ARC Journal of Hepatology and Gastroenterology
Volume 2, Issue 2, 2017, PP 12-22
www.arcjournals.org

Agreement between Endoscopic assessment and Histological Diagnosis of Helicobacter Pylori−Associated Gastric Atrophy and Intestinal Metaplasia

Adamu Ishaku Akyala[1, 2], Kianoosh. Dadashzadeh[3], Alaba Ovye[4]

David Ishaleku[2], Maikel P. Peppelenbosch[1*]

[1]*Erasmus MC Cancer Institute, Erasmus University, Rotterdam, Netherlands*

[2]*Department of Microbiology, Faculty of Natural and Applied Sciences, Nasarawa State University, Keffi, Nasarawa State, Nigeria*

[3]*Department of Medical Laboratory Sciences, Marand Branch, Islamic Azad University, Marand, Iran*

[4] *Histopathology Department, University of Abuja teaching hospital, Gwagwalada, Abuja, Nigeria*

Corresponding Author: **Maikel P. Peppelenbosch,** 1Erasmus MC Cancer Institute, Erasmus University, Rotterdam, Netherlands, **E-mail:** m.peppelenbosch@erasmusmc.nl*

Abstract: *Atrophic gastritis (AG) and intestinal metaplasia (IM) are generally regarded as a precancerous condition associated with Helicobacter pylori and strongly predispose to the development of gastric cancer. Although accurate diagnosis is essential for preventing gastric cancer, in practice many physicians rely solely on visual endoscopic inspection to rule out the presence of AG. It is thus important to verify the validity of such endoscopic inspection to the gold standard (histological diagnosis by the pathologist) in a variety of settings, also because incidence and presentation of AG is highly variable in geographical terms. This consideration prompted us to conduct a retrospective cohort study involving 248 patients of which, 124are from low-incidence Nigeria and 124from high incidence Iran, all aged 50±30 years. The extent of endoscopic atrophy was classified into five subgroups according to a modified Kimura–Takemoto classification system and was compared with histological findings of atrophy at five biopsy sites according to the updated Sydney system. The strength of agreement between endoscopic and histological atrophy was moderate and showed substantial geographical discrepancy, indicating that relying solely on endoscopic screening for AG requires local validation.*

Keywords: *Stomach / intestinal metaplasia / gastric atrophy / Helicobacter pylori / gastric cancer*

1. INTRODUCTION

Gastric cancer (GC) remains the second most leading cause of cancer-related deaths and ranks 4th in cancer incidence worldwide [1,2]. Incidence rates and presentation of gastric cancer show, however, marked regional differences, European countries tend to have a low incidence [3]. In contrast, in Iran for instance stomach cancer together with breast cancerhas the highest incidence and highest mortality of all types of oncological disease in this country [4]. In contrast, gastric cancer has a low prevalence in sub- Saharan Africa with the lowest incidence rates in Western Africa[5]. Thus, gastric cancer is constitutes a global health issue, but presentation is markedly different in various parts of the world, raising questions as to whether screening strategies should to be tailored according to geography.

Appropriate screening is important as the prognosis of gastric cancer varies dramatically according to disease stage. The 5-year survival rate for advanced gastric cancer is less than 20%. In contrast, early gastric cancer (EGC) has a good prognosis, with reported 5-year survival rates being in excess of 90% or even 95% [6,7]. The main risk factors for gastric cancer are *Helicobacter pylori infection*, salt intake, smoking, alcohol, a family history of gastric cancer, atrophic gastritis (AG), and intestinal metaplasia (IM) [8].Especially AG and IM are important as they are considered to be premalignant lesions of gastric cancer [9,10].Hence accurate detection of AG and IM is essential for effective combat of gastric cancer.

AG and IM have multiple etiologies but the most important risk factor for these conditions is *Helicobacter pylori* infection [11,12] and according *H. pylori* eradication therapy provides

a preventive effect with respect to gastric cancer development [13,14]. Thus it is especially important to establish that screening for *H. pylori*-associated is adequate and appropriate irrespective of the geographical context. Currently the gold standard for the diagnosis of AG and IM is histological evaluation of biopsies by the pathologist [15]. In practice, however, in many cases physicians rely on endoscopic evaluation, especially for making a diagnosis of atrophy. Especially the endoscopic atrophy classification (EAC) according to Kimura and Takemoto[16,17] is frequently been used to evaluate the atrophic degree of gastric mucosa. However, although intraobserver agreement for gastric mucosa atrophy using the Kimura-Takemoto Classification.tends good to excellent, interobserver agreement is moderate even in experienced endoscopists[18], suggesting that histology-free evaluation may be suboptimal. Surprisingly, however, the correlation between endoscopic evaluation and histological final diagnosis has been relatively underexplored. Generally speaking published studies support that endoscopic evaluation performs well with respect to the detection of histological IM and AG [19,20]. However, these studies were performed in specific east-Asian high risk cohorts and the extent as to which these results can be extrapolated to the global situation remains uncertain, Data in patients specifically following *H. pylori* eradication are not present at all. Thus there is paucity in studies assessing the accuracy of endoscopic detection of AG in different settings.

The above mentioned considerations prompted us to investigate the concordance between histological diagnosis and endoscopic diagnosis employing the Kimura-Takemoto Classification of AG in a variety of geographical settings. The results show that irrespective of the context endoscopic evaluation performs well.

2. Materials and Methods

2.1. Study Population

The study population consisted of a total of 248 (Nigeria-cohort: 124, Iran-cohort: 124) patients who underwent both upper gastrointestinal Zoom endoscopy and examination for detection of *H. pylori*. The Nigeria cohort was collected at the University of Abuja Teaching Hospital, Gwagwalada. Abuja. Nigeria and the Iran cohort at the Department of Medical Laboratory Sciences.Marand Branch, Islamic Azad University, Marand, Iran. Only patients presenting between January 2007 and August, 2017 were evaluated in this study. Exclusion criteria were as follows: patients with prior history of gastrectomy, endoscopic evidence of reflux esophagitis, peptic ulcer disease, or malignancy and patients who had been treated with antibiotics, proton-pump inhibitors, bismuth-containing compoundsor histamine H2 receptor blockers within four weeks before the endoscopic procedure. Patients were also excluded if they had received *H. pylori* eradication therapy in the past or had been treated with any non-steroidal anti-inflammatory drug in the two weeks leading up to the endoscopic procedure. The protocol was approved by the Ethics Committee of the University of Abuja Teaching Hospital, Gwagwalada. Abuja. Nigeria and Department of Medical Laboratory Sciences.Marand Branch, Islamic Azad University, Marand, Iran. All patients gave written informed consent before entering the study. Two-hundred and forty-eight patients satisfied the criteria, and systemic map biopsies were taken. In total, 131 men and 117 women; mean age, 46 years; range, 20–80 years were studied.

2.2. Histological Examination

Records of biopsy sampling and the subsequent histological analysis by the gastroenterological pathologist were retrieved and reviewed. Biopsy samplesused for the analysis were those obtained using standard biopsy forceps from the five sites specified in the updated Sydney system (Figure 1) and had to be processed according to convention procedures. With respect to the latter, each tissue sample included was placed in a separate bottle of 10% formalin and embedded in paraffin for sectioning. Sections were stained with hematoxylin and eosin (HE) and evaluated according to established procedures. All the specimens were scored by expert gastrointestinal pathologists. For analysis of specimens with IM, PAS and Alcian blue 2.5 staining had to be used to identify the IM subtypes. Gastric atrophy was defined as apparent chronic inflammation of the gastric mucosa with concomitant loss of the gastric glandular cells and their replacement by intestinal-like epithelium, pyloric-like glands, and fibrous tissue. In each single biopsy, atrophy was scored as a percentage of atrophic glands. Non-metaplastic and metaplastic atrophy were considered together. For each biopsy sample, atrophy was scored on a four-tiered scale (no atrophy = 0%, score = 0; mild atrophy

= 1–30%, score = 1; moderate atrophy = 31–60%, score = 2; and severe atrophy >60%, score = 3). The OLGA stage resulted from the combination of the overall "antrum score" with the overall "corpus score"[21]. In each specimen, IM was subject to Markov classification(absent or present), and "extensive intestinal metaplasia" was deemed present if IM appeared in two or more specimens of the same patient. A patient was considered to have incomplete IM subtype if the incomplete subtype appeared in at least one specimen. Gastric dysplasia was assessed according the revised Vienna classification [22].In this study, the expert gastrointestinal pathologists were blinded to the age and sex of the subjects. The graded features were scored according to the updated Sydney system for atrophy[23]. Patients were considered positive for histological atrophy if the score was mild, moderate or marked in each location.

2.3. Endoscopy Examination

All of the endoscopic examinations were performed and assessed by one experienced endoscopist (G.A and K.D) who had been trained to evaluate EGA at the University of Abuja Teaching Hospital, Gwagwalada. Abuja. Nigeria and Department of Medical Laboratory Sciences.Marand Branch, Islamic Azad University, Marand, Iran respectively. Olympus video-scopes with conventional white light (model GIF-160; Olympus) were used. The endoscopic mucosal atrophy was evaluated according to the location of the endoscopic atrophic border described by Kimura and Takemoto [17]. This atrophic border is the boundary between the pyloric and fundic gland regions, which is endoscopically recognized by the difference in color and height of the gastric mucosa between the two sides of the border (Fig. 1). There are three grades of EGA: severe (O2 – O3), moderate (C3 – O1), and mild (C1 – C2). Six specimens were taken from each patient: five specimens were taken from specific locations according to the updated Sydney System and were put in separate boxes for pathologic examination; the 6th specimen used for rapid urease test was taken from the greater curvature of the antrum.

2.4. Level of Agreement Definition

The endoscopic findings of the extent of atrophy were compared with the histological findings of glandular atrophy at five biopsy sites (Figure 1). To be able to compare the extent of atrophy strictly, both classifications were modified to five grades according to definitions of those anatomical locations. Histological grading was scored as 1, none; 2, antrum (site 1 and/or 2); 3, angulus (up to site 3); 4, the middle body of the lesser curvature (up to site 4) and 5, the middle body of the greater curvature (up to site 5). Endoscopic atrophic grading according to the modified Kimura–Takemoto classification was scored as 1, none; 2; antral (C-1); 3, antral predominant (C-2); 4, corpus predominant (C-3, O-1, O-2) and 5, pan-atrophy (O-3) (Figure 3). Inasmuch as extensive atrophy is associated with a much higher cancer risk than limited atrophy, the Kimura–Takemoto classification was simplified to three grades of cancer risk oriented atrophy as: normal (no atrophy), limited atrophy (antral and antral predominant atrophy; C-1, C-2) and extended atrophy (corpus predominant and pan-atrophy; C-3, O-1, O-2, O-3). Agreement was defined as matching of endoscopic and histologic grades, with all other findings defined as disagreement.

2.5. Serum Pepsinogen Levels

Fasting serum was collected from all subjects. The samples were centrifuged immediately at 4 °C and serum stored at −70 °C until used. Serum concentrations of pepsinogen (PG) I and II were measured using a latex-enhanced turbidimetric immunoassay, and the PG I to PG II ratios (PG I/II) were calculated.

2.6. Helicobacter Pylori detection

Serum samples from all patients were tested by enzyme linked immunosorbent assay for the presence and concentration of IgG antibodies to *H. pylori* (HM-CAP; Enteric Products Inc., Westbury, NY). A concentration ≥1.8 was defined as positive (sensitivity 98.7%, specificity 100%).We also employ the gold standard for H. pylori detection by culture. Following collection of gastric biopsy, samples were homogenized and cultured onto Brucella agar supplanted with 5% sheep blood and antibiotics (Vancomycin, Amphotericin B and Trimethoprim). Culture plates were incubated at microaerophilic condition, 37 ºC and high humidity for 5-7 days. Organisms were identified as H. pylori based on colony

morphology, gram staining and positive oxidase, catalase and urease tests.

2.7. Statistical Analysis

STATA software (version 10.0; StataCorp, College Station, TX, USA) was used. Chi-squared test and Fisher's exact test were applied to evaluate endoscopic, histological, and serological parameters in patients with gastric atrophy. Agreement between endoscopic and histologic evaluations of the grade of gastric atrophy was assessed by determining the weighted kappa value. Factors associated with extensive atrophy were estimated by univariate logistic regression analysis. Covariates showing a significant association with extensive atrophy by the χ^2 or *t* test were included in multiple logistic regression analyses. Odd ratios (ORs) and 95% confidence interval (CI) were calculated to assess the strength of association between variables. A P value < 0.05 was considered statistically significant.

3. RESULTS

3.1. Demographic Data

A total of 248 patients aged 50±30 years were included in this study, including 124 patients from Nigeria and 124 from Iran. Mean ± SD patient age was 46.4 (± 15.3) years. Of these patients, 131(52.8%) were male, 117 female; (47.2%). Gender ratio F/M: 0.89 and 138 (55.6%) were serologically *H. pylori-positive*. The detailed characteristics of the two subgroups are shown in **Table 1**.

Table1: *Demographic, Endoscopic, and Pathologic Characteristics of Study Population with H Pylory Associated Gastric Atrophy*

	Nigeria (n = 124)(%)	Iran (n =124)(%)	Total (n =248)(%)	P value (Nigeria vs Iran)
Clinical parameters				
Sex				
Male	62 (50.0)	69 (55.6)	131 (52.8)	
Female	62 (50.0)	55 (44.4)	117 (47.2)	0.37
Age (yr)				
≥ 40	69 (55.6)	68 (54.8)	137 (55.2)	
<40	55 (44.4)	56 (45.2)	111 (44.8)	0.89
Helicobacter pylori Ag				
Positive	40 (32.3)	88 (71.0)	128 (51.6)	
Negative	84 (67.7)	36 (29.0)	120 (48.0)	0.84
Helicobacter pylori IgG				
Positive	89 (71.8)	49 (39.5)	138 (55.6)	
Negative	35 (28.2)	75 (60.5)	112 (45.4)	0.00
Serologic features (ng/mL), mean ± SD				
Pepsinogen I	49.9 ± 39.2	57.8 ± 38.1	53.1 ± 38.7	0.731
Pepsinogen II	12.9 ± 7.2	12.1 ± 10.1	12.9 ± 8.65	0.621
Pepsinogen I/II ratio	5.4 ± 1.8	<5		0.471
Endoscopicatrophy				
No atrophy	50 (40.3)	67 (54.0)	117 (47.2)	
Antral (C-1)	43 (34.7)	36 (29.2)	79 (31.9)	
Antralpredominant (C-2)	26 (20.9)	0 (0.0)	48 (19.4)	
Corpus predominant (C-3-O-2)	5 (4.03)	21 (17.0)	26 (10.5)	0.00
Histologicalatrophy				
None	50 (40.3)	57 (46.0)	107 (43.1)	
Antrum	38 (30.2)	41 (33.0)	79 (31.8)	
Angulus	20 (16.13)	26 (20.5)	46 (18.5)	
Lesser curvature of middle body	16 (12.9)	0 (00.0)	16 (6.5)	0.00
Greater curvature of middle body	0 (0.0)	0 (00.0)	0 (0.0)	
IntestinalMetaplasia	85(68.5)	63(50.8)	148 (59.7)	
Complete subtype	46(37.1)	32(25.8)	78(31.4)	
Incomplete subtype	30(24.2)	26(20.9)	56(22.5)	0.06
Unidentified	9(7.2)	5(4.1)	14(5.6)	

There were significant differences between the groups from the Nigeria and Iran, especially with respect tothe extent of atrophy. In the Nigerian population, only 60.%were diagnosed histologically of having corpus atrophy, whereas, in Iran, 54% had gastric atrophy while 57 (46.0%) showed no evidence of histological atrophy. Hence geographical origin influences disease presentation necessitating comparison of the relative performance of endoscopy with respect to the diagnosis of AG.

3.2. Agreement between Endoscopic and Histological Atrophy

The comparisons between endoscopic and histological atrophy scores are shown in **table 2**.

Table 2: *Endoscopic and Histological Atrophy Cases Cross-Tabulation with H Pylori-Associated Atrophy*

		Histologicalatrophy						
		None	**Antrum**	**Angulus**	**Middle body LC**	**Middle body GC**	**Total**	**Weighted κvalue**
Endoscopicatrophy	No atrophy	**71**	21	14	11	0	117	0.89
	Antrum (C-1)	18	**42**	9	10	0	79	
	Antrumpredominant (C-2)	0	2	**3**	0	0	5	
	Corpus predominant (C-3-O-2)	12	3	10	**22**	0	47	
	Pan-atrophy(O-3)	0	0	0	0	**0**	0	
	Total	101	68	36	43	0	248	
	Misdiagnosis	30	26	33	21	0	110 (44.35%)	
	Concordance		Endoscopic over-diagnosis		Endoscopicunder-diagnosis			

Taking the study population *in toto*, of the 248 patients, 138 (55.0%) showed complete agreement between endoscopic assessment and final histological diagnosis. Importantly, the strength of agreement between the modified Kimura–Take moto classification and histological atrophy, as defined by the updated Sydney system, showed good reproducibility, with a weighted kappa value of 0.89 [95% confidence interval (CI) 0.68–0.96]. However, a total of 110 patients were endoscopically misdiagnosed, including 45 (18.14%) who were over-diagnosed and 65 (26.2%) who were under-diagnosed. Of the 43 patients histologically diagnosed with atrophy in the middle of the body of the greater curvature, 21 (49 %) were under-diagnosed endoscopically. Moreover, 30 of 110 (127.3%) patients without histological atrophy were endoscopically over-diagnosed with antral or antral predominated atrophy. Thus generally speaking endoscopic assessment performs well but is not sufficient for accurate diagnosis.

3.3. Factors Affecting Agreement

To identify factors affecting the agreement between endoscopic and histological atrophy, univariate analyses were performed; factors analyzed included geopgraphy (Nigeria vs Iran), age, sex, *H. pylori* infection, endoscopic atrophy (no atrophy *vs* others) and PG I/II ratios. Factors significantly associated with reduced performance of endoscopy included Iran ethnicity ($P < 0.001$), older age ($P < 0.001$), a low pepsinogen I/II ratio ($P = 0.015$), the endoscopic dwetection of atrophy ($P < 0.001$) and *H. pylori* infection ($P = 0.001$) (**Table 3**).

Table3: *Factors that Significantly Associated with Reduced Concordance between Endoscopic and Histological Atrophy with H Pylori Associated Gastric Atrophy Cases.*

	Agreement group(*n* = 180) (%)	**Disagreementgroup (*n* = 58) (%)**	OR(95%CI)	P value
Country				
Nigeria	98 (51.6)	38 (65.5)	0.22 (0.23 -0.76)	<0.001
Iran	92 (48.4)	20 (34.5)	1	
Age (yr)				
≥ 40	109 (57.4)	30 (51.7)	0.14 (0.09 -0.40)	P=0.148
< 40	71 (42.6)	28 (48.3)	1	
Helicobacter pylori IgG				
Positive	111 (58.2)	32 (55.2)	0.40 (0.30 -0.55)	P=0.001
Negative	69 (36.3)	26 (44.8)	1	
Serologic features (ng/mL)				
Pepsinogen I	120 (63.2)	38 (65.5)	0.23 (0.20 -0.45)	P=0.001
Pepsinogen II	70 (36.8)	20 (34.5)	1	
Endoscopicatrophy				
No atrophy	89 (46.8)	22 (37.9)	1	
Others	101 (53.2)	36 (62.1)	0.38 (0.22 -0.67)	<0.001

OR: Odds ratio; CI: Confidence interval.

In contrast, age was not significantly associated with reduced Agreement (P = 0.138). Multivariate analysis showed that only three factors were independently associated with reduced agreement: Iranianethnicity, older age and endoscopic atrophy (**Table 4**). Thus the performance of endoscopic evaluation is influenced by the geographical context.

3.4. Further Assessments According to Factors Significant on Multivariate Analysis

To further assess the disagreement between histological and endoscopic atrophy, patients were cross-tabulated by each factor found to be significant (**Table 4**).

Table 4. *Factors that Significantly Associated with Reduced Concordance between Endoscopic and Histological Atrophywith H Pylori-Associated Gastric Atrophy Cases.*

	Adjusted OR (95%CI)	**P values**
Country		
Nigeria	1	<0.001
Iran	0.23 (0.11–0.56)	
Age (yr)		
≥ 40	1	0.268
< 40	0.6 (0.31–1.38)	
***Helicobacter pylori* IgG**		
Positive	1	
Negative	0.32 (0.16–0.66)	0.008
Pepsinogen I/II ratio		
> 3.0	1	
≤ 3.0	0.50 (0.67–3.35)	0.328
Endoscopicatrophy		
No atrophy	1	0.256
Others	0.09 (0.04–0.56)	

Although the performance of endoscopic evaluation was diminished in extensive atrophy in both populations, the geographical context influenced the extent of this misdiagnosis. More

specifically, 24 (19.35%) of the 124 Nigeria patients were misdiagnosed, including 15 who were over-diagnosed with histological atrophy of the antrum or angulus. In contrast, 57 (45.2%) of the 126 Iranian patients, of all histological grades, were misdiagnosed, including 22 who were over-diagnosed and 35 who were under-diagnosed. This further analysis supports the notion that the performance of endoscopic evaluation solely is significantly influence by the different presentation of disease in alternative geographical locations.

3.5. Cancer Risk-Oriented Atrophy Grading

Table 5. *Endoscopic and Histological Atrophy Cross Tabulation According to Populationswith H Pylori Associated Gastric Atrophy*

		Histologicalatrophy					Total	Weighted κvalue
Nigeria		None	Antrum	Angulus	Middle body LC	Middle body GC		
Endoscopicatrophy	No atrophy	**40**	4	4	2	0	56	0.79
	Antrum	8	**30**	5	**0**	0	40	
	Antrumpredominant	0	2	**3**	0	0	24	
	Corpus predominant	4	0	10	**12**	0	6	
	Total	52	36	22	14	0	124	
Iran								
Endoscopicatrophy	No atrophy	**31**	17	10	09	0	67	0.96
	Antrum	10	**12**	4	**10**	0	36	
	Antrumpredominant	0	0	**0**	0	0	0	
	Corpus predominant	8	3	0	**10**	0	21	
	Total	49	32	14	29	0	124	

GC: Greater curvature; LC: Lesser curvature

Table 6: *Risk Factors-Associated with Cancer*

		Histologicalatrophy			Total	Weighted κvalue
		Normal	Limited	Extended		
Endoscopicatrophy	Normal	**70**	5		75	0.79
	Limited (C-1~2)	24	**80**	7	107	
	Extended (C-3~O-3)		12	**52**	62	
	Total	92	97	59	248	
	concordance		endoscopic over-diagnosis			endoscopicunder-diagnosis

When classified according to cancer risk-oriented atrophy grading defined above, 110 (88.1%) of the 248 patients were concordant (**Tables5 and 6**). The strength of agreement between endoscopic and histological assessment by cancer risk-oriented grading showed good reproducibility, with a weighted kappa value of 0.79 (95%CI: 0.60–0.97). No marked differences between the two geographical locations involved appeared. Thus with respect to assessing cancer risk endoscopic evaluation performs well irrespective from the geographical context.

3.6. Association between OLGA Gastritis Stage, Endoscopic Gastric Atropy and Intestinal Metaplasia

Intestinal metaplasia, extensive IM, and incomplete IM subtype also clustered to the subgroup of patients with high-stage OLGA gastritis (**Table 8**).

Table8. *The Association between OLGA Gastritis Stage and Intestinal Metaplasia*

	OLGA gastritis stage			
	Stage 0–II (n = 121)	**Stage III, IV (n = 47)**	**p (Fisher's exact)**	**Oddratios (95% CI)**
IM	49.58 (60/121)	38.29 (18/47)	**<.001**	**24.6 (05.7–72.5)**
Extensive	26.45 (32/121)	25.53 (12/47)	**<.001**	**22.6 (07.8–82.9)**
Incomplete subtype	18.18 (22/121)	21.27 (10/47)	**<.001**	**33.7 (04.5–62.8)**
Unidentifiedsubtype	4.13 (7/121)	0 (0/47)		

OLGA, Operative Link on Gastritis Assessment; IM, intestinal metaplasia

Seven cases with unidentified IM subtype were all in OLGA gastritis stage 0–II. When we subsequently analyzed only patients with gastritis stage 0–II only, there was no homogenous distribution of IM subgroup: We rarely found patients with IM none-to-mild EGA, while it clustered to patients with moderate-to-severe endoscopic gastric atrophy (**Table 7**). We also found that there was an association between the gastric atrophy and the subtype of IM. From a total of 59.7% (148 /248) in our entire study population, 46(37.1%) and 32(25.8%) from Nigeria and Iran respectively had the complete subtype of IM while 30(24.2%) and 26(20.9%) patients from Nigeria and Iran respectively presented with the incomplete IM. In addition, 9(7.2%) and 5(4.1%) patients from Nigeria and Iran respectively were classified asindeterminate IM. Thus also with respect to the presentation of IM, important regional differences are apparent, further highlighting the necessity to tailor screening strategies to local needs.

Table7. *Association between Endoscopic Gastric Atrophy and Metaplasia*

	Endoscopicgastricatrophy			
	Moderate-to severe (n = 40)	**None-to-mild (n =38)**	**P (X^2test)**	**AdjustedOddratios(95% CI)**
Complete **IM**	27.5% (11/40)	47.34% (18/38)	**<0.001**	21.3 (8.7–35.2)
Incomplete	30.0% (12/40)	31.6% (12/38)	**<0.001**	33.5 (7.4–37.3)
Unidentified	42.5 % (17/40)	36.84(14/38)	**<0.001**	41.7 (4.1–74.1)

IM, Intestinalmetaplasia

4. DISCUSSION

The natural history of the development and progression of gastric cancer in general and especially the role of *H. pylori* infection in this process is now fairly well understood and involves sequence of gastric mucosal atrophy, intestinal metaplasia, and gastric cancer [24]. This has led to the realization that endoscopic screening in high-risk individuals is essential for preventing the associated mortality. The efficacy of such screening obviously depends on adequate diagnosis in which histological assessment of biopsies taken by the endoscopist remains the gold standard. The updated Sydney system was designed to assess histological gastritis and atrophy more objectively and has become the international standard [25]. Although this classification includes assessment of five biopsy sites, this extensive approach is not common in daily practice, because of patient discomfort, cost, logistic and time restrictions. Hence, many physicians rely to an important extent on endoscopic evaluation for the detection of AG. To which extent this is a problem is not well understood. A Swedish study found a sensitivity and specificity for moderate to severe atrophic gastritis in the gastric corpus of 67 % and 85 %, respectively [26]and concluded that macroscopic features as observed during gastroscopy are of very limited value in the evaluation of whether or not gastritis or H. pylori infection are present. AKorean study, however, reported that endoscopic and histological atrophic gastritis show relatively good correlations [27]. Hence further studies, investigating presentation in different geographical contexts are necessary to clarify to which extent endoscopic observation

alone can accurately assess AG. The present study was initiated to fill this void.

Our results show that the efficacy of endoscopy to detect AG is moderate and shows substantial regional variation, possibly caused by different presentation and incidence of AG at different locations around the globe. Generally speaking the performance of endoscopic screening is not good enough to rely on it alone and histological confirmation of the endoscopic diagnosis remains necessary. In conjunction with geographical variations in the performance of endoscopic observation to detect AG, it is fair to say that local validation remains essential. The agreement rate for atrophy was significantly higher for patients in the Nigerian than for those in Iran. Much more patients, however, in the Iranian cohort displayed extended atrophy, which is more easily misdiagnosed. The two populations also had different concordance between endoscopic diagnosis and microscopic diagnosis in the multivariate analysis, suggesting that this difference may be associated with differences in the background of the two populations. Indeed, the two populations differed in host genetic factors, diet, and bacterial virulence. For example, there are ethnicand.or geographical differences in the *H. pylori*cytotoxin associated gene A (CagA), one of the most important virulence factors for gastric mucosal injury and atrophy. The CagA gene is polymorphic and is primarily classified into East Asian and Western types based on sequences in its 3′ coding region [11]. Previous studies have clarified the differences in gastritis and atrophy among patients infected with East Asian CagA-positive, Western CagA- positive, and CagA-negative *H. pylori* [28], with differences in virulence ppotentially provoking differences in agreement rates. In Iran the cagA gene genotype was found to predominate in gastric adenocarcinoma patients [29]. But obviously further studies, linking such variations directly to concordance between endoscopic and histological diagnosis are necessary to substantiate this notion.

We observed that older age predisposes for discordance between the endoscopic assessment and the histological diagnosis, the histological structures of the normal antral and corpus mucosa differ, with the border between these two areas located at the angulus. This anatomically defined border is difficult to detect clearly using conventional endoscopy, although it can be better detected using high definition equipment. However, a slight difference in color between the antrum and the corpus may occur in the absence of histological atrophy. Mistaking this anatomical border for the atrophic border may result in over-diagnosis. We found that older patients, particularly older Iranians, tended to be over-diagnosed. Two possibilities may explain this finding. The first may have been bias in the endoscopist prompted by the notion that elderly Iranians are more likely to be infected with *H. pylori*. The second reason is that gastric mucosal blood flow decreases with age[30,31], which may affect mucosal appearance. Because of the slight differences in mucosal color, the endoscopist may mistake normal for atrophic antral mucosa in older patients. It is clear, however, that special care should be taken in older patients and that the practitioner should not submit to the temptation to rely solely on endoscopic diagnosis.

5. Conclusion

Although routine endoscopy can assess precancerous conditions by evaluating the extent of gastric atrophy, agreement between endoscopic and histological atrophy is unclear and always requires local validation. Endoscopic atrophy grading can predict extensive histological atrophy and may serve as a practical assessment of precancerous conditions during endoscopy in routine clinical practice, especially for patients in Western countries.

References

[1] Hunt R.H., Camilleri M., Crowe S.E., El-Omar E.M., Fox J.G., Kuipers E.J, Malfertheiner P., McColl K.E., Pritchard D.M., Rugge M., Sonnenberg A., Sugano K., Tack J. The stomach in health and disease.Gut. 64 (10):1650-1668 (2015).

[2] Ferlay J., Shin H.R., Bray F., Forman D., Mathers C., Parkin D.M. .Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008.Int J Cancer 127(12):2893-917. (2010).

[3] den Hoed C.M., Kuipers E.J. Gastric Cancer: How Can We Reduce the Incidence of this Disease? Curr Gastroenterol Rep18(7):34 (2016).

[4] Parkin D.M., Bray F., Ferlay J., Pisani P.Global cancer statistics, 2002.CA Cancer J Clin. 55:74-108 (2005).

[5] Oluwasola A.O., Ogunbiyi J.O. Gastric cancer: aetiological, clinicopathological and

management patterns in Nigeria. Niger J Med, 12(4): 177-186 (2003).

[6] Ortiz J.,.Ragunath, K. Long-term survival after endoscopic resection for early gastric cancer in the remnant stomach: comparison with radical surgery. Ann Gastroenterol, . 28(1): 1-2 (2015).

[7] Park JM, Ryu WS, Kim JH, Park SS, Kim SJ, Kim CS, Mok YJ.Prognostic factors for advanced gastric cancer: stage-stratified analysis of patients who underwent curative resection. Cancer Res Treat. 38(1):13-8 (2006).

[8] Yoon, H..Kim N., Diagnosis and Management of High Risk Group for Gastric Cancer. Gut Liver, 9(1): 5-17 (2015).

[9] Mommersteeg M.C., Yu J., Peppelenbosch M.P, Fuhler G.M. Genetic host factors in Helicobacter pylori-induced carcinogenesis: Emerging new paradigms.BiochimBiophysActa.2017 Nov 14.pii: S0304-419X(17)30158-0.

[10] Park Y.H., Kim N. Review of atrophic gastritis and intestinal metaplasia as a premalignant lesion of gastric cancer.J Cancer Prev. 20(1):25-40 (2015).

[11] Yamaoka Y. Pathogenesis of Helicobacter pylori-Related Gastroduodenal Diseases from Molecular Epidemiological Studies. Gastroenterol Res Pract.2012:371503 (2012).

[12] Uemura N., Okamoto S., Yamamoto S., Matsumura N., Yamaguchi S., Yamakido M., Taniyama K., Sasaki N., SchlemperR.J.Helicobacter pylori infection and the development of gastric cancer.N Engl J Med. 345(11):784-9 (2001).

[13] Fukase K., Kato M., Kikuchi S., Inoue K., Uemura N., Okamoto S., Terao S., Amagai K., Hayashi S., Asaka M.; Japan Gast Study Group.Effect of eradication of Helicobacter pylori on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label,randomised controlled trial.Lancet. 372(9636):392-397 (2008).

[14] Rugge M., Genta R.M., Di Mario F., El-Omar E.M., El-Serag H.B., Fassan M., Hunt R.H., Kuipers E.J., Malfertheiner P., Sugano K., Graham D.Y. Gastric Cancer as Preventable Disease.ClinGastroenterolHepatol. 15(12):1833-1843 (2017).

[15] el-Zimaity H.M., Graham D.Y., al-Assi M.T., Malaty H., Karttunen T.J., Graham D.P., Huberman R.M., Genta R.M..Interobserver variation in the histopathological assessment of Helicobacter pylori gastritis.Hum Pathol. 27(1):35-41 (1996).

[16] Kimura, K., Chronological transition of the fundic-pyloric border determined by stepwise biopsy of the lesser and greater curvatures of the stomach. Gastroenterology, . 63: 584-592 (1972).

[17] Kimura, K.,. Takemoto T. An endoscopic recognition of the atrophic border and its significance in chronic gastritis. Endoscopy, . 1(03): 87-97 (1969).

[18] Miwata T., Quach D.T., Hiyama T., Aoki R., Le H.M., Tran P.L., Ito M., Tanaka S., Arihiro K., Uemura N., Chayama K. Interobserver and intraobserver agreement for gastric mucosa atrophy. BMC Gastroenterol.15:95 (2015).

[19] Lim J.H., Kim N., Lee H.S., Choe G., Jo S.Y., Chon I., Choi C., Yoon H., Shin C.M., Park Y.S., Lee D.H., Jung H.C.Correlation between Endoscopic and Histological Diagnoses of Gastric Intestinal Metaplasia. Gut Liver. 2013 7:41-50.

[20] Eshmuratov A., Nah J.C., Kim N., Lee H.S., Lee H.E., Lee B.H., Uhm M.S., Park Y.S., Lee D.H., Jung H.C., Song I.S.The correlation of endoscopic and histological diagnosis of gastric atrophy..Dig Dis Sci. 55(5):1364-7135 (2010).

[21] Rugge M., Meggio A., Pennelli G., Piscioli F., Giacomelli L., De Pretis G., Graham D.Y. Gastritis staging in clinical practice: the OLGA staging system.Gut 56(5):631-536 (2007).

[22] Schlemper R.J., Riddell R.H., Kato Y., Borchard F., Cooper H.S., Dawsey S.M., Dixon M.F., Fenoglio-Preiser C.M., Fléjou J.F., Geboes K., Hattori T., Hirota T., Itabashi M., Iwafuchi M., Iwashita A., Kim Y.I., Kirchner T., Klimpfinger M., Koike M., Lauwers G.Y., Lewin K.J., Oberhuber G., Offner F., Price A.B., Rubio C.A., Shimizu M., Shimoda T., Sipponen P., Solcia E., Stolte M., Watanabe H., YamabeH..The Vienna classification of gastrointestinal epithelial neoplasia.Gut. 47(2):251-5 (2000).

[23] Dinis-Ribeiro M., Areia M., de Vries A.C., Marcos-Pinto R., Monteiro-Soares M., O'Connor A., Pereira C., Pimentel-Nunes P., Correia R., Ensari A., Dumonceau J.M., Machado J.C., Macedo G., Malfertheiner P., Matysiak-Budnik T., Megraud F., Miki K., O'Morain C., Peek R.M., Ponchon T., Ristimaki A., Rembacken B., Carneiro F., Kuipers E.J.; European Society of Gastrointestinal Endoscopy; European Helicobacter Study Group; European Society of Pathology; Sociedade Portuguesa de EndoscopiaDigestiva.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 EndoscopiaDigestiva (SPED). Endoscopy 44(1):74-94 (2012).

[24] Kuipers E.J. Editorial: the risk of cancer in patients with gastric intestinal metaplasia.Aliment PharmacolTher46(3):374-375 (2017).

[25] Price A.B. The Sydney System: histological division. J GastroenterolHepatol.6:209-222 (1991).

[26] Redéen S., Petersson F., Jönsson K.A., Borch K. Relationship of gastroscopic features to histological findings in gastritis and Helicobacter pylori infection in a general population sample. Endoscopy 35(11): 946-950 (2003).

[27] Lee J.Y., Kim N., Lee H.S., Oh J.C., Kwon Y.H., Choi Y.J., Yoon K.C., Hwang J.J., Lee H.J.1, Lee A1, Jeong Y1, Jo HJ1, Yoon H1, Shin CM1, Park YS1, Lee DH2J Cancer Prev. 2014 Mar;19(1):47-55.

[28] Azuma, T., Helicobacter pylori CagA protein variation associated with gastric cancer in Asia. Journal of gastroenterology 39(2):97-103 (2004).

[29] Dadashzadeh, K., MilaniM. , and SomiM.H., The prevalence of Helicobacter pylori CagA and IceA genotypes and possible clinical outcomes. Actamedicamediterranea, 31: p. 1345-1349 (2015).

[30] Lee, M., Age-related changes in gastric blood flow in rats. Gerontology, 42(5): 290-293 (1996).

[31] Tarnawski, A.S., AhluwaliaA. . Jones, M.K, Increased susceptibility of aging gastric mucosa to injury: the mechanisms and clinical implications. World journal of gastroenterology: WJG, 20 (16): 4467 (2014).

Citation: *Adamu Ishaku Akyala, Kianoosh. Dadashzadeh, Alaba Ovye, David Ishaleku, Maikel P. Peppelenbosch. Agreement between Endoscopic assessment and Histological Diagnosis of Helicobacter Pylori−Associated Gastric Atrophy and Intestinal Metaplasia. ARC Journal of Hepatology and Gastroenterology 2017; 2(2):12–22.*