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ORIGINAL ARTICLE

Interobserver reproducibility in pathologist interpretation of columnar-lined esophagus

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Abstract Confirmation of endoscopically suspected esophageal metaplasia (ESEM) requires histology, but confusion in the histological definition of columnar-lined esophagus (CLE) is a longstanding problem. The aim of this study is to evaluate interpathologist variability in the interpretation of CLE. Thirty pathologists were invited to review three ten-case sets of CLE biopsies. In the first set, the cases were provided with descriptive endoscopy only; in the second and the third sets, ESEM extent using Prague criteria was provided. Moreover, participants were required to refer to a diagnostic chart for evaluation of the third set. Agreement was statistically assessed using Randolph's free-marginal multirater kappa. While substantial agreement in recognizing columnar epithelium (K=0.76) was recorded, the overall concordance in clinico-pathological diagnosis was low (K=0.38). The overall concordance rate improved from the first (K=0.27) to the second (K=0.40) and third step (K=0.46). Agreement was substantial when diagnosing Barrett's esophagus (BE) with intestinal metaplasia or inlet patch (K=0.65 and K=0.89), respectively, in the third step, while major problems in interpretation of CLE were observed when only cardia/cardia-oxyntic atrophic-type epithelium was present (K=0.05–0.29). In conclusion, precise endoscopic description and the use of a diagnostic chart increased consistency in CLE interpretation of esophageal biopsies. Agreement was substantial for some diagnostic categories (BE with intestinal metaplasia and inlet patch) with a well-defined clinical profile. Interpretation of cases with cardia/cardia-oxyntic atrophic-type epithelium, with or without ESEM, was least consistent, which reflects lack of clarity of definition and results in variable management of this entity.

Keywords Columnar-lined esophagus · Barrett's esophagus · Interobserver variation · Histological diagnosis

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Introduction

Interest in Barrett's esophagus (BE) diagnosis, surveillance, and treatment has steadily increased in the last decade in relation to the increased incidence of esophageal and gastroesophageal junction adenocarcinoma. BE is a recognized risk factor for intraepithelial and invasive neoplasia, with a cancer incidence rate between 0.14 and 0.5 % [1, 2]. For these reasons, periodic endoscopic surveillance with four-quadrant biopsies every 1–2 cm is recommended in patients with previously diagnosed BE [3, 4]. A correct diagnosis of BE is therefore mandatory in order to plan cost-effective follow-up. Unfortunately, however, overdiagnosis of BE is a common event and implies increased health care and insurance costs as well as inappropriate cancer risk perception by patients [5]. The current diagnostic interpretation of columnar-lined esophagus (CLE) is based on the following algorithm: endoscopy + histology = diagnosis [6, 7]. Three main issues generate problems for pathologists in CLE interpretation: (1) definition of BE, (2) biopsy sampling, and (3) endoscopic description.

1. Definition of BE. The definition of BE has changed over time and in relation to geography (US/mainland Europe vs UK/Asia) [1, 8–15]. The principal reason for disagreement has been whether intestinal metaplasia should be an essential requirement for a diagnosis of BE. The American Association of Gastroenterologists defined BE as the condition in which "any extent of metaplastic columnar epithelium, that predisposes to cancer development, replaces the stratified squamous mucosa that normally lines the distal esophagus." As yet, intestinal metaplasia (IM) is "the only type of esophageal columnar epithelium that clearly predisposes to malignancy," thus implying that IM is a requisite for BE diagnosis [1]. Conversely, the British Society of Gastroenterologists guidelines [8] state that BE is any metaplastic change of the esophagus irrespective of the presence of IM. This is based on the possibility of sampling error and the inability to demonstrate goblet cells when biopsies are few and endoscopic CLE is long. A recent American study [16] evaluated the possible effects of adopting the British criteria for BE diagnosis and clinical outcomes depending on the presence or absence of IM. The authors concluded that BE diagnoses would increase by 147 % if IM were no longer a requisite (impacting greatly on health care costs). Furthermore, only 12 % of patients who did not have IM at initial endoscopy were found to have IM in subsequent biopsies, and these also had a much larger average endoscopic extent of CLE.
2. Biopsy sampling. The number of biopsies required in case of endoscopic CLE depends on its length, and multiple biopsies on the four quadrants are suggested, even though recommended protocols are impractical in routine and often not implemented [17–21].
3. Endoscopic description. Endoscopy is crucial and it requires widespread use of standardized criteria for the following: (1) recognition of well-defined landmarks, (2) identification of endoscopically suspected esophageal metaplasia (ESEM) which describes endoscopic findings consistent with BE that await histological evaluation according to the Montreal Consensus and its validation [7, 22], and (3) reproducible description of ESEM extent [23–29]. High reliability coefficient values have been demonstrated using validated Prague C&M criteria [23]. Even so, the reliability of recognition of ESEM extension less than 1 cm is weak, which complicates the distinction between so-called "ultra-short Barrett" and IM of the cardia [23, 27].

Different trials have been conducted to test agreement among endoscopists in evaluating endoscopic landmarks and BE extension. However, only few reports address agreement between pathologists and these are mostly limited to IM recognition in BE diagnosis [30, 31] or dysplasia in BE [32–34]. The present study is aimed at evaluating agreement among pathologists in the diagnostic interpretation of columnar epithelium in routine esophageal biopsies performed above the gastroesophageal junction (GEJ), in relation to the availability of endoscopic description and the use of a shared diagnostic chart.

Materials and methods

Study design

Thirty pathologists, recruited nationwide and working in community and teaching hospitals in Italy, were invited to participate in a working group (Assessment of Barrett and its Reproducibility with Aim on Management working group (ABRAM) in June 2012. Ten were pathologists with specific expertise in gastrointestinal (GI) pathology. They had a median working experience of 27 years (range 10–

Table 1 Diagnostic flowchart sent to participants for step 3 evaluation

Histology	Endoscopy	Diagnosis
Intestinal-type epithelium	Normal or Irregular Z-line	Suggestive of intestinal metaplasia of the cardia
	ESEM length >1 cm	Diagnostic for Barrett's esophagus with intestinal metaplasia
Cardia/cardia-oxyntic-type epithelium	Normal or irregular Z-line	Suggestive of site-appropriate gastric mucosa
	ESEM length >1–3 cm	Descriptive diagnosis of epithelium type with no conclusion
	ESEM length >3 cm	Possible Barrett's esophagus without intestinal metaplasia which requires confirmation[a]
Non-atrophic oxyntic-type epithelium	In distal esophagus	Suggestive of hiatus hernia
	In proximal esophagus	Diagnostic for ectopia (inlet patch)

Modified from Fiocca et al. [33]

ESEM endoscopically suspected esophageal metaplasia

[a] The term possible BE without IM is suggested because ESEM length is considerable (>3 cm) and subsequent bioptic sampling may show the presence of IM, not previously identified due to sampling error

34), worked in a subspecialty model organization subdivided in fields of interest allowing them to coordinate and/or participate in GI pathology, and had published a median number of 55 papers in GI pathology. Ten were general pathologists with no specific interest or expertise in GI pathology and working in an organization model with pathologists seeing all types of histological specimens. They had a median working experience of 15.5 years (range 4–24). Finally, ten trainees, between the second and fifth year of anatomic pathology training, participated.

Participants were required to complete a three-step slide revision study, each step comprising ten cases. For each case, participants were asked to note which type of

Table 2 Diagnostic interpretation and agreement of CLE based on endoscopic description and epithelium recognition

	CASE	Endoscopic description	Histology of columnar epithelium[a]	Agreement (%)		Diagnosis[b]	Agreement (%)	
Step 1	1	Irregular Z-line with tongue	Intestinal type	100 % (30/30)	K=0.7074	BE with IM	83 % (25/30)	K=0.2693
	2	Small tongues extending from GEJ	Intestinal type	80 % (24/30)		BE with IM	33 % (10/30)	
	3	Irregular mucosal transition	Cardial type	90 % (27/30)		Site-appropriate GM	33 % (10/30)	
	4	Columnar mucosa between GEJ and Z-line	Intestinal type	97 % (29/30)		BE with IM	73 % (22/30)	
	5	Tongue of columnar epithelium	Intestinal type	83 % (24/29)		IM of the cardia	41 % (12/30)	
	6	Tongue of gastric type mucosa	Oxyntic type	97 % (29/30)		Site-appropriate GM	33 % (10/30)	
	7	Tongue of columnar epithelium	Intestinal type	93 % (28/30)		BE with IM	90 % (27/30)	
	8	Columnar epithelium in proximal esophagus	Oxyntic type	93 % (28/30)		Inlet patch	83 % (25/30)	
	9	Circumferential columnar mucosa	Cardial type	93 % (28/30)		Possible BE without IM	53 % (16/30)	
	10	Proximal extension of gastric columnar mucosa	Oxyntic type	53 % (16/30)		Site-appropriate GM	37 % (11/30)	
Step 2	11	ESEM C4M7	Intestinal type	100 % (30/30)	K=0.7918	BE with IM	97 % (29/30)	K=0.399
	12	ESEM C3M5	Cardial type	90 % (27/30)		Possible BE without IM	40 % (12/30)	
	13	ESEM C1M2	Intestinal type	90 % (27/30)		BE with IM	77 % (23/30)	
	14	ESEM C0M2	Cardial type	90 % (27/30)		Descriptive diagnosis[c]	50 % (15/30)	
	15	Erythematous area in proximal esophagus	Oxyntic type	77 % (23/30)		Inlet patch	80 % (24/30)	
	16	ESEM C2M3	Intestinal type	100 % (29/29)		BE with IM	93 % (27/29)	
	17	Irregular Z-line	Intestinal type	93 % (28/30)		IM of the cardia	50 % (15/30)	
	18	ESEM C0M2	Intestinal type	97 % (29/30)		BE with IM	80 % (24/30)	
	19	Irregular Z-line	Oxyntic type	83 % (25/30)		Hiatus Hernia	57 % (17/30)	
	20	Irregular Z-line	Cardial type	100 % (30/30)		Site-appropriate GM	67 % (20/30)	
Step 3	21	ESEM C4M6	Intestinal type	93 % (28/30)	K=0.7783	BE with IM	97 % (29/30)	K=0.4632
	22	Salmon pink area in proximal esophagus	Oxyntic type	90 % (27/30)		Inlet patch	90 % (27/30)	
	23	Irregular Z-line	Intestinal type	97 % (29/30)		IM of the cardia	80 % (24/30)	
	24	ESEM C4M7	Cardial type	93 % (28/30)		Possible BE without IM	80 % (24/30)	
	25	ESEM C1M3	Intestinal type	100 % (30/30)		BE with IM	97 % (29/30)	
	26	Irregular Z-line	Oxyntic type	97 % (29/30)		Hiatus Hernia	60 % (18/30)	
	27	ESEM C0M1	Cardial type	70 % (21/30)		Descriptive diagnosis[d]	37 % (11/30)	
	28	ESEM C2M4	Intestinal type	100 % (29/29)		BE with IM	93 % (27/29)	
	29	ESEM C1M2	Cardial type	87 % (26/30)		Descriptive diagnosis[e]	37 % (11/30)	
	30	Irregular Z-line	Intestinal type	97 % (29/30)		IM of the cardia	43 % (13/30)	

CLE columnar-lined esophagus, *GEJ* gastroesophageal junction, *ESEM* endoscopically suspected esophageal metaplasia (Prague C&M criteria), *BE* Barrett's esophagus, *IM* intestinal Metaplasia, *GM* gastric mucosa

[a] When cardia type is mentioned, pure cardia or mixed cardia/oxyntic atrophic-type epithelium is intended

[b] Diagnosis which had the highest consensus among participants

[c] Case 14: descriptive diagnosis (cardia/cardia-oxyntic-type epithelium with no diagnostic conclusion/distinction between site-appropriate cardia epithelium and possible BE without intestinal metaplasia is not achievable) was chosen by 15 participants (15/30–50 %). Less frequent diagnoses were possible BE without IM (8/30) or suggestive of site-appropriate gastric mucosa (4/30)

[d] Case 27: descriptive diagnosis (cardia/cardia-oxyntic-type epithelium with no diagnostic conclusion/distinction between site-appropriate cardia epithelium and possible BE without intestinal metaplasia is not achievable) was chosen by 11 participants (11/30–37 %). Less frequent diagnoses were suggestive of site-appropriate gastric mucosa (8/30) or possible BE without IM (3/30)

[e] Case 27: descriptive diagnosis (cardia/cardia-oxyntic-type epithelium with no diagnostic conclusion/distinction between site-appropriate cardia epithelium and possible BE without intestinal metaplasia is not achievable) was chosen by 11 participants (11/30–37 %). Less frequent diagnoses were suggestive of site-appropriate gastric mucosa (8/30) or possible BE without IM (3/30)

columnar epithelium was present on the slide (intestinal, atrophic cardia/cardia-oxyntic, non-atrophic oxyntic) and to provide a diagnosis. When several types of columnar epithelium were present, they were asked to identify the type of epithelium on which they had based their diagnosis.

Participants were asked to submit their diagnoses, taking into account endoscopic findings. Diagnoses were then grouped into the following categories: (1) BE with IM; (2) possible BE, without IM; (3) site-appropriate gastric mucosa; (4) heterotopic gastric mucosa of the esophagus (inlet patch); (5) non-atrophic oxyntic epithelium suggestive of hiatus hernia; (6) IM of the cardia; (7) intestinal metaplastic epithelium, distinction between origin in the cardia or in BE with IM impossible; (8) cardia-type epithelium, distinction between site-appropriate cardia mucosa or BE without IM impossible; (9) Descriptive diagnosis without diagnostic conclusion; and (10) other, such as obsolete terminology (i.e., BE oxyntic type) or sample inadequate for diagnosis.

Fig. 1 (**a** Case no. 23. Endoscopy: esophago-gastric junction (GEJ) is at 40 cm from superior dental arch (SDA). Squamo-columnar junction (Z-line) is at the same level and has an irregular outline. Type of epithelium: intestinal (29/30; 97 %). Diagnosis: suggestive of intestinal metaplasia of the cardia (24/30; 80 %). **b** Case no. 21. Endoscopy: GEJ is at 41 cm from (SDA). Z-line is at 37 cm with tongues extending to 35 cm (ESEM C4M6 according to Prague classification). Type of epithelium: intestinal (28/30; 93 %). Diagnosis: diagnostic for Barrett's esophagus with intestinal metaplasia (29/30; 97 %). **c** Case no. 20. Endoscopy: GEJ is at 40 cm from SDA, and Z-line is irregular with small tongues extending proximally for a maximum length of 0.5 cm. Type of epithelium: cardia-oxyntic atrophic (30/30; 100 %). Diagnosis: suggestive of site-appropriate gastric mucosa (20/30; 67 %). **d** Case no. 24. Endoscopy: GEJ is at 40 cm from SDA. Z-line is at 36 cm with tongues extending to 33 cm (ESEM C4M7 according to Prague classification). Type of epithelium: cardia-oxyntic atrophic (28/30; 93 %). Diagnosis: possible Barrett's esophagus without intestinal metaplasia (24/30; 80 %). **e** Case no. 26. Endoscopy: gaping cardia is at 41 cm from SDA with associated hiatal hernia. GEJ is at 40 cm from SDA. Z-line is at 40 cm and has an irregular outline. Type of epithelium: oxyntic non-atrophic (29/30; 97 %). Diagnosis: suggestive of hiatus hernia (18/30; 60 %). **f** Case no. 22. Endoscopy: GEJ is at 38 cm from SDA. Z-line is at the same level and has a regular outline. A *salmon pink area* of columnar mucosa (diameter 1.8 cm) can be seen proximally in the esophagus at 22 cm from Z-line. Type of epithelium: oxyntic non-atrophic (27/30; 90 %). Diagnosis: diagnostic of ectopia(inlet patch) (27/30; 90 %) (hematoxylin and eosin, magnification ×20)

Sample selection

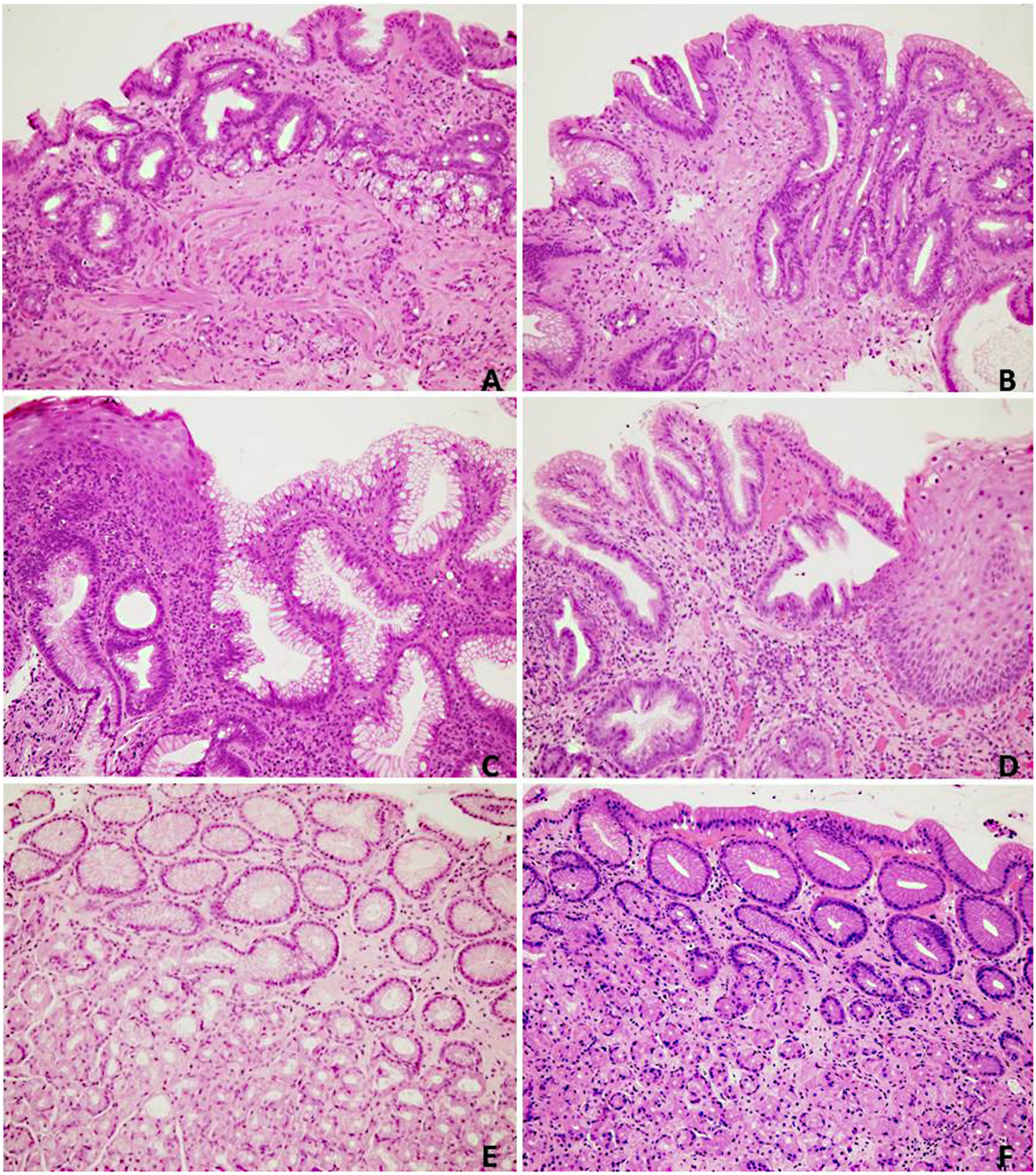
Thirty cases of esophageal biopsies were retrieved from routinely obtained tissue biopsies, archived at the Pathology Unit of IRCCS S. Martino-IST University Hospital in Genoa between July 2010 and June 2012. Selection was limited to biopsies for which the endoscopist indicated sampling above the GEJ, and columnar epithelium had been identified at histology. Moreover, cases were selected to represent all possible types of columnar epithelium. The number of biopsies per case varied between cases (min 1; max 9; median 3 biopsies), which reflects the lack of standardization in the number of biopsy samples taken in daily practice. A description of the endoscopy findings was provided for the first ten cases (step 1 cases 1–10) and consisted of a free-text endoscopy report without any standardization (e.g., no C&M criteria or no measures at all). In the second and third steps of the study (cases 11–20 and 21–30), endoscopy findings were described following Prague C&M criteria [23].

For each case, two slides were available: one stained with hematoxylin and eosin and one with Alcian blue-PAS. Whole slides were digitally scanned at ×40 magnification (Olympus ×40/0.90 UPlanSApo) with the Olympus virtual slide microscope and with Olympus "dotSlide" software at the Department of Medical Sciences, University of Turin; digital slides were saved with .vsi file extension (Olympus proper file format). Subsequently, images were uploaded on Web Image Server and made accessible to all participants with a different username and password at each step. No additional software was needed, and participants visualized digital slides via a web browser (i.e., Explorer, Firefox, Safari, Chrome, etc.).

Instructions and the first step were made available to participants in July 2012, and evaluations were concluded by October 2012. The second step started in November 2012 with conclusion in February 2013. Before the third step, a diagnostic chart (Table 1), based on the Italian Guidelines on Microscopic esophagitis and BE [35], was sent to all participants. Participants were asked to apply this diagnostic chart for evaluation of the third-step biopsies (March–June 2013).

Statistical analysis

Categorical variables were expressed as number and percentage. Agreement was statistically assessed using multirater kappa. The kappa statistic is frequently used to measure the degree of agreement between raters. Originally, Cohen kappa was proposed to measure agreement between two raters when the scale of measurement is nominal. However, its use has since been extended to other issues including multiple raters [36]. The kappa-statistic measure of agreement is scaled to be 0 when the amount of agreement is what would be expected to be observed by chance and 1 when there is perfect agreement. For intermediate values, Landis and Koch [37] suggest the



following interpretations: below 0.0, poor; 0.00–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; and 0.81–1.00, almost perfect. Data analysis was performed with STATA statistical package (release 13.1, 2013, Stata Corporation, College Station, TX, USA).

Results

Main results, including a synthesis of the endoscopy description, the type of columnar epithelium, the diagnosis chosen by the majority of participants, and

Table 3 Concordance in columnar-lined esophagus diagnostic interpretation between categories of pathologists

	GI pathologists	General pathologists	Trainees
Step 1	K=0.2852 (0.248–0.322)	K=0.3242 (0.284–0.364)	K=0.1829 (0.146–0.219)
Step 2	K=0.5099 (0.470–0.550)	K=0.3180 (0.278–0.358)	K=0.3726 (0.332–0.413)
Step 3	K=0.4551 (0.414–0.496)	K=0.4880 (0.447–0.529)	K=0.4253 (0.384–0.467)
Steps 1 + 2 + 3	K=0.4187 (0.397–0.441)	K=0.3806 (0.358–0.403)	K=0.3311 (0.309–0.353)

percentage of agreement, are listed in Table 2. Examples of histological findings in selected cases are shown in Fig. 1.

Agreement in the recognition of epithelium type

The overall concordance (all steps) in recognizing epithelium (intestinal vs cardia/cardia-oxyntic atrophic vs oxyntic non-atrophic type) was comprehensively substantial (K=0.76, 95 % confidence interval (CI) 0.75–0.77; range in different steps between 0.71 and 0.79) with a higher concordance in recognizing intestinal epithelium (K=0.85, 95 %CI 0.83–0.87) than cardia/cardia-oxyntic atrophic and oxyntic non-atrophic-type epithelium (K= 0.68 and =0.74, respectively).

Agreement on diagnostic categories between different steps

The overall diagnostic agreement for the three steps considered together was fair (K=0.38, 95 %CI 0.37–0.39). Concordance was lower for the first set (K=0.27 95 %CI 0.26–0.28) compared to the second (K=0.40 95 %CI 0.39–0.41) and third set (K=0.46 95 %CI 0.45–0.48).

Agreement in diagnosis between pathologists

Agreement was higher among GI pathologists (K=0.42 95 %CI 0.40–0.44) than general pathologists (K=0.38 95 %CI 0.36–0.40) and trainees (0.33 95 %CI 0.31–0.35) (Table 3). An improvement in agreement from step 1 to step 3 was noted for all the groups, and this was more evident for trainees (from K=0.18 in step 1 to K=0.43 in step 3) than for general pathologists and GI pathologists. Similar moderate concordance rates (K between 0.43 and 0.49) were obtained by all three groups in the third step (Table 3).

Agreement for specific diagnosis

Considering the different diagnoses (Table 4), BE with IM had a moderate-substantial agreement rate among participants (overall K=0.60 95 %CI 0.58–0.62) and the highest concordance rate was reached in steps 2 and 3 (K=0.65) after introduction of standardized measurement of ESEM extension. An almost perfect agreement was observed for inlet patch with an overall K value of 0.81 (95 %CI 0.80–0.83). A moderate agreement was reached in step 3 for other two diagnoses:

Table 4 Overall agreement according to diagnostic categories

Diagnosis	All steps K (CI)	Step 1 K (CI)	Step 2 K (CI)	Step 3 K (CI)
BE with intestinal metaplasia	0.5996 (0.582–0.617)	0.4847 (0.455–0.514)	0.6536 (0.624–0.683)	0.6473 (0.618–0.877)
Intestinal metaplasia of the cardia	0.3667 (0.350–0.384)	0.191 (0.161–0.221)	0.2774 (0.248–0.307)	0.5131 (0.483–0.543)
Possible BE without intestinal metaplasia	0.1743 (0.157–0.191)	0.0182 (–0.012–0.048)	0.05 (0.02–0.08)	0.2742 (0.244–0.304)
Site-appropriate gastric mucosa	0.2268 (0.210–0.241)	0.1931 (0.163–0.222)	0.2993 (0.270–0.329)	0.1313 (0.102–0.161)
Inlet patch	0.8144 (0.797–0.832)	0.7764 (0.747–0.806)	0.7751 (0.745–0.805)	0.8863 (0.857–0.916)
Non-atrophic oxyntic epithelium (suggestive of hiatus hernia)	0.3561 (0.339–0.373)	0.0345 (0.005–0.064)	0.4421 (0.412–0.472)	0.4993 (0.470–0.529)

BE Barrett's esophagus, *CI* confidence interval

"intestinal metaplasia of the cardia" and "non-atrophic oxyntic epithelium suggestive for hiatus hernia." On the other hand, two diagnoses (possible BE without IM; site-appropriate gastric mucosa) had a concordance rate of poor/fair (K between 0.05 and 0.29), and both involved the interpretation of cardia/cardia-oxyntic-type mucosa.

Discussion

Numerous international and national guidelines have been developed to improve standardization of BE diagnosis in terms of endoscopic description, number of biopsies, and histologic interpretation, but these are not always adequately followed in daily practice. We studied how the histological diagnosis of BE is made in daily practice and explored which factors may influence interobserver agreement.

In the study by Corley et al. [30], the reported interobserver agreement between two pathologists was 88.3 % with a kappa value of 0.41. The study limited the agreement evaluation to the description of columnar epithelium present in a large cohort of 616 patients, 580 with previously reported IM. The strength of our study is that it includes a large number of assessors, as well as the double aspect of recognizing epithelium and interpreting it to reach a precise diagnosis. The use of routine cases is both a strength, in that it more closely mimics real life, and a limitation, as this means that a low median (3) of biopsies may have influenced histology (too few biopsies to reliably detect IM in cases with suspected ESEM, for example).

The substantial/near-to-perfect agreement in recognizing epithelial type in our study proves that problems are not related to the histologic recognition of lesions; i.e., pathologists recognize the type of columnar-lined epithelium. This is particularly clear if we consider intestinal-type epithelium, which has an extremely high concordance rate (K=0.85). This is consistent with recently reported data on agreement in the recognition of IM in gastric mucosa (K=0.77 in corpus and 0.69 in antrum) [31]. The distinction between cardia/cardia-oxyntic atrophic and oxyntic non-atrophic-type epithelium is slightly less reliable, but still within substantial agreement rate. Disagreement in recognizing epithelium type could be due to the minimal presence of goblet cells, the use of digital slides, or the erroneous interpretation of pseudogloblet cells on the Alcian blue stain.

Histological diagnosis of CLE, however, shows overall poor agreement. This may be explained, at least in part, by the need for an integrated approach with endoscopy. Indeed, pathologists may encounter difficulty in understanding endoscopic reports which are descriptive and do not follow up-to-date criteria [23, 38]. In our experience, for example, up to 30–40 % of endoscopic reports in our institution do not report Prague criteria for ESEM description. The improvement of concordance observed from first to second step may therefore be related to the improvement in endoscopic description with the use of a clearer and shared system of ESEM extension reporting. A learning curve leading to an improvement in concordance between steps is unlikely, as no consensus meeting was organized between pathologists and no feedback was given after each step. This could also represent a limit of the study, as we cannot be sure that all participants applied the diagnostic chart correctly. Indeed, the use of a diagnostic chart among participants was shown to only mildly improve the concordance rate in the third step, without reaching the expected near perfect agreement. While general pathologists (from K=0.31 to K=0.49) and trainees (from K=0.37 to K=0.43) improved with the use of a chart, specialist GI pathologists did not (from K=0.51 to K=0.46). A possible explanation for the latter result is that GI pathologists may be less prone to change their personal views, matured during years of experience. On the other hand, trainees showed the greatest increase in overall concordance between steps, as they are probably more open to novelties and not as set in their ways as their more experienced colleagues. Furthermore, in-depth analysis of the various discrepancies for each case reveals that some participants (in all three groups) were more prone to interpret the lesions in a different way with respect to the majority of participants. This probably reflects individual characteristics (reduced attention, lack of time, etc.) and falls into the variability of human behavior. Finally, the poor understanding of the biological behavior of cardia/cardia-oxyntic atrophic-type BE and the open debate regarding its neoplastic potential may influence pathologists in their diagnoses. In particular, when only cardia/cardia-oxyntic atrophic-type epithelium is present, a simple description of histological findings may be preferred to a diagnosis of BE without IM, thus leaving the precise categorization of the patient and consequent management to the gastroenterologist.

Concluding remarks

Despite the aforementioned problems, overall recognition of the most clinically relevant category—i.e., BE with IM—shows substantial agreement among all categories of pathologists. Lower concordance was observed in cases of CLE with cardia/cardia-oxyntic atrophic-type epithelium, both associated and not associated with ESEM, and such variability

possibly reflects the changing definition of BE in time and between different countries.

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Compliance with ethical standards

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Conflict of interest The authors have no conflicts of interest to declare.

Appendix

*A*ssessment of *B*arrett and its *R*eproducibility with *A*im on *M*anagement (*ABRAM*) Study Group participants:

Alò PL (Pathology Unit, Fabrizio Spaziani Hospital, Frosinone); Al Omoush TMM (Pathology Unit, Riuniti University Hospitals, Trieste); Asioli S (Pathology Unit, G.B. Morgagni-L. Pierantoni Hospital, Forlì); Buffelli F (Pathology, Diagnostic, Bioimaging and Public Health Department, Pathology Unit, University of Bari and Policlinico Consorziale University Hospital, Bari); Conforti F (Pathology Unit, University of Magna Graecia and Mater Domini Hospital, Catanzaro); Cornaggia M (Diagnostic and Therapeutic Department, Pathology Unit, San Carlo Clinic, Paderno Dugnano, Milan, Italy); Cossu S (Pathology Unit, San Francesco Hospital, Nuoro); D'Armiento FP (Morphologic and Functional Diagnostic, Radiotherapy and Forensic Medicine Department, Pathology Unit, Federico II University Hospital, Napoli); De Marco L (Pathology Unit, S. Maria Nuova Arcispedale, Reggio Emilia), Fiocca R (Department of Surgical and Diagnostic Sciences, Pathology Unit, IRCCS S. Martino-IST University Hospital, Genoa); Foscolo AM (Pathology Unit, Castelli Hospital, Verbania); Fraternali Orcioni G (Pathology Unit, IRCCS S. Martino-IST University Hospital, Genoa), Ingravallo G (Pathology, Diagnostic, Bioimaging and Public Health Department, Pathology Unit, Policlinico Consorziale University Hospital, Bari), Locatelli F (Biomedic and Neuromotor Sciences Department, Pathology Unit, University of Bologna and M. Malpighi Bellaria Hospital, Bologna); Luinetti O (Diagnostic Medicine and Medicine of Services Department, Pathology Unit, IRCCS San Matteo, Pavia), Marchio C (Laboratory Medicine Department, Pathology Unit, Le Molinette University Hospital, Torino), Montinari E (Diagnostic and Sperimental Medicine Department, Pathology Unit, Arcispedale Sant'Anna University Hospital, Ferrara); Melchiorri L (Clinical Medicine, Public Health, Life and Environment Sciences Department University of l'Aquila and "San Salvatore" Hospital, l'Aquila); Messerini L (Pathology Unit, Careggi University Hospital, Firenze); Migliora P (Pathology Unit, S. Andrea Hospital, Vercelli); Pizzi M (Pathology Unit, University of Padova and Padova University Hospital, Padova), Rugge M (Pathology Unit, University of Padova and Padova University Hospital, Padova), Saragoni L (Pathology Unit, AUSL Forlì, Forlì,); Tamponi E (Pathologic Anatomy and Histopathology Department, University of Cagliari and San Giovanni di Dio University Hospital, Cagliari); Tomezzoli A (Pathology and Diagnostic Department, Pathology Unit, Verona University Hospital, Verona); Trisolini MP (Pathology Unit, Vito Fazzi University Hospital, Lecce); Trombatore M (Laboratory Diagnostic Department, Pathology Unit, Paolo Giaccone University Hospital, Palermo); Vanoli A (Diagnostic Medicine and Medicine of Services Department, Pathology Unit, IRCCS San Matteo, Pavia); Vellone VG (Laboratory and Services Department, Pathology Unit, Giovanni Paolo II Foundation of Research and Cure, Campobasso); and Villanacci V (Pathology Unit, Spedali Civili, Brescia).

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