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The Orientation of Gastric Biopsy Samples Improves the Inter-observer Agreement of the OLGA Staging System

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ABSTRACT

Background & Aims: Evaluation of severity and extension of gastric atrophy and intestinal metaplasia is recommended to identify subjects with a high risk for gastric cancer. The inter-observer agreement for the assessment of gastric atrophy is reported to be low. The aim of the study was to evaluate the inter-observer agreement for the assessment of severity and extension of gastric atrophy using oriented and unoriented gastric biopsy samples. Furthermore, the quality of biopsy specimens in oriented and unoriented samples was analyzed.
Methods: A total of 35 subjects with dyspeptic symptoms addressed for gastrointestinal endoscopy that agreed to enter the study were prospectively enrolled. The OLGA/OLGIM gastric biopsies protocol was used. From each subject two sets of biopsies were obtained (four from the antrum, two oriented and two unoriented, two from the gastric incisure, one oriented and one unoriented, four from the gastric body, two oriented and two unoriented). The orientation of the biopsy samples was completed using nitrocellulose filters (Endokit®, BioOptica, Milan, Italy). The samples were blindly examined by two experienced pathologists. Inter-observer agreement was evaluated using kappa statistic for inter-rater agreement. The quality of histopathology specimens taking into account the identification of lamina propria was analyzed in oriented vs. unoriented samples. The samples with detectable lamina propria mucosae were defined as good quality specimens. Categorical data was analyzed using chi-square test and a two-sided p value <0.05 was considered statistically significant.
Results: A total of 350 biopsy samples were analyzed (175 oriented / 175 unoriented). The kappa index values for oriented/unoriented OLGA 0/I/II/III and IV stages have been 0.62/0.13, 0.70/0.20, 0.61/0.06, 0.62/0.46, and 0.77/0.50, respectively. For OLGIM 0/I/II/III stages the kappa index values for oriented/unoriented samples were 0.83/0.83, 0.88/0.89, 0.70/0.88 and 0.83/1, respectively. No case of OLGIM IV stage was found in the present case series. Good quality histopathology specimens were described in 95.43% of the oriented biopsy samples, and in 89.14% of the unoriented biopsy samples, respectively (p=0.0275).
Conclusion: The orientation of gastric biopsies specimens improves the inter-observer agreement for the assessment of gastric atrophy.

Key words: Gastric atrophy – nitrocellulose filters – gastric cancer – gastric biopsy.

Abbreviations: *H. pylori: Helicobacter pylori*; OLGA: operative link for gastritis assessment; OLGIM: operative link on intestinal metaplasia assessment.

INTRODUCTION

Gastric cancer is one of the most common cancers worldwide, being the third leading cause of cancer death in both genders [1, 2]. The global incidence of gastric cancer has declined in the last few decades. However, in some regions, including Eastern Asia, South America, Eastern Europe, and Portugal, the incidence rates are still high [1-3]. One of the major factors responsible for this could be the high prevalence of *Helicobacter pylori* (*H. pylori*) infection [4, 5]. *H. pylori* is considered to be the promoter of the cascade described by Correa [6], consisting of chronic inflammation, mucosal atrophy, intestinal metaplasia, dysplasia, and cancer. The higher the extension and severity of gastric atrophy, the higher the risk of dysplasia and gastric cancer [7, 8]. For this reason, the current recommendation is to establish the extension and the severity of gastric atrophy using multiple biopsies standardized protocols [9]. A staging system using the severity and extension of gastric mucosal atrophy has been proposed

[the operative link for gastritis assessment (OLGA) staging system] [10]. The main problem in assessing gastric atrophy is the low inter-observer agreement [11]. For this reason, a new staging system similar to the OLGA staging system, but using intestinal metaplasia instead of gastric atrophy, was developed [the operative link on intestinal metaplasia assessment (OLGIM)] [12]. The rationale behind this new staging system is that intestinal metaplasia is easier to assess histologically. However, the OLGIM staging system takes into account only intestinal metaplasia, and for this reason could be less sensitive in identifying subjects at high risk for gastric cancer compared to the OLGA staging system [13].

The aim of the present study was to evaluate the inter-observer agreement for the assessment of the severity and the extension of gastric atrophy using oriented and unoriented gastric biopsy samples. Furthermore, the quality of the histopathology specimens of oriented versus unoriented biopsy samples was analysed.

MATERIAL AND METHODS

A total of 35 gastric biopsy sets (350 biopsy specimens, 175 oriented / 175 unoriented) from 35 patients (12 male/23 female, mean age of 67 ± 8.34 years) with dyspeptic symptoms examined by upper gastrointestinal endoscopy were analyzed in the present study. Patients with active bleeding during examination, and/or with severe comorbidities were not included into the study. Only subjects that had agreed to and signed the informed consent were included in the study. The subjects with gastric cancer detected during the examination were excluded.

The endoscopic examination was performed under superficial sedation (local 10% Xylocaine and i.v. Midazolam) or deep sedation (i.v. Propofol). The endoscopic equipment used was Olympus® Evis Exera II, CV-180 Processor, GIF-H180 scope (Olympus Medical System Corp, Tokyo, Japan). The protocol used for the gastric sampling was the standardized OLGA/OLGIM gastric biopsy sampling protocol (1 biopsy sample from the lesser curvature of the antrum, 1 from the greater curvature of the antrum, 1 from the gastric incisure, 1 biopsy sample from the anterior part of the gastric body, and 1 from the posterior part of the gastric body) [10]. The OLGA/OLGIM III and IV stages were considered high risk stages. From each subject, two sets of gastric biopsies were collected during the same examination using the above protocol: one set of oriented biopsy samples, and one set of unoriented biopsy samples. The unoriented biopsy samples were taken 5 mm to the left of each previous biopsy area of the oriented sample. In the end, at least ten biopsy samples were obtained from each subject (five oriented / five unoriented). Complementary biopsy samples were taken from any supplementary lesion detected during endoscopy, and labeled in separate vials. However, the analysis of the histopathology results of the complementary biopsy samples was not included in the present study.

The orientation of gastric samples was performed using nitrocellulose filters (Endokit®, BioOptica, Milan, Italy). The biopsy samples were applied from the biopsy forceps on the nitrocellulose filters with the luminal part uppermost (Fig. 1).

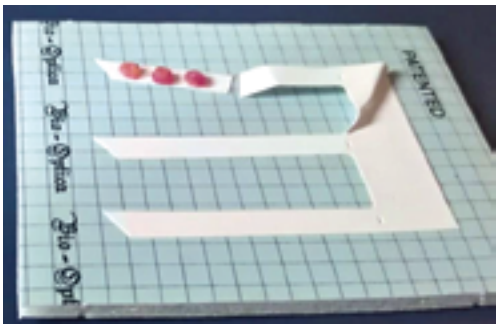

Fig. 1. Orientation of gastric biopsy specimens using nitrocellulose filters.

After orientation, the samples were placed in 10% formalin vials separately labeled for each gastric region. The unoriented biopsy samples were placed directly from the biopsy forceps in 10% formalin vials separately labeled for each gastric region.

The samples were stained using hematoxylin and eosin. No special stains for subtyping of intestinal metaplasia were used. A minimum of six histology sections from each sample were performed (each 4 μm thick). The most severe score for gastric atrophy and intestinal metaplasia was taken into account for the final histopathology result. The histology examination was performed by two experienced pathologists (Pathologist 1- G.B., and Pathologist 2 – M.D.) in a blind manner. The oriented biopsy samples were examined in a different session from the unoriented ones. The pathologists had no information regarding the endoscopy or medical reports of the patients. The quality of biopsy samples was defined using the identification of lamina propria mucosae on histology assessment. If the lamina propria mucosae was identified, the biopsy specimen was considered as being good quality.

Inter-observer agreement for each OLGA/OLGIM stage was computed using the kappa test for inter-rater agreement [14, 15]. Furthermore, the inter-observer agreement of high-risk/low-risk scores for atrophy and intestinal metaplasia for antrum and gastric body was computed using the same test. The high-risk/low-risk scores for atrophy and intestinal metaplasia in the two gastric regions were defined according to the visual analogue scale of the Houston-updated Sydney system (0 - no atrophy/intestinal metaplasia; 1 – mild atrophy/intestinal metaplasia (<30%); 2 – moderate atrophy/intestinal metaplasia (30-60%); 3 – severe atrophy/intestinal metaplasia (>60%) [10]. The Kappa test values less than 0.4 indicate low inter-rater agreement, values between 0.4-0.75 indicate medium agreement and values > 0.75 indicate high agreement between raters. Chi-square test was used to analyze the differences in good quality biopsy samples in oriented and unoriented biopsy specimens. A two-sided p value <0.05 was considered statistically significant.

The study was approved by the Fundeni Clinical Institute Committee of Science and Research Ethics (Reg.No. 3898/2013). All participants provided written informed consent to participate in the study.

RESULTS

Overall, 35 subjects were included in the study: 12 males, and 32 females with a mean age of 67 ± 8.34 years. A total

of 350 biopsy samples were analyzed: 175 oriented and 175 unoriented. The distribution of OLGA and OLGIM stages according to each pathologist examinations are presented in Tables I and II. The OLGA and OLGIM III and IV stages were considered high risk stages. OLGA high risk stages were found in 17.14 % of the cases examined by Pathologist 1, and in 28.56% of the cases examined by Pathologist 2 in the unoriented series. In the oriented series, the OLGA high risk stages have been found in 20% of the cases examined by the Pathologist 1, and in 25.72% of the cases examined by the Pathologist 2. For the OLGIM staging system, the high risk stages were found in 5.72 % of the cases examined by both pathologists in the unoriented series, and in 17.14%, and 11.42 % of the cases examined by the Pathologist 1, and by the Pathologist 2, respectively, in the oriented series.

Table I. Distribution of OLGA stages according to histopathology examination

	OLGA - n (%)			
	Unoriented		Oriented	
	P1	P2	P1	P2
OLGA 0	13 (37.14)	2 (5.72)	14 (40)	10 (28.56)
OLGA I	9 (25.72)	12 (34.29)	10 (28.56)	12 (34.29)
OLGA II	7 (20)	11 (31.43)	4 (11.42)	4 (11.42)
OLGA III	2 (5.72)	4 (11.42)	3 (8.58)	6 (17.14)
OLGA IV	4 (11.42)	6 (17.14)	4 (11.42)	3 (8.58)
OLGA HIGH RISK (III+IV)	6 (17.14)	10 (28.56)	7 (20)	9 (25.72)

n: number of cases; P1: Pathologist 1; P2: Pathologist 2.

Table II. Distribution of OLGIM stages according to histopathology examination

	OLGIM - n (%)			
	Unoriented		Oriented	
	P1	P2	P1	P2
OLGIM 0	14 (40)	17 (48.56)	16 (45.71)	16 (45.71)
OLGIM I	10 (28.56)	9 (25.72)	7 (20)	9 (25.72)
OLGIM II	9 (25.72)	7 (20)	6 (17.14)	6 (17.14)
OLGIM III	2 (5.72)	2 (5.72)	6 (17.14)	4 (11.42)
OLGIM IV	0 (0)	0 (0)	0 (0)	0 (0)
OLGIM HIGH RISK (III+IV)	2 (5.72)	2 (5.72)	6 (17.14)	4 (11.42)

nn: number of cases; P1: Pathologist 1; P2: Pathologist 2.

The inter-observer agreement for the OLGA stages in the unoriented series was poor to moderate in all stages (kappa index = 0.06-0.50). When the high risk stages, III and IV, were evaluated together, the inter-observer agreement was better (kappa index = 0.65). However, in the oriented series, the inter-observer agreement was substantial in all OLGA stages (kappa index = 0.61 – 0.77). Furthermore, when high risk OLGA stages were taken together, the agreement between the two examiners was high (kappa index = 0.88).

Overall, the agreement between pathologists was high for intestinal metaplasia both in the oriented and unoriented histopathology samples analysis (kappa test: oriented series = 0.70-0.83 / unoriented series = 0.83 – 1). Table III shows the complete results of the inter-observer agreement for the OLGA and OLGIM stages.

The kappa-indexes for the low risk (0/1) and high risk (2/3) atrophy/intestinal metaplasia scores in the antrum and gastric body are summarized in Table IV.

The lamina propria mucosae was identified in 167 (95.43%) of the 175 oriented biopsy samples, and in 156 (89.14%) of the 175 unoriented biopsy samples, respectively (p=0.0275).

Table III. Kappa index values for OLGA / OLGIM stages

	Kappa index Oriented	Kappa index Unoriented		Kappa index Oriented	Kappa index Unoriented
OLGA 0	0.62	0.13	OLGIM 0	0.83	0.83
OLGA I	0.70	0.20	OLGIM I	0.88	0.89
OLGA II	0.61	0.06	OLGIM II	0.70	0.88
OLGA III	0.62	0.46	OLGIM III	0.83	1
OLGA IV	0.77	0.50	OLGIM IV	-	-
OLGA HIGH RISK (III+IV)	0.88	0.65	OLGIM HIGH RISK (III+IV)	0.83	1

Table IV. Kappa index values for atrophy/intestinal metaplasia high-risk/low-risk scores in antrum and gastric body

	ANTRUM		GASTRIC BODY	
	Kappa index Oriented	Kappa index Unoriented	Kappa index Oriented	Kappa index Unoriented
Atrophy low-risk score (0/1)	0.70	0.45	1	0.70
Atrophy high-risk score (2/3)	0.70	0.45	1	0.70
Intestinal metaplasia low-risk score (0/1)	0.76	0.83	0.86	1
Intestinal metaplasia high-risk score (2/3)	0.76	0.83	0.86	1

DISCUSSION

Gastric cancer is a high mortality condition due to the limited curative therapeutic options by the time of diagnosis [16]. For this reason, detection in early stages would be mandatory in order to improve morbidity and survival. This has been suggested by the Japanese mass screening programs that showed a possible reduction of gastric cancer mortality associated with a higher detection rate of early stages [17]. However, endoscopic mass screening is a difficult and unrealistic task, and for this reason, defining a more targeted high risk population would be more useful. Atrophic gastritis

and intestinal metaplasia are well-defined risk factors for gastric cancer. These conditions are the result of a long-standing mucosal inflammation, which in certain instances can progress into advanced precancerous lesions, and eventually into invasive cancer [18].

The Sydney system and its updated version have the purpose to uniformly report gastric preneoplastic lesions (gastric atrophy, intestinal metaplasia, and dysplasia) [19]. However, the prediction of high gastric cancer risk cannot be done using this classification system. The OLGA staging system has the capability to differentiate the high-risk cancer population (stages III/IV) from low risk gastric cancer population (stages 0/I/II) [13, 20, 21]. The low reported inter-observer agreement of the gastric atrophy staging [11] conducted to the proposal of a new staging system based on the assessment of severity and extension of intestinal metaplasia [12]. However, the OLGA staging system includes intestinal metaplasia subtyping. By focusing on intestinal metaplasia alone, the OLGIM system is less sensitive in identifying high-risk subjects by the down-staging of the high-risk groups to whom follow-up should be offered [13, 22].

In the present study, a moderate-high inter-observer agreement for all the OLGA stages was obtained using the orientation of the gastric biopsy samples (kappa index = 0.61-0.77 in oriented series versus 0.06-0.50 in unoriented series). However, the biggest improvement of the inter-observer agreement was noted in OLGA 0/I/II stages (low-risk stages). This can be explained by the fact that a full thickness section of the gastric mucosa with a proper orientation is essential in assessing the density of the glands, and especially the pits/glands ratio that defines a normal mucosa. If the atrophy is present, the proper orientation is essential especially to define the severity of the atrophy (e.g. >60%) [10].

For intestinal metaplasia, the inter-observer agreement was high both in the oriented and unoriented series.

The OLGA staging system is based on the combination of atrophic changes in the two gastric mucosal compartments: antrum and body. In each compartment, atrophy is scored in a four-tiered scale (0 – no atrophy; 1- mild atrophy; 2 – moderate atrophy; 3- severe atrophy) according to the visual analogue scale of the Houston-updated Sydney system [10, 19]. We noticed in our series that the biggest improvement of the inter-observer agreement with sampling orientation was noted in the antral atrophy assessment (from 0.45 in unoriented samples to 0.70 in oriented samples). This could be explained by the different type and architectural pattern of the specific glands in the two regions of the stomach. The branched antral glands form lobules with an opening in the pits, whereas the oxyntic glands are straight, tubular, and parallel [10]. For this reason, the assessment of the glands density in the antral mucosa is more subjective than in the gastric body.

In a previous study (unpublished data), we analyzed the inter-rater index for the assessment of gastric atrophy and intestinal metaplasia using OLGA/OLGIM classification systems in 87 dyspeptic subjects (42 males/45 females, mean age 57 ± 15.8 years) addressed for upper gastrointestinal endoscopy. The OLGA high risk (III+IV) stages were detected in 10.4% of the cases. All the biopsy samples were oriented using the nitrocellulose filters (no unoriented case series were analyzed). The inter-observer agreement for gastric atrophy was at least substantial (moderate to high) for all the OLGA stages (kappa index - OLGA 0 = 0.80; OLGA I = 0.65; OLGA II = 0.90; OLGA III = 0.77; OLGA IV = 0.65, and OLGA high-risk (III+IV) = 0.90). For the OLGIM stages the inter-rater agreement was high in all stages (kappa index = 0.84-0.94). The OLGA high-risk stages were associated with age over 50 years, a personal history of cancer, except gastric cancer, and with gastric cancer. No gastric cancer was detected in the OLGA low-risk subjects. However, when intestinal metaplasia alone was analyzed, a downstaging of the high-risk OLGA stages was noted. Six cases of high-risk OLGA stages were down-staged to low-risk OLGIM stages. Furthermore, in one of the down-staged cases, gastric cancer was detected. To confirm the results, the present study was performed with oriented and unoriented gastric biopsies from the same gastric areas of the same subjects. A dramatic improvement of the inter-observer agreement in the oriented series for the gastric atrophy assessment was noted. For intestinal metaplasia the agreement was high in both the oriented and unoriented series.

Intestinal metaplasia can be very conveniently assessed because the goblet cells can easily be recognized with only a little training. However, for an accurate evaluation of the gastric mucosal atrophy, the pathologist needs a perpendicular full thickness mucosal section [10]. This can be difficult to

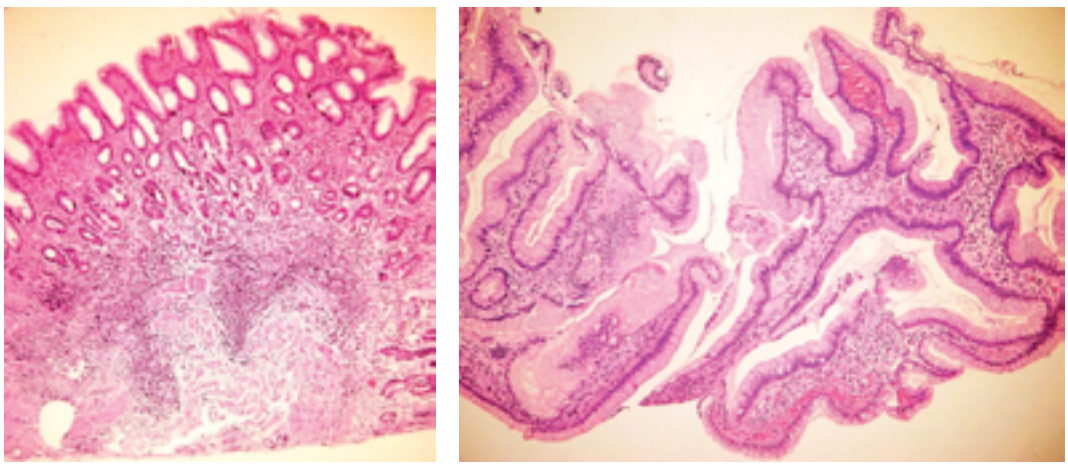

Fig. 2. a) good quality oriented gastric biopsy specimen using nitrocellulose filter (H&E, 50x); b) poor quality unoriented gastric biopsy specimen (H&E, 50x).

be obtained by the histo-technician if the biopsy fragment is not oriented after sampling. Using orientation, the histo-technician will know how to properly cut the paraffin slices perpendicular to the lamina propria mucosae, and in this way, a full thickness mucosal section can be obtained (Fig. 2a, b). In our study, the lamina propria mucosae could be detected in 95.43% of the oriented biopsy specimens compared to 89.14% of the unoriented samples. This difference was found to be statistically significant. Unfortunately, the orientation of biopsy specimens is not a common practice [23]. In our center, the orientation of biopsy specimens is also not usual. The main complaint of the personnel involved in the endoscopic procedures is the time dedicated to the procedure. However, using the nitrocellulose filters for the orientation of the biopsy samples is easy, and at least for the evaluation of the gastric and small bowel mucosa, it adds valuable information for the pathologist [10, 24]. The biopsy sample is easily fixed by the endoscopy nurse from the biopsy forceps directly on the nitrocellulose filter with the luminal part uppermost. The filter is designed to tightly adhere to the biopsy specimen during the whole processing of the sample. Up to 10 biopsy samples can be placed close one to another in a row on a single filter stripe. The tissue processing, after fixation, will not influence the sample orientation. After processing, the histo-technician embeds the filter and biopsy samples rotating the filter paper by 90 degrees. The first biopsy sample is easily recognized because the proximal end of the filter has a special angled shaped design for this purpose. For this reason, the technique permits a better and constant topographical localization of each biopsy specimen. There is no minimal size for proper orientation. The larger the size of the specimen, the higher the probability to have multiple layers for examination: mucosa, lamina propria with the specific components, muscularis mucosae, and submucosa, ideally. The use of the nitrocellulose filter orientation method does not prolong the histologic work-up in the laboratory. On the contrary, the processing time is shortened because the histotechnician will usually prepare a single filter stripe with all the biopsy samples fixed on it. This will reduce the embedding, cutting, and staining time. The cost is also reduced by diminishing the necessary paraffin blocks to one.

The present study showed an important improvement of the inter-observer agreement in gastric atrophy evaluation using orientation of the biopsy samples. The drawbacks could be represented by the small number of cases, and by the fact that the pathologists involved in the study have high expertise in gastrointestinal pathology. However, the number of samples analyzed was high (175 oriented and 175 unoriented), with both series of biopsy samples being obtained from the same subjects, and the same gastric areas.

CONCLUSION

The orientation of gastric biopsy samples increases the quality of the biopsy specimens and improves the inter-observer agreement of the gastric atrophy assessment. For this reason, if the results are confirmed in future studies, the orientation of gastric biopsy samples should be used routinely in clinical practice.

Conflicts of interest: No conflict to declare.

Authors' contribution: B.C. and C.G.: subjects' enrollment, data-acquisition, design of the study, data interpretation and manuscript drafting; M.D. and G.B.: histopathology examination of the biopsy samples and critical review of the scientific data; C.R. and I.B.: subjects' enrollment and data-acquisition; R.I.: subjects' enrollment, statistical analysis, data interpretation and manuscript drafting. All the authors critically revised the manuscript, read and approved its final version.

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