

Lower esophageal palisade vessels and the definition of Barrett's esophagus

K. Ogiya,¹ T. Kawano,¹ E. Ito,² Y. Nakajima,¹ K. Kawada,¹ T. Nishikage,¹ K. Nagai¹

¹Departments of Surgery and ²Pathology, Tokyo Medical and Dental University, Tokyo, Japan

SUMMARY. The designated area of the columnar-lined esophagus (CLE) is anatomically defined by the distal limit of the lower esophageal palisade vessels (LEPV) and the term 'Barrett's esophagus' is equally used along with the name CLE in Japan. The aim of this study was to investigate the actual prevalence of CLE based on the Japanese criteria and to evaluate the criteria per se. A total of 42 esophagi consecutively resected at this institute were included. All subjects underwent a surgical resection for squamous cell carcinoma of the esophagus. The position of the LEPV, squamocolumnar junction, the prevalence of CLE and intestinal metaplasia were investigated both pre- and postoperatively. Preoperative endoscopy revealed CLE based on the Japanese criteria in half of all patients. In the resected specimens the distal limit of LEPV was lower than the squamocolumnar junction in 95.2%. In other words, almost all cases had CLE (equivalent to Barrett's mucosa in Japanese criteria). However, most of the CLE areas were very short and their average maximum length was only about 5 mm. In addition, no intestinal metaplasia was observed in any of the CLE cases. Almost all individuals might therefore be diagnosed to have CLE or Barrett's mucosa based on precise endoscopic observations in Japan. The CLE located in a small area, e.g. less than 5 mm, defined according to the LEPV criteria without any other factor concerning typical Barrett's esophagus such as signs of gastroesophageal reflux should therefore be excluded from consideration as a high-risk mucosa.

KEY WORDS: Barrett's esophagus, columnar-lined esophagus, lower esophageal palisade vessels.

INTRODUCTION

Due to the absence of a universally accepted definition, the esophagogastric junction (EGJ) has clinically resulted in confusion regarding the diagnosis of Barrett's esophagus, not only in Japan but also in Western countries. The widely accepted definition of the EGJ is where the distal limit of the lower esophageal sphincter, namely the proximal limit of the longitudinal gastric mucosal folds and the distal limit of esophageal peristalsis.¹⁻³ However, these comprehensive definitions are vague, and it is difficult to accurately make a diagnosis of short-segment Barrett's esophagus.

In Japan the anatomical definition of EGJ is described to be the distal limit of the lower esophageal palisade vessels (LEPV).^{4,5} In addition, the condition named columnar-lined esophagus (CLE) as

defined by LEPV is equally called Barrett's esophagus in Japan. In Western countries, except for the UK, a pathophysiological definition that is confirmed to be intestinal metaplasia in addition to the vague anatomical definition has been standardized for the diagnosis of Barrett's esophagus.⁶ Therefore, the prevalence of Barrett's esophagus in Japan tends to be higher than that observed in Western countries.^{4,5,7}

This study observed the position of the distal limit of LEPV and the squamocolumnar junction (SCJ), while also examining the prevalence of CLE in resected specimens and investigating the significance of LEPV in the diagnosis of EGJ, CLE and Barrett's esophagus.

PATIENTS AND METHODS

A total of 42 specimens from consecutive surgeries performed between December 2004 and April 2006 were used in this study. Twenty-two of the 64 cases in which the carcinoma invaded the SCJ and preoperative endoscopy could not be sufficiently performed

Address correspondence to: Dr Kazuo Ogiya, Department of Surgery, Tokyo Medical and Dental University, Yushima 1-5-45, Bunkyo-ku, Tokyo 113-8519, Japan. Email: ogiya.srg1@tmd.ac.jp

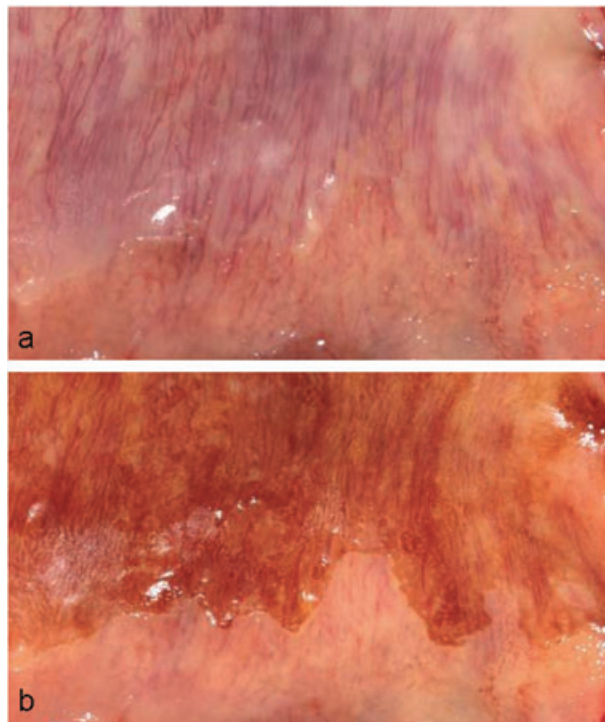


Fig. 1 Observation of (a) the lower esophageal palisade vessels in a fresh resected specimen. (b) The squamocolumnar junction is clearly observed after iodine staining.

were excluded. The subjects had a mean age of 62.9 ± 10.6 years (range 35–79 years); and 39 were males and three were females.

All subjects underwent a surgical resection for squamous carcinoma of the thoracic esophagus, which was performed at the hospital by the surgical staff.

The existence of a hiatus hernia and reflux esophagitis, which was classified according to the Los Angeles classification,⁸ LEPV and CLE were identified based on the preoperative endoscopy findings. EGJ was defined as the distal limit of the LEPV but when the LEPV could not be visualized, the upper end of gastric folds was used. Therefore, a hiatus hernia was defined as a case in which the distal limit of the LEPV was proximal side of the hiatus. These observations were made retrospectively on still images not acquired for the purpose of this study by one endoscopist. In addition, the endoscopic diagnostic concordance between the distal limit of LEPV and the upper end of gastric folds was also evaluated. The area of CLE was not pathologically examined.

The resected specimens were opened longitudinally along the greater curvature of the stomach after injecting a marker from the left gastric artery into the specimens. About 10 mL of the patient's blood, barium or indigo carmine were used for markers. The specimens were thereafter pinned out for examination. The specimens that were stained by iodine solution were then photographed with a visible scale (Fig. 1).

The distal end of the LEPV and the SCJ were macroscopically observed in the resected specimen and in the photographic images. According to the definition of EGJ in Japan, the area of the columnar epithelium at the proximal side of the distal limit of LEPV is CLE. The prevalence of a CLE and the endoscopic findings were investigated. In cases which had a CLE, the area, ratio of the area and the width of the esophagus, and the longest longitudinally length were measured using the ImageJ 1.34n software program (NIH, Bethesda, MD, USA) as seen in Figure 2.

Multiple full-thickness tissue samples that were cut at a width of 5 mm were obtained after 24 hours of formalin fixation. The samples were embedded in paraffin, and 5- μ m thick sections were cut and stained with hematoxylin-eosin. The first 20 consecutive cases were evaluated histologically. In 12 of 20 cases a proper esophageal gland that could be recognized within 10 mm on both sides of the SCJ were observed in detail. The gaps between the SCJ and the proper esophageal glands were measured in the same sections (Fig. 2). The extent of intestinal metaplasia was investigated from the SCJ to 2 cm distal to the SCJ in these 12 cases. The squamous island and double muscularis mucosa adjacent to the SCJ were evaluated according to the guidelines of the British Society of Gastroenterology.⁹

A univariate analysis was performed by means of the Mann–Whitney *U*-test. The correlation test was performed using Pearson's correlation coefficient. The values were expressed as the mean \pm standard deviation. All statistical evaluations were performed by the Stat View 5.0 software program for Macintosh (HULINKS, Inc., Tokyo, Japan). A value of $P < 0.05$ was considered to be statistically significant.

RESULTS

Endoscopic findings

In preoperative endoscopy, a hiatus hernia was recognized in 21 patients (50%) and eight patients (19%)

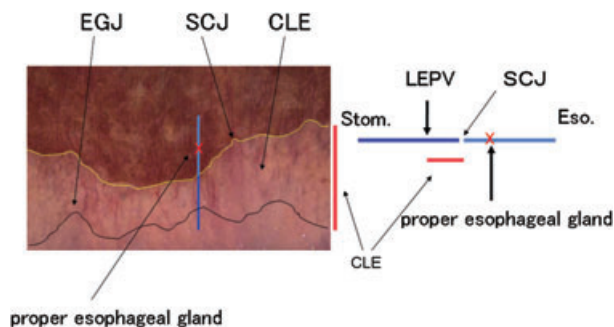


Fig. 2 Observation and measurement of the columnar-lined esophagus (CLE). The distal limit of a proper esophageal gland is compared microscopically with the squamocolumnar junction (SCJ) and lower esophageal palisade vessels (LEPV). EGJ, esophagogastric junction; Eso, esophagus; Stom, stomach.

Table 1 Preoperative endoscopic findings

	Exist	Absent
Columnar lined esophagus (%)	25 (59.5)	17 (40.5)
Hiatal hernia (%)	21 (50)	21 (50)
Esophagitis (%)	8 (19.0)	34 (81.0)

had reflux esophagitis that was more severe than Grade A (Los Angeles classification). The LEPV could be observed in 38 patients (90.5%) as shown in Table 1. In addition 25 patients (59.5%) had CLE (Barrett's esophagus as defined by the Japanese definition); 15 (60%) with a hiatus hernia; seven (28%) with reflux esophagitis more severe than Grade A; and 6 (24%) with both a hiatus hernia and reflux esophagitis (Table 2). The diagnostic concordance between the distal limit of the LEPV and upper end of gastric folds was 83%.

Macroscopic findings

The corresponding rate of the distal end of LEPV between that measured by preoperative endoscopy and postoperative macroscopic examination was 90.5%. In resected specimens, a columnar epithelium was recognized in 40 cases (95.2%) on the proximal side of the distal limit of LEPV. In other words CLE was recognized in 40 cases (95.2%). In addition, CLE could be observed in 25 of 40 patients (62.5%) in the preoperative endoscopy findings. The cases in which CLE was recognized were then measured and the metric area of the CLE (in square mm) was calculated. Almost all cases had a small area and the length of the vertical line direction ranged from 0 mm to 19 mm (mean 5.6 ± 3.6 mm). The area of CLE ranged from 0 mm² to 395.0 mm² (mean 99.8 ± 82.8 mm²). In each case the value in which the area of CLE was divided by the width of the esophagus ranged from 0 mm to 7.3 mm (mean 1.5 ± 1.4 mm) as shown in Table 3 and Figure 3.

Microscopic findings

The proper esophageal glands were recognized on the distal side of the SCJ in four cases. These cases were confirmed to histologically have CLE.^{10,11} The gaps of

Table 2 Relationship of columnar-lined esophagus (CLE), hiatus hernia and esophagitis

	CLE Exist (n = 25)	CLE Absent (n = 17)
Hiatal hernia alone (%)	9 (36)	6 (35)
Esophagitis alone (%)	1 (4)	1 (6)
Hernia + esophagitis (%)	6 (24)	0 (0)
Neither hernia nor esophagitis (%)	9 (36)	10 (59)

Table 3 Columnar-lined esophagus (CLE) in the resected specimens

Length of longest CLE (mm)	
Mean \pm standard deviation (SD)	5.6 ± 3.6
Median	5
Area of CLE (mm ²)	
Mean \pm SD	99.8 ± 82.8
Median	80.5
Width of esophagus	
Mean \pm SD	66.0 ± 8.8
Area of CLE/width of esophagus (mm)	
Mean \pm SD	1.5 ± 1.4

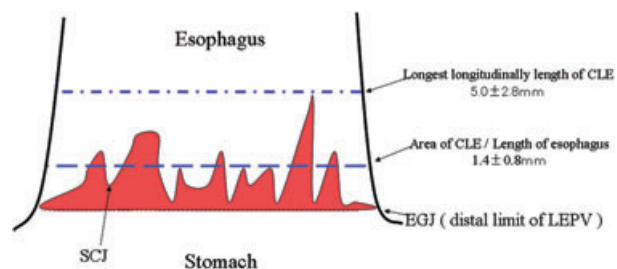
the SCJ and the distal limit of the proper esophageal gland could be evaluated in these cases. When the distal side was assumed to be a minus, then the gaps ranged from -3.0 mm to 5.0 mm (mean 0.8 ± 2.2 mm) in each of the same sections. Regarding the site of the SCJ, the distal limit of the LEPV and the distal limit of the proper esophageal gland, four different patterns were observed (Fig. 4). In the cases in which the proper esophageal glands were recognized on the distal side of the SCJ, the gap of the SCJ and the proper esophageal gland was shorter than the length of the gap of the SCJ and the distal limit of the LEPV. Intestinal metaplasia was recognized in seven of 12 cases. However, no intestinal metaplasia was seen in the area of the CLE.

The squamous island was recognized in 13 of 20 cases microscopically and the double muscularis mucosa underneath the columnar epithelium was recognized in four of 20 cases. In total, 14 of 20 cases had one or more components of Barrett's esophagus according to the guidelines of the British Society of Gastroenterology.⁹

In this study, neither age nor clinical esophagitis were significantly associated with the length and the area of the CLE. However, the hiatus hernia was significantly associated with the length and the area of the CLE (Table 4 and 5).

DISCUSSION

The gastroesophageal reflux disease (GERD) Society Study Committee in Japan reported Barrett's mucosa

**Fig. 3** Area and length of the columnar-lined esophagus (CLE). LEPV, lower esophageal palisade vessels.

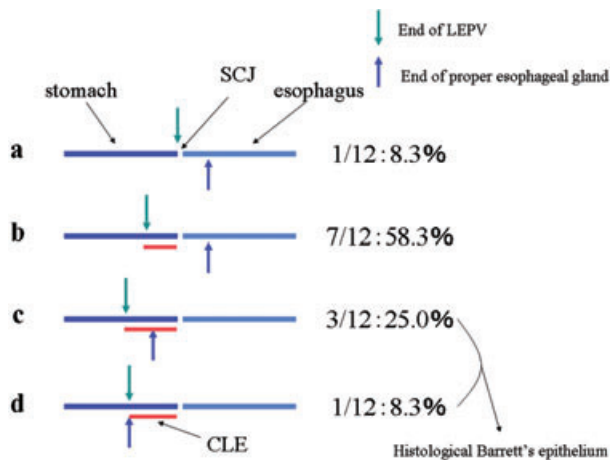


Fig. 4 Site of the squamocolumnar junction (SCJ), distal limit of the lower esophageal palisade vessels (LEPV) and the distal limit of proper esophageal gland in the same section. Eleven cases have columnar-lined esophagus (CLE) because the distal end of the LEPV is located more distal to the SCJ (b,c,d) according to the Japanese criteria. In four cases the distal end of the proper esophageal gland was located more distal to the SCJ (c,d) and they are diagnosed as Barrett's esophagus histologically.

to be observed in 536 (20.8%) of 2577 patients who underwent endoscopy for the first time. In addition, correlations were observed between the length of Barrett's mucosa and an esophageal hiatus hernia.⁵ In this study Barrett's mucosa was recognized in 59.5% of the patients by endoscopy according to Japanese definition.

Table 4 Columnar-lined esophagus (CLE) and hiatus hernia

	HH+	HH-	P-value
Length of longest CLE (mm)			
Mean \pm standard deviation (SD)	6.0 \pm 2.7	5.1 \pm 4.4	0.033
Median	6.0	4.0	–
Area of CLE (mm ²)			
Mean \pm SD	118.4 \pm 71.0	81.2 \pm 91.0	0.009
Median	112.2	50.6	–
Area of CLE/width of esophagus (mm)			
Mean \pm SD	1.7 \pm 1.1	1.3 \pm 1.7	0.010
Median	1.6	0.8	–

Table 5 Columnar-lined esophagus (CLE) and esophagitis

	RE+	RE-	P-value
Length of longest CLE (mm)			
Mean \pm standard deviation (SD)	6.0 \pm 3.1	5.5 \pm 3.7	0.283
Median	6.5	5.0	
Area of CLE (mm ²)			
Mean \pm SD	105.7 \pm 78.1	98.4 \pm 84.9	0.471
Median	97.6	73.2	
Area of CLE/width of esophagus (mm)			
Mean \pm SD	1.6 \pm 1.4	1.5 \pm 1.4	0.543
Median	1.5	1.2	

RE, reflux esophagitis.

In Western countries Ronkainen *et al.* recently reported the prevalence of Barrett's esophagus in a randomly selected sample of 1000 Swedish people who underwent endoscopy. The prevalence of any type of Barrett's disease was 1.6%, while for long-segment Barrett's disease (≥ 2 cm in length) the prevalence was 0.5%.¹²

There are large differences in the prevalence of Barrett's esophagus between Japan and the Western countries. The cause of the difference in the prevalence between Japan and the Western countries is mainly the difference in the definition of Barrett's esophagus. The definition of Barrett's esophagus is similar in Japan and the UK. This suggests that because of the difference in the definition of Barrett's esophagus, the prevalence of esophageal adenocarcinoma in Japan is therefore artificially low.⁵

In most Western countries the diagnosis of Barrett's esophagus is based on the endoscopic findings of suspected columnar-lined esophagus in the distal esophagus, as confirmed by the presence of specialized intestinal metaplasia in the esophageal biopsy specimens.^{12–15}

In Japan the definition of Barrett's esophagus is the columnar epithelium that extends from the stomach to the esophagus without considering the presence of intestinal metaplasia.⁵ Histologically, any findings of the existence of a proper esophageal gland beneath the columnar epithelium continuing to the distal esophageal squamous mucosa, squamous island in the columnar area and/or double muscularis mucosa are required.

When a small area of CLE was recognized, i.e. short-segment Barrett's esophagus, the EGJ is very important. In this study the EGJ was considered to be the distal limit of the LEPV. The unique existence of a proper esophageal gland on the distal side of the SCJ is histological proof of CLE.¹¹ In cases that could be evaluated, the gap of the SCJ and the distal limit of the proper esophageal gland were shorter than the length of CLE. This indicates that a proper esophageal gland was not present on a more distal side of the distal limit of the LEPV. As a result, this phenomenon cannot rule out the possibility that the distal limit of the LEPV is EGJ. However, according to a recent report in Japan, the upper end of the gastric folds, as used in circumferential (C) and maximum (M) (C&M) criteria,¹⁶ may be a more suitable landmark than the palisade vessels for identifying the distal end of the esophagus by endoscopy.¹⁷

In this study, the columnar epithelium recognized at the proximal side of the distal limit of the LEPV was very frequently observed. The CLE was observed in almost all patients. However, these areas tended to be very small. The CLE recognized in this study was short in the direction of the longitudinal axis. The longest length of the CLE was 19 mm and the mean length was 5.6 mm. Histological Barrett's esophagus,

according to the guidelines of the British Society of Gastroenterology, was recognized in 14 of 20 patients; however, each area of Barrett's esophagus was very narrow. However, the clinical implications of such a tiny histological Barrett's esophagus are unclear.

No intestinal metaplasia was observed in the CLE among the cases investigated in this study. According to the definition of Barrett's esophagus in Western countries except for the UK, the CLE cases observed in this study were not diagnosed to be Barrett's esophagus. Similar to Western countries, there have been some reports stating that many small-sized case of CLE could be observed,^{18,19} however, the clinical significance appears to be low regarding the CLE cases investigated in this study. From the standpoint of the risk of adenocarcinoma, the presence of intestinal metaplasia plays a very important role in the definition of Barrett's esophagus.²⁰⁻²³ Barrett's esophagus is a condition that has risk of adenocarcinoma and it is appropriate that Barrett's esophagus could thus be classified as having intestinal metaplasia according to the common definition used by Western countries.

LEPV is therefore considered to be useful for the diagnosis of the CLE, however, according to the definition of LEPV, CLE will therefore be observed in almost all individuals. That seems to be why there are large differences in the prevalence of Barrett's esophagus between Japan and Western countries.

Spechler described that until the cancer risk is better defined, endoscopists should not routinely obtain biopsy specimens from a healthy-appearing distal esophagus in order to look for specialized intestinal metaplasia.²⁴ In order to solve this problem, the CLE located in a small area defined according to the LEPV criteria, e.g. an area measuring less than 5 mm in longitudinal length, without any other factors associated with typical Barrett's esophagus, such as the sign of gastroesophageal reflux, should therefore be excluded from consideration as a high risky mucosa.

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