Original Article

Comparison of the diagnostic accuracy of the updated Sydney system and single biopsy

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Abstract

Background: Updated Sydney system (USS) recommends taking biopsies from certain areas of the stomach for the diagnosis of precancerous lesions associated with *Helicobacter pylori*. Our aim was to evaluate the contribution of each of the biopsy sites to the diagnosis.

Methods: This prospective study included 97 patients aged 40 and over with dyspeptic complaints. Biopsies were taken from five regions: the lesser curvature of the antrum (LCA), the lesser curvature of the corpus (LCC), incisura angularis (IA), the greater curvature of the antrum (GCA), and the greater curvature of the corpus (GCC). Biopsy specimens were stained with hematoxylin–eosin stain, periodic acid Schiff–alcian blue, and Giemsa histochemical stain and evaluated according to the Sydney classification.

Results: Thirty-seven (38%) patients were positive for *H. pylori* in at least one biopsy site. Atrophic gastritis without intestinal metaplasia (IM) was found in 17 (17.5%) of the patients (6.2% in IA, 5.2% in each of LCA, GCA, and LCC, and 2% in GCC). The prevalence of atrophic gastritis with IM was 42.3% (21.6% in LCA, 20.6% in GCA, 20.6% in IA, 14.4% in LCC, and 5.2% in GCC). Endoscopic follow-up was planned in 21 (22%) patients due to the presence of extensive atrophy or incomplete IM. If a single biopsy of the LCA or a biopsy of both LCA and GCA was taken, endoscopic follow-up would have been missed in 12 (57%) or 6 (29%) patients, respectively.

Conclusion: Taking biopsies in accordance with the USS had higher sensitivity in detecting atrophic gastritis with or without IM compared to single biopsy. One or two biopsies is not sufficient to identify patients for whom endoscopic follow-up is recommended.

Keywords: Gastric Atrophy, *Helicobacter pylori*, intestinal metaplasia, updated Sydney system

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INTRODUCTION

Gastric cancer ranks third in the world in malignancy-related deaths.[1,2] *Helicobacter pylori* is the strongest recognized risk factor for gastric adenocarcinoma.[3]

H. pylori infects approximately 50% of the world's population.[4] In *H. pylori* infection, the process that begins with chronic gastritis in the gastric mucosa may continue with atrophic gastritis and intestinal metaplasia (IM).

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Atrophic gastritis and IM are considered as precancerous lesions.[5] Early diagnosis of these precancerous lesions and treatment of *H. pylori* can slow down or prevent the development of gastric cancer.[6-8]

Recently developed endoscopic techniques such as chromoendoscopy (CE), narrow-band imaging, and magnifying endoscopy have improved the diagnosis of precancerous lesions.[9] These techniques are very valuable in guiding the selection of the biopsy site, but their use has not yet become widespread.

The Sydney System, created in 1990 at the World Congress of Gastroenterology and updated in 1994, recommended taking two biopsies each from the antrum and corpus and one biopsy from the incisura angularis (IA) during endoscopy, for the diagnosis of gastric diseases.[10-12] However, since increased number of biopsies creates disadvantages in terms of time, cost, and patient comfort, these recommendations are not followed frequently both in our country and in the world. There are few prospective studies investigating the contribution of each of the five biopsy sites recommended by the updated Sydney System (USS) in the diagnosis of *H. pylori* and precancerous gastric lesions.[13] Thus, this study aimed to assess the efficiency of taking five biopsies according to USS instead of a single biopsy, for minimalization of missed diagnosis needing surveillance due to precancerous lesions.

PATIENTS AND METHODS

This prospective study included 97 patients aged ≥40 years who presented to the gastroenterology outpatient clinic with dyspeptic complaints (heartburn, bloating, or stomach pain) between November 2020 and February 2021. Patients with complaints of at least 1 month were included in the study.

Those who used proton-pump inhibitor (PPI) in the last 2 weeks, antibiotics and bismuth-containing drugs in the last 1 month, who had gastric malignancy, a history of gastric operation, pregnant ladies, and those who had previously received *H. pylori* eradication therapy were excluded from the study. All patients provided written informed consent for endoscopy, and the study was approved by the ethical committee of our institution. The principles of the Declaration of Helsinki were followed throughout the study.

Endoscopies were performed in the same clinic by two gastroenterologists. Initially, a single biopsy was taken from the lesser curvature of the antrum (LCA) for rapid urease test. The biopsy specimens were taken from the lesser and greater curvatures of the antrum, IA, and lesser and greater curvatures of the corpus into labeled formaldehyde bottles and sent for histopathologic examination.

Biopsy materials from each site were separately fixed in 10% neutral formaldehyde solution for a minimum of 6 h and a maximum of 24 h. In the macroscopic examination, biopsy materials were placed in coded cassettes according to their localization, by specifying their size and number of pieces, and wrapped in blotting papers, so that they would not be lost. After routine tissue follow-up (Leica TP1020; Leica Biosystems, Nussloch, Germany), tissue samples were embedded in paraffin blocks. Sections prepared with a thickness of 4 μm from paraffin blocks in the microtome were stained with hematoxylin–eosin (H&E) stain in an automatic staining device, as well as with periodic acid Schiff–alcian blue (PASAB) and Giemsa histochemical stain. Then, the preparations were blindly examined histomorphologically by two pathologists specialized in gastroenterology, under a light microscope (Olympus Bx51). Pathologists consulted each other and wrote a consensus report in cases where they were in doubt.

In the histopathologic examination, chronic inflammation (lymphoplasmacytic inflammation), neutrophilic activation, IM, atrophy, and presence of *H. pylori* were evaluated according to Sydney classification. Giemsa stain was used to detect *H. pylori*. IM was evaluated using both H and E and PASAB stains and categorized as complete or incomplete type. Additionally, dysplasia, lymphoid aggregates, and lymphoid follicles were noted in the report.

Statistical analysis

The values are expressed as mean ± standard deviation (SD), and statistical analysis included Student's *t*-test for numerical and Chi-square test and Fisher's exact test for categorical comparisons, by Statistical Package for the Social Sciences (SPSS) v20 (Armonk, NY, USA; IBM). A *P* value less than 0.05 was considered statistically significant.

RESULTS

Ninety-seven patients were included in the study. Fifty-seven of the patients (58.8%) were female. The mean age was 51.9 ± 8.6 years, with a range of 40–79 years. Twenty-five of the patients (26%) were current smokers or had used more than 20 packs/year in the past and quit smoking. Seventy-two patients (74%) had never smoked. Two patients had a history of gastric adenocarcinoma in their first-degree relative. Fifty-three (54.6%) of the patients had active gastritis, and 40 (41.2%) had inactive gastritis. Gastric mucosa

Table 1: Characteristics of patients

	Patients who need endoscopic follow-up	Patients who do not need endoscopic follow-up	*P* value
Gender			0.865*
Male	9	31	
Female	12	45	
Tobacco smoking			0.01*
Current/previous smoker	10	15	
Nonsmoker	11	61	
Family history of gastric cancer	2/21	0	
Diabetes mellitus	6/21	11/76	
Hypertension	6/21	16/76	
Age, years			0.493*
<50	9	39	
≥50	12	37	

*Chi-square test is used

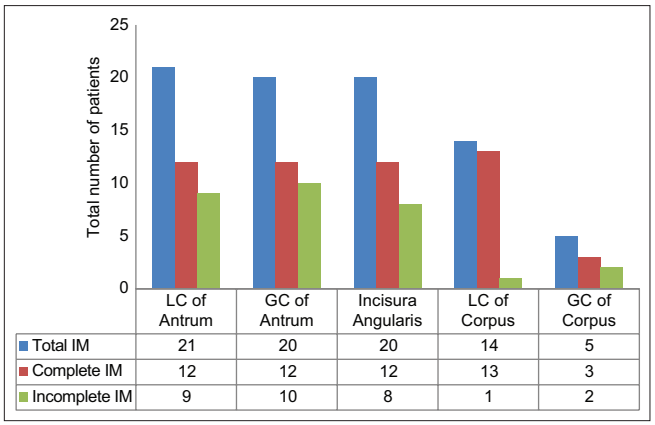

Figure 1: Distribution of IM and its subtypes by site. GC = greater curvature, IM = intestinal metaplasia, LC = lesser curvature

appeared normal only in four patients. Characteristics of patients are shown in Table 1.

Thirty-seven (38%) patients were positive for *H. pylori* in at least one biopsy site (37.1% in LCA, 36% in greater curvature of antrum [GCA], lesser curvature of the corpus [LCC], and greater curvature of the corpus [GCC], and 34% in IA). The sensitivity, specificity, positive predictive value, and negative predictive value of the rapid urease test were 91.8%, 95%, 91.8%, and 95.0%, respectively. There was no significant difference in the diagnosis of *H. pylori* between a single biopsy from any site and biopsies in accordance with the USS.

Atrophic gastritis without IM was determined in 17 (17.5%) of the patients (6.2% in IA, 5.2% in each of LCA, GCA, and LCC, and 2% in GCC). Taking biopsies in accordance with the USS had a higher sensitivity in detecting atrophic gastritis, compared to a single-site biopsy. Sensitivity of biopsy sites in the diagnosis of atrophic gastritis without IM is shown in Table 2 (the case where five biopsies were taken in accordance with the USS was accepted as the reference value).

Extensive atrophy with or without IM (atrophy of both antrum and corpus) was detected in nine (9%) patients. If a single biopsy were taken from the LCA or IA, as clinicians often do, extensive atrophy would have been missed in three (33%) and two (22%) patients, respectively. If two biopsies were taken from the LCA and GCA, extensive atrophy would have been missed in one (11%) patient.

Atrophic gastritis with IM was found to be more common in patients aged ≥50 years compared to those <50 years ($P = 0.016$).

Atrophic gastritis with IM was determined in 41 (42.3%) of the patients (21.6% in LCA, 20.6% in GCA, 20.6% in IA, 14.4% in LCC, and 5.2% in GCC). Sensitivity of biopsy sites in the diagnosis of atrophic gastritis with IM is shown in Table 2 (the case where five biopsies were taken in accordance with the USS was accepted as the reference value). Complete IM was present in 31 (31.9%) patients and incomplete IM in 19 (19.5%) patients.

Distribution of IM and its subtypes by site is shown in Figure 1. (Complete and incomplete IM were found together in GCA of two patients. Other biopsies revealed features of a single type of IM.)

IM was found to be more common in smokers than in nonsmokers (total IM $P = 0.01$, complete IM $P = 0.042$, and incomplete IM $P = 0.005$). Compared to patients under

Table 2: Sensitivity of biopsy sites in the diagnosis of atrophic gastritis without intestinal metaplasia

Single bio.	%	*P**	Two bio.	%	*P**	Three bio.	%	*P**	Four bio.	%	*P**
LCA	29.4	<0.01	LCA + GCA	52.9	0.01	LCA + GCA + IA	76.7	0.051	EXC GCC	100	
GCA	29.4	<0.01	LCA + IA	58.8	0.04	LCA + GCA + LCC	76.7	0.051	EXC IA	76.7	0.051
IA	35.2	<0.01	LCA + LCC	52.9	0.01	LCA + IA + LCC	82.3	0.114			
LCC	29.4	<0.01	GCA + IA	52.9	0.01	GCA + IA + LCC	76.7	0.051			
GCC	11.7	<0.01	GCA + LCC	47	<0.01						
			IA + LCC	52.9	0.01						

bio.=biopsy, EXC=except, GCA=greater curvature of the antrum, GCC=greater curvature of the corpus, IA=incisura angularis, LCA=lesser curvature of the antrum, LCC=lesser curvature of the corpus. *Fisher's exact test is used

Table 3: Sensitivity of biopsy sites in the diagnosis of atrophic gastritis with intestinal metaplasia

Single bio.	%	*P**	Two bio.	%	*P**	Three bio.	%	*P**	Four bio.	%	*P**
LCA	51.2	<0.01	LCA + GCA	73.1	<0.01	LCA + GCA + IA	85.3	0.013	EXC GCC	100	
GCA	48.7	<0.01	LCA + IA	73.1	<0.01	LCA + GCA + LCC	90.2	0.058	EXC GCA	90.2	0.058
IA	48.7	<0.01	LCA + LCC	70.7	<0.01	LCA + IA + LCC	90.2	0.058	EXC LCA	80.4	0.03
LCC	34.1	<0.01	GCA + IA	65.8	<0.01	GCA + IA + LCC	80.4	0.03	EXC IA	90.2	0.058
GCC	12.1	<0.01	GCA + LCC	65.8	<0.01						
			IA + LCC	68.2	<0.01						

bio.=biopsy, EXC=except, GCA=greater curvature of the antrum, GCC=greater curvature of the corpus, IA=incisura angularis, LCA=lesser curvature of the antrum, LCC=lesser curvature of the corpus. *Chi-square and Fisher's exact tests are used

50 years of age, patients aged 50 years and older had an overall increase in IM, but significant increase was found in complete IM ($P = 0.015$).

Compared to the *H. pylori*-negative patients, IM was more common in *H. pylori*-positive patients ($P = 0.318$). The frequency of IM in the GCC was found to be lower than in all other sites ($P < 0.05$). Taking biopsies in accordance with the USS had higher sensitivity in detecting IM, compared to single-site biopsy ($P < 0.01$).

If a single biopsy were taken from the LCA or IA, incomplete IM would be missed in 10 (53%) and 11 (58%) patients, respectively. If only one biopsy was taken from the GCA, IM would be missed in nine (47%) patients. If two biopsies were taken from the LCA and GCA, incomplete IM would be missed in five (26%) patients [Table 3].

Endoscopic follow-up was planned in 21 (22%) of the patients due to the presence of extensive atrophy or incomplete IM. Neither atrophy nor IM was detected in 12 (57%) of these patients in LCA and IA, 10 (48%) in GCA, 18 (86%) in LCC, and 19 (90%) in GCC. Table 4 and Table 5 demonstrate how many of the patients would be missed for endoscopic follow-up if biopsies had been taken from a single site or from two or three sites.

No adenocarcinoma was detected in any of the patients. Only two patients had "indefinite dysplasia" in the antrum and both patients had incomplete IM.

DISCUSSION

Several studies showed that virtual CE is a more accurate modality for diagnosing gastric precancerous conditions than white light endoscopy.[9,14] However, new endoscopic techniques have not yet become widespread in Turkey as in many other developing countries. Therefore, the regions from where it would be more beneficial to take a biopsy for the diagnosis of precancerous conditions still remains an important issue.

Since the discovery of *H. pylori*, studies have been conducted to determine which part of the stomach would be more useful in the diagnosis of *H. pylori* during endoscopy. In some of these studies, *H. pylori* was found to be at a similar rate in all areas of the stomach,[15] while there was a significant difference in some other studies.[16,17] In this study, we showed that taking a single-site biopsy enables detection of *H. pylori* in all infected patients.

To understand the reason for this difference between studies, it is necessary to remember the microbiological characteristics of *H. pylori*. Outer membrane proteins, which play a role in the adhesion of *H. pylori* to the gastric mucosa and initiation of inflammation, can bind to intact gastric mucosa.[18] Therefore, atrophic gastritis and IM sites are inhospitable to *H. pylori*.[19,20]

After the general acceptance of the USS, studies on the effectiveness and adequacy of the biopsy protocol have

Table 4: Frequency of precancerous lesions and failure to recognize patients requiring endoscopic follow-up if a single or two biopsies are taken

Biopsy site (s)	Atrophy without IM	Atrophy with IM	Extensive atrophy false negative	Incomplete IM false negative	Missed endoscopic surveillance
LCA	5	21	3 (33%)	10 (53%)	12 (57%)
GCA	5	20	1 (11%)	9 (47%)	10 (48%)
IA	6	20	2 (22%)	11 (58%)	12 (57%)
LCC	5	14	0 (0%)	18 (95%)	18 (86%)
GCC	2	5	6 (67%)	17 (89%)	19 (90%)
LCA and GCA	9	30	1 (11%)	5 (26%)	6 (29%)
LCA and IA	10	30	1 (11%)	4 (21%)	5 (24%)
LCA and LCC	9	29	0 (0%)	9 (47%)	9 (43%)
USS	17	41	0 (0%)	0 (0%)	0 (0%)

GCA=greater curvature of the antrum, GCC=greater curvature of the corpus, IA=incisura angularis, IM=intestinal metaplasia, LCA=lesser curvature of the antrum, LCC=lesser curvature of the corpus, USS=updated Sydney system

Table 5: Missed endoscopic surveillance

Single bio.	%	*P**	Two bio.	%	*P**	Three bio.	%	*P**
LCA	12 (57%)	<0.01	LCA + GCA	6 (29%)	0.01	LCA + GCA + IA	3 (14%)	0.116
GCA	10 (48%)	<0.01	LCA + IA	5 (24%)	0.024	LCA + GCA + LCC	5 (24%)	0.024
IA	12 (57%)	<0.01	LCA + LCC	9 (43%)	<0.01	LCA + IA + LCC	3 (14%)	0.116
LCC	18 (86%)	<0.01	GCA + IA	6 (29%)	0.01	GCA + IA + LCC	4 (19%)	0.053
GCC	19 (90%)	<0.01	GCA + LCC	8 (38%)	<0.01	GCA + IA + GCC	6 (29%)	0.01
			IA + LCC	10 (48%)	<0.01			

bio.=biopsy, GCA=greater curvature of the antrum, GCC=greater curvature of the corpus, IA=incisura angularis, LCA=lesser curvature of the antrum, LCC=lesser curvature of the corpus. *Fisher's exact test is used

been conducted. In the study of Satoh *et al*.,[16] one of the first prospective studies conducted for this purpose, it was revealed that biopsy should be taken from the LCA, GCA LCC, and GCC, as in the Sydney system, in order to evaluate *H. pylori* colonization and extension of the atrophy. In this study, endoscopy was performed in 76 patients with *H. pylori* (+) chronic gastritis. Similar to our study, *H. pylori* was detected equally in all regions, in patients with nonatrophic and mild atrophic gastritis. However, in the same study, *H. pylori* positivity was found to be higher in the GCC than in other regions in the presence of moderate and severe atrophy. The small number of patients (9%) with extensive atrophic gastritis in our study and the large number of patients with extensive atrophy in the study of Satoh *et al*. may explain this difference. Because of the presence of widespread and severe atrophy, *H. pylori* can colonize only in areas with intact gastric mucosa.[20,21]

In another prospective study, Erikkson *et al*.[13] evaluated the diagnostic contribution of additional IA biopsy recommended in the USS. While *H. pylori* was detected only in IA in one (0.4%) of 272 patients, atrophy was detected in three (1.1%) patients and IM was detected in 13 (4.7%) patients only in IA biopsy. Routine biopsy of the IA would provide little additional clinical information compared to that obtainable from antrum and corpus biopsies.

In the study of el-Zimaity *et al*.,[22] patients with IM who had previously been biopsied with the mapping protocol were re-evaluated and it was investigated how many of the patients would have missed *H. pylori* and IM if biopsy was taken according to the USS. Both the original and the revised Sydney systems identified 100% of patients with *H. pylori* infection. Using the original Sydney recommendation, IM was found in only 48% of those with confirmed IM. The USS was more accurate, but IM was identified in only 75% of those already proven to have it.

It is estimated that the prevalence of *H. pylori* in developing countries, including our country, is around 50%.[23] Serological tests are frequently used in epidemiological studies. However, this test cannot distinguish current and past infection. The low prevalence of *H. pylori* in our study compared to other studies in developing countries may be related to the use of methods indicating only current infection. The high socioeconomic development level of the region where the study was conducted may also have contributed to this result.

Atrophic gastritis without IM was detected in 17 (17.5%) of the patients. Atrophy was most common in IA (6.2%), followed by the LCA, GCA, and GCC (5.2% each). Multiple-site biopsies had greater diagnostic power than single-site biopsies in the case of gastric atrophy.

IA is thought to undergo more severe atrophic, metaplastic, and chronic inflammatory changes than the other sites. Thus, the USS recommends taking a biopsy from IA as well as biopsies of the corpus and antrum. Studies following the USS also show that biopsy of IA has an additional contribution to the diagnosis of precancerous lesions.[24-26] The results of our study on atrophy are consistent with previous studies.

Gastric IM is considered to be a precancerous condition.[27] The prevalence of IM is variable due to the geographic variability in the frequency of gastric cancer and the different methods used in the studies. In a study conducted in Finland between 2000 and 2001, the prevalence of IM was found to be 19%.[24] Olmez *et al*.[28] reported that the prevalence of IM was 13.8% in 4050 patients who underwent gastric biopsy in the Van region of Turkey, where the incidence of gastric adenocarcinoma is relatively high. In the study of Almouradi *et al*.,[29] in which they evaluated the endoscopy of 437 patients in the USA, the prevalence of IM was found to be 15%. A study by Craanen *et al*.[30] from the Netherlands showed a 25.3% overall prevalence of gastric IM. Unlike other studies conducted in Europe, the prospective design of Caraanen *et al*.'s study and multiple antrum biopsies from each patient may have resulted in a higher prevalence of IM.

The overall prevalence of IM was 42.3%, with the complete type IM showing 31.9% and the incomplete type IM showing 19.5% prevalence in our study. The high prevalence of IM can be explained by the prospective design of our

study and due to taking biopsies from each of the patients in accordance with the USS. The fact that all of the patients included in the study were ≥40 years old and had long-term dyspeptic complaints may also be the reasons.

The relationship between incomplete IM and gastric cancer is clear and requires endoscopic follow-up. However, endoscopic follow-up is not considered necessary in the presence of nonextensive complete IM.[2] Thus, it is important to distinguish complete and incomplete metaplasia in the pathological examination of endoscopic material in terms of cost-effectiveness.

In our study, taking five biopsies in accordance with the recommendations of the USS was found to be superior to biopsy from a single site in the diagnosis of IM ($P < 0.05$). Numerous studies have been conducted on the benefit of taking biopsies according to the USS, and it has been shown to be superior in the diagnosis of precancerous lesions, consistent with the results of our study.[31]

Our literature review showed that there are few prospective studies on the distribution of IM in the stomach. This study showed that IM was found to be more common in the lesser curvature compared to the greater curvature. The LCA, GCA, and IA are most prone to the development of IM. Similarly, in the study of Eriksson *et al*.[24] to measure the frequency of IM and its distribution in the stomach, IM was observed most frequently in the antrum and IA. In a retrospective study of 78,335 endoscopies performed in China between 2008 and 2013,[32] IA, LCA, and corpus were found to be most prone to the development of IM. These findings confirm our knowledge that chronic gastritis and atrophy begin from the antrum.

The USS and subsequent guidelines recommended taking two biopsies each from the antrum and corpus and one biopsy from the IA during endoscopy, for the diagnosis of gastric diseases.[2,12]

However, it is common in clinical practice to take only one or two biopsies from the antrum properly due to time and cost concerns. In the study carried out to measure compliance with the Sydney system, gastric biopsy samples from a private pathology clinic between 2008 and 2011 were examined. Of the 379,667 patients with no visible lesions, none of the biopsy specimens were taken in accordance with the USS, showing that only 3.9% received two biopsies from the antrum and corpus.[31]

Patients with extensive atrophic gastritis, extensive IM, or focal incomplete IM should be followed up with a high-quality endoscopy every 3 years, according to the recently published guidelines on the management of epithelial precancerous conditions and lesions in the stomach (MAPS II).[2]

In our study, if a single biopsy is taken from any site, due to false-negative results, endoscopic follow-up is neglected in almost one-half of the patients. It has been determined that the need for endoscopic follow-up in approximately one-third to one-fourth of the patients is missed if two biopsies are taken only from the antrum or one biopsy is taken from the antrum and corpus. The results show the importance of compliance with USS for accurate identification of patients who need endoscopic surveillance.

The fact that there are few prospective studies investigating the distribution of *H. pylori* and precancerous lesions in the stomach, increases the importance of our study. The use of tests showing only active infection may have underestimated the frequency of *H. pylori*. The clinical impact of the study results may be insufficient because of methodological limitations (relatively small sample and cross-sectional, observational, single-center study) that preclude a robust conclusion.

In conclusion, taking a biopsy from a single site seems to be sufficient for the diagnosis of *H. pylori* in patients without extensive atrophy. However, it is not reliable for the diagnosis of gastric atrophy with or without IM. Thus, our study confirms the importance of compliance with the USS in the diagnosis of *H. pylori*-associated precancerous lesions of the stomach.

One or two biopsies from the antrum or one biopsy from each of the antrum and corpus, which we frequently encounter in clinical practice, is not an appropriate approach in terms of endoscopic follow-up decision due to high false-negative results for precancerous lesions. We need more comprehensive studies emphasizing the importance of taking biopsies in accordance with the USS recommendations in clinics using white light endoscopy.

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Conflicts of interest

There are no conflicts of interest.

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