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# Gastrointestinal pathologists' perspective on managing risk in the distal esophagus: convergence on a pragmatic approach

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**Here, we discuss recent updates and a continuing controversy in the diagnosis and management of Barrett's esophagus, specifically the recommendation that the irregular Z-line not be biopsied, the diminished status of ultrashort-segment Barrett's esophagus, the evidence basis for excluding and including the requirement of goblet cells for the diagnosis of Barrett's esophagus, and the conclusion that histologically confirmed low-grade dysplasia is best managed with endoscopic ablation rather than surveillance. We reference the American Gastroenterological Association and College of Gastroenterology and the British Society of Gastroenterology guidelines throughout, with the thesis that the field is converging on the concept of applying scarce medical resources to the diagnosis, surveillance, and therapy of patients most likely to derive benefit.**

**Keywords:** Barrett's esophagus; columnar-lined esophagus; intestinal metaplasia; goblet cells; ultrashort segment; irregular Z-line; carditis

## Introduction

As is typically the case when studying a new disease, research efforts in Barrett's esophagus were initially focused on the most obvious and severe cases (i.e., long-segment Barrett's esophagus). The pendulum inevitably swung toward the study of subtler cases (i.e., short and ultrashort-segment Barrett's esophagus). As our body of knowledge has matured, efforts are now being directed toward the investment of scarce medical resources toward the surveillance and treatment of patients most likely to derive benefit. This natural history of the discipline is captured in the form of gastroenterology society guidelines (Table 1).[1–4]

Here, we focus on newer developments and a continued area of controversy in the diagnosis and management of Barrett's esophagus, namely, the strong discouragement of the practice of biopsying an "irregular Z-line," the diminished status of ultrashort-segment Barrett's esophagus, the necessity (or lack thereof) of goblet cells for the diagnosis of Barrett's esophagus, and the embrace of endoscopic eradication therapy as the management of choice in histologically confirmed low-grade dysplasia. This is facilitated by additional review of the definition and localization of the anatomic gastroesophageal junction (GEJ), the distinction of Barrett's esophagus from carditis with intestinal metaplasia (CIM), and the risk of neoplastic progression in various categories of Barrett's esophagus. We do not specifically discuss areas of longer standing and broad agreement (Table 2).

## Definition and localization of the gastroesophageal junction

The GEJ has been variously defined anatomically, manometrically, endoscopically, and histologically. Barrett's esophagus is characterized by proximal

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**Table 1. Comparison of gastroenterology society guidelines**

| | American Gastroenterological Association (2011) | British Society of Gastroenterology (2014, 2017) | American College of Gastroenterology (2016) |
|---|---|---|---|
| **Definition of Barrett's esophagus** | "The condition in which **any extent** of metaplastic columnar epithelium that predisposes to cancer development replaces the stratified squamous epithelium that normally lines the distal esophagus. Presently, **intestinal metaplasia** is required for the diagnosis of Barrett's esophagus because intestinal metaplasia is the only type of esophageal columnar epithelium that clearly predisposes to malignancy." | "Barrett's esophagus is defined as an esophagus in which any portion of the normal distal squamous epithelial lining has been replaced by metaplastic columnar epithelium, which is **clearly visible endoscopically (≥1 cm) above the GOJ** and confirmed histopathologically from oesophageal biopsies." | "BE should be diagnosed when there is extension of salmon-colored mucosa into the tubular esophagus **extending ≥1 cm proximal to the gastroesophageal junction (GEJ)** with **biopsy confirmation of IM**." |
| **Biopsying an irregular Z-line** | No specific mention of "irregular Z-line." | "Biopsies are generally not recommended if there is an irregular Z-line."<br><br>"If biopsy specimens are taken . . . they should be labelled as GOJ and not oesophageal." | "Endoscopic biopsy should not be performed in the presence of a normal Z line or a Z line with <1 cm of variability." |
| **Screening** | "In patients with multiple risk factors associated with esophageal adenocarcinoma (age 50 years or older, male sex, White race, chronic GERD, hiatal hernia, elevated body mass index, and intra-abdominal distribution of fat), we suggest screening for Barrett's esophagus." | "Endoscopic screening can be considered in patients with chronic GORD symptoms and multiple risk factors (at least 3 of age 50 years or older, White race, male sex, obesity). However the threshold of multiple risk factors should be lowered in the presence of family history including at least one first-degree relative with Barrett's or OAC." | "Screening for BE may be considered in men with chronic (>5 years) and/or frequent (weekly or more) symptoms of gastroesophageal reflux (heartburn or acid regurgitation) and two or more risk factors for BE or EAC. These risk factors include: age >50 years, Caucasian race, presence of central obesity (waist circumference >102 cm or waist-hip ratio >0.9), current of past history of smoking, and a confirmed family history of BE or EAC (in a first degree relative." |
| | "We recommend against screening the general population with GERD for Barrett's esophagus." | "Screening with endoscopy is not feasible or justified for an unselected population with gastro-oesophageal reflux symptoms." | "Screening of the general population is not recommended." |
| **Surveillance** | • No dysplasia: 3–5 years<br>• LGD: 6–12 months<br>• HGD in the absence of eradication therapy: 3 months | • Carditis with IM or an irregular Z-line with IM: surveillance not generally recommended<br>• CLE <3 cm without IM or dysplasia: repeat endoscopy with biopsy—if no IM, discharge from surveillance<br>• CLE <3 cm with IM, without dysplasia: 3–5 years<br>• CLE ≥3 cm without dysplasia: 2–3 years<br>• IND: single repeat endoscopy in 6 months after optimization of antireflux therapy<br>• LGD: 6 months (see directly below)<br>• HGD: endoscopic therapy preferred | • No dysplasia: 3–5 years<br>• IND: repeat endoscopy in 3–6 months after optimization of antireflux therapy; if IND persists—12 months<br>• LGD: 12 months (endoscopic therapy preferred)<br>• HGD: endoscopic therapy preferred |

*Continued*

**Table 1.** *Continued*

| | American Gastroenterological Association (2011) | British Society of Gastroenterology (2014, 2017) | American College of Gastroenterology (2016) |
|---|---|---|---|
| **Management of low-grade dysplasia** | "Endoscopic eradication therapy with RFA should also be a therapeutic option for treatment of patients with confirmed low-grade dysplasia in Barrett's esophagus." | "Currently, ablation therapy cannot be recommended routinely until more data are available." (2014)<br>"Patients with LGD should have a repeat endoscopy in 6 months' time. If LGD is found in any of the follow-up OGD and is confirmed by an expert GI pathologist in at least two sets of biopsies, the patient should be offered endoscopic ablation therapy, preferably with RFA." (2017) | "Endoscopic eradication therapy is the procedure of choice for patients with confirmed LGD." |
| **Cost-effectiveness** | No global statement on cost-effectiveness | "There are insufficient data to indicate that endoscopic screening and surveillance for Barrett's oesophagus are cost-effective. Further studies on non-endoscopic diagnostic methods are awaited."<br>"Endoscopic therapy for dysplastic Barrett's oesophagus and early OAC is cost-effective compared with oesophagectomy." | No global statement on cost-effectiveness |

BE, Barrett's esophagus; CLE, columnar-lined esophagus; GOJ, gastro-oesophageal junction; GORD, gastro-oesophageal reflux disease; HGD, high-grade dysplasia; IM, intestinal metaplasia; IND, indefinite for dysplasia; LGD, low-grade dysplasia; OAC, oesophageal adenocarcinoma; OGD, oesophagogastroduodenoscopy; RFA, radiofrequency ablation.

displacement of the squamocolumnar junction (i.e., the Z-line) from the GEJ. Current definitions of Barrett's esophagus require that proximal displacement to extend $\geq$1 cm.[2,3] As such, precise localization of the GEJ is imperative, and endoscopic definitions are the most clinically relevant. Into the 1990s, the distal esophagus was described as normally lined by cardia-type mucosa, typically 1–2 cm in length but occasionally up to 3 cm.[5] These patients would be described today as having columnar metaplasia of the distal esophagus (i.e., Barrett's esophagus in the United States in the presence of goblet cells; Barrett's esophagus in the UK, regardless of the presence of goblet cells).

Two endoscopic definitions of the GEJ predominate: the upper limit of the gastric folds (in the West) and the lower limit of the esophageal palisade vessels (in Japan). Validation of the Prague C&M criteria, which describe the circumferential and maximal extent of a columnar-lined segment relative to the GEJ, found the upper limit of the gastric folds to be a highly reproducible anatomic landmark ($\kappa$ = 0.88).[6] Assessment may be obscured by a number of factors, including deep inspiration, air insufflation, and atrophic gastritis. Kinjo and colleagues compared the impact of the use of Japanese and Western landmarks on the diagnosis of Barrett's esophagus (defined in this study as columnar mucosa of any extent not requiring biopsy confirmation) in a series of 110 consecutive upper endoscopies, finding Barrett's esophagus rates of 39% and 26%, respectively, with nearly all observed Barrett's esophagus regions being short segments (i.e., $<$3 cm), as well as many ultrashort segments ($<$1 cm).[7] Evaluation of the distal extent of the esophageal palisade vessels is obscured by reflux esophagitis, which is much more common in the West than in Japan. Amano and colleagues performed an interobserver variability study comparing the two definitions in a set of 30 endoscopic photographs and reported $\kappa$ values of 0.16 using Japanese and 0.35 using Western landmarks.[8] Thus, the Western definition appears preferable (at

**Table 2. Points of broad agreement**

- The Seattle Biopsy Protocol should be used, including four-quadrant biopsies every 2 cm of nondysplastic and every 1 cm of dysplastic Barrett mucosa, with additional targeted biopsies of any lesions (i.e., nodule, plaque, stricture, erosion, and ulceration).
- Dysplasia assessment by H&E morphology remains the gold standard for risk stratification in Barrett's esophagus.
- Dysplasia assessment is fraught with intra- and interobserver variability, and thus all new diagnoses of dysplasia (including indefinite for dysplasia) should be confirmed by a second pathologist, ideally one with special expertise in gastrointestinal pathology.
- High-grade dysplasia and intramucosal adenocarcinoma are best managed by endoscopic eradication with endoscopic mucosal resection of any visible lesions and (preferably) radiofrequency ablation of the remaining Barrett segment.
- Special attention should be paid to the deep margin of endoscopic mucosal resection specimens, with a positive deep margin necessitating additional (and possibly more intensive) therapy.
- Patients should be maintained in endoscopic surveillance after endoscopic eradication of Barrett-associated (advanced) neoplasia.
- Adenocarcinoma invasive beyond the mucosa is typically treated with esophagectomy, with endoscopic management potentially applied in poor surgical candidates with low-grade tumors confined to the inner third of the submucosa without lymph-vascular space invasion.

least in the West) owing to its better reproducibility, lack of interference by reflux esophagitis, and greater likelihood of identifying Barrett's esophagus patients more likely to benefit from endoscopic surveillance.

Histologically, esophageal submucosal glands and associated squamous-lined ducts are taken as evidence that tissue is derived from the esophagus, and, thus, associated columnar epithelium (e.g., in the same biopsy fragment) is taken to be metaplastic.[9] However, these structures are noted in only a minority of biopsies. Similarly, squamous epithelium is taken to be esophageal in nature, and columnar epithelium directly underlying squamous epithelium is presumed to be metaplastic. The muscularis mucosae is typically reduplicated in Barrett's esophagus, and, thus, this finding has also been used to infer that tissue is esophageal derived.[10,11]

## The Z-line (squamocolumnar junction)

Like descriptions of the normal distal esophagus, those of the normal squamocolumnar junction have varied over time. Savary and Miller stated that the normal Z-line is "serrated and shows four to six small, long, or short tongues towards the esophagus."[12] DeNardi and Riddell related that "the Z-line consists of small projections of red gastric epithelium, up to 5 mm long and 3 mm wide, extending upward into the pink-white squamous epithelium."[5] These descriptions of the squamocolumnar junction imply that it is inherently irregular. This created difficulties in applying earlier definitions of Barrett's esophagus (e.g., 2011 American Gastroenterological Association (AGA) guidelines), which refer to "any extent" of metaplastic columnar epithelium in the distal esophagus.[1] Wallner and colleagues took a hard line on the normal Z-line, defining it in their Z-line appearance (ZAP) classification as "ZAP grade 0: Sharp and circular. May be wavelike because of the mucosal folds, but no tongue-like protrusions are allowed."[13] ZAP grade I constitutes "an irregular Z-line with a suspicion of tongue-like protrusions and/or islands of columnar epithelium." ZAP grades II and III correspond to contemporary endoscopic classifications of short-segment and long-segment Barrett's esophagus, respectively. Implicit in these definitions are use of the upper limit of the gastric folds to define the GEJ. Using this classification in a series of consecutive endoscopies in patients with reflux symptoms, Wallner and colleagues found intestinal metaplasia in 5.4% of 37 grade 0, 15% of 100 grade I, 58.3% of 12 grade II, and 66.7% of three grade III patients. Thus, two-thirds of gastroesophageal reflux disease (GERD) patients in this study had an irregular Z-line, which often demonstrated intestinal metaplasia, and patients with a normal Z-line also occasionally showed intestinal metaplasia. In a subsequent study of 53 consecutive non-GERD patients, 26 (51%) were ZAP grade 0, 24 (47%) were ZAP grade I, and one (2%) was ZAP grade II; intestinal metaplasia was seen in 11.5% and 25% of grade 0 and I patients, respectively.[14]

## Carditis with intestinal metaplasia

CIM refers to inflamed gastric-type (i.e., cardiac, oxyntocardiac, and occasionally fundic) mucosa with associated intestinal metaplasia in the

proximal stomach. The presence of intestinal metaplasia at this anatomic site may be attributable to *Helicobacter* infection, autoimmune atrophic gastritis, or reflux. Patients with Barrett's esophagus may have concurrent CIM.[15,16] CIM patients are not typically placed into endoscopic surveillance owing to a presumed low risk of neoplastic progression. Sharma and colleagues prospectively identified 76 patients with CIM, comparing them to 177 with short-segment Barrett's esophagus. Rates of prevalent (1.3%) and incident (2.9%) dysplasia in CIM were significantly lower than in short-segment Barrett's esophagus (11.3% and 11.5%, respectively).[16] Morales and colleagues reported rates of prevalent and incident dysplasia in 28 CIM patients of 0% and 1.4% per year.[17]

Given a variety of study protocols, patients described as having CIM are a heterogeneous group, including those with intestinal metaplasia in the proximal stomach; at normal, nondisplaced Z-lines; at irregular Z-lines; and even in association with what today would be characterized as short-segment Barrett's esophagus. For example, some studies describe taking cardia biopsies 2 cm distal to the top of the rugal folds (i.e., "true" CIM), while many others describe taking biopsies across the squamocolumnar junction, regardless of its localization.

## Histologic distinction of Barrett's esophagus from carditis with intestinal metaplasia

In the recent past, when definitions of Barrett's esophagus made reference to any extent of metaplastic columnar epithelium, pathologists were relied on to distinguish "histologic Barrett's esophagus" from CIM in the setting of endoscopically ambiguous descriptions like "irregular Z-line," "rule out ultrashort-segment Barrett's esophagus," and "possible short tongue of salmon-colored mucosa." Srivastava and colleagues' biopsy study, including 20 cases of Barrett's esophagus and 20 cases of CIM (defined in this study as intestinal metaplasia in biopsies immediately distal to a straight, nondisplaced squamocolumnar junction) provided a diagnostic framework in this all-too-common scenario.[9] They found several histologic features to be significantly associated with a diagnosis of Barrett's esophagus, including the aforementioned squamous epithelium overlying columnar epithelium with goblet cells (i.e., "buried metaplasia") and esophageal submucosal glands or squamous-lined ducts, as well as diffuse intestinal metaplasia (i.e., involving >50% of the biopsy), incomplete intestinal metaplasia (i.e., intergoblet columnar cells resembling gastric foveolar epithelium), hybrid glands (i.e., single glands containing cardia-type cells and goblet cells), and multilayered epithelium (i.e., a distinctive epithelium with acid mucous cells overlying squamous cells) (Table 3 and Fig. 1). Buried metaplasia, esophageal submucosal glands/squamous-lined ducts, and hybrid glands were found to be specific for Barrett's esophagus.

**Table 3. Histologic features more commonly seen in Barrett's esophagus (BE) than carditis with intestinal metaplasia (CIM)**

| Histologic feature | Frequency in BE versus CIM |
|---|---|
| Squamous epithelium overlying IM | 57%/0% |
| Hybrid glands | 40%/0% |
| Esophageal glands/ducts | 30%/0% |
| Incomplete IM | 100%/50% |
| Diffuse IM | 60%/10% |
| Multilayered epithelium | 70%/15% |

Note: Based on Ref. 9.

## Intestinal metaplasia at the Z-line

As discussed above, intestinal metaplasia is often found in biopsies of irregular Z-lines and occasionally in biopsies of straight, nondisplaced Z-lines (variously abbreviated in studies as EGJ-SIM, SIM-GEJ, and IM-GEJ). Reported rates range from 5% to 43.5% and are typically higher in GERD patients and those with irregular Z-lines.[13,14,18–23] When patients with intestinal metaplasia at the Z-line are compared with those with Barrett's esophagus, they are more likely to be non-White and female and to have fewer GERD symptoms, less endoscopic evidence of esophagitis, and higher lower esophageal sphincter pressures. Similar to patients classified as CIM, the (overlapping) group of patients with intestinal metaplasia at the Z-line has a very low risk of neoplastic progression. Horwhat and colleagues followed 34 EGJ-SIM patients for a mean of 44 months and found no incident dysplasia.[24] Jung and colleagues followed 86 such patients for a median of 8 years, none of whom developed esophageal adenocarcinoma.[25] Five patients with

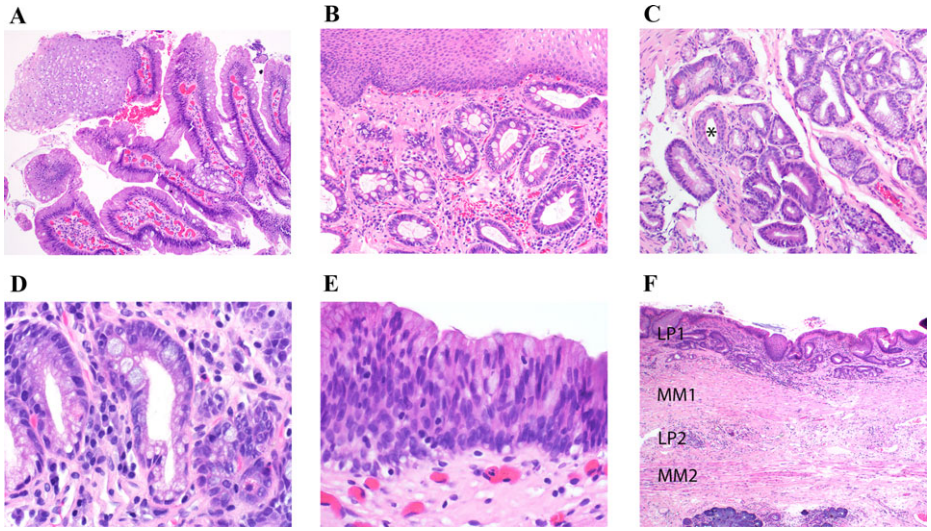


**Figure 1.** Histologic features of Barrett's esophagus. (A) Diffuse, incomplete intestinal metaplasia; (B) buried intestinal metaplasia; (C) squamous-lined duct (*); (D) hybrid gland; (E) multilayered epithelium; (F) reduplication of the muscularis mucosae. LP1, inner lamina propria; MM1, inner, reduplicated muscularis mucosae; LP2, outer lamina propria; MM2, outer, native muscularis mucosae.

prevalent low-grade dysplasia had no dysplasia on subsequent endoscopies, suggesting that these diagnoses may have represented "overcalls" of reactive changes.

## Irregular (and regular) Z-lines should not be routinely biopsied

On the basis of the frequent finding of intestinal metaplasia and the negligible (if any) increased cancer risk relative to the general population, the nondisplaced Z-line, whether regular or irregular, should not be routinely biopsied. The identification of intestinal metaplasia in such a biopsy is not currently diagnostic of Barrett's esophagus, and labeling a patient as such and placing them into endoscopic surveillance has adverse economic implications for the patient and for the entire healthcare system.[26] This conclusion is reflected in the 2014 British Society of Gastroenterology and the 2016 American College of Gastroenterology guidelines.[2,3]

## Ultrashort-segment Barrett's esophagus is a poorly reproducible diagnosis with a negligible cancer risk

Ultrashort segments of Barrett's esophagus are defined as those measuring <1 cm. The distinction of ultrashort-segment Barrett's esophagus from an irregular Z-line is arbitrary and not reproducible, and the presence of intestinal metaplasia in these segments confers no clear increase in cancer risk (Table 4). In the validation of the Prague C&M criteria, while the recognition of Barrett segments >1 cm was reported as substantially reliable ($\kappa = 0.72$), recognition of segments <1 cm was found to be only slightly reliable ($\kappa = 0.21$).[6] Thota and colleagues recently reported a prospective multicenter cohort of 167 patients with Barrett's esophagus <1 cm, which they parenthetically equated to "irregular Z-line;" at a median follow-up of 4.8 years, none had developed high-grade dysplasia or esophageal adenocarcinoma (compared with a 4.4% rate of progression in 1624 patients with ≥1 cm of Barrett's esophagus followed for a median of 6 years).[27] On the basis of the distribution of 1017 T1 cancers in long-segment, short-segment, and ultrashort-segment Barrett's esophagus, and a literature-derived estimate of the population prevalence of long-, short-, and ultrashort-segment Barrett's esophagus of 1.5%, 4.7%, and 14.4%, respectively, Pohl and colleagues estimated annual cancer rates of 0.22%, 0.03%, and 0.01% in these endoscopic categories, concluding that 450, 3440, and 12,365 such patients would need to be screened to detect one cancer.[28] In both the 2014 British Society of Gastroenterology and the 2017

**Table 4. Frequency of neoplastic progression for different histologic categories of Barrett's esophagus**

| Category | Annual incidence rate | Comment |
|---|---|---|
| Barrett's esophagus with no dysplasia | EAC: 0.33% (95% CI 0.28–0.38%) (48) | • Meta-analysis including 57 studies, 11,434 patients, and 58,547 patient-years follow up; patients with EAC that occurred within 1 year of surveillance excluded as "prevalent" |
| Short-segment Barrett's esophagus with no dysplasia | EAC: 0.19% (95% CI 0.08–0.34%) (48) | • Subset of 16 studies, 967 patients, and 4456 patient-years follow up |
| Ultrashort-segment Barrett's esophagus/irregular Z-line with intestinal metaplasia and no dysplasia | EAC and/or HGD: 0% (27) | • Single prospective, multicenter cohort study including 167 patients followed for a median of 4.8 years |
| Columnar-lined esophagus without intestinal metaplasia | EAC and/or HGD: 0.07% (95% CI 0.04–0.11%) (45) | • Population-based study of all adults diagnosed with Barrett's esophagus in Northern Ireland between 1993 and 2005 including 3179 patients without intestinal metaplasia at index endoscopy and 23,417 patients-years follow up |
| Barrett's esophagus with LGD | EAC: 0.54% (95% CI 0.32–0.76%) (49)<br>EAC and/or HGD: 1.73% (95% CI 0.99–2.47%) | • Meta-analysis of 24 studies and 2694 patients<br>• Rates of progression in component studies varied widely (0.02–11.43% for EAC; 0.04–26.67% for EAC and/or HGD)<br>• Rates of progression influenced by "stringency" of LGD diagnosis, estimated based on LGD/BE ratio; EAC rate 0.76% if ratio $<0.15$ and 0.32% if $>0.15$ |
| Barrett's esophagus with HGD | EAC: 6.58% (95% CI 4.97–8.19%) (50) | • Meta-analysis of 4 studies, 236 patients, and 1241 patient-years follow up |

CI, confidence interval; EAC, esophageal adenocarcinoma; HGD, high-grade dysplasia; LGD, low-grade dysplasia.

American College of Gastroenterology guidelines, Barrett's esophagus is defined by the presence of columnar mucosa $\geq 1$ cm from the GEJ.[2,3] As briefly referenced above, the 2011 AGA guideline defines Barrett's esophagus as "any extent of metaplastic columnar epithelium."[1] It is of interest how ultrashort-segment Barrett's esophagus will be regarded in any future AGA guideline, though one is not clearly forthcoming at present.[29]

## Differing viewpoints on the requirement of intestinal metaplasia for the diagnosis of Barrett's esophagus

The British definition of Barrett's esophagus does not require the presence of intestinal metaplasia (i.e., goblet cells), while the U.S. definition does.[2,3] The current British guideline acknowledges that the presence of intestinal metaplasia modifies the risk of neoplastic progression. It distinguishes "Barrett's oesophagus with gastric metaplasia only" from "Barrett's oesophagus with intestinal metaplasia." In short segments ($\geq 1$ and $<3$ cm) of columnar-lined mucosa in which goblet cells are not detected, if the absence of goblet cells persists on follow-up at 3–5 years, patients may be discharged from endoscopic surveillance. The evidence basis of the British and U.S. definitions is reviewed below.

### *British position: goblet cells are not required for the diagnosis of Barrett's esophagus*

Implicit in the British position is the belief that columnar mucosa in the distal esophagus, regardless of our ability to identify goblet cells, bears a risk of neoplastic progression sufficient to warrant placing patients into endoscopic surveillance (or at least warrants one endoscopic follow-up). This position is supported by histologic, epidemiologic, and genetic data.

The British position acknowledges that, in patients who will subsequently be shown to have intestinal metaplasia, it may not be demonstrated at index endoscopy. It is well recognized that goblet cells are more frequently identified in longer segments of columnar mucosa, that they vary in density

from patient to patient, and that rates of intestinal metaplasia detection in columnar-lined segments are a function of the number of biopsies taken. In a set of 1646 individual biopsies from 296 endoscopies in 125 patients with columnar lengths of 1–11 cm (mean 4.9 cm), goblet cells were noted in 64% of patients, 51% of endoscopies, and only 34% of individual biopsies.[30] The likelihood of detecting intestinal metaplasia at any one endoscopy ranged from 35% if one to four biopsies were taken, to 68% (5–8), 74% (9–12), 71% (13–16), and 100% (>16). On the basis of the results of this study, these investigators recommended a minimum of eight biopsies for the detection of intestinal metaplasia in columnar-lined segments, a recommendation that is endorsed in the American College of Gastroenterology guideline.[3] Jones and colleagues had previously shown that, among 43 patients with suspected short-segment Barrett's esophagus without intestinal metaplasia on index endoscopy, 23% had intestinal metaplasia on repeat endoscopy.[31] More recently, Khandwalla and colleagues found that, in 80 patients with columnar-lined segments (85% <3 cm) initially negative for intestinal metaplasia, 29% had intestinal metaplasia on follow-up.[32]

Although it is dogma that esophageal adenocarcinoma arises in association with intestinal metaplasia,[33,34] Japanese and German investigators have shown that the mucosa adjacent to small adenocarcinomas in the distal esophagus is frequently gastric type rather than intestinal type. In a series of 141 endoscopic mucosal resections of small, German (i.e., Western) esophageal adenocarcinomas, investigators found the directly adjacent mucosa to be cardiac or fundic in 71%, intestinal in 22%, and gastric on one side and intestinal on the other side in 7%; of the 71% entirely flanked by gastric mucosa, 19 had intestinal metaplasia elsewhere in the specimen (i.e., goblet cells were present in only 43% of all specimens).[35] These findings have recently been reproduced in a series of 100 endoscopic mucosal resections of small, Japanese cancers.[36]

Two studies demonstrated a similar cancer risk in patients with or without goblet cells identified in columnar-lined segments at index endoscopy. Kelty and colleagues reported a retrospective, single-center study of all patients with the finding of columnar mucosa in a distal esophageal biopsy from 1980 to 1994.[37] Upon rereview of biopsies from 712 patients, 55.1% had and 44.9% lacked intestinal metaplasia. At a median follow up of 12 years, 4.1% with and 3.6% without intestinal metaplasia on index endoscopy had developed esophageal adenocarcinoma ($P = 0.57$). Similarly, in a retrospective, seven-center study of 612 patients with and 322 patients without intestinal metaplasia in nondysplastic, columnar-lined segments at index endoscopy, 3.2% and 3.1%, respectively, developed esophageal adenocarcinoma at a median follow up of 3.5 years ($P = 1$).[38]

Goblet and nongoblet metaplastic columnar epithelium have been shown to harbor similar genetic abnormalities. Chaves and colleagues, in fact, found more frequent gains of chromosomes 7 and 18 in nongoblet than goblet columnar cells.[39] Liu and colleagues, using image cytometry, found similar rates of DNA heterogeneity, mild aneuploidy, and 5N-exceding cells in nongoblet– and goblet-containing metaplastic columnar epithelium.[40]

### *American position: goblet cells are required for the diagnosis of Barrett's esophagus*

The American position that goblet cells are required for the diagnosis of Barrett's esophagus is based on the premise that only those segments (≥1 cm) exhibiting intestinal metaplasia clearly predispose to malignancy.[1,2] It acknowledges (and addresses) each of the British arguments for including those segments without intestinal metaplasia.

Instead of (provisionally) labeling patients without demonstrable goblet cells as "Barrett's esophagus with gastric metaplasia only," the 2016 American College of Gastroenterology guideline withholds any specific diagnosis, stating that a repeat endoscopy in 1–2 years to "rule out Barrett's esophagus" should be considered.[3] Intestinal metaplasia in Barrett segments is known to predominate at the neosquamocolumnar junction, and it is thus reasonable to concentrate initial diagnostic biopsies proximally.[41,42]

Instead of focusing on the epithelium directly adjacent to early esophageal adenocarcinomas, investigators looking for any intestinal metaplasia in endoscopic mucosal resection specimens have typically found it.[43,44] Allanson and colleagues recently reported intestinal metaplasia in 79% of 139 such specimens. Including intestinal metaplasia found in previous or subsequent specimens, the frequency was 86%. Tumors lacking intestinal metaplasia

tended to be larger and, thus, may have obliterated associated intestinal metaplasia. Tumors associated with columnar-lined segments <1 cm were enriched for women and the absence of intestinal metaplasia, with the authors suggesting that these may represent an etiopathogenetically different disease. Even Takubo and colleagues acknowledge that, in focusing on the gastric mucosa directly adjacent to esophageal adenocarcinomas, they are making a "histogenetic" argument and are "unable to assess cancer predisposition."[36]

Regarding the risk of neoplastic progression in nongoblet columnar mucosa, the best epidemiologic evidence suggests no clear increased cancer risk. In a population-based study of all adults in Northern Ireland diagnosed with Barrett's esophagus from 1993 to 2005, including 3179 patients without and 3917 patients with intestinal metaplasia at index endoscopy, Bhat and colleagues reported annual incidences of combined high-grade dysplasia/adenocarcinoma of 0.07% and 0.38%, respectively.[45] Westerhoff and colleagues reported a single-institution study (University of Chicago) similar to that of Kelty but with a very different finding. Among 690 patients between 1987 and 2008 who had undergone biopsy of a columnar-lined segment, 258 (37%) had and 379 (55%) did not have goblet cells in columnar mucosa (8% had squamous mucosa only).[46] In patients with available follow-up, dysplasia developed in 8% of 178 patients with and 0% of 118 patients without goblet cells (mean follow up of 4.8 years in patients with and 5.8 years in patients without goblet cells). Dropping the requirement for goblet cells in this patient cohort would have increased the rate of Barrett diagnoses 2.5-fold, with significantly increased costs in the absence of demonstrable clinical benefit.

Regarding the genetic argument, nondysplastic Barrett's esophagus is known to be a neoplasm, albeit one with a very low rate of neoplastic progression. The demonstration of genetic abnormalities in nongoblet columnar epithelium is interesting, but, like the histogenetic argument, there is no clear demonstration of increased risk.

## Endoscopic eradication is the management of choice in histologically confirmed low-grade dysplasia

The 2016 American College of Gastroenterology and the 2017 Revised British Society of Gastroenterology guidelines both cite a 2014 multicenter randomized controlled clinical trial as the evidence basis for this recommendation.[3,4] Sixty-eight patients each were randomized to radiofrequency ablation or endoscopic surveillance at 6, 12, 24, and 36 months.[47] All diagnoses of low-grade dysplasia were confirmed by central pathology review, and an additional endoscopy was performed within 6 months of randomization to exclude prevalent endoscopic lesions, high-grade dysplasia, or adenocarcinoma. Regarding the importance of second opinion in new diagnoses of dysplasia, among 511 patients initially screened for potential inclusion, low-grade dysplasia was confirmed in 247 (48%), 239 were considered indefinite or nondysplastic (47%), and 25 (5%) were upgraded to high-grade dysplasia or cancer. In the ablation group, one (1.5%) patient progressed to adenocarcinoma, which was managed with an endoscopic resection, 98.4% achieved eradication of dysplasia, and 90% achieved eradication of intestinal metaplasia. By comparison, 18 (26.5%) patients in the control group progressed to high-grade dysplasia or cancer, including six with cancer (8.8%), one of whom required esophagectomy. Eradication of dysplasia was seen in only 27.9% of controls, with no patient achieving eradication of intestinal metaplasia. Twelve percent of patients in the ablation arm developed strictures, all of which were amenable to endoscopic dilation (median of one treatment required).

## Conclusions

Current American and British gastroenterology society guidelines conclude that the irregular Z-line should not be routinely biopsied, that ultrashort-segment Barrett's esophagus is an irreproducible diagnosis with a negligible cancer risk, and that histologically confirmed low-grade dysplasia is best managed with endoscopic ablation. Although American and British guidelines continue to differ regarding the requirement of intestinal metaplasia for the diagnosis of Barrett's esophagus, the British guidelines allow patients with short segments of columnar-lined mucosa (i.e., ≥1 and <3 cm) to be discharged from surveillance if goblet cells are not detected at an initial and single follow-up endoscopy. Future efforts will go toward identifying Barrett patients most likely to benefit from surveillance, as >90% die of unrelated causes;

decreasing the cost of surveillance efforts; and finding a way to identify the 85% of esophageal adenocarcinoma patients who present with frank cancer in the absence of a personal history of Barrett's esophagus.

## Competing interests

The authors declare no competing interests.

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