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Systematic Endoscopy 5 Years After Sleeve Gastrectomy Results in a High Rate of Barrett's Esophagus: Results of a Multicenter Study

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Abstract

Background Recent evidence has indicated an increased risk of Barrett's esophagus (BE) in the long term after sleeve gastrectomy (SG).

Aim The aim of the study is to investigate the spectrum of gastroesophageal reflux disease (GERD) symptoms as well as the prevalence of BE, at minimum 5 years after SG in patients who underwent SG in different bariatric centers of two countries: France and Italy.

Patients and Methods Five high volume outpatient centers dedicated to bariatric surgery that routinely perform upper GI endoscopy before any bariatric procedures were invited to participate in the study. From January 2017 to June 2018, each center during scheduled postoperative evaluation after surgery asked a minimum 10 consecutive patients, which had performed SG at least 5 years before and with no evidence of BE preoperatively, to undergo another upper GI endoscopy.

Results Ninety (66 F) consecutive patients were enrolled. The mean follow-up was 78 ± 15 months, and the mean total body weight loss was $25 \pm 12\%$. The prevalence of BE was 18.8% with no significant difference among centers. Weight loss failure was significantly associated with BE ($p < 0.01$). The prevalence of GERD symptoms, erosive esophagitis, and the usage of PPIs increased from 22%, 10%, and 22% before the SG to 76%, 41%, and 52% at the time of follow-up, respectively ($p < 0.05$).

Conclusions This multicenter study show a high rate of BE at least 5 years after SG. Weight loss failure was significantly associated with BE. We suggest to provide systematic endoscopy in these patients to rule out this condition.

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Introduction

Sleeve gastrectomy (SG) is currently the most common bariatric procedure performed worldwide [1] due to its advantages: the low rate of complications, the short operative time, the absence of foreign material, the lack of gastrointestinal anastomosis and malabsorption, the patient's acceptance, and the feasibility to be converted into multiple other bariatric procedures. Indeed, a recent randomized trial showed that SG results in weight loss and comorbidity resolution and/or improvement that are not significantly different from those recorded after a Roux-en-Y gastric bypass (RYGB) [2, 3]. However, despite all these favorable features, the effect of SG on the risk of gastroesophageal reflux disease (GERD) is still controversial [4–7]. GERD can range from no visible esophageal injury at endoscopy, named non-erosive reflux disease (NERD), to esophageal injury or erosive reflux disease (ERD), which can, in turn, give rise to Barrett's esophagus (BE), The latter is a potential factor for the development of esophageal carcinoma [8, 9]. Recently, two independent series have reported a high prevalence in Barrett's esophagus of around 15% at 5- and 10-year follow-up after SG, respectively [10, 11]. Therefore, as the prevalence of BE is around 1.6% in the general population [12], the association between SG and BE seems to be strong enough to support systematic upper gastrointestinal (GI) endoscopy beyond 5 years independently from the presence or absence of esophageal symptoms [10].

The aim of the present study was to investigate the spectrum of GERD as well as the prevalence of BE, at minimum 5 years after SG in obese patients who underwent SG in different bariatric centers of two countries: France and Italy.

Patients and Methods

Study Design

Five high volume outpatient centers dedicated to the surgical therapy of obesity and related disorders in France and Italy that routinely perform upper GI endoscopy before any bariatric procedures were invited to participate in the study. From January 2017 to June 2018, each center during scheduled postoperative evaluation after surgery asked a minimum 10 consecutive patients, which had performed SG at least 5 years before and with no evidence of BE preoperatively, to undergo another upper GI endoscopy [13, 14]. Inclusion criteria were an upper GI endoscopy performed according to international standard of quality [14], an informed written consent to undergo follow-up endoscopy with detailed information on the risks and benefits of endoscopy especially for the potential findings of BE, and the clinical implications of this condition [13]. Exclusion criteria were patients with SG done as a conversional procedure from any other bariatric operations such as gastric banding, vertical banded gastroplasty, RYGB, or duodenal switch.

The diagnosis of BE was made if the distal esophagus was lined with columnar epithelium with a minimum length of 1 cm (tongues or circular) containing specialized intestinal metaplasia at histological examination [14, 15].

The main investigator of each center collected age, gender, weight, height, body mass index (BMI), GERD symptoms, proton pump inhibitor (PPI) usage, and esophagitis at baseline and at the follow-up visit performed at least 5 years or more after SG. Additionally, the presence of BE and the presence of smoking habit and frequency of GERD symptoms were gathered. Weight loss after surgery (%WL) was calculated. All data were anonymized and pooled in a common database for which the authors had obtained previous authorization (MR003-R019; Number 2003095-CNIL).

GERD was defined on the basis of the presence of typical heartburn symptoms and/or regurgitation according to Montreal definition [16] and considered mild when reported less than two times a week and did not require PPIs and severe when was more than two times a week and require PPI. Furthermore, GERD was defined as "de novo" when no symptom of GERD had been recorded before the SG in concomitance with the absence of endoscopic abnormalities at baseline endoscopy. Esophagitis grade A according to Los Angeles classification was not considered as esophagitis at endoscopy [17]. Total weight loss (%TWL) was calculated as follows: [(weight before surgery − final weight) / weight before surgery] × 100. Excess body weight loss (EBWL) was calculated by using 25 kg/m^2 as the ideal BMI, and weight loss failure (WLF) was defined as an insufficient percentage of excess weight loss 2 years after surgery (< 50% of excess weight loss).

Outcome Parameters

Primary outcome parameter was to investigate the prevalence of BE in a multicentric series of morbidly obese patients undergoing SG in the hands of experienced bariatric surgeons in different bariatric centers of France and Italy.

Secondary outcome parameter was to assess the prevalence of GERD symptoms, the usage of PPI, and endoscopic signs of esophagitis.

Statistical Analysis

Quantitative variables are presented as the mean ± standard deviation (SD). Qualitative variables are presented as the percentage and frequency of the entire study population. Univariate comparisons for categorical variable analyses were performed using Pearson's chi-squared tests or Fisher tests for independent groups. To compare variables before and after surgery, the McNemar test and paired Student's t test were used, as appropriate. Multivariate analysis was performed using a logistic regression model, controlling for age, gender, and relevant clinical characteristics for parameters associated with Barrett's esophagus at 5 years of follow-up. The diagnostic performance of the EWL was determined by constructing a receiver operating characteristic (ROC) curve and by calculating the area under the ROC (AUC) curve for predicting patients with Barrett's esophagus. Sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratio were determined. A significance level of $p < 0.05$ was used in all analyses. All analyses were performed with SAS Enterprise Guide Version 5.1.

Results

Ninety consecutive patients fulfilling the inclusion criteria underwent systematic endoscopy at least 5 years after SG and were included prospectively in the present study by the five investigating centers. There were 24 men and 66 women with a mean age of 41 ± 11 years at the time of intervention and a mean BMI of 46 ± 8 kg/m^2. The mean follow-up was 78 ± 15 months, and at the time of the revaluation, the mean BMI was 34 ± 8 kg/m^2 with a total body weight loss (TBWL) of $25 \pm 12\%$ and an EBWL of $58 \pm 27\%$ (Table 1).

At baseline, patients in the five different bariatric centers were not different for PPI usage and endoscopic signs of esophagitis, while GERD symptoms were significantly more prevalent in one center (Padua) (Table 2). At the time of follow-up, the rate of esophagitis was the only significant difference between the centers (Table 3). Concerning our primary outcome, the total prevalence of BE at least 5 years after SG was 18.8% ($p < 0.01$). The length of BE was always less than 3 cm than all were classified short BE. In this series, no case of dysplasia was found. The prevalence of BE was not significantly different among the five bariatric centers in spite of the higher prevalence of GERD at baseline among centers (Table 3). Most of the patients with BE (94%) also complained of GERD symptoms, which were severe in 12 cases (75%) and mild in four cases (25%). None of BE patients were smokers. Using a univariate analysis, a significant association was found between weight loss failure and the presence of BE.

Table 1 Patients' characteristics before the SG and at the time of follow-up

Patients' characteristics	Before SG	Follow-up	p
Patients (N)	90	90	–
Sex ratio male/female (%)	24/66 (73)	–	–
Age, SD	41 ± 11	48 ± 11	–
Time of follow-up (months), SD	–	78 ± 15	–
Body weight (kg), SD	127 ± 24	94 ± 22	< 0.0001
BMI (kg/m^2), SD	46 ± 8	34 ± 8	< 0.0001
TBWL %, SD	–	25 ± 12	–
EBWL %, SD	–	58 ± 27	–
Barrett's N (%)	0	17 (18.8)	–
GERD N (%)	20 (22)	68 (76)	< 0.0001
Patients on PPI N (%)	20 (22)	46 (52)	< 0.0001
Esophagitis N (%)	9 (10)	37 (41)	< 0.0001

P value was calculated for quantitative or qualitative variables with Student's and χ^2 test, respectively ($p < 0.05$)

SG sleeve gastrectomy, *N* number of patients, *SD* standard deviation, *BMI* body mass index, *TBWL* total body weight loss, *EBWL* excess body weight loss (calculated with a 25 kg/m^2 as ideal BMI), *GERD* gastro-esophageal reflux, *PPI* proton pump inhibitor

WLF was recorded in 32 patients in the whole series (36.8%) among patients with BE was even higher (70.6%) ($p < 0.01$) (Table 4). Using a logistic regression analysis, WLF was still significantly associated with BE, with an adjusted odds ratio (OR) = 6.7 CI95% [1.7–25.7] after controlling for age, gender, GERD symptoms, esophagitis, and PPI usage (Table 5). The ROC curve constructed to investigate the diagnostic performance of WLF showed an AUC of 0.69 CI 95% [0.51–0.81] indicating that the EWL failure at least 5 years might be used to select patients for endoscopy in search of BE (Figs. 1 and 2).

The prevalence of GERD symptoms increased significantly from 21% before surgery to 76% at the time of follow-up ($p < 0.01$). Half of the patients in this series complained of de novo GERD symptoms (Fig. 1) that were mild in 12 patients (18%) and severe in the remaining 56 patients (82%). Among those 20 (21%) patients complaining of GERD before surgery, eight had worse symptoms, nine reported stable symptoms, and three reported improved symptoms.

Concomitantly, the usage of PPIs increased significantly from 22% (20 patients) to 52% (46 patients) at the time of follow-up ($p < 0.0001$). Moreover, the prevalence of esophagitis increased significantly from 10% (9 patients) before the surgery to 41% (37 patients) at the upper GI endoscopy at least 5 years after SG ($p < 0.0001$). Among these 37 patients, seven (19%) were asymptomatic, two (5%) had mild symptoms of GERD, and 28 (76%) had severe GERD symptoms.

Table 2 Preoperative GERD symptoms and endoscopic findings in 90 patients with more than 5 years of follow-up after the SG undergoing a systematic endoscopy according to the international guidelines for the diagnosis of Barrett's esophagus in each investigating bariatric center

Patients' characteristics	Naples	Nice	Lyon	Marseille	Padua	p
Patients (N)	20	18	21	19	12	NS
Barrett's esophagus at histology (N)	0	0	0	0	0	NA
GERD N (%)	5 (25)	1 (6)	2 (10)	2 (11)	9 (75)*	< 0.0001
Patients on PPI N (%)	4 (20)	2 (11)	7 (33)	1 (5)	5 (41)	NS
Esophagitis N (%)	2 (10)	2 (11)	3 (14)	0	2 (17)	NS

p values were calculated with Kruskal-Wallis test ($p < 0.05$)

N number of patients, *GERD* gastroesophageal reflux, *PPI* proton pump inhibitor, *NS* not significant ($p > 0.05$), *NA* not applicable

*Significantly different from the others

Discussion

This multicentric study exploring the prevalence of BE at histology 5 years or more after SG confirms a high prevalence of BE (18.8%).

In this study, we aimed to pool data issued from different bariatric centers to avoid any interference that might have been stemmed from surgeon-related technical issues such as the degree of dissection of the crura, the amount of residual gastric fundus and/or gastric antrum, the shape of stapling (straight or spiraling), the size of the calibration tube, or any other technical details linked to the surgical technique. Indeed, we found no significant difference in the distribution of the prevalence of BE among the five bariatric centers indicating that it is not linked to variations in the surgical technique.

GERD is the main mechanism underlying the transformation of the esophageal squamous mucosa into metaplastic columnar mucosa [13]. GERD was not significantly associated with BE in our study probably for the small size of the sample and the high prevalence of GERD in the whole study population. While it has been argued that SG might decrease GERD because of the reduction in intraabdominal pressure, gastric acid production, the reduction of the gastric volume, and increased gastric emptying [18, 19], it now seems evident from the literature that the true weakness or the *Achilles' heel* of this procedure in spite of overall strength is the long-term

occurrence of GERD [2]. Indeed, in the present study, 52% of patients reported GERD symptoms requiring regular use of PPIs beyond 5 years of follow-up. Many mechanisms have been claimed to be responsible for the increased rate of GERD observed after SG such as the disruption of anatomical antireflux mechanisms after surgery, decreased gastric compliance, increased intragastric pressure, localized stricture or angulation of the gastric tube at the junction between the body and the antrum of the stomach, the gastric twist [20], the final shape of the sleeve (funnel shape) [21], the persistence of a significant part of the gastric fundus, and the presence of a hiatal hernia [4, 20, 22].

Genco et al. first published the alarming systematic endoscopy results of 17.2% of 110 patients with BE after SG at a median follow-up of 58 months [10]. The authors also reported that 26.4% of patients with Barrett's had no GERD symptoms, while the rate of upward migration of the "Z" line was 73% and the incidence and the severity of erosive esophagitis were increased. Soricelli et al. from the same group confirmed that 21% of patients with evidence of BE had no symptoms of GERD [23]. However, in our study, all but one patient with evidence of BE complained of GERD symptoms and 35% of them required systematic PPIs to control the symptoms. The difference in the definition of GERD between the study by Genco et al. and the present study may account for this difference. Felsenreich et al. also reported a high prevalence of BE

Table 3 Postoperative GERD symptoms and endoscopic findings in 90 patients with more than 5 years of follow-up after the SG undergoing a systematic endoscopy according to the international guidelines for the diagnosis of Barrett's esophagus in each investigating bariatric center

Patients' characteristics	Naples	Nice	Lyon	Marsille	Padua	p
Patients (N)	20	18	21	19	12	NS
Barrett's esophagus at histology N (%)	1 (5)	5 (28)	5 (24)	5 (26)	1 (8)	NS
GERD N (%)	15 (75)	14 (78)	14 (67)	14 (74)	11 (92)	NS
Patients on PPI N (%)	9 (45)	8 (44)	12 (57)	8 (42)	6 (50)	NS
Esophagitis N (%)	12 (60)	10 (62)	5 (26)	4 (19)	6 (50)	0.01

p values were calculated with Kruskal-Wallis test ($p < 0.05$)

N number of patients, *GERD* gastroesophageal reflux, *PPI* proton pump inhibitor, *NS* not significant ($p > 0.05$)

Table 4 Postoperative GERD symptoms, endoscopic findings, PPI intake, and weight loss failure in patients with and without Barrett's at histology at least 5 years after SG

Patients' characteristics	No Barrett's esophagus N = 71	Barrett's esophagus N = 17	p
GERD symptoms N (%)	50 (75)	16 (94.1)	0.06
PPIs intake N (%)	38 (53.5)	7 (43.7)	0.50
Esophagitis N (%)	29 (40.8)	8 (47.1)	0.64
Weight loss failure* N (%)	20 (29.0)	12 (70.6)	< 0.01

*Weight loss failure defined by excess body weight loss < 50%

SG sleeve gastrectomy, N number of patients, GERD gastroesophageal reflux, PPI proton pump inhibitor

of 15% at 10 years after SG that was associated with 45% of esophagitis while only 37% of patients complained of GERD symptoms [10]. These data indicate that the decision to adopt the policy of systematic endoscopy beyond five years after SG should not rely on the presence of GERD symptoms.

Furthermore, in our study, there was no significant difference in the prevalence of BE among the five centers at the mean follow-up of 78 months, ranging from 60 to 132 months. These data suggest that it is independently of the surgical technique.

It should be stressed that in the present study, only short BE was found and no case of dysplasia was recorded. The rate of incidence of malignant transformation of BE has been evaluated between 0.6 and 0.7% per year in two large metanalyses [24, 25] while the annual incidence of malignant transformation increased up to 1.4% and 6% only in the presence of low-grade and high-grade dysplasia at histology, respectively [10, 26]. Then, although the yearly progression of non-dysplastic BE to high-grade dysplasia and invasive cancer is low, we believe that a follow-up has to be ensured for these patients.

The novel result of this study was that weight loss failure was significantly associated to BE. This result is in key with the previous study by Angrisani et al. in which the absence of

Table 5 Logistic regression analyses to identify factors associated to Barrett's esophagus 5 years after SG. OR odds ratio, CI 95% confidence limits 95%

Patients' characteristics	Adjusted OR	CI 95%	p
Weight loss failure*	6.7	1.7–25.7	< 0.01
Age 30 to 39 (ref. 18–29)	1.2	0.2–8.7	0.83
Age 40 to 49 (ref. 18–29)	1.6	0.2–11.8	0.76
Age > 50 (ref. 18–29)	1.8	0.2–13.1	0.61
Women (ref. men)	1.1	0.3–4.8	0.88
GERD symptoms at baseline	0.5	0.1–2.6	0.39
Esophagitis	1.7	0.5–6.2	0.39
PPI intake	0.4	0.1–1.7	0.23

SG sleeve gastrectomy, N number of patients, GERD gastroesophageal reflux, PPI proton pump inhibitor, ref reference

*Weight loss failure defined by excess body weight loss < 50%

GERD was associated with better weight loss results at 5 years [27]. The link between BE and WLF is still unclear; however, a few hypotheses can be done. First, in weight loss failure, often the SG is dilated especially at the level of the remnant acid-secreting gastric fundus. This may, in turn, account for the loss of restriction with weight regain and increased GERD. Furthermore, the presence of GERD symptoms might modify eating behavior leading patients to eat more frequently to buffer acid.

Moreover, we further tested the performance of WLF in predicting the presence of BE at endoscopy. This information might be relevant in clinical practice suggesting to perform endoscopy at least 5 years after SG in patients with weight loss failure. However, these data should be confirmed in a larger series of patients because current recommendations on BE screening do not refer specifically to patients in the setting of bariatric surgery. Indeed, whereas SG increased worldwide in the last decade, the occurrence of esophageal adenocarcinoma on BE remains an exceptional clinical entity [28, 29]. This may suggest that the process of malignant transformation due to GERD in the lower esophagus in the setting of SG might be not the same as in individuals without a history of SG. Although there is no clear explanation for this difference yet, a few hypotheses may be proposed. The effect of gastrectomy may alter the chemical characteristics of the refluxate, blunting its carcinogenic effect on the esophageal epithelium, and the time interval required for the malignant transformation may be longer in this setting. Obesity has also been shown to be a risk factor for esophageal adenocarcinoma independently of GERD, and the achieved weight loss may thus exert a protective effect [30].

As the magnitude of risk associated with malignant transformation of BE in the setting of SG is still not clear, the debate concerning the right attitude toward BE in patients with SG is still open. One possibility might be the use of systematic endoscopic surveillance as it is currently done in patients with BE who have no history of SG [13]; the alternative approach is a conversion to RYGB [31, 32]. Indeed, the latter works as an antireflux procedure because the Roux-en-Y loop anatomy avoids bile reflux, and the small, lesser curvature-based gastric pouch excluding the acid-secreting gastric fundus
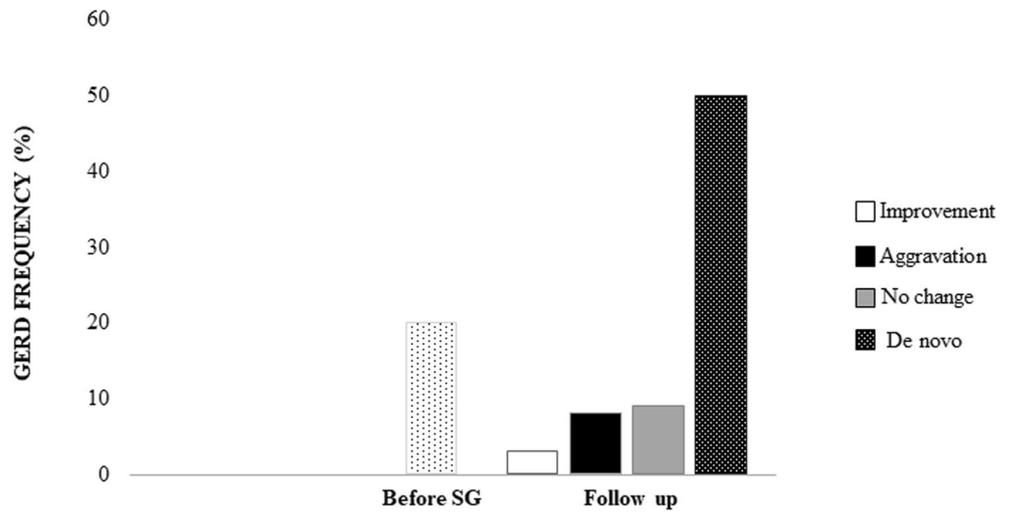
Fig. 1 Prevalence of (%) GERD symptoms before and after (de novo) SG (mean follow-up time 78 ± 15 months)

dramatically limits the production of hydrochloric acid that may come in contact with the esophagus. It should be stressed that a conversional RYGB for GERD to address a SG complication should be done with a short gastric pouch excluding the gastric fundus. In cases of WLF, this tiny pouch can be coupled with a calibrated gastrojejunal anastomosis of 12 mm, which adds a strong restrictive effect to the antireflux effect of the RYGB to induce further weight loss. As the effect of a RYGB conversion on the evolution of Barrett's mucosa is still unclear, endoscopic surveillance should be wisely performed in this setting [33].

Furthermore, as the RYGB also dramatically reduces the symptoms of GERD, it might add further weight loss in patients presenting with insufficient weight loss or weight regain, representing an interesting alternative in those patients with WLF and BE [6]. Indeed, we found a significant association between BE and WLF suggesting that converting a failed SG to RYGB may represent a valuable option in a large proportion of these patients. The use of endoscopic techniques to retrieve metaplastic mucosa has also been proposed [34].

The main strengths of our study was its multicenter nature, which limits surgeon-related technical factors that might impact the postoperative occurrence of GERD, the standardized protocol for the endoscopic exploration required to include patients in the study, and the histologic definition of BE. However, we acknowledge several limitations including the retrospective analysis of the study design; the definition of GERD [16], which was mainly based on symptoms reported by patients at baseline and at the time of follow-up and without a validated questionnaire; and the limited number of patients.
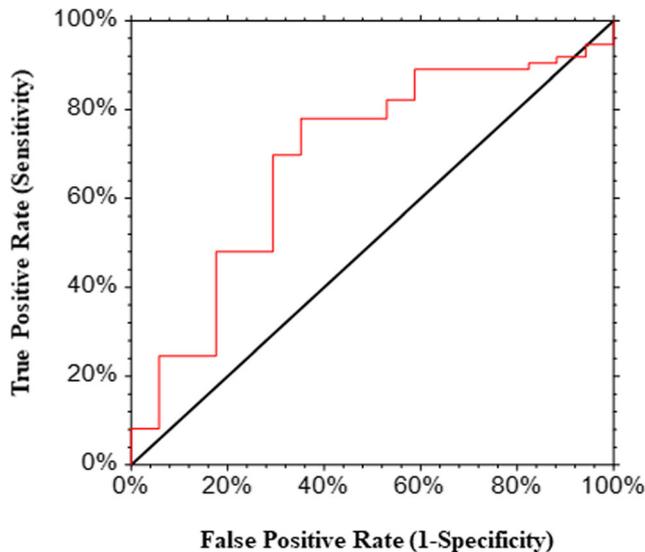
Conclusion

This multicenter study confirms a high rate of BE at histology in 18.8% of patients at least 5 years after SG. Further investigation is needed to confirm the high rate of BE in the esophageal epithelium beyond 5 years after SG and the potential of malignant transformation of this condition. The policy of adopting systematic endoscopic exploration long term after SG seems to be judicious and appropriate especially in young patients.

Compliance with Ethical Standards

Conflict of Interest   The authors declare that they have no conflict of interest.

Informed Consent   Written informed consent was obtained for each individual participant included in the study.

Fig. 2 Receiver operating characteristic (ROC) curves for the diagnosis of Barrett's esophagus. The excess weight loss (EWL) cutoff with the highest sensitivity and specificity for the detection of Barret's esophagus (BE) was 48.1%. At this threshold, sensitivity, specificity, likelihood ratio positive, likelihood ratio negative, and index of Youden were 0.78, 0.65, 2.21, 0.34, and 0.43, respectively

Ethical Approval All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments.

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