Published in final edited form as:

Dig Liver Dis. 2008 July ; 40(7): 497–503. doi:10.1016/j.dld.2008.02.032.

GASTRIC ENDOSCOPY IN THE 21ST CENTURY: APPROPRIATE USE OF AN INVASIVE PROCEDURE IN THE ERA OF NON-INVASIVE TESTING

David Y. Graham, M.D.¹, Mototsugu Kato, M.D. Ph.D.², and Masahiro Asaka, M.D., Ph.D.²

¹ Michael E. DeBakey VA Medical Center and Baylor College of Medicine, Houston, Texas, USA

² Hokkaido University School of Medicine, Sapporo, Japan

Abstract

The acceptance of the premise that *Helicobacter pylori* infection is etiologically related to gastric cancer and peptic ulcer and that the risk of gastric cancer among *H. pylori* infected individuals is related to the extent, severity, and duration of atrophic gastritis has led to major changes in medical and endoscopic practices. The development of non-invasive methods to detect *H. pylori* and to estimate the extent and severity of gastritis has reduced the need for diagnostic endoscopy in asymptomatic individuals. Here we provide recommendations regarding deciding whether noninvasive and for endoscopic assessment of the gastric mucosa is preferred. We also include specific recommendations and caveats regarding the preferred biopsy number and sites as well as the identification of specimens to allow the pathologist to reliably stage the severity and extent of gastritis and thus provide prognostic information needed for patient managements (eg, whether endoscopic surveillance is recommended). In summary, while there clearly is a role for gastric endoscopy and endoscopic biopsy in the *H. pylori* era, obtaining useful diagnostic and prognostic information is critically dependent upon attention to detail with regard to biopsy site and identification as to location where the specimen was taken.

Keywords

Gastroscopy; biopsy; intestinal metaplasia; scoring; pepsinogen; gastrin; histology; biopsy

Introduction

From time immemorial humans have been plagued by gastric diseases [1]. In the 1970s fiberoptic endoscopy allowed the stomach to become a familiar place for gastroenterologists

Corresponding author: David Y. Graham, M.D., Michael E. DeBakey Veterans Affairs Medical Center, RM 3A-320 (111D), 2002 Holcombe Boulevard, Houston, TX 77030, USA, Phone: 713-795-0232, FAX: 713-790-1040, E-mail: dgraham@bcm.tmc.edu.

Conflict of interest statements

Dr. Graham has received small amounts of grant support and/or free drugs or urea breath tests from Meretek, Janssen/Eisai, and TAP, and BioHit for investigator initiated and completely investigator controlled research. Dr. Graham is a consultant for Novartis in relation to vaccine development for treatment or prevention of *H. pylori* infection. Dr. Graham is also paid consultant for Otsuka Pharmaceuticals and a member of the Board of Directors of Meretek, Diagnostics, the manufacturer of the ¹³C-urea breath test. Dr. Graham also receives royalties on the Baylor College of Medicine patent covering the serologic test, HM-CAP. MA and MK have nothing to declare.

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to explore. Steady improvements in endoscopic technology resulted in better images and as well as improved capabilities prompting gastroenterologists to differentiate into gastroenterologists and gastro-enteroscopists defined as those for whom endoscopy consumed a large share of the time spent in patient contact. These advances in endoscopy paralleled advances in other imaging techniques as well as in all areas of Medicine.

The discovery of *Helicobacter pylori* in the 1980s and proof that it played an etiologic role in the major gastric diseases, atrophic gastritis, peptic ulcer disease, gastric cancer, and primary gastric lymphoma was another major turning point in Gastroenterology. It became evident that eradication of the infection should result in the elimination of major causes of gastrointestinal morbidity and mortality and thus reduce the need for upper gastrointestinal endoscopy, or at least endoscopy focused on the stomach. The article addresses the questions about what, if any, are the current role for gastroscopy and how do to logically integrate the currently available testing modalities into modern medical practice

The world can be divided into regions with a low prevalence of *H. pylori* infections and high prevalence areas where *H. pylori* related diseases are still major clinical and public health problems. The populations can be divided into patients (eg, those signs or symptoms suggesting a upper gastrointestinal disease) and subjects or those without signs or symptoms of an upper gastrointestinal disease. The approach varies for the different groups.

Patients

Few would disagree that individuals with signs and symptoms suggestive of an upper gastrointestinal disease (eg, patients with anemia, vomiting, etc) are candidates for endoscopy. For those patients the mucosa of the esophagus, stomach, and proximal duodenum should be inspected carefully and biopsies should be taken from an specious areas. Endoscopy also allows directed therapy such as dilation of strictures, cautery of bleeding or potential bleeding sites, and removal of polyps or early cancers. The endoscopist also can employ more specialized modalities such as endoscopic ultrasound, high resolution endoscopes, chromoendoscopy, to assist in diagnosis and therapy. Routine biopsies from normal appearing mucosa should also be collected to assess *H. pylori* status and the health of the gastric mucosa (see below).

Low *H. pylori* prevalence areas

In many regions the disappearance of *H. pylori* was preceded by a change in the average pattern of gastritis such that non-atrophic gastritis replaced atrophic gastritis as the prevalent type of *H. pylori* gastritis. This change was the result of changes in the environment, primarily diet, and was seen clinically as a marked decline in the incidence of gastric cancer despite the widespread occurrence of *H. pylori* infections. The ultimate disappearance of *H. pylori* was the result of the combination of breaks in the chain of transmission of the infection to children (eg, improved sanitation and standard of living) and as a bystander effect of the widespread use of antibiotics. In populations where *H. pylori* is now rare (eg, <15%) such as in White middle or upper class North Americans, gastritis and its consequences are no longer important problems and the indications and expertise in upper gastrointestinal endoscopy have changed from gastro-duodenal to esophageal diseases. The widespread use of proton pump inhibitors has further reduced the incidence of active ulcers and has made the job of the pathologist more difficult as proton pump inhibitor use is associated with a reduction in *H. pylori* density and an improvement in antral gastritis at the expense of an increase in the severity of corpus gastritis. As many US endoscopists routinely take only antral biopsy specimens, the pathology report in *H. pylori* infected individuals is often more confusing than helpful (see below for recommendations)

High *H. pylori* prevalence areas

Gastric cancer is the second most common cancer world wide. With few exceptions gastric cancer is a consequence of *H. pylori* infection and the risk is proportional to the degree and stage of gastric atrophy. This relationship has led pathologists to devise grading systems to classify gastric mucosal damage in terms of severity and risk for developing gastric cancer. The OLGA system is the most recent iteration [2]. Although eradication of *H. pylori* will essentially eliminate gastric cancer, cure of an individual's active infection will not necessarily eliminate their risk of developing cancer [3,4]. However, *H. pylori* eradication is generally expected to reduce the cancer risk with the degree of reduction being related to the level of risk at the time of eradication therapy [3,4]. Therefore, *H. pylori* infected patients at low risk (eg, those with non-atrophic gastritis) can be assured that their chance of subsequent gastric cancer is very low to non-existent. In contrast, patients with increasingly severe corpus atrophy corresponding to baseline risks ranging from 200 to 4000/100,000 per year can expect a reduction but not an elimination of risk. Patients should reasonably expect that their diagnostic evaluation will also include the studies needed to allow risk stratification [5].

While, all *H. pylori* infected individuals should undergo *H. pylori* eradication, only those with significant baseline risks of gastric cancer should be considered for surveillance programs which are designed to identify gastric cancer at an early and curable stage. Initially, candidates for surveillance programs were selected based on age and most surveillance programs used age as a surrogate marker for risk based on the fact that cancer risk has long been known to increase logarithmically with age. However, that criteria has progressively been undermined by an increasing prevalence of *H. pylori*-related non-atrophic gastritis and individuals without *H. pylori* infections such that age is no longer a valid surrogate for the severity of atrophy. Histology or non-invasive laboratory testing (eg, measurement of pepsinogen and gastrin levels) allow more precise targeting of surveillance candidates [5–8].

Pattern of development of gastric atrophy

Carefully done endoscopy-histology studies have shown that the progression of gastric atrophy follows a pattern in which atrophy progresses out of the antrum into the corpus as an expanding atrophic front (Figure 1) [9]. This front advances more rapidly along the lesser curve such that the last sites to become atrophic are the most proximal portions of the greater curvature [10–12]. This is shown in the commonly used Japanese endoscopic atrophic border grading system (Figures 2A,B) [12]. Pathologists identified multifocal atrophic gastritis as the pattern of atrophy. This pattern is readily seen when one detects metaplastic mucosa macroscopically by staining gross specimen for brush border enzymes such as disaccharidases or alkaline phosphatase [13,14]. Endoscopists see similar patterns using in vivo staining with methylene blue (Figure 3). These scattered foci of intestinal metaplasia provided a misleading understanding of the progression of atrophy which typically tends to occur as an advancing “sheet” of atrophic mucosa often with focal areas of intestinal metaplasia (ie, pseudopyloric mucosa with focal intestinal metaplasia) embedded within it [9]. A better term would have been atrophic gastritis with multifocal intestinal metaplasia. The pathologist is at considerable disadvantage compared to the endoscopist as he/she will often judge mucosal biopsies of pseudopyloric metaplasia to be pyloric mucosa as they are dependent on the endoscopist to correctly identify each specimen in terms of its origin (eg, definitely taken from corpus mucosa). This is particularly important at sites near normal junctional mucosa (eg, lesser curvature proximal to the incisura) where either pyloric or pseudopyloric mucosa can be found. The dilemma can be resolved if the specimen is stained for gastrin (typically found in the antrum) and pepsinogen I (typically found in the corpus) as antral appearing mucosa without positive staining for gastrin and expressing pepsinogen I is pseudopyloric metaplasia [9] (Figure 4). Antral atrophy is defined as the loss of normal glands with and without its

replacement with fibrosis or intestinal metaplasia. Heavy lymphoid infiltration and the presence of lymphoid follicles makes it difficult if not impossible to reliably identify antral atrophy in the presence of an active *H. pylori* infection [15]. Clearly, better and regular communication between pathologists and endoscopists will lead to more useful information for patient management.

Determining the extent of atrophy requires sufficient biopsy specimens taken from predefined locations (see below). Even when this is done only a tiny they percent of the mucosal surface is examined such that sampling areas are likely to occur. Currently, most studies focus on the presence or absence of intestinal metaplasia. Using intestinal metaplasia as a surrogate for the degree and severity of atrophy is fraught with problems because as noted above, intestinal metaplasia is patchy such that even when biopsies are targeted to the same location it may not be found again [16]. In addition, experienced endoscopists can often identify intestinal metaplasia grossly (Figure 5) and unless instructed will tend to target it instead of more normal appearing mucosa thus providing an additional bias. One suspects, and the available data are consistent with the notion that the extent and type of intestinal metaplasia increase (eg, extending the area within the atrophic area with intestinal metaplasia), however it may not be a good measure of the extent and severity of atrophy.

Non-invasive gastric sampling

For those without symptoms, non-invasive testing should suffice (eg, urea breath test or stool antigen testing for *H. pylori*) and in areas and populations with increased risk of cancer, serum pepsinogen levels for atrophic gastritis [5–8]. This combination should allow clinicians to reasonably separate those with significant atrophy (higher cancer risk) from those with minimal to low risk. Asymptomatic patients with normal pepsinogen levels need only *H. pylori* eradication irregardless of age and surveillance is rarely warranted. Those with low pepsinogen levels should also undergo *H. pylori* eradication which, if there are remaining but suppressed parietal cells, will result in a partial return of function [17]. Such individuals are at increased risk for cancer and are also candidates for surveillance. Those with low pepsinogen and high gastrin levels have severe atrophic gastritis and it is likely that the tests for *H. pylori* will be negative. This is one of the highest risk groups [18]. However, the presence of persisting anti-*H. pylori* IgG suggests the presence of residual foci of infection and such patients should receive *H. pylori* eradication therapy. The effectiveness can be followed by noting a fall in *H. pylori* antibody titers as eventually the anti-*H. pylori* IgG antibodies will become negative. Anti-CagA antibodies are likely to remain positive despite all the other tests for *H. pylori* becoming negative and serve as a reminder as to the etiology of the atrophic process [19,20]. A fall in an elevated serum gastrin post treatment signifies that some recovery of function was possibly and probably also signifies a somewhat lower, but still high, risk for developing gastric cancer [21–24].

Recommended biopsy sites and protocol

Biopsy of normal appearing gastric mucosa can answer two important questions: is there an *H. pylori* infection, and is the mucosa atrophic? To adequately access the gastric corpus requires a minimum of 4 biopsy specimen (2 lesser curvature and 2 greater curvature sites) [2] (Figure 6 and 7). Because atrophy extends up the lesser curve faster than along the greater curve, the biopsies along the lesser curve serve to identify if atrophy is present whereas those along the greater curve provide an estimate of the extent [25]. Because the site of the biopsy provides important information, specimens should be separately identified. The specimens do not need to be sectioned in different blocks as the histological technician can embed them into multi-compartment cassette that allows them to be placed on one slide and still maintain their identify as to location.

One should use the largest forceps that will safely fit through the biopsy channel. Alligator type cups provide better specimens than round cups and forceps without a needle cause less damage to the specimen. The endoscopist should communicate whether the patient was receiving proton pump inhibitors, the site of each specimen, and the clinical impression. Additional biopsies should be taken on both sides of the advancing antral-corpus border (Figure 6 and 7) and of any mucosal abnormality [26] (Figure 8).

Summary

There clearly is a role for gastric endoscopy and endoscopic biopsy in the *H. pylori* era. However, the ability to provide useful diagnostic and prognostic information is critically dependent upon attention to detail with regard to biopsy site and identification of the biopsies as to the site from which they were taken.

Practice Points

- The approach to patients with upper gastrointestinal symptoms differs depending on whether they come from a low or high prevalence area in terms of *H. pylori* infections.
- In low *H. pylori* prevalence areas the focus has changed from gastroduodenal to esophageal diseases.
- In high *H. pylori* prevalence areas endoscopy coupled with non-invasive testing allows accurate diagnosis as well as risk stratification in terms of subsequent risk for development of gastric cancer.
- Whether gastric cancer risk is essentially eliminated or simply reduced following *H. pylori* eradication depends on the degree, severity, and pattern of gastritis.
- All those with *H. pylori* infection should undergo treatment with confirmation of cure. Those with significant baseline risk for gastric cancer (eg, those with corpus atrophic gastritis) should be considered for surveillance programs.

Research Agenda

- Identify cut-off points in terms of the pattern and severity of gastritis and/or laboratory test (eg, pepsinogen levels that allow stratification of patients in terms of relative need for surveillance following *H. pylori* eradication).
- Identify the best and most cost effective approaches for surveillance following *H. pylori* eradication including how often and for how many years surveillance is required.
- Identify markers for risk stratification for both low risk (eg, improvement of acid secretion, return of an acid environment in the stomach, serum gastrin normalization) and high risk (eg, failure of acid secretion to return or improve).
- Identify and prioritize effective post *H. pylori* eradication risk reduction strategies (eg, cessation of smoking, increased intake of fresh fruits and vegetables, use of gastroprotectives or inhibitors of inflammation that accelerate elimination of inflammation).

Acknowledgements

This material is based upon work supported in part by the Office of Research and Development Medical Research Service Department of Veterans Affairs and by Public Health Service grant DK56338 which funds the Texas Gulf Coast Digestive Diseases Center.

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Figure 1. Schematic representation of the stomach from a gastric resection. The yellow area represents antral mucosa and its extension into the corpus as pseudopyloric metaplasia (see Figure 4). The hatched blue areas represent areas of intestinal metaplasia as multifocal intestinal metaplasia (see figure 3). The red areas are the sites where the gastric cancer was found on this patient (adapted from reference 9).

Figure 2.

A. The stomach opened along the lesser curvature showing the different regions. B. Schematic representation of the spread of atrophic gastritis from the antrum to the corpus. C = closed-type and O = open type. The most extensive would be scored as O-3. C. An example of the atrophic border seen in a retroflexed view of the lesser curvature (score = C-2).

Figure 3. Methylene blue staining of the gastric mucosa showing multifocal intestinal metaplasia as the blue-staining mucosa scattered over the antral and corpus mucosa.

Figure 4. Gastric mucosal biopsy taken from the mid-corpus on the greater curve (site C-4, Figure 6) A. H&E staining showing pseudopyloric metaplasia with absence of parietal cells and B. Immunostaining for pepsinogen I confirming that the sample was from the corpus. Immunostaining for gastrin was negative (courtesy of Hala El-Zimaity, M.D.)

Figure 5.

A and B show two different endoscopic appearances of intestinal metaplasia. The red and white alternating pappter (A) is the most easily recognized. Biopsy of either the red or white areas shows intestinal metaplasia. Intestinal metaplasia as seen in (B) is commonly confused with erosions. (C) shows intestinal metaplasia presenting as depressive erythema. The insert shows the site at high magnification.

Figure 6. Schematic representation of the stomach showing the preferred biopsy sites: 4 antral and corpus.

Figure 7.

Endoscopic photograph of the distal corpus with the lesser curve on the right and the greater curve on the left. The gastric angle is seen in the distance on the right. The patient has severe atrophic gastritis with a clear demarcation of the atrophic border that has not yet fully involved the greater curvature.

Figure 8. Endoscopic appearance of the lesser curve of the corpus just proximal to the angularis with a Japanese type 0-IIc, Ul- gastric cancer emphasizing the importance of biopsy of any suspicious area [26].