treated for *H pylori* eradication. Posttreatment success was defined by a negative ^{13}C-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

Table 1

Demographic and clinical features of the studied cohort at baseline.

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.

the study. Women were slightly older than men (60.6 ± 11.0 vs 58.1 ± 11.8 years) (Table 1). The prevalence of *H pylor*i 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

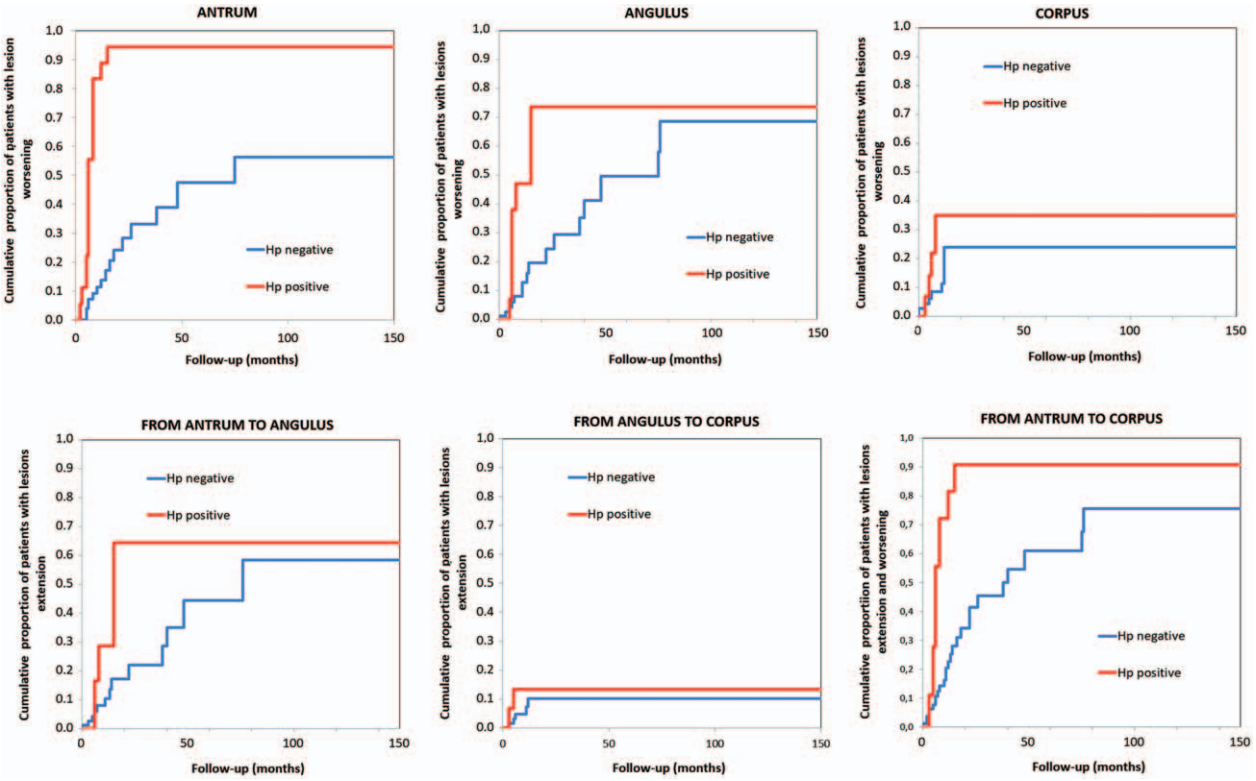

Figure 1. In the upper panel; KM curves show the local worsening of lesions (from atrophy to metapalsia/displasia), subdivided according to *H pylori* status for each gastric segment (antrum, angulus, and corpus). Lower panel; KM curves expressing local extension of lesions (from antrum to angulus and 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	1.000		
≥65	1.011	(0.457–2.233)	.979
Gender			
Female	1.000		
Male	0.636	(0.315–1.287)	.209
H pylori status			
Negative or eradicated	1.000		
Not eradicated	4.392	(2.198–8.779)	<.0001

* HR = hazard ratio.

extention from the antrum to the angulus and from the angulus to the corpus, respectively). More precisely in the 50% of *H pylori* negative patients was observed a delay of 20, 32, and 7 months in the worsening of precancerous lesions of the antrum, angulus, and corpus, respectively, compared with *H pylori* positive patients.

The Cox regression model showed (Table 3) that the only relevant factor for lesion worsening and/or extension was persistence of *H pylori* infection (HR = 4.392; $P < .0001$), whereas age >65 years and sex were not significant predictors.

The chance to have lost gastric cancer in patients with premalignant lesions included in our study, was double checked using the data base of the pathology service as a proxy. The pathology service of the "Azienda Ospedaliero Universitaria" of Sassari, is the reference center for all histological examinations from Northern Sardinia. All specimens were analyzed until May 2017, and not 1 patient followed up in our study developed a gastric malignancy.

4. Discussion

Gastric cancer is one of the most common cancers characterized by a high morbidity and mortality.[18] It was the first cause of death from cancer until the 1980s.[19] The dramatic decline of gastric cancer in the last decades is related to the consistent reduction in the prevalence of *H pylori* infection especially in resources-reach countries.[20] Others environmental factors such as the wide availability of refrigerators to storage groceries, preserved individuals to consume high quantity of food salted, smoked, or contaminated by bacterial and/or fungal toxins.[21–23]

Unfortunately, despite the overall decline, the absolute number of new cases per year is increasing, mainly due to the progressive aging of the world population.[24] A similar trend was also observed in Northern Sardinia.[25] Incidence and mortality rate of gastric cancer did not change significantly in the period between 1992 and 2010, although, among 1227 gastric cancers, only 47.3% were adenocarcinomas, the histological subtype related to *H pylori* infection,[25] suggesting that the histologic pattern of gastric cancer is changing with a decline in the intestinal type compared with the diffuse type.

Standard endoscopic surveillance of patients with intestinal metaplasia is important to decrease the risk of gastric cancer. Timing of surveillance is based on the premalignant lesions subtype at the index endoscopy. Screening and eradication of *H pylori* is a rule of thumb. Treatment of *H pylori* is capable to reverse chronic non-atrophic gastritis and multifocal atrophic gastritis in the majority of patients.[26,27] Moreover, eradication therapy delays the progression of intestinal metaplasia.[28] 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.[29] The risk of malignancy may be related to specific amino acid EPIYA segments, able to increase the phosphorylation-dependent CagA activity.[30] However, differences in cancer risk between virulent and non-virulent *H pylori* strains are approximately doubled.[31] Up to date, no one specific virulence factor identified showed a disease-specific association.[31] 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.[31] 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.[9] 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).[7] 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, $P < .0001$). 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.[7] 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.[17] 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.[32] 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.[1] 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.[33] 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."[34] 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.[35] 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.[36]

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[17] 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.

References

[1] Graham DY. History of Helicobacter pylori, duodenal ulcer, gastric ulcer and gastric cancer. World J Gastroenterol 2014;20:5191–204.

[2] Ota H, Genta RM. Ernst P, Michetti P, Smith PD. Morphological characterization of the gastric mucosa during infection with Helicobacter pylori. The Immunobiology of Helicobacter pylori from Pathogenesis to Prevention. Philadelphia: Lippincott-Raven; 1997;15–28.

[3] Howden CW. Clinical expressions of Helicobacter pylori infection. Am J Med 1996;100:27S–32S.

[4] Lu H, Yamaoka Y, Graham DY. Helicobacter pylori virulence factors: facts and fantasies. Curr Opin Gastroenterol 2005;21:653–9.

[5] Roosendaal R, Kuipers EJ, Buitenwerf J, et al. Helicobacter pylori and the birth cohort effect: evidence of a continuous decrease of infection rates in childhood. Am J Gastroenterol 1997;92:1480–2.

[6] Malaty HM. Epidemiology of Helicobacter pylori infection. Best Pract Res Clin Gastroenterol 2007;21:205–14.

[7] Dore MP, Marras G, Rocchi C, et al. Changing prevalence of Helicobacter pylori infection and peptic ulcer among dyspeptic Sardinian patients. Intern Emerg Med 2015;10:787–94.

[8] Valle J, Kekki M, Sipponen P, et al. Long-term course and consequences of Helicobacter pylori gastritis. Results of a 32-year follow-up study. Scand J Gastroenterol 1996;31:546–50.

[9] Sepulveda AR, Graham DY. Role of Helicobacter pylori in gastric carcinogenesis. Gastroenterol Clin North Am 2002;31:517–35.

[10] Graham DY. Helicobacter pylori update: gastric cancer, reliable therapy, and possible benefits. Gastroenterology 2015;148:719.e3–31.e3.

[11] Zhang W, Lu H, Graham DY. An update on Helicobacter pylori as the cause of gastric cancer. Gastrointest Tumors 2014;1:155–65.

[12] Dore MP, Graham DY. Gastritis, dyspepsia and peptic ulcer disease. Minerva Med 2008;99:323–33.

[13] Uemura N, Okamoto S, Yamamoto S, et al. Helicobacter pylori infection and the development of gastric cancer. N Engl J Med 2001;345:784–9.

[14] Shimoyama T, Fukuda S, Tanaka M, et al. Evaluation of the applicability of the gastric carcinoma risk index for intestinal type cancer in Japanese patients infected with Helicobacter pylori. Virchows Arch 2000;436:585–7.

[15] You WC, Blot WJ, Li JY, et al. Precancerous gastric lesions in a population at high risk of stomach cancer. Cancer Res 1993;53: 1317–21.

[16] Evans JA, Chandrasekhara V, Chathadi KV, et al. ASGE Standards of Practice CommitteeThe role of endoscopy in the management of premalignant and malignant conditions of the stomach. Gastrointest Endosc 2015;82:1–8.

[17] Dinis-Ribeiro M, Areia M, de Vries AC, et al. Management of precancerous conditions and lesions in the stomach (MAPS): guideline from the European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter Study Group (EHSG), European Society of Pathology (ESP), and the Sociedade Portuguesa de Endoscopia Digestiva (SPED). Endoscopy 2012;44:74–94.

[18] Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011;61:69–90.

[19] Haenszel W. Variation in incidence of and mortality from stomach cancer, with particular reference to the United States. J Natl Cancer Inst 1958;21:213–62.

[20] Leja M, Axon A, Brenner H. Epidemiology of Helicobacter pylori infection. Helicobacter 2016;21(Suppl):3–7.

[21] Song P, Wu L, Guan W. Dietary nitrates, nitrites, and nitrosamines intake and the risk of gastric cancer: a meta-analysis. Nutrients 2015;7: 9872–95.

[22] Kneller RW, You WC, Chang YS, et al. Cigarette smoking and other risk factors for progression of precancerous stomach lesions. J Natl Cancer Inst 1992;84:1261–6.

[23] Leung WK, Lin SR, Ching JY, et al. Factors predicting progression of gastric intestinal metaplasia: results of a randomized trial on Helicobacter pylori eradication. Gut 2004;53:1244–9.

[24] Zhu AL, Sonnenberg A. Is gastric cancer again rising? J Clin Gastroenterol 2012;46:804–6.

[25] Cossu A, Budroni M, Pulighe F, et al. Gastric cancer in North Sardinia, Italy: an epidemiological report. Acta Medica Mediterranea 2014;30: 935–40.

[26] Rokkas T, Pistiolas D, Sechopoulos P, et al. The long-term impact of Helicobacter pylori eradication on gastric histology: a systematic review and meta-analysis. Helicobacter 2007;12(Suppl):32–8.

[27] Watari J, Das KK, Amenta PS, et al. Effect of eradication of Helicobacter pylori on the histology and cellular phenotype of gastric intestinal metaplasia. Clin Gastroenterol Hepatol 2008;6:409–17.

[28] Wang J, Xu L, Shi R, et al. Gastric atrophy and intestinal metaplasia before and after Helicobacter pylori eradication: a meta-analysis. Digestion 2011;83:253–60.

[29] Huang JQ, Zheng GF, Sumanac K, et al. Meta-analysis of the relationship between cagA seropositivity and gastric cancer. Gastroenterology 2003;125:1636–44.

[30] Basso D, Zambon CF, Letley DP, et al. Clinical relevance of Helicobacter pylori cagA and vacA gene polymorphisms. Gastroenterology 2008;135: 91–9.

[31] Miftahussurur M, Yamaoka Y, Graham DY. Helicobacter pylori as an oncogenic pathogen, revisited. Expert Rev Mol Med 2017;19:e4.

[32] Fennerty MB, Emerson JC, Sampliner RE, et al. Gastric intestinal metaplasia in ethnic groups in the southwestern United States. Cancer Epidemiol Biomarkers Prev 1992;1:293–6.

[33] Asaka M, Kato M, Sakamoto N. Roadmap to eliminate gastric cancer with Helicobacter pylori eradication and consecutive surveillance in Japan. J Gastroenterol 2014;49:1–8.

[34] Sugano K, Tack J, Kuipers EJ, et al. faculty members of Kyoto Global Consensus ConferenceKyoto global consensus report on Helicobacter pylori gastritis. Gut 2015;64:1353–67.

[35] Malfertheiner P, Megraud F, O'Morain CA, et al. European Helicobacter and Microbiota Study Group and Consensus panel. Management of Helicobacter pylori infection-the Maastricht V/Florence consensus report. Gut 2017;66:6–30.

[36] IARC Helicobacter pylori Working Group. Helicobacter pylori Eradication as a Strategy for Preventing Gastric Cancer. Lyon, France: International Agency for Research on Cancer (IARC Working Group Reports, No. 8); 2014. Available at: http://www.iarc.fr/en/publications/pdfsonline/wrk/wrk8/index.php. Accessed January 2, 2018.