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Usefulness of optical enhancement endoscopy combined with magnification to improve detection of intestinal metaplasia in the stomach

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Authors

Sergio Sobrino-Cossío[1,2], Oscar Teramoto-Matsubara[2,3], Fabian Emura[4,5], Raúl Araya[6], Vítor Arantes[7], Elymir S. Galvis-García[8], Marisi Meza-Caballero[2], Blanca Sinahi García-Aguilar[2], Arturo Reding-Bernal[9], Noriya Uedo[10]

Institutions

1 Hospital Ángeles del Pedregal, Ciudad de Mexico, Mexico
2 Gástrica, Centro Avanzado en Endoscopia y Estudios Funcionales, Mexico City, Mexico
3 Hospital ABC Ciudad de Mexico, Mexico
4 Endoscopia Gastrointestinal Avanzada, EmuraCenter Latinoamérica y Departamento de Gastroenterología de la Universidad de la Sabana, Bogotá, Colombia
5 Departamento de Gastroenterología de la Universidad de la Sabana, Chia, Cundinamarca, Colombia
6 Servicio de Endoscopia y Gastroenterología de la Clínica Universidad de Los Andes y del Hospital Militar de Santiago y Clínica Universidad de los Andes, Santiago, Chile
7 Hospital das Clínicas, Faculdade de Medicina, Universidade Federal de Minas Gerais, Hospital Mater Dei Contorno, Belo Horizonte, Brasil
8 Department of Endoscopy. Hospital General de Mexico “Dr. Eduardo Liceaga,” Mexico City, Mexico
9 Research Division, Hospital General de Mexico “Dr. Eduardo Liceaga,” Mexico City, Mexico
10 Osaka International Cancer Institute, Department of Gastrointestinal Oncology, Osaka, Japan

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Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Corresponding author

Dr. Sergio Sobrino-Cossío, Endoscopy Department of Hospital Ángeles del Pedregal, Camino a Santa Teresa 1055-776, Colonia Héroes de Padierna, CP 10700 Mexico, Mexico
Phone: +56527488 and 56529589
ssobrinocossio@gmail.com

ABSTRACT

Background and study aims The light blue crest observed in narrow band imaging endoscopy has high diagnostic accuracy for diagnosis of gastric intestinal metaplasia (GIM). The objective of this prospective study was to evaluate the diagnostic accuracy of magnifying i-scan optical enhancement (OE) imaging for diagnosing the LBC sign in patients with different levels of risk for gastric cancer in a Mexican clinical practice.

Patients and methods Patients with a history of peptic ulcer and symptoms of dyspepsia or gastroesophageal reflux disease were enrolled. Diagnosis of GIM was made at the predetermined anatomical location and white light endoscopy and i-scan OE Mode 1 were captured at the two predetermined biopsy sites (antrum and pyloric regions).

Results A total of 328 patients were enrolled in this study. Overall GIM prevalence was 33.8 %. The GIM distribution was 95.4 % in the antrum and 40.5 % in the corpus. According to the Operative Link on Gastritis/Intestinal-Metaplasia Assessment staging system, only two patients (1.9 %) were classified with high-risk stage disease. Sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, and accuracy of both methods (95 % C. I.) were 0.50 (0.41–0.60), 0.55 (0.48–0.62), 0.36 (0.31–0.42), 0.68 (0.63–0.73), 1.12 (0.9–1.4), 0.9 (0.7–1.1), and 0.53 (0.43–0.60) for WLE, and 0.96 (0.90–0.99), 0.91 (0.86–0.94), 0.84 (0.78–0.89), 0.98 (0.94–0.99), 10.4 (6.8–16), 0.05 (0.02–0.12), and 0.93 (0.89–0.95), respectively. The kappa concordance was 0.67 and the reliability coefficient was 0.7407 for interobserver variability.

Conclusions Our study demonstrated the high performance of magnifying i-scan OE imaging for endoscopic diagnosis of GIM in Mexican patients.

Introduction

The gastric carcinogenic sequence involves subsequent changes inf the mucosa from normal to chronic gastritis, atrophic gastritis (AG), intestinal metaplasia (IM), dysplasia, and gastric cancer (GC) [1]. The development of IM is an important step in the precancerous cascade of gastric adenocarcinoma, and it has been reported that patients with IM have a 10-fold increased risk of GC [2]. Therefore, identification of gastric IM during esophagogastroduodenoscopy (EGD) is very important to recognize high-risk individuals who may benefit from being enrolled in surveillance for GC [3]. A light blue crest (LBC) is an endoscopic sign used to detect metaplasia. Although IM can be observed using white light, its sensitivity and specificity is lower compared to narrow band imaging (NBI).

IM appears during white light imaging as slightly elevated or flat whitish areas, without contrast (color) with the surrounding mucosa, or as depressed reddish areas of shallow depth. Conventional endoscopic identification of IM has a high rate of interobserver variability and correlates poorly with histological findings.

Although the current standard for diagnosis for IM is histological assessment of a biopsy specimen, high-quality image-enhanced endoscopy enables detection and characterization of premalignant and malignant gastric lesions and determination of how far they extend [4]. NBI with magnifying endoscopy (NBI-ME) visualizes a particular endoscopic sign of IM, LBC, which is defined as a thin, blue-white line on the crest of the epithelial surface, showing high diagnostic accuracy [5–8]: sensitivity of 90 % and specificity of 90 % [8]. Use of NBI increases sensitivity of endoscopy for diagnosing IM compared to white light endoscopy (WLE) diagnosis (87 % vs. 53 %, $P<0.001$) [7].

The i-scan (Pentax Medical, HOYA Corporation, Tokyo, Japan) is a computerized digital image processing system that improves the visibility of vessels, crypts, and surface structures of the superficial mucosa [9]. The OE i-scan-Mode System (Pentax Medical) is a new, computerized, dynamic, digital image processor that provides high-resolution enhanced images. i-SCAN combines high-resolution endoscopy with three adjustable modes of image enhancement: 1) surface enhancement, which delimits the edges of the structures; 2) CE, which shows the areas of low density in color (depressed lesions), sharpening the appearance of the vessels and the texture of the surface; and 3) TE, which modifies the colors of each pixel by accentuating the mucosal (MS) and vascular (MV) pattern. As an example, this technology is reported to be useful for improving detection of dysplasia in Barrett's esophagus with a high diagnostic yield [10]. However, the usefulness of this system for diagnosing gastric IM has not been investigated.

Actual diagnostic criteria for IM are not pathognomonic, nor reproducible using WLE, which may be the reason for the low rate of agreement among examiners. We suggest that with NBI and i-scan, used in combination with histology, it is possible to detect more cases. The aim of this study, therefore, was to evaluate the diagnostic yield of the i-scan system with magnifying endoscopy for detection of gastric IM in clinical practice.

Patients and methods

Study design and settings

This was a prospective cohort study conducted in a private endoscopic center in Mexico City from July 2018 to September 2019. All patients received extensive information about the objective of the study, including benefit of histological confirmation of GC risk and potential increase of risk of bleeding associated with biopsy, and provided consent for study participation. The study protocol was approved by the Ethics and Research Committee of the Hospital Ángeles del Pedregal in Mexico City (HAP 2557).

Participants

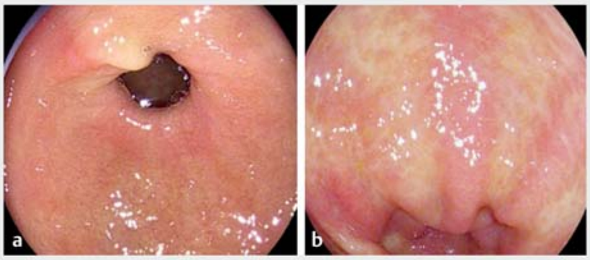
Eligibility criteria were: 1) history of peptic ulcer; 2) symptoms of dyspepsia or gastroesophageal reflux disease; 3) age over 18 years old; and 4) provision of written informed consent for study participation. Exclusion criteria were: 1) poor performance status; 2) bleeding tendency; 3) past history of gastrectomy or stenosis; 4) suspected symptom or clinical information for perforation, intestinal obstruction, advanced GC, gastrointestinal bleeding, or portal hypertension; and 5) dimethicone allergy.

Endoscopic equipment and procedure

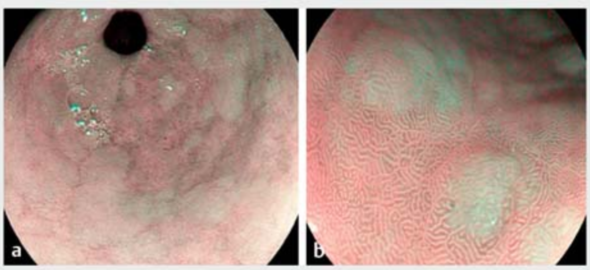
A magnifying videoendoscope (Magniview EG-2990Zi HD, Pentax Medical) and an EPK-i7010 processor (Pentax Medical) that works in WLE and i-scan OE modes were used in this study. We used Mode 2 Pentax Medical (similar NBI-Olympus) and i-scan 2 to detect LBC sign. A distal attachment (OE-A58, Pentax Medical) was placed over the tip of the gastroscope to maintain adequate distance to the mucosa during magnifying observation.

The EGD procedures were performed by two endoscopists separately, and two others (blinded) evaluated the endoscopic images who had experience in NBI-ME diagnosis to determined the presence of IM according to the LBC sign. An anesthesiologist administered intravenous propofol sedation to the patients and monitored their vital signs continuously.

Following a systematic alphanumeric-coded endoscopic (SACE) method [11], gastric mucosa was systematically examined to detect any definite or suspicious neoplastic lesions. Then, after thorough observation of the gastric mucosa, magnifying endoscopic images of WLE and i-scan OE Mode 1 were captured at the two predetermined biopsy sites (antrum and pyloric regions) (▶ **Fig. 1**, ▶ **Fig. 2**): the antral lesser and greater curvature (approximately 2–3 cm proximal to the pylorus), the corpus lesser and greater curvature (approximately 4 cm proximal to the gastric angle), and the incisura angulus [12, 13]. Even though, biopsies were taken from five areas, only two sites were evaluated (one in the antrum and one in the body) to determine the extent of IM. Immediately after observation in each mode, the endoscopic findings were documented in the medical notes and they could not be modified. Finally, biopsy specimens were taken from each site. All procedures were recorded with a high-definition video recorder.



▶ **Fig. 1** Images coded by region and area (systematic alphanumeric-coded endoscopy) using i-scan OE Mode 2 (pentax system). **a** Close-up of pyloric area (A6) and **b** lower curvature in distal body (L12).



▶ **Fig. 2** Images by i-scan coded by region and area (alphanumeric system) using OE i-scan mode 1 (pentax system). We observed a contrast color difference as shown by the white opaque substance in **a** the pyloric area (A6), and **b** the greater curvature in distal body (L14).

Diagnostic criteria for IM in WLE and magnifying i-scan OE images

The diagnosis of IM in WLE was made according to presence of irregularly clustered whitish mucosa, mucosa with a rough or uneven surface, a villous appearance, and patchy redness [14]. The mucosa was diagnosed as IM when it had any of the above-mentioned endoscopic findings, while it was diagnosed as non-IM when it had none of the findings.

The diagnosis of IM in magnifying i-scan OE images was made according to presence of an endoscopic finding of LBC. LBC was defined as a fine, blue-white line on crests of the epithelial surfaces/gyri [5]. It was initially described in NBI-ME images, but we confirmed that the same finding is seen in magnifying i-scan OE images. When the mucosa showed LBC in any part of the image fields, it was diagnosed as IM, while I fthere was no LBC in the endoscopic image field, it was diagnosed as non-IM.

Each biopsy specimen was deposited in a separate pod that contained 10 % formaldehyde and labeled. After fixation, the biopsy specimens were embedded into a paraffin block, sectioned, and stained with hematoxylin and eosin (H&E) and Giemsa. In the case of presence of IM, they were also stained with Alcian blue (pH 2.5) and periodic acid Schiff (PAS) [15]. Diagnosis of complete and incomplete type IM was made according to Updated Sydney System criteria [12]. Pathologists were blinded to clinical and endoscopic findings. Presence of histological IM in the biopsy specimen was used as a reference standard for calculation of diagnostic accuracy.

Grade of IM, and *Helicobacter pylori* was evaluated according to the updated Sydney system [12]. The Operative Link for Gastric Intestinal Metaplasia Assessment (OLGIM) was used for staging of histological severity and topography of IM [16].

Measured outcomes and statistical analyses

Descriptive statistics were used out for frequencies and proportions. For comparisons of demographic data, Pearson's chi-square tests and Student's t tests were used for categorical and continuous variables, respectively. The prevalence of IM was reported. For evaluation of diagnostic yield, the sensitivity, specificity, positive predictive values (PPVs), negative predictive values (NPVs), positive likelihood ratios (LR +), and negative (LR –) and diagnostic accuracy of each endoscopic diagnostic method were calculated. Differences in diagnostic yield between WLE and magnifying i-scan OE were compared using MacNemar's test. The interobserver kappa concordance test between endoscopists was calculated. To measure internal consistency, we also calculated the Cronbach's alpha.

Results

A total of 328 patients were included in this study. Demographic characteristics are shown in ▶ **Table 1**. IM was histologically detected in 111 individuals (30.1 %). For patients over 45 years old, IM was noted in 111 of 302 subjects (36.7 %). There were statistically significant differences in mean age ($P < 0.001$), intake of proton pump inhibitors, tobacco ($P < 0.0001$), alcohol ($P < 0.0001$), nonsteroidal anti-inflammatory drugs (0.0005), family history of GC ($P < 0.0005$), and *H. pylori* infection (0.0001) between patients with IM and those without IM.

Histological characteristics of IM patients are shown in ▶ **Table 2**. IM was more predominant in the antrum (106 patients, 95.4 %) than in the corpus (45 patients, 40.5 %). According to the OLGIM staging system, patients were stratified as stage I, II, III, and IV in 25 (7.62 %), nine (2.74 %), one (0.3 %), and one (0.3 %), respectively. Only two of them (0.6 %) were classified as have high risk for GC.

Antrum and pyloric regions were observed using WLE (▶ **Fig. 1**) and i-scan OE Mode 2 (▶ **Fig. 2**) with magnification (▶ **Fig. 3**). Sn, Sp, PPV, NPV, LR +, LR-, and diagnostic accuracy of both methods for histological IM are shown in ▶ **Table 3**. The kappa concordance was calculated as 0.67. The reliability coefficient was calculated as 0.7407.

Discussion

This prospective study provided evidence that magnifying i-scan OE imaging improved diagnosis of GIM compared to only WLE diagnosis in Mexican patients.

H. pylori was classified as a definite carcinogen in 1994 [17]. However, it is known that *H. pylori* infection is a necessary but not sufficient causal factor for GC [18], and having only *H. pylori* infection does not increase GC risk substantially [19]. Persistent

▶ **Table 1** Demographic characteristics of the study participants.

Variables	Total n = 328 (100 %)	Intestinal metaplasia		
		Absent N = 217	Present N = 111	*P* value
Age, mean years (SD)		53 (17)	61 (13)	< 0.001
Sex (men/women)	116/212	72/145	44/67	0.070
BMI mean (SD)		24.5 (0.4)	25.8 (0.4)	0.075
Cigarette smoking (% > 20/day)	39 (11.9)	25 (11.5 %)	14 (12.6 %)	0.00001
Drinking habit, n (%)	57 (17.3)	41 (18.9 %)	16 (14.4 %)	0.00001
Regular NSAID intake, n (%)	99 (30.1)	51 (23.5)	48 (43.2 %)	< 0.00001
Family history of GC in first-degree relatives	34 (10.3)	21 (9.6 %)	13 (11.7 %)	0.0005
H. pylori infection, n (%)	52 (15.8)	35 (16.1 %)	17 (15.3 %)	0.00001
Indication of EGD				
▪ Dyspepsia, n (%)	118 (44.0 %)	68 (43.3 %)	50 (45.0 %)	0.014
▪ GERD symptom, n (%)	72 (26.8 %)	40 (25.4 %)	30 (27.0 %)	0.072
▪ Dyspepsia + GERD symptoms	58 (21.6 %)	36 (22.9 %)	22 (19.8 %)	0.014
▪ History of peptic ulcer	18 (6.7 %)	12 (7.64 %)	6 (5.4 %)	0.962
▪ Others	2 (1.7 %),	1 (0.63 %)	3 (2.7 %)	0.080

BMI, body mass index; NSAID, bonsteroid antiinflammatory drug; GC, gastric cancer; CI, confidence interval; SD, standard deviation.

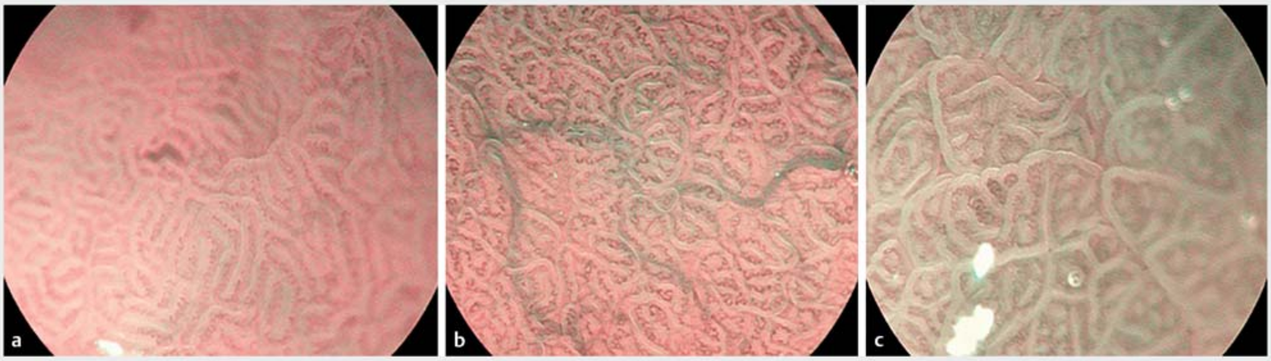
▶ **Table 2** Histological characteristics of IM patients.

Intestinal metaplasia	N = 111
Prevalence	
▪ Antral	106 (95)
▪ Corpus	45 (41)
▪ Both	27 (24.3)
Subtype	
▪ Complete	4 (3.2)
▪ Incomplete	107 (96)
Distribution	
▪ Focal	94 (85)
▪ Multifocal	17 (15)
OLGIM stage	
▪ I	25 (22.5)
▪ II	9 (8.1)
▪ III	1 (0.9)
▪ IV	1 (0.9)

IM, intestinal metaplasia; OLGIM, Operative Link for Gastric Intestinal Metaplasia Assessment.

infection with *H. pylori* causes subsequent AG and IM in the gastric mucosa, which signify high risk of GC [20]. In particular, the risk of GC increases significantly when IM is present in the gastric mucosa [21]. We found the prevalence of IM in our study subjects was 33.8 %, but according to the OLGIM staging system, only two of the study subjects (2 %) were classified as high risk for GC. Accordingly, identification of IM and surveillance for patients with IM enables detection of GC in an early stage [22] and would improve mortality from GC in our country.

In 1964, Takemoto described the presence of white-grayish elevations dispersed in the antrum and the angularis incisura as a specific finding of IM [23]. Although this finding is highly specific (specificity of 98 %-100 %) for histological IM, the sensitivity was quite low (6 %-13 %) [24] because IM exists in not only white-grayish elevated areas but also areas without color difference, or in shallow, depressed, reddish areas [25]. Fukuta, et al. included several endoscopic findings of IM other than whitish slight elevation and showed good diagnostic values: sensitivity of 86.1 % to 94.6 % and specificity of 65.9 % to 69.1 % [14]. Although the same endoscopic findings were used for the diagnostic criteria of WLE for IM in this study, the diagnostic ability of WLE (sensitivity of 50 % and specificity of 55 %) was not as good as that in the previous Japanese study [14]. A recent online survey and imaging test indicated that the accuracy for endoscopic diagnosis of IM was significantly higher among Japanese and Korean endoscopists compared to the rest of the world [26], and it may be attributed to training and routine practice of endoscopic diagnosis of IM in East Asian countries.



► **Fig. 3** Close-up Mode 2 images of the antrum using OE Ii-scan mode (pentax system). **a**, **b**, **c**, A mucosal pattern with light blue crest sign is visible.

► **Table 3** Diagnostic accuracy for detecting the endoscopic sign of the light blue crest by combining Magniview EG-2990Zi HD and i-scan OE mode.

Method	White light endoscopy n = 328	Magnifying i-scan OE n = 328
Sensitivity	50 (41–60)	96 (90–99)
Specificity	55 (48–62)	91 (86–94)
Positive predictive value	36 (31–42)	84 (78–89)
Negative predictive value	68 (63–73)	98 (94–99)
Positive likelihood ratio	1.12 (0.9–1.4)	10.4 (6.8–16)
Negative likelihood ratio	0.9 (0.7–1.1)	0.05 (0.02–0.12)
Diagnostic accuracy	53 (43–60)	93 (89–95)

Data are presented with percentage (95 % confidence interval). OE, optical enhancement.

Usefulness of NBI for diagnosis of gastric IM was first reported in a Japanese study with sensitivity of 89 % and specificity of 93 % [5]. An American study described sensitivity and specificity of 89 % and 93 %, respectively, for detection of gastric IM with NBI endoscopy [27]. Our previous study demonstrated that non-magnifying NBI imaging had sensitivity, specificity, PPV, NPV, and diagnostic accuracy for diagnosing gastric IM as 80%, 96 %, 84 %, 95 %, 93 %, and 87 %, respectively [12]. Moreover, we found that i-scan OE showed good LR (LR + of 10.4 [95 %CI 6.8–16] and LR- of 0.05 [95 %CI 0.02–0.12]), which is the ratio between the probability of observing an alteration in patients with disease versus the probability of this result in healthy patients [28]. Values of LR greater than 10 have a higher probability of disease and close to 0 to rule it out. According to the meta-analysis, NBI has the pooled LR + of 8.98 (95 % CI 6.42–12.58) and LR- of 0.12 (95 % CI 0.09–0.16 [8]. Unlike sensitivity, specificity, and predictive values, LR incorporates both sensitivity and specificity, and is not influenced by the prevalence of the disease [28]. The use of LR enables an evaluation closer to reality because the combination of such optical technology using band limited lights and digital image processing technology is reported to yield improved diagnostic accuracy for not only gastric IM but also other diseases in the upper gastrointestinal tract compared to WLE [29].

In this study, we focused on one representative endoscopic finding of gastric IM: LBC. In normal gastric mucosa, the microsurface structure has been described as the foveola type in the body and the groove type in the antrum [30]. MS structure of IM shows a groove type or villiform structures that mimics the normal antral or intestinal mucosa. As in NBI, the LBC was observed on the edge of the ridged or villiform MS of the gastric IM. Kanemitsu et al. reported that the sensitivity and specificity of white opaque substance (WOS) for histologically diagnosed IM were 50.0 % (95 % IC 40.0 %–50.0 %) and 100.0 % (95 %CI 85.0 %–100.0 %), respectively [31]. In our study, the sensitivity and specificity of WOS to diagnose IM were poor (data not shown). The different diagnostic values of MTB and WOS in this study may be a result of differences in endoscopy systems and ethnic backgrounds of study subjects.

The white light anomalies reported as IM [14] have an area under the receiver operating curve between 0.55 to 0.8 in this paper, different among each anomaly and different in the antrum and gastric body. We observed that i-scan sensitivity and specificity do not differ between the antrum and corpus. Using the diagnostic criteria, there were no differences in sensitivity or specificity. Although the structural characteristics of the mucosa differ between the antrum and the gastric body, the diagnostic criteria for IM are considered to be the same.

Finally, American Gastroenterological Association guidelines do not recommend routine surveillance for GIM, and it should be reconsidered in patients with any potential risk.

This study has some limitations. It was conducted by only two operators and both experienced difficulties while trying to focus the mucosa, even using an endoscopic cap. Furthermore, this study only used i-scan, and even though NBI and i-scan have similar diagnostic accuracies for histological prediction, they are not identical [32]. A comparative study between NBI and i-scan could be very informative for validating our findings across these two techniques, but such a study would require a larger group of patients. Therefore, refinement of endoscopic technology and provision of adequate training is necessary before this method can be widely used.

Conclusions

In conclusion, our study demonstrated that the accuracy of magnifying i-scan OE by means of identification of the LBC sign was better than WLE for diagnosis of gastric IM in a Mexican clinical practice.

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Competing interests

Drs. Sobrino-Cossío and Teramoto-Matsubara are consultants for Endomédica S.A. de CV (distributor of Pentax Medical) in Mexico City. Dr. Emura is a speaker for Fuji. Dr. Uedo is a speaker for Olympus speaker.

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