The normal anatomy around the oesophagogastric junction: A histopathologic view and its correlation with endoscopy

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The incidence of primary oesophageal adenocarcinoma in Caucasian men has recently been increasing rapidly. Therefore, primary oesophageal adenocarcinoma, columnar-lined oesophagus (CLO) or Barrett’s oesophagus and the normal condition of the lower segment of the oesophagus are currently receiving worldwide attention in the medical field. Precise definitions of the anatomical features of the oesophagogastric junction (OGJ) are essential before accurate assessment of CLO can be made. This article reviews the normal morphological features in the OGJ zone to give a closer insight into the histopathology and endoscopic appearance of the OGJ and CLO. We review definitions of the OGJ, the pattern of the squamocolumnar junction (SCJ), oesophageal cardiac-type glands beneath the squamous epithelium, the normal squamous epithelium, columnar islands in squamous-lined mucosa, squamous islands in CLO and newly reported metaplastic changes in the OGJ zone. The nature of the OGJ is clarified in detail through comparison between endoscopically evident and histological features.

Key words: Columnar-lined oesophagus; Oesophagogastric junction; Barrett’s oesophagus; Squamous metaplasia; Columnar island; Squamous island.

INTRODUCTION

In Western countries, the incidence of primary oesophageal adenocarcinoma in Caucasian men has recently been increasing rapidly and has exceeded 50% of all oesophageal malignancies in some series, whereas in Asian countries, including Japan, more than 90% of primary oesophageal malignancies are squamous cell carcinomas. For detailed information about oesophageal carcinoma in Japan, the reader is referred to the Comprehensive Registry of Esophageal Cancer in Japan. In Asian countries, lifestyle and diet are rapidly becoming westernised and, as a result, it is anticipated that primary oesophageal adenocarcinoma will increase. Therefore, primary adenocarcinoma of the oesophagus, its origin in columnar-lined oesophagus (CLO) or Barrett’s oesophagus (BO) and the normal condition of the lower segment of the oesophagus are currently under scientific scrutiny worldwide from the viewpoints of gastroenterology, oncology and pathology.

When trying to understand the actual condition of CLO (which is considered to be BO in Japan) or BO, the definition of the oesophagogastric junction (OGJ) has always been problematical. This article reviews the normal morphological features of the OGJ zone to provide a better understanding of CLO histopathology and its correlation with endoscopic findings. This article also describes the histological patterns and squamous and columnar islands at the OGJ and the nature of CLO. This review is intended primarily for clinicians and pathologists with an interest in CLO or BO as an aid to understanding and recognising CLO.
LOCATION OF THE OGJ

The upper limit of the gastric folds or lower limit of the palisade longitudinal vessels

Although short-segment CLO and ultrashort-segment CLO have received a good deal of attention, there has been no clear definition of the OGJ, microscopically, macroscopically or endoscopically. Precise definitions of the anatomical features of the OGJ are essential before an accurate diagnosis of CLO can be made. In Western countries, the definition has usually been the ‘upper limit of the gastric mucosal folds’. Gastroenterologists worldwide now support the definition of the OGJ as ‘being at the proximal margin of the gastric mucosal folds’. In Japan, the OGJ is usually defined endoscopically as ‘the lower limit of the palisade longitudinal vessels’ (Figure 1). Histologically, in oesophageal transverse sections, large veins exceeding 100 μm in diameter are observed much more frequently in the lamina propria of the lower oesophageal sphincter (LOS) than in that of the middle and upper oesophagus, and are considered to be the palisade vessels revealed by endoscopy (Figure 2). They are also revealed in salmon pink metaplastic columnar mucosa by conventional endoscopy using light from a xenon lamp. Therefore, in Japan, when palisade vessels are seen through metaplastic columnar epithelium, a diagnosis of CLO can be made by endoscopic examination alone without histological examination.

Most Western authors have considered that the Japanese definition based on palisade vessels is not infallible because discrimination between these vessels and other vascular patterns is sometimes difficult and palisade vessels cannot be adequately visualised in all patients. Furthermore, it has been reported that palisade vessels are not always evident in Western patients. Indeed, palisade vessels cannot always be observed by endoscopy in patients with minimal-change oesophagitis, gastro-oesophageal reflux disease (GORD), CLO, or BO. In such cases, in Japan, proton pump inhibitor therapy is recommended before endoscopic examination to check for the presence of vessels. The incidences of GORD, BO, and Barrett’s

Figure 1. Endoscopic features of palisade vessels seen through squamous epithelium. The palisade vessels can be seen through squamous epithelium at the entrance of the lower oesophageal sphincter.
adenocarcinoma (BA) are all very low in the Japanese population and reflux induces minimal-change oesophagitis characterised by mucosal cloudy whiteness and redness. Japanese gastroenterologists can clearly observe palisade vessels in Japanese patients usually without cloudy whiteness or redness. The differences in the ability to visualise the palisade vessels between Western and Japanese gastroenterologists and in the definition of the OGJ may be attributable to differences in the incidence of minimal-change oesophagitis between Western and Japanese populations.

During endoscopic examination, the squamocolumnar junction (SCJ) is observed to move slightly at inspiration and expiration. The CLO should be scrutinised during deep inspiration on the basis of palisade vessels. For this reason, it is impossible to check the location of the lower limit of the palisade vessels in patients under anaesthesia. In Western countries endoscopy is frequently performed under anaesthesia, whereas in Japan it is usually performed without anaesthesia.

In any event, it is very important to define the OGJ in order to know whether BO is present, because BO is associated with a risk of malignant transformation. To achieve this aim, an East–West exchange of views between gastroenterologists is desirable.

### Macroscopic features of the SCJ and OGJ

The distance between the OGJ and the SCJ on macroscopic examination at autopsy has been reported in two articles. Bombeck et al reported that in 21 autopsy cases this distance ranged from 5 to 21 mm (mean = 11 mm), whereas Takubo et al reported a range of 0–10 mm (14 cases: mean = 3 mm) in 50 Japanese autopsy cases. In the latter study, the OGJ was defined as the line between the angles of the opened oesophagus and the stomach curvature. These results suggest that the incidence of CLO is higher in Western countries than in Japan.

In Japanese subjects, it is considered that the OGJ coincides with the SCJ, as the distance between them is frequently 0 mm. Thus, it may be possible to define the OGJ as the SCJ in many Japanese. Shimoda et al also reported that the normal OGJ...
almost matched the straight line of the SCJ and that the OGJ coincided with the SCJ in most Japanese individuals.\(^\text{11}\)

**Is the lower oesophagus normally lined with columnar mucosa?**

Some histology or anatomy textbooks consider that the lower oesophagus, 2–3 cm in length, is lined with columnar mucosa. However, when the OGJ is defined as the lower limit of palisade vessels endoscopically, or as the line connecting the angles of the opened oesophagus and the stomach curvature macroscopically, the lower oesophagus is usually lined with squamous epithelium up to the OGJ.

**NORMAL MUCOSAL EPITHELIUM**

The oesophagus is usually lined with flat stratified squamous epithelium, except for CLO and ectopic gastric mucosa in the upper oesophagus. The normal squamous epithelium is thick and non-keratinised, comprising about 10–20 layers of cells that are about 300–500 µm thick in surgically resected specimens. Biopsy specimens usually have much thicker epithelium than surgically resected and endoscopic mucosal resection specimens, because the superficial layers are likely to be lost during surgical manipulation, Lugol’s iodine staining and peri- and postoperative handling. In Japan, resected oesophagi are stretched to their original length before fixation and, thus, a difference in epithelial thickness between biopsy and surgical materials is evident.

The layers of basal and parabasal cells reportedly account for 15% or less of the thickness of the epithelium. Subjects with reflux oesophagitis have thicker basal and parabasal layers.\(^\text{12}\) However, some normal subjects also have histological features in the lower segment of the oesophagus similar to those of patients with reflux oesophagitis.\(^\text{13}\) The epithelial cells become flatter as they approach the surface and those in the uppermost layer are very thin, attenuated, and disk-like.

The turnover time of the oesophageal epithelium is about 4–7 days in rats and mice. The corresponding period in humans is said to be 10 days or less, although no definite data are available. Mitotic figures are found in the deeper parabasal layer, but not in the basal layer: Ki-67 (MIB-1) immunostaining of biopsy specimens usually shows a negative reaction in the basal layer and a positive reaction in the parabasal layer (Figure 3), very few basal cells being Ki-67-positive.\(^\text{14,15}\) One to two layers of basal cells around the tops of papillae are occasionally positive for Ki-67. However, Ki-67-positive cells are increased in various conditions, such as reflux oesophagitis. Telomerase immunostaining and in situ hybridisation for hTERT, a catalytic subunit of telomerase, show a positive signal in both the basal and parabasal layers.\(^\text{16}\) Telomeres of basal cells are longer than those of parabasal and prickle cells. These findings suggest that epithelial stem cells and early differentiated cells may be located in the basal layer, but that proliferative activity occurs in the parabasal layer.\(^\text{16}\) Transit amplifying cells may be located in the parabasal layer whereas terminally differentiated cells are present in the prickle cell layer (Figure 4).

**PATTERNS IN THE OGJ ZONE**

**Histological patterns**

Three histological patterns can be observed in the SCJ: (1) the clear-cut demarcation type, (2) the subepithelial gland type (Figure 5), and (3) the CLO type (Figure 6).\(^\text{3}\) The
clear-cut demarcation type is defined as an abrupt change from squamous to columnar mucosa. There is an abrupt change from squamous to cardiac mucosa, but there are no oesophageal cardiac-type glands beneath the squamous epithelium. The subepithelial gland type is defined as an overlapping of columnar and squamous mucosae. Cardiac-type glands beneath the oesophageal squamous epithelium (oesophageal cardiac-type

Figure 3. Normal mucosal epithelium of the oesophagus immunostained for Ki-67. The basal cells do not stain, but parabasal cells are positive for Ki-67.

Figure 4. Cellular organisation of the human oesophageal squamous epithelium. It is considered that stem and early differentiated cells are located in the basal layer on the basement membrane, transit amplifying cells are located in the parabasal layer and terminal differentiated cells are located above the parabasal layer.
glands also known as superficial glands) show continuity from gastric cardiac glands and they can be observed by endoscopy (Figure 7). The CLO type has squamous islands or ducts in columnar-lined mucosa. Because identification of oesophageal glands proper (OGPs, submucosal glands) is a definite indicator that tissue is of oesophageal origin, a diagnosis of CLO can be made purely on the basis of histology. Squamous islands or ducts will be described in detail below.

Serial examination of the histological patterns in the OGJ zone in 110 cases has demonstrated that the CLO type accounted for 7%, the clear-cut demarcation type 19% and the subepithelial gland type 74% of these cases. Other reports have indicated

Figure 5. The subepithelial gland type oesophagogastric junction (OGJ) zone. Cardiac-type glands are located beneath the squamous epithelium in the lamina propria extending continuously from the gastric mucosa.

Figure 6. 'Ultrashort-segment' columnar-lined oesophagus. The duct of an oesophageal gland proper opens in columnar-lined mucosa. Several dilated ducts (D) can be seen. In this case, the distance from the squamo-columnar junction (SCJ) and the distal duct is 3.1 mm. Two layers of original (M) and newly developed (m) muscularis mucosae are evident.
that the subepithelial gland type was replaced in all\textsuperscript{17} and 95\%\textsuperscript{18} of OGJ specimens. These data suggest that the prototype of the OGJ is the subepithelial gland type.

The lengths of overlapping segments in histological sections

The lengths of the overlapping segments of squamous epithelium and cardiac-type glands extending continuously from the gastric cardia, as revealed by histological examination, have been reported in three articles. The maximum lengths in all Japanese subjects reported by Takubo\textsuperscript{3}, Watanabe et al\textsuperscript{17} and Nakanishi\textsuperscript{18} were 12, 14 and 13 mm, respectively. Only 13 (12.7\%) of our series of 102 cases had segments that overlapped by more than 6 mm. The mean length of the overlapping segments is reported to be 4 mm.\textsuperscript{18}

ENDOSCOPIC CORRELATION WITH HISTOLOGICAL PATTERN

Endoscopically, oesophageal cardiac-type glands beneath squamous epithelium in the OGJ zone usually appear yellowish in colour and are flat or slightly elevated (Figure 7). Oesophageal cardiac-type glands are observed to extend continuously from the gastric cardia or as isolated islands. Based on the experience of one of the authors (H.K.), cardiac-type glands beneath squamous epithelium were observed through the squamous epithelium in 82 (55.0\%) out of 149 Japanese cases in a consecutive endoscopic examination series, and were found in areas from the SCJ to the proximal 15 mm of the squamous-lined mucosa. However, most of them were observed in the areas between the SCJ and the proximal 5 mm of the squamous-lined mucosa (H.K., unpublished data).

Cardiac-type glands beneath squamous epithelium can be observed clearly or vaguely depending on the manufacturers of the endoscope employed.
TWO POSSIBLE CONDITIONS OF THE LOWER SEGMENT OF CLO

Columnar islands in the OGJ

Columnar islands are observed endoscopically in squamous mucosa and are similar in colour to those of the gastric cardiac mucosa, being unstained with Lugol's iodine. Columnar islands can often be found in the distal 10-mm segment of the oesophagus.\cite{19} They were observed in 57% of 131 subjects with oesophageal and gastric carcinomas.\cite{20} Columnar islands may or may not be associated with cardiac-type glands (Figures 8 and 9). Some columnar islands are surrounded by cardiac-type glands

Figure 8. Endoscopic features of columnar islands in the lower oesophagus. A columnar island (arrow) is surrounded by cardiac-type glands that appear yellowish in colour through the squamous epithelium. Palisade longitudinal vessels are evident in the mucosa.

Figure 9. Columnar island in squamous-lined mucosa. A columnar island shows cardiac-type mucosa without goblet cells in this case. The island is surrounded by squamous epithelium. Cardiac-type glands are also evident beneath the squamous epithelium.
beneath squamous epithelium, possibly due to desquamation of the surface squamous epithelium above the glands through reflux, whereas columnar islands not surrounded by cardiac-type glands occur due to reflux oesophagitis.

**Lower 15-mm segment of CLO**

The maximum lengths of the overlapping segments of columnar and squamous epithelium or the distribution of cardiac-type glands are considered to be 12–14 mm histologically and 15 mm endoscopically in the lower oesophagus. The presence of columnar islands in the lower segment of CLO, within 15 mm in length, may be either metaplastic CLO or CLO due to desquamation of the squamous epithelium covering the cardiac-type glands. In other words, CLO within 15 mm in length may contain original oesophageal cardiac-type glands located beneath squamous epithelium. However, both conditions can be considered to be 'metaplastic CLO'.

**SQUAMOUS ISLANDS IN CLO**

The relationship between squamous islands (Figures 7 and 10) and the underlying histology of OGPs has been reported in several papers. The squamous island(s) were endoscopically identified in the columnar mucosa in 78% of patients with CLO. They can be observed by conventional endoscopy, but staining with iodine helps to demonstrate the smaller squamous islands.

When targeted biopsy specimens were obtained from the islands, OGPs or their ducts were evident histologically in 67% of cases with squamous islands, which accounted for 52% of patients with CLO. Ducts of OGPs were found in 10–15% of random biopsy specimens from cases of CLO.

Complete serial sections were taken through 15 squamous islands within CLO to assess their underlying histology and all were found to be continuous with an underlying gland duct. Therefore, squamous islands always appear to be ductal orifices of

![Figure 10. Squamous island in columnar-lined mucosa. A squamous island (arrow) is located in the cardiac-type mucosa. The duct of an oesophageal gland proper (arrowhead) is also evident in the cardiac-type mucosa just beneath the squamous island.](image-url)
OGPs. OGPs always develop from squamous epithelium and they develop after squamous epithelialisation, which begins in the 7th month of gestation. The presence of squamous islands, OGPs or their ducts demonstrates that squamous-lining mucosa once surrounded them continuously from the proximal squamous mucosa. Therefore, the identification of the openings of OGPs into columnar-lined mucosa indicates that squamous-lined mucosa has changed to columnar-lined mucosa. This is a pathognomonic feature of CLO.

Microscopic diagnosis of CLO based on OGPs and related findings (Figure 10) should be borne in mind at histological examination. When squamous islands are endoscopically evident in columnar mucosa at locations distant from the SCJ, a diagnosis of CLO can be made without histological examination.

RECENTLY REPORTED METAPLASTIC CHANGES AT THE OGJ

Pancreatic metaplasia

Pancreatic acinar-like cells, also known as pancreatic metaplasia (Figure 11), have been reported in the gastric cardiac mucosa and oesophageal cardiac-type glands in several papers. Pancreatic metaplasia can be seen in gastric cardiac mucosa in cardiac-type glands under squamous epithelium (oesophageal cardiac-type glands) and in CLO. Pancreatic metaplasia has been reported to be present in the stomach or oesophagus in 65% of specimens obtained by total gastrectomy or oesophagectomy for gastric or oesophageal cancer. These cells, which are easily visualised by hematoxylin and eosin (H&E) staining, have many fine eosinophilic cytoplasmic granules in their apical and mid-regions, while the cytoplasm in the basal region is basophilic. The appearance of these cells is similar to that of the acinar cells of pancreatic exocrine glands.

If the pancreatic metaplasia and fundic mucosa in CLO secrete pancreatic and gastric juices, they may be factors that induce oesophagitis. They may also be exacerbation factors of CLO. In fact, ‘crackleware oesophagus’, characterised by acanthotic and keratinised squamous epithelium due to diffuse pancreatic metaplasia, has recently been reported.

Figure 11. Pancreatic metaplasia. Metaplastic cells have basophilic cytoplasm adjacent to the basement membrane and granular eosinophilic cytoplasm adjacent to the lumen.
Squamous metaplasia-like change, also known as multilayered epithelium

Squamous metaplasia-like change (SMLC) or multilayered epithelium (ME) has been widely reported (Figure 12). Although the incidence of primary adenocarcinoma of the oesophagus is rare in Japan, SMLC was reportedly seen in 49% of 43 OGJs from Japanese patients. The pattern of immunostaining for tubulin and cytokeratins was very similar to that of normal bronchial epithelium and multiple cilia were detected on the luminal surface. The morphological features strongly suggest that SMLC/ME is ciliated pseudostratified epithelium, probably bronchial metaplasia. As SMLC is frequently surrounded by columnar mucosa, SMLC or ME may arise from columnar-lined mucosa.

Although the SMLC reported in some articles was thought to be a precursor of BO, the following five observations suggest that this is not the case:

1. This change is common in Japanese subjects, who have a very low incidence of BO.
2. The lesion is located in ectopic gastric mucosa in the hypopharynx and oesophagus.
3. The change is also seen in cardiac-type glands just beneath the squamous epithelium.
4. The lesions have multiple cilia, suggesting not intermediate cells but differentiated cells.
5. The lesions are often surrounded by columnar epithelium.

Therefore, this lesion is believed to represent only metaplastic change, similar to pancreatic metaplasia at the OGJ. When histological examination of biopsy specimens reveals pancreatic metaplasia and SMLC, the specimens may have been obtained from the mucosa of the OGJ zone.

Pseudoregression/buried glands/squamous re-epithelialisation

Pseudoregression or buried glands after ablation by plasma argon coagulation or photodynamic therapy with a proton pump inhibitor has been reported in several
papers.\textsuperscript{31–33} One report has indicated that adenocarcinoma arose from buried glands.\textsuperscript{33} However, mucosal adenocarcinoma frequently spreads into the lamina propria beneath intact squamous epithelium far from BO and not from buried glands. Therefore, there is a need to differentiate these two conditions and also to examine the likelihood of carcinogenesis in buried glands.

**SUMMARY**

This review has clarified the nature of the OGJ in detail. In Japan, the OGJ is defined endoscopically as the lower limit of the palisade longitudinal vessels, whereas in Western countries it is considered to correspond to the upper limit of the gastric folds. The lower oesophagus is usually lined with squamous epithelium extending to the OGJ. Squamous epithelium demonstrates differences in thickness between biopsy and surgical specimens. The histological prototype of the OGJ is the subepithelial gland type that shows cardiac-type glands beneath squamous epithelium. There are many columnar islands with or without cardiac-type glands in the lower oesophagus. The columnar-lined segment of the lower oesophagus, within a length of 15 mm, may be either metaplastic CLO or CLO due to desquamation of the squamous epithelium covering cardiac-type glands. However, we believe that both can be called ‘metaplastic columnar-lined segment of the oesophagus’. Identification of openings from OGPs into columnar-lined mucosa indicates that it has changed from squamous-lined mucosa and is a pathognomonic feature of CLO. Recently, pancreatic metaplasia, SMLC and pseudoregression have been reported at the OGJ. SMLC is not thought to be a precursor of CLO. When biopsy specimens contain pancreatic metaplasia and SMLC, they may have been obtained from the mucosa of the OGJ zone. As there are still many changes at the OGJ that have not been reported and many aspects of OGJ pathophysiology are still unresolved, further studies are essential.

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**Practice points**

- The oesophagogastric junction (OGJ) is defined endoscopically as the upper limit of the gastric mucosal folds in Western countries and as the lower limit of the palisade vessels in Japan.
- Cardiac-type glands are endoscopically and histologically observed beneath squamous-lined mucosa within 15 mm from the squamocolumnar junction (SCJ).
- When squamous islands are endoscopically evident in columnar mucosa, a diagnosis of columnar-lined oesophagus (CLO) can be made solely by endoscopy.
- When oesophageal glands proper (OGPs) and their ducts are histologically evident in columnar-lined mucosa of biopsy specimens, a diagnosis of CLO can be made solely by histological examination.
- When biopsy specimens are found to contain pancreatic metaplasia and squamous metaplasia-like change (SMLC), they may have been obtained from the OGJ zone.
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Research agenda

- Gastroenterologists in the West and the East need to exchange views on the oesophagogastric junction (OGJ).
- It is necessary to clarify the histogenesis of columnar-lined oesophagus (CLO) within 15 mm of the OGJ.
- There is a need to clarify the role of pancreatic metaplasia and fundic glands within CLO as exacerbation factors of CLO.
- It needs to be confirmed whether or not squamous metaplasia-like change (SMLC) is a precursor of Barrett’s oesophagus.
- The likelihood of carcinogenesis in buried glands needs to be clarified.


