Original Article

Anatomical Predilection of Intestinal Metaplasia Based on 78,335 Endoscopic Cases

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ABSTRACT

Background/Aims: Gastric intestinal metaplasia (IM) is an important risk factor for intestinal-type gastric carcinoma, and successful treatment critically depends on its timely detection. In order to guide appropriate endoscopic surveillance, objective knowledge on the anatomical predilection of intestinal metaplasia development is urgently needed. **Materials and Methods:** A total of 78,335 cases who underwent gastroduodenoscopy from 2008 to 2013 in Jiangsu and Anhui provinces in China, were studied. Demographic and clinical characteristics, as well as biopsy location and histological results, were analyzed. **Results:** This study revealed that intestinal metaplasia incidence was 28.5% in angulus, 20.24% in lesser curvature of the antrum, and 25.48% in corpus; and all these were significantly higher than those observed in other sites ($P < 0.01$). Histological grading of intestinal metaplasia in the lesser curvature of the antrum and angulus was generally worse than the grading observed in the greater curvature of the antrum. For *Helicobacter pylori*-positive patients, acute inflammation was more severe in the lesser curvature of the antrum compared with the greater curvature. In the *H. Pylori*-negative group, both acute and chronic inflammations were more severe in the lesser curvature of the antrum. **Conclusions:** The angulus, lesser curvature in the antrum, and corpus are most prone to the development of intestinal metaplasia. Inflammation is most severe in the lesser curvature of the antrum, which corresponds to a higher predilection to develop intestinal metaplasia at this site. The lesser curvature of the antrum and corpus require the most attention during endoscopic biopsy surveillance.

Key Words: Angulus, biopsy sites, gastric cancer, intestinal metaplasia, predilection sites

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Intestinal metaplasia (IM) in the gastric mucosa is characterized by the transformation of normal gastric epithelium and gastric glands into intestinal epithelium and intestinal glands, and it is considered an important precursor to gastric cancer. Patients with histologically confirmed gastric intestinal metaplasia have up to a sixfold increased risk for developing gastric cancer, compared with the population at large.[1] Gastric cancer represents the fifth most common cancer type worldwide, and is the third leading cause of cancer-related mortality.[2] Although its incidence has declined over the past decades, it remains a prominent disease in China; and its early detection represents an important goal for health care.

According to the widely accepted multistep model of gastric carcinogenesis, progression to cancerous disease involves the sequential development of inflammation and atrophy, followed by metaplasia and dysplasia, ultimately leading to carcinoma. Thus, the presence of IM is an important risk factor for gastric cancer development. Therefore, improving the early diagnosis of IM is the cornerstone of strategies aimed at improving the selection of patients that require vigilant surveillance.

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Endoscopic biopsy has developed into the most important avenue for identifying IM. Diagnosis requires histological assessment by a pathologist, which in turn requires representative sampling of the gastric mucosa by taking biopsies. To this end, a standardized protocol is usually followed, which involves taking biopsies at five predetermined sites (two samples from the antrum, two samples from the corpus, and one sample from the angulus). However, whether this standardized protocol maximizes the chance for the adequate diagnosis of premalignant gastric lesions remains controversial. In the study of de Vries *et al.*,[3] involving a Western non-Asian cohort nontargeted biopsies from the lesser curvature had a significantly higher yield as compared with those conventionally obtained of the greater curvature of the corpus in diagnosing atrophic gastritis and IM ($P = 0.05$ and $P = 0.03$). Although these data still require validation in an Asian cohort the study of de Vries *et al.* strongly suggests that further assessment as to which anatomical parts of the stomach are most likely to develop IM are needed. This consideration prompted us to comprehensively characterize the anatomical predilection for developing IM in the stomach in a large well-characterized Chinese cohort. The results indicate that the standard protocol for biopsy sampling in patients with potential IM may require anatomical adjustment in order to obtain more effective monitoring of gastric cancer risk.

MATERIALS AND METHODS

Ethics statement

This study was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University.

Study population

We identified and obtained data from 109,840 patients who underwent gastroendoscopy with sampling of gastric biopsies between January 2008 and December 2013 at the Digestive Endoscopy Center of The First Affiliated Hospital of Nanjing Medical University. All upper gastrointestinal (GI) endoscopic results were retrieved from the Endoscopy Information System (EIS, Angelwin, Beijing, China). Inclusion criteria for this study were endoscopic diagnosis of chronic gastritis (CG), duodenal ulcer (DU), gastric ulcer (GU), reflux esophagitis (RE), duodenogastric bile reflux, and so on. Exclusion criteria were diagnosis of active gastrointestinal hemorrhage, esophageal and gastric varices, esophageal cancer, duodenal neoplasms, pyloric obstruction, cases without definite endoscopic or pathological diagnosis, and rare diseases such as gastric lymphoma or eosinophilic gastroenteritis. In cases where multiple endoscopies were performed for the same patient, only the first report was included in the analysis. Finally, applying these criteria, 78,335 cases were included in this study. All available demographic data (age, gender, address, and others), endoscopic images, endoscopic and pathological findings, and rapid urease test results were retrieved from the EIS. An algorithm written using the Perl programming language was used for data processing (The algorithm is available at the scientific community upon request.).

Endoscopy with biopsy

All 78,335 cases underwent conventional upper GI endoscopy using a standard forward-viewing video gastroscope (Olympus GIF-Q160, Olympus Optical Co., Tokyo, Japan). For subanalysis, the 7019 cases that fulfilled the inclusion criteria (sufficient number of biopsies, no overt cancer, and so on) were analyzed separately in more detail; and among these selected cases, 2012 were *Helicobacter pylori* (*H. pylori*)-positive patients. All procedures were performed by experienced senior endoscopists, who have more than three years experience in endoscopic procedures. For all included cases, biopsies were taken from the following sites according to standard protocol: The lesser and greater curvature of the antrum and the body, the posterior and anterior wall of the antrum, the angulus, the cardia, and the fundus. Generally, three or four biopsies were taken from each person. IM status was evaluated through histology data by expert gastrointestinal pathologists of the Department of Pathology. We considered the diagnosis of IM as confirmed if at least one biopsy displayed IM, irrespective of the anatomical site where it was obtained.

Histological assessment of *H. pylori* status and IM

Biopsy specimens were fixed in 10% PBS-buffered formalin, and embedded in paraffin. The slide sections were stained with hematoxylin and eosin (H and E). A rapid urease test (Pronto Dry, Medical Instruments Corporation, Solothurn, Switzerland) was used to directly examine the status of the *H. pylor*i infection. If *H. pylori* infection exists, the breakdown of the urea would produce high concentrations of ammonia. This would then cause the pH to rise and provoke color change from yellow to bright magenta. IM was morphologically recognized by the presence of goblet cells, absorptive cells, and cells resembling colonocytes. The degree of activity of CG was scored by a pathologist based on the number of histologically determined lymphoid follicles, whereas the severity of acute inflammation was scored based on the extent of the neutrophil infiltration. All subjects were assessed according to the updated Sydney classification system.[4] The severity of inflammation, activity, atrophy, and intestinal metaplasia was graded as "no," "mild," "moderate," and "marked," and was scored on a 0–3 scale, respectively.

Statistical analysis

SAS 9.2 software was used for statistical analysis. Chi-square test was used to compare categorical variables (such as the comparison of IM detection rates among various parts of the

gastric antrum and gastric corpus). The Cochran–Armitage trend test was also carried out for IM when appropriate. Differences in scores were examined using the Kruskal–Wallis test, and all *P*-values calculated were two-tailed with a significance level of 0.01.

RESULTS

Baseline characteristics

A total of 78,335 patients were included in this study, and data obtained from these patients were included in the analysis. All patients have been previously diagnosed with a digestive system disease [Table 1a]. The mean age of patients in this study was 47.91 ± 14.30 years (range, 5–100 years), and male-to-female ratio was almost 1:1. For the analysis, patients were grouped into seven age groups: <20, 20–29, 30–39, 40–49, 50–59, 60–69, and ≥70. The total incidence of IM in this study cohort was 22.14% [Table 1b], and there was a statistically significant difference in IM incidence among all age groups, compared with this large cohort ($P < 0.01$). Thus, the existence of IM strongly depends on age. In apparent agreement, after determining IM grade trends by the Cochran–Armitage test in relation to the different age groups, it became apparent that IM incidence increased with age [Figure 1]. The incidence of IM was higher in the male population than in the female population (OR =1.05, 95% CI: 1.01–1.08, $P < 0.01$). These characteristics of our cohort are in agreement with those described in previous literature,[5] and we concluded that it was appropriate to analyze the anatomical predilection of gastric IM incidence.

Table 1a: Demographic characteristics (*n*=78,335)

Age-year median (range)	47.91	(5-100)
Gender no. (%)		
Male	40,027	(51.10)
Female	38,308	(48.90)
Gastric ulcer no. (%)[a]		
Positive	4,763	(6.52)
Negative	68,298	(93.48)
Duodenal ulcer no. (%)[b]		
Positive	5,624	(7.61)
Negative	68,298	(92.39)
Bile reflux no. (%)		
Positive	5,564	(7.10)
Negative	72,771	(92.90)
Reflux esophagitis no. (%)		
Positive	8,591	(10.97)
Negative	69,744	(89.03)
Metaplasia no. (%)		
Positive	17,340	(22.14)
Negative	60,995	(77.86)
Atrophy no. (%)		
Positive	2,837	(3.62)
Negative	75,498	(92.38)
Dysplasia no. (%)		
Positive	4,537	(5.79)
Negative	73,798	(94.21)

[a,b]Missing date a=5,274, b=4,413

Table 1b: Correlation among age, gender, and intestinal metaplasia

Characteristics	With IM (*n*=17,340)		OR	95% CI	*P* value
	Number	(%)			
Age (year, mean±SD)	53.84±12.69				
<20	55	0.32			<0.01
20-29	435	2.51			<0.01
30-39	1,926	11.11			<0.01
40-49	3,756	21.66			<0.01
50-59	5,299	30.56			<0.01
60-69	3,824	22.05			<0.01
≥70	2,045	11.79			<0.01
Gender			1.05	1.01-1.08	
Male	9,012	51.97			
Female	8,328	48.03			<0.01

IM incidence at different anatomical sites observed in nontargeted biopsies

When the anatomical location of IM diagnoses based on targeted biopsies was considered, the highest IM incidence appears to be present in the angulus (28.5%, 14,063 of 49,345 nontargeted angulus biopsies; Table 2 and Figure 2). Compared to the greater curvature of the antrum and corpus, the lesser curvature also had a significantly higher incidence of IM diagnoses ($P < 0.01$). Importantly, significant differences were observed when the five standard proctors for establishing IM diagnosis (the lesser and greater curvature of the antrum, the lesser and greater curvature of corpus, and the angulus) were compared [Table 3], in which the angulus was substantially more prone to display IM compared with the other sites ($P < 0.01$). Thus, it seems that the standard protocol for sampling the stomach for potential IM does not capture anatomical preferences for the development of this condition.

Severity of IM at the three main sites for IM development

The tendency of IM to develop into a full-blown cancer strongly depends on the severity of the IM process. Anatomical incidence *per se* is not a sufficient basis with respect to the guidance of endoscopic biopsy sampling; thus, the severity of IM must be taken into account as well. Hence, we analyzed the severity of IM at three anatomical sites that are most likely to develop IM, which are the lesser curvature of the antrum, the lesser curvature of the corpus, and the angulus [Figure 3]. In agreement with the overall incidence, the incidence of mild, moderate, and severe IM in the angulus (19.48%, 10.39%, and 1.20%) and the lesser

Table 2: Incidence of IM in nontargeted biopsies

Biopsy location	Biopsy (*n*)	IM (*n*, %)	χ^2_1	P_1	χ^2_2	P_2
Antrum	72,603	15,107 (20.81)	*	*		
Lesser curvature	51,632	11,056 (20.24)			*	*
Greater curvature	50,841	5,240 (9.38)			2224.17	<0.01
Anterior wall	4,455	1,054 (23.66)				
Posterior wall	3,285	626 (19.00)				
Corpus	58,822	2,918 (4.96)	6,895.65	<0.01		
Lesser curvature	45,083	11,487 (25.48)			*	*
Great curvature	46,153	2,321 (5.03)			7,426.23	<0,01
Angulus	49,345	14,063 (28.50)	955.06	<0.01		
Cardia	2,724	332 (12.19)				
Fundus	1,179	101 (8.57)				

Target biopsy (the anterior and posterior wall of the antrum, cardia, and fundus) is not comparable with nontarget biopsy, even though the incidence rate of IM in the cardia and fundus was low in targeted biopsy. Hence, IM appears to be not frequent in these sites. *The baseline for comparison

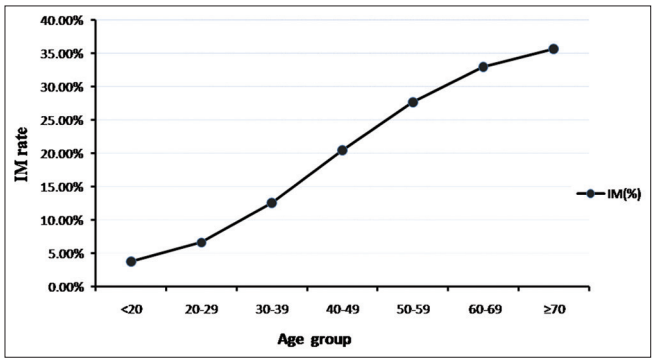

Figure 1: The distribution of intestinal metaplasia (IM) in the seven age groups. IM data observed in the stomach of 78,335 cases that underwent gastroduodenoscopy from 2008 to 2013 in Jiangsu and Anhui provinces in China are shown. The percentage of biopsies displaying IM stratified by age group is shown

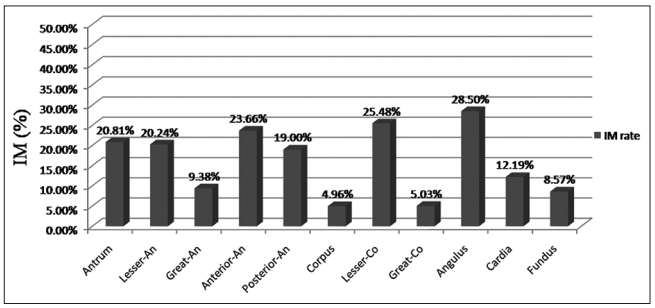

Figure 2: The distribution of IM in the stomach. IM data observed in the stomach of 78,335 cases that underwent gastroduodenoscopy from 2008 to 2013 in Jiangsu and Anhui provinces in China are shown. The percentage of biopsies at specific anatomical locations is shown

curvature of the antrum (12.56%, 3.22%, and 0.25%) were significantly higher, compared with the greater curvature (6.12%, 1.32%, and 0.09%) [Table 4]. These results further support the adjustment of sampling procedures when screening for IM.

Different inflammation scores in the lesser and greater curvature of the antrum

Biopsy samples were simultaneously taken from both the lesser and greater curvatures of the antrum of 7019 cases. This allowed us to compare the relative severity of inflammation in these two anatomical structures. To this end, the incidence of IM in these two sites of the same subjects were compared used a matching Chi-square test. Inflammation was more common in the lesser curvature of the antrum (18.79%, 1319/7019 of all cases) than in the greater curvature of the antrum (4.67%, 328/7019 of all cases; Table 5a). When analyzed according to the updated Sydney classification system, acute and chronic inflammation scores were significantly different in the lesser and greater curvatures of the antrum. For this analysis, patients were stratified according to *H. pylori* status [Table 5b]. In the *H. pylori*-positive group, acute-inflammation scores were higher and chronic-inflammation scores were lower in the lesser curvature of the antrum. However, both acute and chronic inflammation scores were higher in the lesser curvature of the antrum than in the greater curvature of the antrum in the *H. pylori*-negative group (all $P < 0.01$). This suggests that both IM incidence and inflammation relate to the anatomical location, even if the latter is also strongly influenced by *H. pylori* status.

DISCUSSION

IM is an important stage in the multistep process that finally leads to full-blown cancer. The progression toward GC is initiated by the development of chronic gastritis, followed by gastric atrophy, intestinal metaplasia and dysplasia, and ultimately resulting in gastric carcinoma.[6] This process typically involves the *H. pylori*-dependent corruption of gastric morphogen signaling.[7] Gastric cancer is the third leading cause of cancer-related mortality.[2] Vigilant

monitoring of IM, especially incomplete colonic metaplasia, appears to be a way forward to reducing mortality.[8,9] Hence, the optimal and early detection and treatment of IM is very important, and is considered to be of utmost importance in this field.[10]

In general, precancerous lesions and early gastric cancer do not have obvious clinical symptoms; and endoscopy, especially endoscopic sampling of gastric biopsies, play a decisive role in the diagnosis. Standard protocols for sampling biopsies have been established, but these have not been linked to the actual incidence of IM at different anatomical locations or to the regional differences of IM severity.[3] This current study aims to fill this void, at least for Asian populations.

This study has demonstrated that age and gender are independent risk factors for intestinal metaplasia. Consistent with a study carried out by Genta *et al*.,[11] IM was found in 8.4% of 810,821 unique patients; increased with age, and was found to be more common in male patients than in female patients. With regard to nontargeted biopsy locations, our results have illustrated that IM is prone to occur in the lesser curvature of the stomach; which is consistent with the study of de Vries *et al*.[3] On this basis, this study further proves that the incidence rate and severity of IM is relatively high in the lesser curvature of the antrum and the angulus. This observation is consistent with the regional differences of *H. pylori* colonization in the stomach, which occurs more frequently in the lesser curvature.[11] Infection with *CagA*-positive *H. pylori* strains is significantly associated with the overexpression of proapoptotic proteins and antiapoptotic proteins in the gastric mucosa, which is mainly in the antral lesser curvature; and this may in turn relate to altered epithelial cell turnover and malignant transformation.[12] A possible reason for the differential *H. pylori* colonization in the stomach is that the propagation velocity of the antral contraction waves in the greater curvature of the stomach is much faster than in the lesser curvature.[13] Low fluid flow rates of the lesser curvature lead to the accumulation of food, and then the colonization of *H. pylori*. Our results suggest that the angulus and antrum deserve more attention with respect to biopsy sampling.

In addition to IM *per se*, we also focused on the inflammation status of the antrum in this study, since gastritis would most likely occur in this site. Our results reveal that the regional severity of gastritis stratifies according to *H. pylori* status. In the *H. pylori*-positive group, our results revealed that acute inflammation was more severe and chronic inflammation was milder, compared with the lesser curvature of the antrum. We expect that the reason for this dichotomy lies in differential colonization (the antrum is more prone to be colonized by *H. pylori*[14]) and patients with *H.*

Table 3: Comparison of IM status at five standard biopsy sites

Biopsy site	IM (*n*)		χ^2	*P*
AL-AG	(AL+ AG+) 2,428	(AL− AG+) 1,582		
	(AL+ AG−) 5,835	(AL− AG−) 30,763	4,436.48	<0.01
AL-An	(AL+ An+) 7,682	(AL− An+) 4,993		
	(AL+ An−) 3,848	(AL− An−) 12,452	148.29	<0.01
AL-CL	(AL+ CL+) 4,330	(AL− CL+) 2,830		
	(AL+ CL−) 5,703	(AL− CL−) 14,320	967.32	<0.01
An-AG	(An+ AG+) 4,387	(An− AG+) 7,216		
	(An+ AG−) 1,930	(An− AG−) 13,344	3,055.08	<0.01
An-CL	(An+ CL+) 1,790	(An− CL+) 499		
	(An+ CL−) 2,373	(An− CL−) 3,539	1,222.80	<0.01
CL-CG	(CL+ CG+) 42	(CL− CG+) 42		
	(CL+ CG−) 208	(CL− CG−) 2,540	110.22	<0.01

AL: Lesser curvature of the antrum, AG: Greater curvature of the antrum, An: Angulus, CL: Lesser curvature of the corpus, CG: Great curvature of the corpus

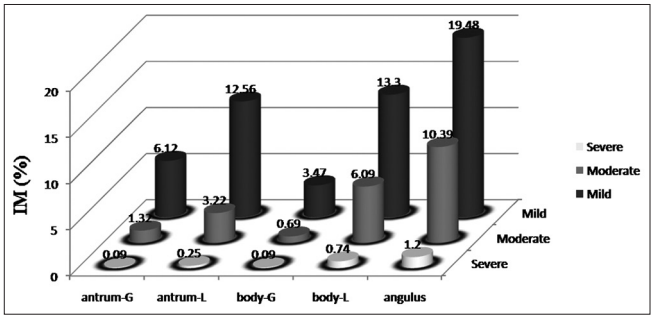

Figure 3: Severity of IM at the five standard anatomical sites. IM data observed in the stomach of 78,335 cases that underwent gastroduodenoscopy from 2008 to 2013 in Jiangsu and Anhui provinces in China are shown. The percentage of biopsies displaying IM and severity of the extent of IM is shown

Table 4: Comparison of IM grades observed in three main gastric locations

Biopsy site	Biopsy	IM (*n*, %)			χ^2_1	P_1	χ^2_2	P_2	χ^2_3	P_3
	n	Mild	Moderate	Severe						
An-GC*	55,841	3,415 (6.12)	738 (1.32)	52 (0.09)						
An-LC	54,632	6,864 (12.56)	1,759 (3.22)	136 (0.25)	1,360.75	<0.01	450.36	<0.01	39.46	<0.01
Angulus	49,345	9,612 (19.48)	5,127 (10.39)	592 (1.2)	4,311.41	<0.01	4,091.82	<0.01	527.18	<0.01

An-GC: Greater curvature of the antrum, An–LC: Lesser curvature of the antrum. χ^2_{1-3}, P_{1-3}: Mild, moderate, and severe IM in the lesser curvature of the antrum or angulus vs. the greater curvature of the antrum; *Baseline for comparison; IM was most severe in the angulus, followed by the lesser curvature of the antrum and the greater curvature of antrum

Table 5a: Paired* comparison results in the antrum

Biopsy site	Antrum-lesser curvature		*P* value
	IM (+)	IM (−)	
Antrum-greater curvature			
IM positive (+)	682	328	
IM negative (−)	1,319	4,690	<0.05

*Matching Chi-square test was used to compare the IM status of the lesser and greater curvature of the antrum from the same patients

Table 5b: Inflammation scores in the lesser and greater curvature of the antrum

Anutrum L-G	Number	Average	SD	Min	Max
N-biopsy	7,019	0.0208	0.3027	−3.0000	5.0000
C-score	7,019	0.01151	0.3880	−2.0000	2.0000
A-score	7,019	0.0403	0.5560	−3.0000	3.0000
N-biopsy-HpY	2,012	0.0378	0.4021	−3.0000	5.0000
C-score-HpY	2,012	−0.0109	0.4478	−2.0000	2.0000
A-score-HpY	2,012	0.0919	0.7592	−3.0000	3.0000
N-biopsy-HpN	4,666	0.0148	0.2467	−3.0000	3.0000
C-score-HpN	4,666	0.0199	0.3575	−2.0000	2.0000
A-score-HpN	4,666	0.0168	0.4369	−3.0000	3.0000

SD: Standard deviation, Based on Kruskal–Wallis Test, the comparison of the *D*-value between the lesser and greater curvature of the antrum between the *H. pylori*-positive and *H. pylori*-negative groups were analyzed, respectively (all *P*<0.01). In the *H. pylori*-positive group, acute-inflammation score was higher and chronic-inflammation score was lower in the lesser curvature. However, both acute and chronic inflammation scores were higher in the *H. pylori*-negative group. Anutrum L-G, the *D*-value of inflammation scores between the lesser and greater curvature of the antrum in different conditions; N-biopsy, biopsy number; C-score, score of chronic inflammation; A-score, score of acute inflammation; HpY, *H. pylori*-positive; HpN, *H. pylori*-negative

pylori infection have a significantly higher neutrophil-to-lymphocyte ratio, compared with those without *H. pylori*.[15] The degree of neutrophil infiltration decreases spatially from the lesser curvature to the greater curvature. In early-stage infection, lesions display acute inflammation characterized by neutrophil infiltration, which changes into chronic inflammation characterized by lymphatic infiltration, and the wide formation of lymphatic follicles at later time points.[16] Hence, differential induction of chronic inflammation may underlie regional differences in IM. Further effects of provoking regional differences in IM incidence in the stomach may relate to mixed infections. It was reported that 23.3% of *H. pylori*-infected patients had mixed infections, and such infections were associated with distinct histological features in the antrum and corpus.[17] Mixed infection may exist in our specimens, and may show regional differences; explaining the findings of this current study. A final factor may be the non–*H. pylori*-related gastritis or other digestive tract diseases that are likely to occur at these sites. IM is closely related to acute and chronic inflammation, and inflammation not related to *H. pylori* might be important.[18] Nonetheless, these exact factors underlying the anatomical distribution of IM in the stomach remain largely speculative and require further research. Biopsies from the lesser and greater curvature of the antrum should be routinely taken for patients infected with *H. pylori*, whereas biopsies should be more exclusively taken from the lesser curvature in noninfected patients. Our results generally provide anatomical guidance for biopsy and evidence for the notion that patients should be stratified according to *H. pylori* status. With this recommendation, we would also like to consider the study conducted by Liu *et al.*,[19] which revealed that there were major geographical differences in the overall prevalence of atrophy and intestinal metaplasia. Scores for intestinal metaplasia were generally low except for Xi-an (55%), Japan (44%), and Shanghai (32%). It is possible that our results only fit the Southeast-China population (mainly in Jiangsu and Anhui), in which the prevalence of precancerous lesions differs from others. Thus, we call for studies similar to ours in other cohorts.

CONCLUSION

IM is most likely to develop in the angulus and the lesser curvature of the stomach. An adequate biopsy scheme for diagnosing IM should involve generous sampling from the lesser curvature of the antrum, lesser curvature of the corpus, and the angulus; especially in *H. pylori*-negative patients.

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Conflicts of interest

There are no conflicts of interest.

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