

Diagnostic Yield of Gastric Biopsy Specimens When Screening for Preneoplastic Lesions

JEANNETTE GUARNER, MD, ROBERTO HERRERA-GOEPFERT, MD,
ALEJANDRO MOHAR, MD, PhD, CHALANDA SMITH,
AMANDA SCHOFIELD, DAVID HALPERIN, MD,* LUZ SANCHEZ,
AND JULIE PARSONNET, MD

The Sydney system recommends sites and numbers of stomach biopsies (mapping) for evaluation of *Helicobacter pylori*-associated lesions. The diagnostic yield of the recommended mapping technique in populations at high risk for gastric preneoplastic lesions has not been established. We evaluated pathology data from 733 endoscopies performed as part of an intervention study that assessed the effects of *H. pylori* treatment on preneoplastic conditions. Two pathologists assessed whether the mapping sequence of the 7 biopsy specimens obtained during each endoscopy was correctly followed and graded the specimens using the Sydney classification for gastritis. If the mapping sequence was followed, then we evaluated whether the amount of information obtained from 3 biopsy samples approximated that obtained from 5 and 7 biopsy samples. The mapping sequence was followed in only 239 (33%) endoscopies, indicating that experienced endoscopists can inadvertently misidentify sites in the

Endoscopically obtained biopsy specimens of the stomach are essential to establish the pattern of gastritis and the presence of preneoplastic gastric lesions.^{1,2} Several gastric mapping techniques, each using multiple biopsies, have been proposed. These techniques have typically evolved from mapping studies of particular gastric lesions.³⁻¹¹ Currently, the updated Sydney classification and grading of gastritis is the most widely accepted system.¹² It specifies taking 5 biopsy specimens, 2 from the antrum (both at 2 to 3 cm from the pylorus, 1 from the lesser curvature and the other from the greater curvature), 2 from the corpus (both at 8 cm from the cardia, 1 from the lesser curvature and the other from the greater curvature), and 1 from the incisura angularis. All samples should be identified and studied separately.

From the Infectious Disease Pathology Activity, Centers for Disease Control and Prevention, Atlanta, GA; Instituto Nacional de Cancerologia, Mexico DF, Mexico; Instituto de Investigaciones Biomedicas, Universidad Autonoma de Mexico, Mexico DF, Mexico; El Colegio de la Frontera Sur, Chiapas, Mexico; and Stanford University School of Medicine, Stanford, CA. Accepted for publication September 26, 2003.

*Deceased.

Supported in part by National Institutes of Health grant ROI CA67488-04.

Address correspondence and reprint requests to Jeannette Guarner, MD, Infectious Disease Pathology Activity, Centers for Disease Control and Prevention, Mail Stop G32, 1600 Clifton Rd. NE, Atlanta, GA 30333.

Copyright 2003, Elsevier Science (USA). All rights reserved.

0046-8177/03/3401-0005\$30.00/0

doi:10.1053/hupa.2003.3

stomach when obtaining specimens. When data from 7 specimens were used, *H. pylori* was found in 205 endoscopies, atrophy in 152, metaplasia in 135, and dysplasia in 22. When data from 3 specimens were used, the sensitivity was 99% for presence of *H. pylori*, 82% for atrophy and metaplasia, and 81% for dysplasia. When data from 5 specimens were used, the sensitivity was 100% for *H. pylori*, 96% for atrophy, and 95% for metaplasia and dysplasia. Although site-specific biopsy mapping is difficult in practice, the recommendations of the Sydney system as to the location and number of gastric biopsy specimens can adequately identify significant gastric histopathology. HUM PATHOL 34:28-31. Copyright 2003, Elsevier Science (USA). All rights reserved.

Key words: gastric biopsy, preneoplasia, screening, diagnosis.

Abbreviations: A, antrum; C, corpus; H&E, hematoxylin and eosin.

El-Zimaity and Graham¹³ evaluated whether the site and number of biopsy samples recommended by the Sydney system for the identification of *Helicobacter pylori* and intestinal metaplasia were adequate. They concluded that the system was unreliable because it underestimated the presence of intestinal metaplasia, and they recommended that the reproducibility of this mapping technique be studied. The predictive value of a test—in this case, the mapping technique—varies depending on the prevalence of disease in a specific population. The prevalence and distribution of gastric preneoplastic lesions, particularly intestinal metaplasia, have been shown to have geographic differences.¹⁴ Thus studies that evaluate the site and the minimal number of biopsy specimens necessary to document *H. pylori* infection and associated preneoplastic gastric lesions in populations at high risk are indispensable. This information is important not only because it will help establish parameters for research, but also because it has practical implications that directly affect patient care.

In an effort to define the minimal number of biopsies necessary to diagnose *H. pylori*-associated gastric lesions, we studied the pathologic data obtained from 733 endoscopies performed during an intervention study that evaluated the effect of *H. pylori* treatment on preneoplastic conditions in a high-risk population. We determined the accuracy of the endoscopist's assessment of the gastric site by evaluating the histologic mucosal type. We then evaluated whether the amount of information obtained from 3 and 5 biopsy

TABLE 1. Diagnoses, Sensitivity, Negative Predictive Value, and Accuracy for 3, 5, and 7 Biopsy Specimens

Pathology	Seven biopsy specimens	Five biopsy specimens			Three biopsy specimens				
	Diagnoses	Diagnoses	Sensitivity	Negative PV	Accuracy	Diagnoses	Sensitivity	Negative PV	Accuracy
<i>H. pylori</i>	205	205	100	100	100	203	99	94	99
Atrophy	152	146	96	93	97	125	82	76	88
Metaplasia	135	129	95	94	97	111	82	81	89
Dysplasia	22	21	95	99	99	18	81	98	98

Abbreviation: PV, predictive value.

specimens approximated that obtained from 7 biopsy specimens.

MATERIALS AND METHODS

Asymptomatic volunteers were recruited through radio announcements of a prevention study of gastric cancer in the highlands of Chiapas, Mexico. People included in the study were asymptomatic volunteers >40 years old. After receiving informed written consent from respondents, we selected people at high risk for atrophic gastritis and/or intestinal metaplasia by testing serum for antibodies to the *H. pylori* cytotoxin-associated gene A protein (cag-A).¹⁵ A cohort of participants were randomly assigned to 1 of 2 treatment groups: a 3-drug *H. pylori* eradication regimen or placebo. In each of these groups, 3 endoscopies were performed, the first before starting medications, the second 4 weeks after completing the intervention, and the last 1 year after treatment. Endoscopies were performed by 2 trained physicians; at each endoscopy, 7 biopsy specimens for histologic examination were obtained in a specific order: (1) antrum (A), (2) corpus (C), (3) A, (4) A, (5) A, (6) C, and (7) C.

Biopsy specimens were formalin-fixed, paraffin-embedded, and stained with hematoxylin and eosin (H&E). Separately, 2 pathologists studied each gastric specimen, recording the mucosal type as corpus if the biopsy specimen included glands with parietal, chief, and mucous cells and as antrum if it included mucous glands only. Each pathologist also graded the amount of *H. pylori*, acute and chronic gastritis, atrophy, and intestinal metaplasia using the visual analogue scale of the Sydney classification.¹² Quantification of *H. pylori* using special stains was necessary only in cases where bacteria were scant or could not be identified by H&E staining. A final conjoint diagnosis encompassing the different histologic features for a case was reached when the pathologists reviewed discrepant diagnoses and reached a consensus. Interobserver variability of the different parameters was assessed in the first 150 cases as described previously.¹⁶

Pathology data of 733 endoscopies were used for this study. Individual pathology reviews were used to define the endoscopies for which the mapping sequence was correctly followed. A database of the histologic parameters for each biopsy of each endoscopy was then created. From this database, the number of cases with *H. pylori*, atrophy, metaplasia, and dysplasia were determined after study of the first 3 biopsy specimens (A, C, A) and 5 biopsy specimens using the first 3 specimens plus biopsy 4 (A) and biopsy 6 (C). The 3- and 5-specimen diagnoses (individual reviews) were compared with the conjoint final diagnoses (hereafter referred to as 7-biopsy specimen diagnoses). Using 7-biopsy specimen diagnoses as reference and the results of 3 and 5 biopsy specimens as tests, sensitivity, specificity, predictive values, and the accu-

racy (sum of true positive and true negative cases, over the total number of cases that followed the mapping sequence) were obtained for *H. pylori*, atrophy, metaplasia, and dysplasia. The term “preneoplastic lesions” included diagnoses of atrophy, intestinal metaplasia, and dysplasia. Finally, we analyzed the final diagnoses for the cases as they were reached with 3, 5, and 7 biopsy specimens. Final diagnoses were defined as the combined coexisting histopathologic features for a case at each number of biopsy specimens; for example, an endoscopy at 3 specimens may have *H. pylori*, atrophy, and intestinal metaplasia.

RESULTS

We examined 3,969 biopsy specimens from 733 endoscopies. Histologically, 2,262 (57%) of the specimens were from the corpus (compared with 43% predicted by the mapping scheme), 1,350 (34%) from the antrum (compared with 57% predicted), and 357 (9%) from an indeterminate site (too superficial). Thus endoscopists frequently misidentified corpus and antrum. The correct mapping sequence was followed in 239 (33%) endoscopies.

Table 1 summarizes the diagnoses, sensitivity, negative predictive value, and accuracy for *H. pylori*, atrophy, metaplasia, and dysplasia using 7, 5, and 3 biopsy specimens. It should be noted that if we had used only the pathology data from the first 3 specimens, then we would have missed 2 *H. pylori* diagnoses, 27 cases with atrophy, 24 cases with metaplasia, and 4 cases with dysplasia. Using data from 5 specimens, we would have missed no *H. pylori* diagnoses but 8 cases with atrophy, 6 cases with metaplasia, and 1 case with dysplasia. The specificity and positive predictive values were 100% for all diagnoses of both 3 and 5 specimens, because no false-positive results were obtained. In summary, with the first 3 biopsy specimens, we had a 99% test sensitivity for detecting *H. pylori* infections and an 80% sensitivity for detecting preneoplastic lesions; using 5 biopsy specimens, sensitivity increased to 95% for preneoplastic lesions. The accuracy for a biopsy specimen exceeded 95% for 5 biopsy specimens and 85% for 3 biopsy specimens in all categories.

Table 2 shows the results of the final diagnoses after review of 3, 5, and 7 biopsy specimens for each endoscopy. We were able to establish final diagnoses in 187 (78%) endoscopies after review of 3 biopsy specimens, in 224 (94%) after review of 5 biopsy specimens,

TABLE 2. Number and Percentage of Cases with Final Diagnoses After Review of 7, 5, and 3 Biopsy Specimens

Pathology	Seven specimens number	Five specimens number (%)	Three specimens number (%)
No histopathology	8	8 (100)	8 (100)
Gastritis alone	3	3 (100)	3 (100)
Hp gastritis	38	38 (100)	38 (100)
Atrophy	6	6 (100)	6 (100)
Hp with atrophy	46	45 (98)	36 (78)
IM	4	4 (100)	4 (100)
Hp with IM	32	29 (91)	20 (62)
Atrophy & IM	10	9 (90)	7 (70)
Hp, atrophy & IM	70	63 (90)	50 (71)
Dysplasia*	3	1 (33)	1 (33)
Hp and dysplasia	19	18 (95)	14 (74)
Total	239	224 (94)	187 (78)

Abbreviations: Hp, *H. pylori*; IM, intestinal metaplasia.

*Dysplasia was usually accompanied by either atrophy and/or intestinal metaplasia.

and in 239 (100%) after review of 7 biopsy specimens. Thus in 37 (15%) cases we needed to review 2 additional biopsy specimens (for a total of 5) to reach a final diagnosis, and in 15 (6%) cases we needed 4 additional specimens (a total of 7). All cases with *H. pylori* exhibited varying degrees of neutrophilic inflammatory infiltrate. The final diagnoses gained after review of 5 and/or 7 biopsies were always in the preneoplastic lesions category but did not necessarily include the worst diagnosis (dysplasia). For example, of the 22 endoscopies in which the final diagnosis included dysplasia, 15 were considered to have a final diagnosis after 3 specimens, whereas 7 needed either 5 or 7 biopsy specimens for a final diagnosis. In the group that obtained final diagnosis after 5 biopsy specimens, 1 case had dysplasia diagnosed in the first 3 biopsy specimens, but atrophy was not apparent in those specimens until 5 biopsy specimens were studied; thus the case was considered to have a final diagnosis after review of 5 biopsy specimens.

Table 3 lists the grades according to the Sydney classification for atrophy, intestinal metaplasia (complete, incomplete, and mixed), and dysplasia for the cases after review of 7 biopsy specimens. Notably, most of the cases with intestinal metaplasia were of the complete type, which was most frequently graded as marked. Of the 29 cases with incomplete intestinal metaplasia, 20 were graded mild, and of the 18 cases with mixed intestinal metaplasia, 13 were graded marked. For dysplasia, all of the cases had a mild grade except for 1 moderate.

DISCUSSION

The updated Sydney system recommendations have become the gold standard for obtaining and reporting gastric biopsy specimens. Thus many reports now present findings as having been evaluated by the Sydney system.¹² Controversy exists, however, concern-

ing the reliability of the system to have maximum diagnostic yield, because biopsy specimen number and sites were chosen arbitrarily.¹³ By studying how frequently endoscopists can reliably follow a set mapping technique, we addressed some of the practical issues related to biopsy site. By analyzing the sensitivity and accuracy using the site and number suggested by the Sydney classification (5), as well as 2 fewer (3) and 2 more (7) biopsy specimens, we assessed the question of the ideal number of specimens necessary to obtain a meaningful diagnosis of the stomach during endoscopic examination.

Endoscopic examination and specimen sampling should not only include the number of biopsy specimens taken from grossly visible lesions, but also should reflect the pathology present in the entire stomach. To this end, various mapping techniques have been proposed.³⁻¹¹ Mapping studies showing specific locations of different gastric lesions have used multiple sections from resected stomachs and endoscopically obtained biopsy specimens. Our findings indicate that experienced endoscopists with careful training can still misidentify sites in the stomach when using a set mapping technique to obtain biopsy specimens. Because most studies consider only biopsy results from successful endoscopic mapping, it is difficult to extract the frequency of unsuccessful endoscopic mapping from the literature.^{5,6,8-10} Two reports briefly address this issue; 1 stated that complete mapping was accomplished in 70% of cases, and the other noted that for their study the number of biopsy specimens ranged from 4 to 12.^{7,14} In our study, we attribute the site misidentification by endoscopists to naturally occurring peristaltic movements, problems in identifying different mucosal textures, normal anatomic variation of each patient, differences in endoscopic equipment, or improperly embedded tissues. In our experience, endoscopists most often obtained corpus biopsy specimens thinking they were in the antrum.

Studies of the distribution of *H. pylori* in the stomach have shown increased density of the bacteria in the cardia followed by the antrum, with bacteria rarely found in areas with intestinal metaplasia.^{4,17-19} Thus at least 2 biopsy specimens, 1 from the antrum and 1 from the corpus, should be obtained to demonstrate *H. pylori* infection. In this study, we were able to detect 99% of *H. pylori* infections with 3 biopsy specimens (2 from the antrum and 1 from the corpus), a ratio similar to that

TABLE 3. Grading According to the Sydney Classification for Atrophy, Intestinal Metaplasia, and Dysplasia

Pathology	Mild	Moderate	Marked	Total
Atrophy	70	66	16	152
Complete IM	16	28	44	88
Incomplete IM	20	8	1	29
Mixed IM	2	3	13	18
Dysplasia	21	1	0	22

Abbreviation: IM, intestinal metaplasia.

found by other authors.¹³ When the recommended 5 biopsy specimens were obtained the sensitivity reached 100%. Thus, for detection of *H. pylori* infection, the number and site of specimens suggested by the Sydney system is adequate.¹²

The preneoplastic gastric lesions associated with *H. pylori* infection have shown topographical predilection for the antrum.^{5,6,10,11} Atrophy tends to show a diffuse pattern, whereas intestinal metaplasia and dysplasia are multifocal. In this study, the sensitivity for preneoplastic lesions was 80% when 3 biopsy specimens were reviewed and 95% when 5 specimens were reviewed. In a previous study, we determined that higher grades of intestinal metaplasia in an individual specimen and increasing number of specimens with metaplasia are associated with moderate and severe grades of atrophy.²⁰ This observation suggests that fewer biopsy specimens are required to find the lesion in patients with extensive preneoplastic conditions than in patients with less severe and/or extensive lesions. Some authors have recommended a minimum of 8 biopsy specimens; however, it is uncertain whether 8 is the ideal number because it is possible that lesions can still be missed, particularly in patients with small, localized lesions.¹³ In our study, 7 biopsy specimens were considered the gold standard; however, because more specimens were not obtained, we do not know whether we missed diagnoses.

Different populations vary in the incidence of gastric cancer and associated preneoplastic lesions despite similar frequencies of *H. pylori* infection.¹⁴ The study presented here was performed in a population with high prevalence of *H. pylori* infection and preneoplastic lesions.²¹ Our results show that most subjects had moderate and severe grades of metaplasia. Thus in this population fewer biopsy specimens may be required to obtain a diagnosis of preneoplastic lesions. If the same study were performed in a population with low prevalence of preneoplastic conditions, then a greater number of specimens may be needed to make an accurate diagnosis.

In conclusion, our study demonstrates that experienced endoscopists misidentify sites in the stomach when following a set mapping technique to obtain biopsy specimens. We observed an excellent sensitivity to identify *H. pylori* and gastric cancer precursor lesions with 5 biopsy specimens. Thus we agree with the recommendations of the Sydney system of location and number for obtaining gastric specimens in populations in which there is a high prevalence of preneoplastic lesions. However, further research needs to be performed in areas with a lower incidence of preneoplastic gastric lesions.

Acknowledgment. We gratefully thank Raul Belmonte, Cecilia Limón, Juan Antonio Moguel, and Rosario Moreno for assistance with data collection. We are especially grateful to El Centro de Investigaciones en Salud de Comitán and El

Colegio de la Frontera Sur in Chiapas, Mexico, for the use of their facilities.

REFERENCES

- Misiewicz JJ: The Sydney system: A new classification of gastritis. Introduction. *J Gastroenterol Hepatol* 6:207-208, 1991
- Price AB: The Sydney system: Histological division. *J Gastroenterol Hepatol* 6:209-222, 1991
- Bayerdorffer E, Oertel H, Lehn N, et al: Topographic association between active gastritis and *Campylobacter pylori* colonization. *J Clin Pathol* 42:834-839, 1989
- Genta RM, Huberman RM, Graham DY: The gastric cardia in *Helicobacter pylori* infection. *HUM PATHOL* 25:915-919, 1994
- Stemmermann GN: Intestinal metaplasia of the stomach: A status report. *Cancer* 74:55-564, 1994
- Genta RM: Recognizing atrophy: Another step toward a classification of gastritis. *Am J Surg Pathol* 20:S23-S30, 1996
- Genta RM, Graham DY: Comparison of biopsy sites for the histopathologic diagnosis of *Helicobacter pylori*: A topographic study of *Helicobacter pylori* density and distribution. *Gastrointest Endosc* 40:342-345, 1994
- Genta RM, Hamner HW, Graham DY: Gastric lymphoid follicles in *Helicobacter pylori* infection: Frequency, distribution and response to triple therapy. *HUM PATHOL* 24:577-583, 1993
- Kimura K: Chronological transitions of the fundic-pyloric border determined by stepwise biopsy of the lesser and greater curvatures of the stomach. *Gastroenterology* 63:584-592, 1972
- Kimura K, Takemoto T: An endoscopic recognition of the atrophic border and its significance in chronic gastritis. *Endoscopy* 3:87-97, 1969
- Stemmermann GN, Hayashi T: Intestinal metaplasia of the gastric mucosa: A gross and microscopic study of its distribution in various disease states. *J Natl Cancer Inst* 41:627-634, 1968
- Dixon MF, Genta RM, Yardley JH, et al: Participants in the International workshop on the histopathology of gastritis, Houston 1994. Classification and grading of gastritis: The updated Sydney system. *Am J Surg Pathol* 20:1161-1181, 1996
- el-Zimaity HM, Graham DY: Evaluation of gastric mucosal biopsy site and number for identification of *Helicobacter pylori* on intestinal metaplasia: Role of the Sydney system. *HUM PATHOL* 30:72-77, 1999
- El-Zimmaity HMT, Gutierrez O, Kim JG, et al: Geographic differences in the distribution of intestinal metaplasia in duodenal ulcer patients. *Am J Gastroenterol* 96:666-672, 2001
- Ley C, Mohar A, Guarner J, et al: Screening markers for chronic atrophic gastritis in Chiapas, Mexico. *Cancer Epidemiol Biomarkers Prev* 10:107-112, 2001
- Guarner J, Herrera-Goepfert R, Mohar A, et al: Interobserver variability in application of the revised Sydney classification for gastritis. *HUM PATHOL* 30:1431-1434, 1999
- Lewy-Trenda I, Trenda P, Wierchniewska A: Non-ulcer dyspepsia and *Helicobacter pylori* infection—morphological analysis according to the Sydney system—changes before and after treatment. *Pol J Pathol* 47:57-63, 1996
- Fiocca R, Villani L, Luinetti O, et al: *Helicobacter* colonization and histopathological profile of chronic gastritis in patients with or without dyspepsia, mucosal erosion, and peptic ulcer: A morphological approach to the study of ulcerogenesis in man. *Vichows Arch A Pathol Anat Histopathol* 420:489-498, 1992
- Genta RM, Gurer IE, Graham DY, et al: Adherence of *Helicobacter pylori* to areas of incomplete intestinal metaplasia in the gastric mucosa. *Gastroenterology* 111:1206-1211, 1996
- Guarner J, Herrera-Goepfert R, Mohar A, et al: Gastric atrophy and extent of intestinal metaplasia in a cohort of *H. pylori*-infected patients. *HUM PATHOL* 32:31-35, 2001
- Guarner J, Mohar A, Parsonnet J, et al: The association of *Helicobacter pylori* with gastric cancer and preneoplastic gastric lesions in Chiapas, Mexico. *Cancer* 71:297-301, 1993