Diagnostic accuracy of magnifying chromoendoscopy with detection of intestinal metaplasia and dysplasia using acetic acid in Barrett’s esophagus

Stéphane RÉAUD (1), Anne CROUE (2), Jean BOYER (1)
(1) Service d’hépato-gastroentérologie, (2) Service d’anatomopathologie, CHU d’Angers, Angers.

SUMMARY
Objectives — Endoscopy with systematic randomized biopsies aims to improve the detection of intestinal metaplasia (IM) and dysplasia in Barrett’s esophagus (BE). Magnifying chromoendoscopy with alcoholic acetic acid might allow directed biopsies to improve detection of IM and dysplasia.

Patients and methods — Twenty-eight patients were studied with magnifying chromoendoscopy (Optical power zoom x 115, alcoholic acetic acid). Endoscopy biopsies were performed on one or several zones of BE chosen randomly, for which the chromoendoscopic pattern was determined according to Guelrud’s classification.

Results — Among seventy-two biopsies, the agreement between magnifying chromoendoscopy and histology and the positive predictive value of the association of patterns III and IV for the diagnosis of IM were 72.4%; sensitivity and specificity were respectively 95.5% and 42.9%. The diagnostic accuracy was 75%. Among the six biopsies that showed high-grade dysplasia, three were suspected because of two particular patterns: local loss of ridged cerebriform pattern due to the disorganization of the mucosal folds and hypervascularization of the mucosa.

Conclusion — Magnifying chromoendoscopy with acetic acid allows targeted biopsies of the IM in BE and may help to detect high-grade dysplasia.

RÉSUMÉ
Performance diagnostique de la vidéoendoscopie grossissante couplée à l’acide acétique dans la détection de la métaplasie intestinale et dysplasie sur endobrachyœsophage
Stéphane RÉAUD, Anne CROUE, Jean BOYER
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Objectifs — L’exploration endoscopique avec biopsies systématiques au hasard d’un endobrachyœsophage (EBO) a pour but de dépister la métaplasie intestinale (MI) et la dysplasie. La chromoendoscopie grossissante à l’acide acétique permettrait des biopsies dirigées pour améliorer le dépistage de la MI et de la dysplasie.

Malades et méthodes — Vingt-huit malades ont été étudiés en chromoendoscopie grossissante [zoom optique x 115, acide acétique alcoolique à 6 %]. Les zones de l’EBO étaient choisies au hasard et décrites selon la classification de Guelrud puis biopsiées.

Résultats — Sur 72 biopsies, la concordance endoscopie/histologie et la valeur prédictive positive pour le diagnostic de MI de l’association des types III et IV étaient de 72,4 %, la sensibilité de 95,5 % et la spécificité de 42,9 %. La performance diagnostique globale était de 75 %. Parmi les 6 biopsies avec dysplasie de haut grade, 3 présentaient en chromoendoscopie grossissante une perte localisée de l’aspect cérébriforme par désorganisation des plis muqueux et un aspect d’hypervascularisation de la muqueuse.

Conclusion — La chromoendoscopie grossissante à l’acide acétique alcoolique permet des biopsies ciblées sur la MI au sein d’un EBO et permet de suspecter dans certains cas une dysplasie de haut grade.

Introduction
Barrett’s esophagus (BE) is histologically defined as a replacement of the non-keratinized squamous epithelium of the lower esophagus by cylindrical metaplastic epithelium. This metaplasia presents three different histological aspects which may frequently coexist within the same patient with BE: gastric (or fundic) metaplasia, transitional (or cardial) metaplasia and intestinal (or specialized) metaplasia [1]. Among these, only intestinal metaplasia (IM) can degenerate into adenocarcinoma [2-8] determined by the sequence - intestinal metaplasia/dysplasia/adenocarcinoma [9-11].

Endoscopically, the metaplastic glandular mucosa which defines BE presents an orange tone close to that of the gastric mucosa, while the esophageal squamous mucosa has a grey-pink tone. However, even in the presence of confirmed BE, the three types of glandular metaplasia remain endoscopically indistinguishable.

A consensus conference has advised endoscopic and histological monitoring for BE patients, with IM detection using the planimetric method: one biopsy from all four quadrants at 1 to 2 centimeters intervals over the entire length of BE [10, 12-15].

However, this protocol, referred to as the Seattle protocol, currently used as the gold standard for diagnosis, has certain limitations: use of multiple disseminated biopsies due to the lack of recognisable gross pattern of IM, sample errors inherent in blind biopsies (biopsies outside zones of IM), long expensive procedure because of the number of biopsies needed to minimize the risk of missing a zone of dysplasia or a micro-invasive adenocarcinoma and non-demonstrated impact on survival [16-17]. It is however noteworthy that in a selected population, the planimetric method permits the discovery of degenerative lesions at an earlier stage and is thus potentially curable [18-21].

Because of the inherent limitations of the Seattle protocol, several techniques are in the course of evaluation; some still rely on endoscopic exploration, but are aimed at achieving guided biopsies in zones of previously identified IM. Combining optical and electronic advances with different dyes has enabled the
development of magnifying chromoendoscopy which enables improved detection of IM in BE by revealing specific gross patterns of IM or dysplasia distinguished by superficial irregularities (erythema, irregularity or excessive thickness of the mucosal surface, heterogeneous discoloration of mucosa) invisible with standard endoscopy.

Nevertheless, to date none of these newer techniques has yielded undeniable proof of superiority in comparison with the Seattle protocol.

Our goal was therefore to evaluate the results and the reproducibility of magnifying chromoendoscopy coupled with acetic acid for screening for IM and dysplasia in BE.

Materials and methods

Patients

The patients were included in an uncontrolled prospective study. They presented with either proven or suspected BE and had an indication for upper gastrointestinal endoscopy for confirmation and/or monitoring. Were excluded all patients at increased risk of bronchial inhalation or presenting serious cardio-pulmonary symptoms; patients with severe ulcerated esophagitis (temporary counter-indication before anti-secretor treatment); patients presenting portal hypertension due to cirrhosis or another cause (potential for esophageal varices); patients with severe coagulation disorders, or taking anticoagulant treatment rendering a biopsy dangerous.

Patients gave informed consent prior to entering the study. A physical examination was not performed for the sole purpose of the present study since all patients had an indication for screening for IM, dysplasia or adenocarcinoma.

Definitions

Any endoscopic suspicion of BE was considered, whatever the height or circumference. The height was measured from the anatomical esophago-gastric junction defined as the most proximal part of the gastric folds and extending to the transitional squamous-glandular mucosa. Short BE was defined as < 3 cm, and long BE as ≥ 3 cm.

The chromoendoscopic aspect of the mucosal crypts after application of acetic acid was defined according to the classification described by Guelrud et al. [22]: pattern I = pits with a regular and orderly arranged circular dots; pattern II = reticular pits that are circular or oval and are regular in shape and arrangement; pattern III = fine villiform appearance with regular shape and arrangement; pattern IV = thick villous convoluted shape with a cerebriform appearance with regular shape and arrangement (figure 1).

Endoscopic protocol

The equipment was composed of an Olympus endoscope (GIF Q160Z, light source EVIS EXERA (CLV-160)) with architectural enhancement (video processor EVIS EXERA, CV-160) and a 115x zoom. A transparent hood placed on the tip of the endoscope enabled an ideal zoom/mucosa distance for optimal focusing. The endoscope was equipped with a coather spray (Olympus PW203L) and pediatric biopsy forceps (Boston Scientific, Radial Jaw Gastro-pediatric). Alcoholic acetic acid was 6% commercial vinegar.

Fig. 1 – The Guelrud classification (x 115, 6% alcohol acetic acid) using the Guelrud classification.

Type I: cryptes arrondies de disposition régulière.
Type II: cryptes circulaires ou ovalaires régulières et d’aspect réticulé.
Type III: reliefs muqueux villoïdes fins et réguliers.
Type IV: reliefs muqueux villoïdes épais et réguliers donnant un aspect cérébriforme.
High-resolution esophage-gastro-duodenal endoscopy was the standard first-intention procedure to search for spontaneously visible zones of abnormal mucosa which were biopsied. Then, 10 to 15 mL of alcoholic acetic acid was flushed from the upper to the lower portion of the lower esophageal without previous washing. The suspected zone of BE was then rapidly scanned using the architectural enhancement option and magnification. The chromoendoscopic aspect of several mucosal zones after application of acetic acid was noted using the Guerud classification [22]. These zones chosen at random within the BE were biopsied.

Biopsies were performed starting from the lowest portion of the esophagus and moving upward so that bleeding induced by sampling would not interfere with the exploration of the remaining mucosa. A video of the mucosal scan and photographs of the biopsy zones were recorded. Each biopsy was labeled with a number and conditioned separately.

Since this protocol was designed to study the diagnostic performance of a specific technique, the same operator performed all of the endoscopic procedures in order to limit operator-dependent variability.

**Mechanism of action of acetic acid**

Since it is a contrast dye, acetic acid does not actually stain the mucosa. It does however have a transient denaturing effect on the protein structures of the esophageal epithelium and the mucus that covers it. This removes the mucus and whitens the mucosa [23], a reversible transitory phenomenon that disappears when the acetic acid is neutralized spontaneously after a few minutes [24]. In the 30 seconds that follow application of acetic acid, a generalized mucosal whitening can be seen, encompassing the normal squamous epithelium of the esophagus, the BE, and the gastric mucosa together. Thereafter, the BE and gastric mucosa redden while the esophageal squamous epithelium regains its normal coloring. The mucosa does not require any specific preparation before application of acetic acid.

**Pathological examination**

After fixing in 10% buffered formalin, biopsy specimens were included in paraffin blocks before cutting into 5μm sections with a microtome. Standard hematoxilin-phloxin-saffran staining was followed by a second stain associating Periodic Acid-Schiff and blue alcian to highlight any IM. The use of acetic acid did not modify the microscopic aspect or the behavior of stains useful for histological characterization.

Microscopic examination allowed the histological classification as intestinal metaplasia, cardial or junctional metaplasia, gastric or fundic metaplasia, low grade dysplasia, high grade dysplasia and adenocarcinoma. Pathologists were informed of the endoscopic aspect. When a first pathologist retained a diagnosis of high-grade dysplasia, confirmation was requested from a second pathologist.

**Statistical analysis**

Results were analyzed with SPSS (Statistical Package for the Social Sciences) for Windows; version 11.1 software packages (SPSS Inc., Chicago, Illinois, USA) to search for a correlation between the endoscopic and histological findings. The sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy for the detection of IM in BE with magnifying chromoendoscopy were determined.

**Results**

**Patients**

Our study population was composed of 28 patients, 26 men and 2 women, average age 59.7 years (range: 29.2 - 88.4 years). Twenty-seven patients presented BE with know histologically-confirmed IM. Twenty-six were on long-term treatment with proton pump inhibitors (PPI). Thirteen patients had previous endoscopic treatment of their BE: argon plasma electrocoagulation associated with high dose PPI in case of dysplasia (four patients with low-grade dysplasia and four patients with high-grade dysplasia), mucosectomy for in situ carcinoma for four patients, and dynamic photocoagulation for in situ carcinoma for one patient after two procedures for subtotal mucosectomy.

Twelve patients had long BE (between 3 and 9 cm) and 16 patients short BE (between 0.5 and 2 cm); among these, the height was less than 1 cm in 13. The average height of the examined BE was therefore 2.9 cm (0.5 cm to 9 cm).

Before acetic acid application, three patients presented with mucosal abnormalities. The first one presented two node-like supra-cardial lesions: histology reported IM with low-grade dysplasia for one nodule and simple IM for the other. The second patient also had a nodular lesion of cardial corresponding to IM with high-grade dysplasia. The third one presented with moderate erosive peptic lesions despite long-term PPI treatment. Altogether, 75 biopsies were performed, with an average of 2.7 biopsies per patient. Three of the biopsies did not allow a satisfactory histological analysis.

**Detection of intestinal metaplasia (table I)**

Of the 72 studied biopsies, the chromoendoscopic aspect was noted pattern III or IV in 58, and pattern I or II in 14. Also, among these 72 biopsies, 44 exhibited IM (61.1%), of which 42 (95.5%) were suspected from the chromoendoscopic aspect to have a III or IV pattern.

The correlation between the endoscopic aspect and the histological diagnosis of intestinal metaplasia was 12.5% for pattern I (1/8), 16.7% for pattern II (1/6), 43% for pattern III (3/7), 76.5% for pattern IV (39/51) and 72.4% for the association of patterns III and IV (42/58). Sensitivity was 95.1% for pattern IV and 95.5% for the association of patterns III and IV. Specificity was 50% for pattern IV and of 42.9% for the association of patterns III and IV. The positive predictive value was 76.5% for pattern IV and 72.4% for the association of patterns III and IV. The negative predictive value was 85.7% for pattern IV as well as for the association of patterns III and IV.

The diagnostic accuracy or global value was 78.5% for pattern IV and 75% for the association of patterns III and IV.

**Detection of high-grade dysplasia**

Among the 72 studied biopsies, low-grade dysplasia was detected in seven biopsies and high grade dysplasia in six (18.1% of dysplasias); three of the six high-grade dysplasias (50%) were suspected endoscopically as pattern IV zones presenting two characteristics: localized pitting with loss of the uniform convoluted pattern and disruption of the mucosal folds and hypervascularization suggestive of neoangiogenesis (figure 2).

The positive predictive value of high-grade dysplasia for these endoscopic patterns was 75% (three high-grade dysplasia on four biopsies, the fourth corresponding histologically to low-grade dysplasia).

**Study conditions and secondary effects**

Twenty-one patients underwent examination using oro-pharyngeal local anesthesia, four were sedated with midazolam, and three were given general anesthesia. For these last seven patients, the indication for anesthesia was poor tolerance during a previous procedure using the Seattle protocol. No incident was noted during the endoscopy or during the post procedure period. The average length of the procedure was 7.5 minutes.

**Discussion**

Devising a method allowing reliable targeted surveillance solely on zones of IM in Barrett's mucosa could improve the yield
of dysplasia and adenocarcinoma screening and thus enable earlier diagnosis and improved outcome. The current literature lacks controlled studies to validate chromoendoscopy as a routine method, although staining with Lugol solution [25-29], indigo carmin [30, 31], toluidine blue [32-34], cresyl purple [35] and especially methylene blue [36-50] has been used in combination with high-resolution and/or magnifying endoscopy for detection of IM.

Nine studies on magnifying chromoendoscopy for the detection of IM reported in the literature have described the predictive gross aspects of IM, and sometimes of dysplasia. Of these studies, six have concerned BE patients [22, 30, 31, 51-52, 54] while the three others were devoted to patients with involvement of the esophago-gastric junction without proven BE [53, 55-56]. Classification systems for the detection of IM on BE by magnifying chromoendoscopy have been presented in three studies, including the acetic acid system established by Guelrud and used here as a reference [22]. The two other methods use methylene blue with 80 x magnification [51] and indigo carmin with 115 x magnifications [31].

We chose the acetic acid method because it offers a double advantage in comparison with the methylene blue method. First, there is no need for preparation -washing with an application of the N-acetyl cysteine followed by abundant rinsing- and requires less time and involving less risk of inhalation. The second advantage is the simpler classification system with only 4 patterns. Moreover, a recent study suggests methylene blue could have a harmful carcinogenetic effect provoking cellular DNA lesions within the zone of IM [57]. On the other hand, unlike absorbed dyes, acetic acid does not induce any coloring effect indicative of IM, implying the need for a complete magnifying examination to search for BE.

Guelrud et al. [52] first used diluted acetic acid (1.5%) without endoscopy amplification to display possible residual islets of glandular metaplasia in patients previously treated by multipolar electrocoagulation for eradication of BE. Acetic acid allowed the visualization of residual islets in 52% of patients in whom high-resolution standard monitoring endoscopy did not disclose further areas of glandular metaplasia. There was however no specific chromoendoscopy aspect evocative of IM. Then in 2001, the same authors [22] used magnifying endoscopy (×35) coupled with acetic acid diluted to 1.5% for the detection of IM within BE in 129 biopsies from 48 patients with short BE (≤ 3 cm). They established a classification of 4 patterns and found good agreement between the magnifying chromoendoscopy pattern and the histological findings: 87% (40/46) for pattern III, 100% (17/17) for pattern IV, and 90.5% (57/63) for the association of patterns III and IV. Sensitivity, specificity, the positive predictive value and negative predictive value of the association of patterns III and IV were respectively: 96.6%, 88.7%, 87.5% and 96.9%. Diagnostic accuracy rose to 92.2%.

Shrestha et al. [54] studied nine patients with a long BE using magnifying endoscopy (×70) associated with 1% acetic acid, applying the Guelrud classification. For their 28 biopsies, the magnifying chromoendoscopy-histology agreements were 67% (6/9) for pattern III, 100% (3/3) for pattern IV, and 75% (9/12) for the association of patterns III and IV. When combining patterns III and IV they obtained a sensitivity of 100%, a specificity of 50%, a positive predictive value of 87%, a negative predictive value of 100% and a diagnostic accuracy of 63% (17/27).

Our study is therefore the third to evaluate the usefulness of magnifying chromoendoscopy with acetic acid for the detection of IM in BE. Our study included very short (N = 13), short (N = 3) and long (N = 12) BE in order to evaluate the technical reliability in ordinary conditions of clinical practice. Shrestha et al. [54] only examined long BE and Guelrud et al. [22] only short BE. In order to optimize the technique, we used the highest magnification (×115) and pediatric forceps for the biopsies in order to diminish the effect of sampling errors on the endoscopy-histology correlation. In fact, using standard forceps, biopsies would have been much larger than the field examined with the high-magnification optical zoom.

The results of the three studies using acetic acid are compared in table I. It can be noted that the endoscopy-histology agreement in our study is closer to that reported by Shrestha et al. [54] compared to the series by Guelrud et al. [22] with a diagnostic accuracy in between these two studies. Sensitivities are similar. On the other hand, specificity is inferior to the one found by Guelrud (42.9% vs. 88.7%), very probably because of the small number of pattern I and II biopsies in our study (14/80 = 18% vs. 66/129 = 51.2%). Also, pattern III was found in only 8 biopsies, insufficient to establish with certainty the correlation with IM.

Certain authors have attempted to validate the use of magnifying chromoendoscopy with acetic acid staining for the detection of IM in ultra short BE or to screen for IM at the esophagogastric junction [53, 55, 56]. In clinical practice, it is well known that very short BE can be confused with an irregular Z line or a

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Table I. – Studies of magnifying chromoendoscopy with acetic acid in diagnosis of intestinal metaplasia according to Guelrud’s classification

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients (N) and types of BE</th>
<th>Zoom</th>
<th>Biopsies (N)</th>
<th>Endoscopy-histology agreement for patterns III+IV</th>
<th>Sensitivity III+IV</th>
<th>Specificity III+IV</th>
<th>Diagnostic accuracy III+IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guelrud et al. [22]</td>
<td>48 short BE</td>
<td>x 35</td>
<td>129</td>
<td>90.5% (57/63)</td>
<td>96.5%</td>
<td>88.7%</td>
<td>92.2% (119/129)</td>
</tr>
<tr>
<td>Shrestha et al. [54]</td>
<td>9 long BEs</td>
<td>x 70</td>
<td>28</td>
<td>75% (9/12)</td>
<td>100%</td>
<td>50%</td>
<td>63% (17/27)</td>
</tr>
<tr>
<td>This series</td>
<td>28 (12 long and 16 short BE)</td>
<td>x 115</td>
<td>72</td>
<td>72.4% (42/58)</td>
<td>95.5%</td>
<td>42.9%</td>
<td>75% (54/72)</td>
</tr>
</tbody>
</table>

(N) = number of biopsies.

BE: Barrett’s esophagus.
Magnifying chromoendoscopy in Barrett’s esophagus

hiatus hernia. This diagnostic difficulty was addressed in our study with the 13 patients with BE measuring less than 1 cm. Magnifying chromoendoscopy with acetic acid was found to be quite reliable in these difficult cases.

Regarding screening for dysplasia, among the three studies using acidic acid, ours alone describes a chromoendoscopy aspect at high magnification indicative of high-grade dysplasia (however found in only three of the six concerned zones). On the other hand, none of the seven zones of low grade dysplasia presented an indicative chromoendoscopic aspect at high magnification.

Three other studies of magnifying chromoendoscopy, two using acetic acid, have described a specific aspect of the dysplasia on BE. Rey et al. [58] used 1% acetic acid in 37 patients with short and long BE and described a characteristic hypervascular pattern with depression of the mucosa suggestive of dysplasia. Similarly, Weerth et al. [59] obtained 96 biopsies from eight patients with BE, and found that magnified endoscopy coupled with the acetic acid was superior to the Seattle protocol with 1% methylene blue since four biopsies with suspected dysplasia and identified by magnifying chromoendoscopy were confirmed while the Seattle protocol failed to identify the suspected zone of dysplasia.

Finally, using magnifying chromoendoscopy with indigo carmine, Sharma et al. [31] described a characteristic aspect yielding 100% agreement with histology on their six biopsies containing high-grade dysplasia.

In our study, the diagnostic endoscopy-histology agreement for high-grade dysplasia was only 50% (3/6). The degree of magnification could affect the description of an aspect suggestive of dysplasia. In fact, the characteristic pattern reported here has also been described by others using the same magnification (x115) but with different dyes. Guelrud used the same dye, acetic acid, but a weaker magnification (x35) and did not find any endoscopic pattern characteristic of high-grade dysplasia comparable to ours. The importance of the degree of magnification would be further supported by the fact that a year after their first classification, Guelrud et al. used an intermediary magnification (x80) to establish a new classification with 7 patterns but without describing any endoscopic aspect suggestive of dysplasia [60].

This suggests that detection of IM, and especially dysplasia, does not depend basically on the type of dye used but can best be optimized by an appropriate combination of the dye and the zoom. The results of our study nevertheless must be interpreted with caution, taking certain weak points into account. First, the presence of IM was already known in 27 of the 28 patients. Nevertheless, BE was considered like a mosaic of the three types of glandular metaplasia and the areas randomly studied; the analyses could also have been interpreted as cardial or junctional metaplasia. Besides, in practice the goal is to monitor only the IM areas at risk of degeneration. Based on these two arguments, we considered therefore that the bias of knowing the presence of IM did not compromise the validity of our results.

Also, the study was not conducted in a blinded manner since the operator was aware of the presence of IM, and the pathologists were informed of the suspicion of IM.

In addition, 16 of the 28 patients had short BE (< 20 mm) with known IM, of which 13 were ultra short BE (< 10 mm). Within our population, eight patients had previously benefited from an endoscopic treatment of their BE with IM and therefore presented with BE with IM of which the size had diminished. This could have positively influenced our results in terms of detection.

Fig. 2 – Architectural disorganization and hypervascularisation of the mucosa suggesting high-grade dysplasia.

Désorganisation architecturale et hypervascularisation de la muqueuse évoquant une dysplasie de haut grade.
of IM. Likewise, this was a non-randomized study, since there was no control group using the standard Seattle protocol. Finally, all procedures were performed by the same operator, not allowing evaluation of inter-observer reproducibility; but this was voluntary since we were seeking to determine the validity of this technique and wished therefore to avoid bias due to insufficient operator experience.

In this respect, using magnifying chromoendoscopy with 1.5% acetic acid or methylene blue, Meining et al. showed in a population of 51 patients without BE or known IM, an elevated inter-observer variability for endoscopic diagnosis of IM and also a lack of diagnostic benefit in terms of sensitivity, specificity, and diagnostic accuracy for the detection of IM at the time of the utilization of the two dyes in comparison with the habitual endoscopic technique [61]. Concerning the conditions for conducting the procedure, only the patients under general anesthesia were intubated and ventilated. Intubation was not needed for patients sedated with midazolam because a very small quantity of liquid was used (10 to 15 mL) and quickly aspirated in the stomach after application. This allowed enough time to achieve the acetic acid contrast and coloration without lengthening the time of the examination.

To summarize, magnifying chromoendoscopy coupled with acetic acid is a very sensitive though not very specific method with an interesting positive predictive value for the detection of IM in BE, notably in case of suspected short BE. Our study does not reproduce the results of the reference study of Guelrud et al. but describes rather a magnifying chromoendoscopic pattern indicative of high-grade dysplasia. Further large-scale randomized blinded studies will be necessary to obtain confirmation and to assess inter-observer reproducibility.

Among the three dyes used to date in magnifying chromoendoscopy, acetic acid has provided promising results for the definition of a chromoendoscopic pattern well correlated with the histological type of glandular metaplasia on Barrett’s esophagus. Our results do not provide conclusive evidence of the superiority of this technique in comparison with the widely used and currently recommended Seattle protocol; magnifying chromoendoscopy coupled with acetic acid should be considered as a useful complement.

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