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Kyoto international consensus report on anatomy, pathophysiology and clinical significance of the gastro-oesophageal junction

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2022-327281).

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Received 1 March 2022
Accepted 3 May 2022

To cite: Sugano K, Spechler SJ, El-Omar EM, *et al*. *Gut* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/gutjnl-2022-327281

ABSTRACT

Objective An international meeting was organised to develop consensus on (1) the landmarks to define the gastro-oesophageal junction (GOJ), (2) the occurrence and pathophysiological significance of the cardiac gland, (3) the definition of the gastro-oesophageal junctional zone (GOJZ) and (4) the causes of inflammation, metaplasia and neoplasia occurring in the GOJZ.

Design Clinical questions relevant to the aforementioned major issues were drafted for which expert panels formulated relevant statements and textural explanations.

A Delphi method using an anonymous system was employed to develop the consensus, the level of which was predefined as ≥80% of agreement. Two rounds of voting and amendments were completed before the meeting at which clinical questions and consensus were finalised.

Results Twenty eight clinical questions and statements were finalised after extensive amendments. Critical consensus was achieved: (1) definition for the GOJ, (2) definition of the GOJZ spanning 1 cm proximal and distal to the GOJ as defined by the end of palisade vessels was accepted based on the anatomical distribution of cardiac type gland, (3) chemical and bacterial (*Helicobacter pylori*) factors as the primary causes of inflammation, metaplasia and neoplasia occurring in the GOJZ, (4) a new definition of Barrett's oesophagus (BO).

Conclusions This international consensus on the new definitions of BO, GOJ and the GOJZ will be instrumental in future studies aiming to resolve many issues on this important anatomic area and hopefully will lead to better classification and management of the diseases surrounding the GOJ.

INTRODUCTION

In the previous consensus conference held in Kyoto, we have reached a consensus to classify gastritis based on aetiology, *Helicobacter pylori*-associated dyspepsia, methodologies to evaluate gastritis, and, most importantly, to prevent gastric cancer by prescribing eradication of *H. pylori*.[1] However, the important issue of 'carditis' was left untouched, as it requires full discussions on the definition of cardia as well as the definition of gastro-oesophageal junction (GOJ), which is closely linked the definition of Barrett's oesophagus (BO). Indeed, there are a number of differences in the definition of BO among guidelines published by professional societies[2–7] (table 1). To resolve these issues, extensive discussions between specialists with different backgrounds (gastroenterology, pathology and surgery) having expertise on BO and gastric diseases are mandatory. We had a chance to organise the second international consensus meeting dedicated to these issues that have been left in a state of confusion for a long time thanks to financial support from the fund of the Asia Pacific Digestive Week (APDW) held in Kobe in 2016 deposited to the Organisation of Japan Digestive Disease Week (JDDW).

After formulation of the draft for clinical questions (CQ) and statements concerning the issues on GOJ which were amended through two rounds of voting by the faculty members, the draft CQs and statements were further discussed and finalised at the face-to-face meeting again in Kyoto. Fortunately, we could reach consensus on all the important issues including a new conceptual definition of BO, a desirable anatomical landmark for GOJ, a definition of 'cardiac mucosa', a new proposal for the gastro-oesophageal junctional zone (GOJZ) concept and unique pathophysiological factors affecting GOJZ, all of which, we hope, will form the basis for future research and thereby improve our understanding, classification and management of the diseases occurring in the area of GOJ.

METHOD

Consensus development process

Draft plan for CQs and statements were developed by the Japanese faculty members who are experts in

Summary box

What is already known about this subject?

⇒ Definitions of Barrett's oesophagus (BO) among guidelines are inconsistent in terms of the minimum length of metaplastic mucosa and of the requirement of intestinal metaplasia (IM, often called specialised columnar metaplasia or specialised IM).

⇒ The endoscopic landmarks for identifying gastro-oesophageal junction (GOJ) adopted in these guidelines are discordant, the proximal end of gastric folds (PEGF) on the one hand, the distal end of palisade vessels (DEPV) on the other.

⇒ Presence and nature of the cardia type mucosa have been debated.

⇒ Classification of cancers arising in the GOJ are ill-defined or confusing.

What are the new findings?

⇒ A new definition of BO, which does not require the length criteria nor IM, is proposed.

⇒ Preferred use of DEPV as an endoscopic landmark of GOJ is agreed.

⇒ Existence of the cardia type columnar mucosa without parietal cells as an innate structure in the limited extent of the GOJ (usually several millimetre of length) is agreed.

⇒ A new concept of gastro-oesophageal zone (GOJZ), defined as an area straddling 1 cm proximal and 1 cm distal to the GOJ, is proposed for practical purposes.

⇒ Cancers arising in the GOJZ as defined above is proposed as a substitute of the Siewert's type II cancer in the junctional zone.

How might it impact on clinical practice in the foreseeable future?

⇒ Adoption of new definition of BO will help resolving the inconsistencies among the reported results and provide a new platform for future studies.

⇒ Use of unified endoscopic landmark (DEPV) observed under proper methodology will reduce the diagnostic inconsistencies of the short (including ultra-short) segment BO.

⇒ Limited distribution of the cardia-type epithelium calls for a revamp of the current category of 'cardia cancer' or 'cancer in the cardia'.

⇒ Adoption of GOJZ cancer concept will better serve to elucidate the aetiology of cancers arising from this area and to improve the classification for health statistics.

the relevant topics. International faculty members were selected from the faculty members who had contributed to international guidelines and from renowned pathologists with extensive publications on the topics. The first drafts of CQs and statements edited and revised by core faculty members (KS, KM, EME-O and PM) were sent to each faculty members who agreed to participate via the internet voting. This internet-based platform to develop consensus based on the Delphi method allowed the faculty members to anonymously choose their level of agreement for each set of CQ and statement. Faculty members were entitled to vote on all set of CQs and statements from the first round of voting. The voting platform was designed for the voters to make any comments and provide references, irrespective of their levels of agreement with the statements. However, when they disagree with the CQs and/or statements, they were obliged to specify their reasons for the objecting. Consensus level was predefined as ≥80% voting either agree (A) or agree with minor reservation (B). The first round of voting involved 27 CQs and statements. Among the 38 faculty members, 37 completed voting. Although all the CQs and statements cleared the consensus threshold of 80% of agreement (A+B), a considerable number of amendments were implemented to omit the redundant CQs and to provide a more logically consistent orders of CQs, based on comments provided by faculty members before the second round of voting. Textural explanations and references attached to support each statement were also revised. For the second round of voting, 23 set of CQs and statements were uploaded to the voting platform, and all the faculty members have completed the voting. Again consensus level was achieved for all the CQs and statements. Further revisions of wording, though minor, were made and presented at the face-to-face meeting.

Table 1 Different definitions of Barrett's oesophagus

Society	Length of CE	Intestinal metaplasia	GOJ
AGA	Any length	Required	PEGF
BSG	≥1 cm	Not required	PEGF
JES	Any length	Not required	DEPV
APAGE	≥1 cm	Not required	PEGF
ACG	≥1 cm	Required	PEGF
ESGE	≥1 cm	Required	PEGF

ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; APAGE, Asian Pacific Association of Gastroenterology; BSG, British Society of Gastroenterology; CE, Columnar epithelium; DEPV, distal end of palisade vessels; ESGE, European Society of Gastrointestinal Endoscopy.; GOJ, Gastrooesophageal Junction; JES, Japan Esophageal Society; PEGF, proximal end of gastric folds.

At the face-to-face meeting, faculty members were asked to vote the evidence level and recommendation to the statements according to the predefined category based on the Grade system,[8 9] which rates the quality of evidence into four tiers (high to very low) and the strength of recommendation into three levels (strong, weak and not applicable) (online supplemental table 1A,B).

Each CQ, statement and supporting evidence was presented by the Japanese faculty member assigned to prepare them, followed by a question and discussion session. Voting at the meeting was accomplished with a key-pad system distributed to faculty members to ensure anonymity, and the polling results were shown on the screen immediately after voting.

One ad-hoc CQ concerning the definition of BO was proposed at the face-to-face meeting in order to facilitate discussions on the entire group of CQs and statements. Although it did not go through the two rounds of internet voting process, adoption of this CQ (initially designated as CQ zero, but renumbered as CQ 1 in this report) was approved and a statement to accompany this CQ was formulated through discussion. Faculty members attending to the meeting were asked to vote to this ad hoc CQ in the same manner as the other CQs, and the wording was modified until the level of agreement was reached. Therefore, this particular CQ did not reflect the opinions of several faculty members who could not attend the meeting. The textual explanation for CQ 1 was prepared by KS and SJS.

Role of the funding sources

This consensus conference was fully supported by a fund from the APDW meeting held in Kobe 2016, which was deposited to the Organisation of JDDW. The funding source also provide

assistance in preparatory works, but had no roles in the planning, formulation of CQ, literature search, writing the manuscript, nor decision to submit for publication.

RESULTS

CQ 1

How can we define BO conceptually?

Statement 1

BO is the condition in which a metaplastic columnar mucosa predisposed to neoplasia replaces the squamous mucosa of the distal oesophagus.

Agreement

Strongly agree 97%.
Agree with minor reservation 3%.
Disagree with major reservation 0%.
Strongly disagree 0%.

Quality of evidence

High 72%.
Moderate 28%.
Low 0%.
Very low 0%.

Strength of recommendation

Strong 90%.
Weak 10%.
Not applicable 0%.

Textural explanation

As stated in the Introduction section, diagnostic criteria for BO among international guidelines are discrepant[2–7] regarding two major points: the length of metaplastic mucosa required and the requirement for the presence of intestinal metaplasia (IM), previously often denoted as specialised columnar epithelium (SCE) or specialised IM, (SIM) (table 1). As for the length of columnar metaplasia, guidelines by the American Gastroenterological Association (AGA) and the Japan Esophageal Society accept any length of metaplastic change, while other societies require a minimum length of 1 cm of metaplastic mucosa for a diagnosis of BO. One major reason for setting this minimum length threshold presumably is rooted in the reports showing unreliability in identifying columnar metaplasia extending less than 1 cm.[10 11] However, even in the cases with longer segments of oesophageal columnar metaplasia, length measurements are imprecise,[12 13] raising doubt regarding the reliability of any length requirement. Moreover, the GOJ landmark used to measure the length of oesophageal metaplasia that is advocated in most guidelines, that is, the proximal end of gastric folds (PEGF), also is imprecise (eg, its location varies with respiration and extent of insufflation), making measurements of the length of metaplastic mucosa inaccurate and unreliable (see CQ 2 and 3 for more detailed explanation).

Although a number of reports have shown that the risk of oesophageal adenocarcinoma (OAC) increases with the extent of Barrett's metaplastic mucosa,[14–17] it is important to consider several factors that can confound the interpretation of endoscopic and histologic findings in BO. First, a relative large number of biopsy samples (minimum of eight) is required to demonstrate IM reliably,[18] and community endoscopists often do not take so many biopsies in routine clinical practice. Indeed, one study documented poor reproducibility in the finding of IM between two endoscopic examinations performed only 6 weeks apart, even when a fairly large number of biopsy samples were taken (mean 13.6 for the first endoscopy and 11.4 for the second endoscopy) conducted in a short interval (6 weeks).[19] Therefore, a substantial proportion of metaplastic oesophageal epithelium containing IM would be missed, and hence cannot be diagnosed as BO. Second, 'pseudogoblet cells' are mucinous, gastric foveolar-type columnar cells that have distended cytoplasmic vacuoles that give them a histologic appearance close to goblet cells. Biopsies containing pseudogoblet cells can easily be misinterpreted as IM,[20] which has been surmised as a clonal event involving multiple cell lineages.[21–23] Third, in biopsies of the GOJ region, it can be difficult to distinguish IM involving the stomach (an atrophic condition frequently caused by chronic *H. pylori* infection) from IM in the metaplastic oesophageal mucosa, since gastric and oesophageal IM can appear identical even when immunohistochemical staining or with gene expression analyses are employed.[24 25] Moreover, IM at the GOJ can exhibit proliferative abnormalities similar to those found in the IM of long-segment BO,[26] implying an increased risk for neoplastic changes. Fourth, a longitudinal follow-up study found that a substantial proportion of patients with IM on an initial endoscopy did not have positive IM in a follow-up procedure and, conversely, those without IM at the first endoscopy often had IM found in the follow-up.[27] Finally, a number of emerging studies have shown that metaplastic columnar epithelium without IM can have genetic alterations that might predispose to cancer development.[28–30] Indeed, several reports have contended that adenocarcinomas can develop in columnar epithelium without IM[31–36] (see CQ 21 for more detailed explanation). Collectively, these problems raise a serious concern regarding the validity of the requirement for IM and the minimum length definition of 1 cm as diagnostic criteria for BO. Thus, in this consensus conference, the new definition of BO was created in which both length limitation and the presence of IM were lifted from the definition of BO.

To circumvent the above problems, we feel it is useful to separate a conceptual definition of BO from its diagnostic criteria. As noted above, there can be considerable disagreement among authorities regarding diagnostic criteria requirements, there are limitations in endoscopic and histologic techniques for identifying those criteria, and diagnostic criteria might change with future studies regarding their importance. However, the conceptual definition of BO as the condition in which a metaplastic columnar mucosa predisposed to neoplasia replaces the squamous mucosa of the distal oesophagus need not change. It should be noted that this new concept of BO does not imply that all the BO in this category should undergo surveillance. On the contrary, we do not recommend endoscopic surveillance of ultrashort segment BO (USSBO) with less than 1 cm of columnar metaplasia since an overall risk of developing OAC is very low despite that it has an increased risk per unit area comparable to short segment BO (SSBO) with 1–3 cm of columnar metaplasia (SSBO).[37]

CQ 2

Which of the two, the distal end of the palisade vessels (DEPV) or the PEGF, is more appropriate anatomical landmark of the GOJ?

Statement 2

Anatomically, the DEPV is more appropriate than the PEGF for defining the GOJ.

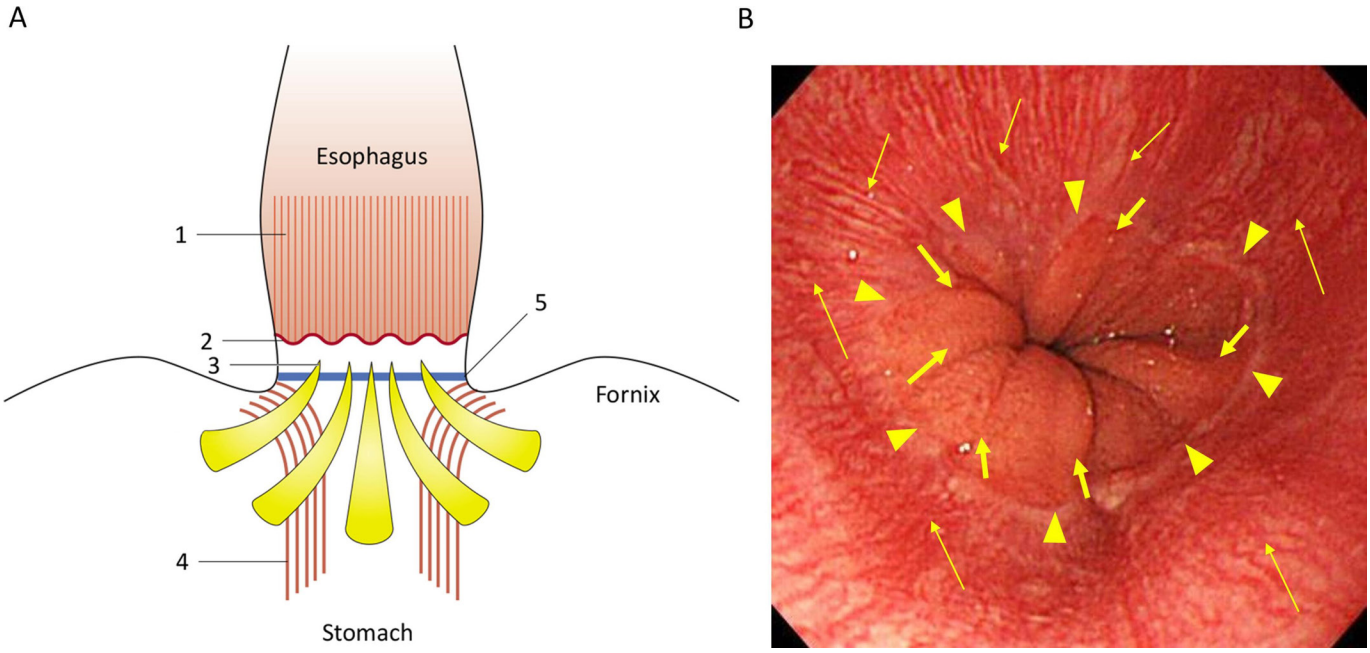

Figure 1 Landmarks of gastro-oesophageal junction (GOJ). (A) Schema of the landmarks used for GOJ. Endoscopic view of the GOJ. (1) palisade vessels, (2) squamocolumnar junctional line (Z line), (3) proximal end of the gastric folds, (4) gastric sling fibres and (5) angle of His. (B) Palisade vessels (thin arrows), squamocolumnar junctional line (Z-line) (arrow heads) and the end of gastric folds (thick arrows) are shown. These three landmarks (distal end of palisade vessels, Z-line and proximal end of gastric folds) are closely aligned with each other in normal subjects. (This endoscopic Image was provided by Prof. MF.).

Agreement

Strongly agree 71%.
Agree with minor reservation 11%.
Disagree with major reservation 14%.
Strongly disagree 4%.

Quality of evidence

High 36%.
Moderate 39%.
Low 4%.
Very low 21%.

Strength of recommendation

Strong 57%.
Weak 36%.
Not applicable 7%.

Textural explanation

Several landmarks have been used to define the GOJ such as the squamocolumnar junction (SCJ), the PEGF and the DEPV[38] (figure 1A, IB). As the SCJ shifts towards proximally when there is columnar metaplasia of the oesophagus[39 40] or in rare cases, the SCJ shifts distally into the stomach,[41] it cannot be used as an anatomical landmark of the GOJ.

PEGF has been used by many Western gastroenterologists for defining the GOJ, since 1987, when McClave *et al* proposed PEGF as an optimal endoscopic landmark for diagnosing the columnar-lined oesophagus.[39] Although those investigators described PEGF as a stable landmark in subjects with hiatus hernia, the study included only four normal control subjects. Moreover, the biopsies taken from the PEGF in the control subjects contained junctional-type mucosa (corresponding to cardiac type mucosa), which might not be a gastric mucosa at all (see below). Furthermore, the literature[42] provided by the authors to support their contention that PEGF represents the GOJ was not convincing.

It is well known that PEGF can vary with different observation methods and pathologic changes in the stomach. In severe gastric atrophy, for instance, gastric folds can become indistinct. The location of the PEGF is susceptible to change with air insufflation during endoscopic observation (see CQ 3 and 4). In the surgically resected oesophagogastrectomy specimens, Chandrasoma *et al* reported that oesophageal submucosal glands, an established anatomical hallmark of the oesophagus, were present distal to the PEGF, raising doubts on its validity as a landmark of the GOJ.[43] A recent report has presented evidence to support Chandrasoma's assertion.[44] In this large multicentre study, biopsies taken at the PEGF by experienced endoscopists were histologically diagnosed as containing the 'cardiac mucosa' in the majority.[44] Furthermore, cardiac mucosa at the GOJ was found to be associated with symptoms of GORD and/or oesophagitis, supporting Chandrasoma's contention that 'cardiac mucosa' represent columnar metaplasia of the oesophagus, not the stomach.[44]

In contrast, DEPV has been shown to mark the anatomical site where the lower oesophageal sphincter (LOS) ends and merges with gastric muscle structures.[45 46] This vascular landmark is not altered by oesophageal columnar metaplasia or by gastric pathology such as atrophy or IM. Moreover, DEPV has been used as a landmark for identifying the LOS during per oral oesophageal myotomy for the treatment of achalasia[47 48] and palisade vessels (PV) has been used to identify the end of the oesophagus in the resected specimen.[49–51] In a recent review, DEPV was deemed more accurate than PEGF as a mucosal landmark for GOJ.[52]

Another proposed anatomic landmark for the GOJ is the angle of His, which has been used for surgically resected or autopsy specimens. Although the angle of His can be surmised during

endoscopy with retroflexed views,[38] it can be difficult to determine its precise location if hiatal hernia is present.

CQ3

Which of the two landmarks, DEPV or PEGF, is more appropriate for clinically defining the GOJ?

Statement 3

Clinically, if the DEPV is clearly identifiable, it should be used for defining the GOJ. In case the PV are not identifiable, the PEGF should be used as a landmark of the GOJ.

Agreement

Strongly agree 78%.
Agree with minor reservation 11%.
Disagree with major reservation 11%.
Strongly disagree 0%.

Quality of evidence

High 57%.
Moderate 29%.
Low 14%.
Very low 0%.

Strength of recommendation

Strong 68%.
Weak 32%.
Not applicable 0%.

Textual explanation

As described in CQ2, DEPV is considered a preferred landmark as it is not influenced by epithelial changes[53] and it has been validated by anatomical, histologic and in vivo dissection studies (see the textural explanation in CQ2). However, identification of the DEPV requires proper training and appropriate control of air insufflation during endoscopic examinations.[54–58] High-resolution endoscopy with image-enhanced modalities may increase the visibility of PV.[59 60] Nevertheless, inflammation in the terminal oesophagus can compromise the recognition of this landmark (online supplemental figure 1). In such cases, PEGF can be used as a surrogate landmark for the GOJ. Use of proton pump inhibitors (PPIs) for several weeks prior to endoscopy to resolve the oesophageal inflammation was reported to be beneficial in increasing the diagnostic yield for USSBO.[61] In this study, PEGF was used as a landmark for GOJ, but it is possible that this kind of pretreatment may increase the visibility of DEPV in the columnar metaplasia as well. Similarly, therapeutic use of PPIs for GORD was shown to reduce mucosal thickness of the distal inflammatory squamous epithelium,[62] and, hence, may facilitate recognition of PV, though this has to be tested in the future.

To distinguish which landmark is used to define GOJ for research purposes, we propose that endoscopists specify either GOJp (the subscript 'p' for palisade vessel) or GOJg (the subscript 'g' for gastric folds) is used to define the site when biopsies in this zone are taken. Refer to CQ4 to CQ6 for more detailed description of proper endoscopic methods to observe these landmarks.

CQ 4

What is the most appropriate endoscopic method to identify the DEPV?

Statement 4

White light imaging (WLI) with/without image-enhanced endoscopy (IEE) in both forward and retroflexed views with air insufflation is the most appropriate method for identifying the DEPV.

Agreement

Strongly agree 71%.
Agree with minor reservation 29%.
Disagree with major reservation 0%.
Strongly disagree 0%.

Quality of evidence

High 57%.
Moderate 36%.
Low 7%.
Very low 0%.

Strength of recommendation

Strong 79%.
Weak 21%.
Not applicable 0%.

Textual explanation

Textural explanation for statements 3–5 are combined together (see CQ5).

CQ 5

What is the most appropriate endoscopic method to identify the PEGF?

Statement 5

To clearly identify the PEGF by endoscopy, the air insufflation must appropriately be controlled as excessive air inflation or deflation changes the position and shapes of the PEGF.

Agreement

Strongly agree 89%.
Agree with minor reservation 11%.
Disagree with major reservation 0%.
Strongly disagree 0%.

Quality of evidence

High 78%.
Moderate 18%.
Low 4%.
Very low 0%.

Strength of recommendation

Strong 93%.
Weak 7%.
Not applicable 0%.

CQ6

Can IEE improve visibility of the PV?

Statement 6

IEE can improve the visibility of PV.

Agreement

Strongly agree 72%.
Agree with minor reservation 21%.
Disagree with major reservation 7%.

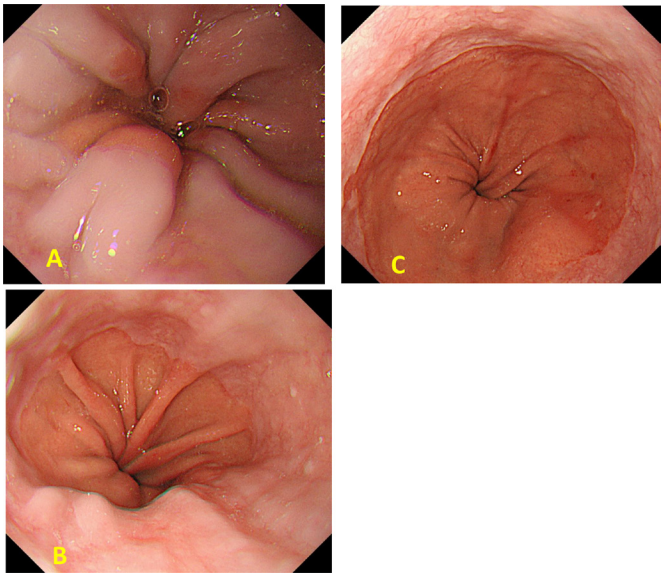

Figure 2 Changes of endoscopic images at the GOJ depending on the different observation conditions. (A) This white light image was taken with deflated condition. Note that oesophageal mucosa on the left side of this image forms as a fold-like configuration, but can be identified as oesophageal mucosa as the whitish colour of the squamous epithelium. Whereas the columnar metaplasia seen at the upper right folds with columnar metaplasia, such a fold-like configuration can be misinterpreted as PEGF. (B) When the distal end of the oesophagus was inflated with moderate amount of air, the distal end of the gastric folds was clearly recognisable. Although palisade vessels can be seen on the right side of the same fold pointed out in A, they are not visible on the other side of this image, indicating a very short area of metaplastic mucosa. (C) Image taken under further air insufflation during deep inhalation, separation between the PEGF and SCJ became more obvious, partly due to flattening of the gastric mucosa. On the right side of this image, DEPV in the columnar mucosa distal to the squamous epithelium became clearly visible, indicating the presence of metaplastic mucosa in this case. (These endoscopic images were provided by Prof. TG.). DEPV, distal end of palisade vessel; GOJ, gastro-oesophageal junction; PEGF, proximal end of gastric fold; SCJ, squamocolumnar junction.

Strongly disagree 0%.

Quality of evidence

High 21%.
Moderate 57%.
Low 18%.
Very low 4%.

Strength of recommendation

Strong 39%.
Weak 61%.
Not applicable 0%.

Textual explanation for statements 4–6

As mentioned in the explanation for the statements 1 and 2, DEPV is considered a preferable landmark for the GOJ based on the anatomical evidence. However, identification of DEPV depends on the endoscopic observation method, requiring standardisation to ensure reproducibility. For instance, Kusano *et al*[57] evaluated whether there were differences between American and Japanese endoscopists in the recognition of PV. A total of 82 patients were enrolled in this study. After an appropriate training, both American and Japanese endoscopists identified the GOJ with the DEPV as a landmark in 87.8% (72/82) and 89.0% (73/82) of cases, respectively. In another study, presence of PV was assessed in endoscopic images obtained from Western patients in eight conditions by a panel of six endoscopists from Japan and Netherland.[58] The results showed visible PV in 25 patients (100% (95% CI 87 to 100)) during insufflation of the four available insufflation images per patient, namely, forward approach–WLI–insufflation, forward–narrow band imaging (NBI)–insufflation, retroflexed–WLI–insufflation and retroflexed–NBI–insufflation, whereas PV were recognised in 15 patients (60% (95% CI 41 to 77)) in the deflated condition of the four desufflation images per patient); $p<0.001$, suggesting adequate air insufflation for identifying PV.

Endoscopic identification of the PV, however, can be difficult in cases with reflux oesophagitis or BO since inflammation and/or mucosal dysplastic changes may obscure them. Insufficient air inflation can also render them difficult to visualise. Therefore, PEGF has been widely adopted as the landmark for GOJ[3 5–7 39 54 63] despite uncertain anatomic evidence as discussed in previous CQs.

It should be noted that the endoscopic observation method appropriate for identifying the PEGF is rather opposite to that of PV; namely, air must be properly deflated by endoscopy as air insufflation flattens the gastric folds obscuring the tips of the folds. However, caution must be exerted not to excessively suck the air, as it may change the position of the PEGF and/or cause artificial plication of the oesophageal mucosa that simulates the gastric folds (pseudogastric folds) (figure 2A–C). This precaution should particularly be taken in patients with columnar metaplasia as the metaplastic mucosa cannot be discriminated by mucosal colour. Also, in patients with dilated distal oesophagus, oesophageal folds can erroneously be interpreted as gastric folds.[43 64] Moreover, respiratory movement was shown to affect the position of diaphragm causing separation of the PEGF from the DEPV by deep inspiration.[55 56 65] Other factors including heart pulsation and contraction of the LOS may further complicate accurate identification of the GOJ. Therefore, in order to identify the PEGF, standardised endoscopic observations with proper desufflation of air should be applied.

Although fairly good results in identifying PV have been reported if trained properly under an appropriate air insufflation, improved endoscopic imaging modalities may further facilitate recognition of PV.

NBI is well known as an excellent tool to highlight microvascular details and may, thus, improve visualisation of the PV.[66] However, a study comparing high-resolution WLI with NBI did not show difference in identifying DEPV.[58]

A different modality of image enhancement, called flexible intelligent colour enhancement, may increase the visibility of PV,[59] but another report questioned the superiority of this modality over WLI in identifying BO.[67] Inconsistent results of the two studies might be explained by the difference in the spectral settings. Thus, further studies are required for validating the utility of this modality.

Recently, a new modality of IEE, linked colour imaging (LCI), was shown to improve visibility of short segment Barrett's mucosa as compared with WLI in a single-centre retrospective clinical study.[60] Intraclass correlation coefficient (ICC) for the inter-rater reliability for LCI compared with WLI was 0.77 (95% CI 0.67 to 0.84). ICC for the intrarater reliability of LCI compared with WLI ranged from 0.45 to 0.57 for trainees and 0.49–0.79 for experts. Intrarater reliability for LCI was 'moderate' for trainees and 'moderate-substantial' for experts, indicating better visibility

even in trainees. Although their study used PEGF as the landmark for GOJ, the visibility of PV was also reported to be superior to WLI. These data support a promising role of LCI for better identification of PV in patients with SSBO, but should be validated in a prospective, multicentre study involving a larger number of subjects under a standardised condition of endoscopic observation. In contrast, however, another modality of IEE, blue laser imaging (BLI) did not show an improvement over WLI on the visibility of BO in this study. More recent reports also described a high rate of diagnosis of SSBO with LCI due to technical enhancement of colour difference.[68 69]

CQ 7

What is the location of the SCJ in the fully developed fetus?

Statement 7

The SCJ is located at the terminal end of the oesophagus in the fully developed fetus. There is no congenital columnar metaplastic change.

Agreement

Strongly agree 75%.
Agree with minor reservation 21%.
Disagree with major reservation 4%.
Strongly disagree 0%.

Quality of evidence

High 47%.
Moderate 39%.
Low 14%.
Very low 0%.

Strength of recommendation

Strong 68%.
Weak 32%.
Not applicable 0%.

Textual explanation

In the human fetus, the oesophagus is initially lined with simple columnar epithelium, and then ciliated cells appear.[70 71] Formation of squamous epithelium becomes evident initially in the middle oesophagus. Ciliated cells disappear after 36 weeks of gestation[71] but may persist until birth. During this period of conversion of ciliated epithelium into squamous epithelium, scattered foci of superficial columnar glands (oesophageal cardiac glands) originating from the foetal columnar epithelium develop most prominently in the upper and distal ends of the oesophagus.[70] After 20 weeks of gestation, well-defined acidic mucin-positive cardiac glands and pits become recognisable at the SCJ (or Z-line).[71] However, more precise cellular composition of these glands was not described in these studies. Zhou *et al* reported that a transitional zone with the characteristics of cardiac mucosa was universally present between squamous epithelium and oxyntic mucosa in the fetus and neonates.[72] In this study, mixed glands containing mucous cells with isolated parietal cells (corresponding to oxyntocardiac gland) appeared at 15 weeks of gestational age when parietal cells in the stomach emerge, indicating the transitional mucosa during prenatal period is predominantly of gastric origin. The proportion of transitional mucosa with pure mucous glands increases after birth. Similarly, Park *et al* identified the transitional epithelium mucous glands with scattered parietal cells abutted the squamous epithelium in 78% of fetal and paediatric autopsy cases.[73] Their autopsy cases, however, only covered cases up to 34 weeks of gestation and only three neonatal (within 1 month after birth) cases were included. Although these studies showed that well-identifiable SCJ is formed by full-term in the fetus, none of them described the location of SCJ in reference to the anatomical landmarks described in CQ 1 and 2 or the angle of His.

De Hertogh *et al* reported that the tiny area of cardiac mucosa (0.3–0.6 mm) in neonates lie at the same level (in 41-week fetus) or just distal to (0.3 mm at 7 months infant) the GOJ with the angle of His[74] as a reference marker. In contrast, Kilgore *et al* described the SCJ as aligned with the angle of His, which corresponded to the PEGF in paediatric autopsy series (mean age 6.3 years, range 16 days to 18 years).[75] In all of their cases, cardiac-type mucosa was present as a narrow zone (mean length of 1.2 mm on the gastric side of the oesophageal squamous epithelium.[75] Note that they were prudent enough to use the term ‘cardiac-type mucosa’ instead of ‘cardiac mucosa’. In any event, SCJ aligns with the anatomical GOJ with the angle of His as a reference.

In a detailed anatomical landmark study, the line connecting the DEPV is not straight but is concave and about 5 mm distal to the angle of His on the lesser curvature in adult specimens.[76] If similar anatomic relation between the angle of His and DEPV is maintained in neonates, the cardiac-type mucosa might be originated from the oesophageal mucosa at least on the lesser curvature side. However, further detailed histological studies in the fetal and neonatal specimens are required to ascertain if this anatomical relation between DEPV and the angle of His can be replicated in full-term neonates.

CQ 8

Does cardiac mucosa exist in fetuses and infants?

Statement 8

Cardiac mucosa exists in fetuses and infants, but its extent is minimal.

Agreement

Strongly agree 82%.
Agree with minor reservation 18%.
Disagree with major reservation 0%.
Strongly disagree 0%.

Quality of evidence

High 43%.
Moderate 50%.
Low 7%.
Very low 0%.

Strength of recommendation

Strong 50%.
Weak 50%.
Not applicable 0%.
Textual explanation for CQ 8, 9 are combined (see CQ 9).

CQ 9

What are the definition and histological features of cardiac-type mucosa?

Statement 9

Cardiac-type mucosa is histologically defined as mucosa, which consists of a foveolar epithelium with only mucous glands and no parietal cells.

Agreement

Strongly agree 61%.
Agree with minor reservation 39%.
Disagree with major reservation 0%.
Strongly disagree 0%.

Quality of evidence

High 48%.
Moderate 45%.
Low 7%.
Very low 0%.

Strength of recommendation

Strong 55%.
Weak 45%.
Not applicable 0%.

Textual explanation for statements 8 and 9

There has been a controversy as to whether the cardiac mucosa is a normal native constituent or an acquired metaplasia of the oesophageal squamous epithelium.[70–73 75–85] Researchers in the University of Southern California (USC) have asserted that the cardiac mucosa develops through metaplastic change of the oesophageal squamous epithelium as a consequence of reflux.[79–85] Park *et al* also demonstrated the presence of the transitional mucosa with oxyntocardiac glands but without pure cardiac glands in fetal and paediatric autopsy materials,[73] supporting their concept. However, Chandrasoma, a representative researcher from USC, acknowledged the presence of the cardiac mucosa (mostly oxyntocardiac type) in four out of seven autopsy specimens of infants.[79] In contrast, other groups demonstrated the existence of the cardiac mucosa in autopsy studies of fetuses and infants, though its extent was very limited.[72 74–77 86 87] For instance, De Hertogh *et al*[74] identified the cardiac mucosa as containing only mucous glands with a mean length of 1.0 mm (range 0.1–3 mm) and present distal to the squamous epithelium in all autopsy cases of fetuses, neonates and an infant (up to 7 month), but it spanned only 0.3–0.6 mm after birth. The same group confirmed their previous findings that the cardiac mucosa with pure mucous glands (mean length: 0.612 mm, range 0.160–1.308 mm) was present in fetuses, neonates and may grow in length with age, which showed similar cytokeratin staining with the Barrett's epithelium.[86] Derdoy *et al*[87] reported that cardiac mucosa with pure mucous glands was present in all paediatric autopsy cases including premature babies (mean age: 2.2 years, range: 1 day to 18 years). Zhou *et al*[72] also showed the presence of a very short stretch of transitional epithelium composed of simple columnar epithelium, pure mucous glands or mixed (oxyntocardiac) glands (mean length: 0.226 mm in foetuses, 0.167 mm in postnatal infants) between the oesophageal squamous epithelium and the gastric oxyntic mucosa in 78% of their series. The rest of their cases (22%) lacked this transitional mucosa in which the oxyntic mucosa directly abutted the squamous epithelium. Therefore, the majority of the autopsy studies involving neonates and infants supported the presence of the cardiac mucosa with pure mucous glands, if not completely circumferential, at the GOJ. Therefore, we agreed that the genuine cardiac mucosa exists as a native structural component at the GOJ, but the mean length is less than 1 mm. Kilgore *et al*[75] examined the mucosa of the GOJ in paediatric autopsy cases (mean age: 6.3 years, range 16 days to 18 years) and found cardiac-type mucosa with pure mucous gland in all specimens with a mean length of 1.8 mm (range: 1.0–4.0 mm). They also noted that this cardiac-type mucosa was adjacent to the transitional mucosa (cardio-oxyntic mucosa) in 59% cases, while the rest lacked the transitional mucosa and directly faced to the oxyntic fundic mucosa. The maximal length of combined cardiac-type and transitional-type mucosa was 8 mm. Therefore, the cardiac-type mucosa is still less than 5 mm during childhood, indicating that the traditional concept of cardiac mucosa extending several centimetres in the proximal stomach[88–90] is false as 'the cardiac glands' described in these papers contained parietal cells. Furthermore, this proposal by Hayward not based on tangible data more than half a century ago that the cardiac epithelium, for which his preferred term was the junctional epithelium, occupies about 1 cm to 2 cm of the most distal portion of the oesophagus[91] seems to be inappropriate in view of the current concept of the cardiac mucosa but might have been due to a mislabelling of the columnar metaplasia. In contrast, Miyagawa described two types of cardiac glands, one without oxyntic cells and another with oxyntic cells, present in the small area (0.5 cm) of the orifice of the stomach,[92] which is consistent with the current observations.

Regarding the GOJ in the adults, Sarbina and colleagues reported the length of cardiac mucosa ranged from 1 mm to 15 mm in surgically resected specimens in adult patients (median 55 years, range 24–82 years) with squamous cell carcinomas.[93] Nakanishi *et al* reported in their series of surgical specimens in patients with oesophageal squamous cell carcinomas (mean age: 63 years, range 46–94 years) that the mean length of the cardiac mucosa in the oesophagus was 4 mm (range 1–26 mm) and that of the gastric side was 13 mm (range 2–64 mm) with the angle of His as a reference point for GOJ.[94] More recently, Stojsic *et al* verified the presence of cardiac-type mucosa in all the adult autopsy cases (mean 59 years) at the angle of His (incisura).[95] Although they found areas with pure mucus glands (cardiac-type mucosa), they are always intermingled with the oxyntocardiac-type glands in the same section. The mean length of total transitional mucosa including oxyntocardiac type glands was 6.7 mm (range: 0.927–19.5 mm). As mentioned in CQ6, the line connecting the angle of His lies proximal to the GOJ with the DEPV as a reference,[75] the extension of the cardiac-type mucosa in to the gastric lesser curvature side should be minimal, if present.

Since the lengths of the 'cardiac mucosa' observed in adults were longer than those of neonates and infants, metaplastic changes, either in the adjacent oesophageal squamous epithelium or in the gastric mucosa would be contributing to this extension of the cardiac-type mucosa.[96]

Can we discriminate these three types of 'cardiac mucosa', namely, the pure cardiac mucosa consisting of mucous glands, the columnar metaplastic mucosa of the oesophagus and the atrophic oxyntocardiac or fundic mucosa devoid of parietal cells or chief cells? Currently, these three-types of mucosa are hardly discernible not only with H&E staining but with mucin histochemistry. Thus, in this consensus, we propose the umbrella term 'cardiac-type mucosa' instead of 'cardiac mucosa' to be used for describing the mucosa found at the adult GOJ. Indeed, this term has already been used by some of the prescient investigators.[75 89]

CQ 10

Which direction does the cardiac-type mucosa lengthen?

Statement 10

Cardiac-type mucosa expands proximally due to GORD.

Agreement

Strongly agree 71%.
Agree with minor reservation 29%.
Disagree with major reservation 0%.
Strongly disagree 0%.

Quality of evidence

High 68%.
Moderate 32%.
Low 0%.
Very low 0%.

Strength of recommendation

Strong 82%.
Weak 18%.
Not applicable 0%.
Textual explanation for CQ 9 and 10 is combined (see CQ10).

CQ 11

What is the role of hiatus hernia in the lengthening of cardiac mucosa?

Statement 11

In hiatus hernia, cardiac-type mucosa extends proximally due to reflux.

Agreement

Strongly agree 86%.
Agree with minor reservation 14%.
Disagree with major reservation 0%.
Strongly disagree 0%.

Quality of evidence

High 68%.
Moderate 32%.
Low 0%.
Very low 0%.

Strength of recommendation

Strong 79%.
Weak 21%.
Not applicable 0%.

Textual explanation for statements 10 and 11

As already described in the explanation for CQ7 and 8, several investigators have noted the association of longer cardiac-type mucosa with age, and inflammation at the GOJ,[77–83] though not confirmed by others.[74 75 87] However, these studies were retrospective observations and, thus, inadequate for establishing the cause–consequence relationship.

Recently, McColl's and colleagues demonstrated in their elegant prospective studies that the cardiac-type mucosa extends proximally in association with increasing age, central obesity and hiatus hernia in *H. pylori*-negative healthy volunteers.[97 98] In the healthy subjects, however, the LOS function remained intact and thereby limited the regurgitation within the LOS. Thus, the extension was confined within the LOS and further development of BO was prevented. This proximally extended cardiac-type mucosa closely resembled non-IM BO immunohistochemically.[99] This association with risk factors predisposing to GOR (age, central obesity and hiatus hernia) and resemblance to BO suggest that this proximal extension of cardiac-type mucosa is due to columnar metaplasia of the most distal oesophageal mucosa secondary to intrasphincteric GOR, which is associated with central obesity and may provoke the columnar metaplasia and consequently promote proximal extension of cardiac-type mucosa in these subjects.[97]

In contrast, in *H. pylori*-positive subjects, atrophic changes most frequently progress from the incisura to the proximal corpus mucosa, but also spreads from the GOJ mucosa to a more distal part in some cases.[100–103] In a recent study that examined parietal and chief cell density in biopsy specimens, the incisura and the GOJ were the two sites where a highest rate of reduction of both parietal cells and chief cells was observed in patients with *H. pylori* infection resulting in the longer length of mucosa without parietal cells distal to the GOJ.[104] This atrophic loss of parietal and chief cells distal to the SCJ mucosa can be accounted for as the consequence of extensive progression of atrophy from the distal gastric mucosa in the majority but may be due to the isolated atrophic change in the oxyntocardiac or fundic mucosa independent from the atrophic changes in the distal stomach. In a study with surgically resected specimens due to squamous cell carcinoma of the oesophagus, isolated IM below the SCJ was noted in 21% of them, whereas IM were continuous from the distal stomach in the majority (42%). About half of the isolated IM at the SCJ would be oesophageal mucosal origin as indicated by the presence of submucosal oesophageal glands.[105] Occurrence of atrophy and IM at the GOJ independent from those of the distal stomach in *H. pylori*-positive patients was reported in a Western population as well.[106] Another recent report investigating a large number of biopsies taken at the GOJ in the US population also demonstrated that IM in three subset of patients, one with columnar metaplasia in the distal oesophagus (BO), second with distal gastric IM and the rest without BO or distal gastric IM (isolated IM at the GOJ).[107]

It has been well-established that hiatus hernia is a prominent risk factor for BO (according to the traditional definition requiring the presence of SIM) irrespective of the length.[108 109] Although more prospective studies showing the cardiac-type mucosa proximally extends with hiatus hernia are required, it would be reasonable to assume that this condition facilitates the proximal extension of the cardiac-type mucosa.

CQ 12

What is the role of impedance and pH monitoring in the analysis of GOJ mucosal pathophysiology?

Statement 12

Currently available impedance and pH monitoring equipment have a limited role for investigating oesophageal junctional mucosal pathophysiology.

Agreement

Strongly agree 66%.
Agree with minor reservation 31%.
Disagree with major reservation 3%.
Strongly disagree 0%.

Quality of evidence

High 38%.
Moderate 55%.
Low 7%.
Very low 0%.

Strength of recommendation

Strong 55%.
Weak 45%.
Not applicable 0%.

Textual explanation

The presence of liquid and/or gas reflux is measured by the oesophageal impedance technique,[110] and intraoesophageal acid exposure time is measured by 24-hour ambulatory pH monitoring.[111] The combination of these modalities allows us to analyse the effect of acidic, weakly acidic and non-acidic reflux on oesophageal junctional mucosal pathophysiology.[112–114]

In general, intraoesophageal acid exposure time is known to be associated with the degree of oesophageal mucosal injury.[115] Recent studies suggest that mucosal injury is caused by immunological mechanisms triggered by inflammatory mediators or cytokines that are released from oesophageal mucosal cells by stimulation with acid.[116 117] There is an argument whether pH monitoring data truly reflect the acidic environment because the pH probe used for 24-hour pH monitoring is placed 5 cm above the GOJ, not at the GOJ itself. However, it is known that the acidic environment 5 cm above the GOJ reflects the true environment at the GOJ well.[118 119] It is also known that intraoesophageal acid exposure time (pH <4) results in columnar epithelialisation with increased expression of intestinal differentiation factors such as CDX1, CDX2 and BMP4 in oesophageal epithelial cells and stromal cells, respectively.[120] Therefore, measurement of intraoesophageal acid exposure time by 24 hour pH monitoring is useful for analysing oesophageal junctional mucosal pathophysiology as a method of predicting columnar epithelialisation. In fact, it has been reported that intraoesophageal acid exposure time is an important factor determining the length of Barrett's mucosa.[121–123] Regarding liquid and/or gas reflux, not only an acidic environment (pH <4) but also a weakly acidic environment (pH >4) is assumed to affect oesophageal junctional mucosal pathophysiology. It has been reported that a weakly acidic environment (pH >4) enhanced mucosal permeability, which results in dilation of intraepithelial spaces (DIS).[124 125] Experimentally, even a weakly acidic environment (pH >4) is known to release inflammatory mediators such as ATP from oesophageal mucosal cells.[126] However, the mechanisms of how a weakly acidic, as well as an acidic, environment induces mucosal permeability, mucosal impedance and metaplastic change are unknown.

It has been reported that baseline impedance represents mucosal integrity, which is related to changes of mucosal permeability, tight junctions and DIS.[127–130] If mucosal permeability increases, baseline impedance decreases, thereby it can be regarded as a new measure of oesophageal mucosal integrity, though the specific cause of lowering the baseline mucosal integrity cannot be inferred.

In this regard, the pathophysiological roles of bile acids need to be taken into consideration. The Bilitec that detects bilirubin in gastroduodenal refluxate has been used as a surrogate measurement of toxic bile acid. Increased oesophageal exposure of bile refluxate detected with this monitoring has been documented to be associated with the occurrence of Barrett's mucosa and mucosal injury.[131–136] Moreover, development of Barrett's metaplasia was less frequent in patients with acidic reflux alone, but was more prevalent in those with mixed bile and acid reflux.[131–134 136] Even higher bile reflux was observed in patients with complicated BO.[137] Clinically, it is also known that the injurious bile acid composition of the refluxate or gastric juice was higher in patients with BO than in patients without.[138 139] From these studies, it is thought that bile reflux affects oesophageal junctional mucosal pathophysiology. Since impedance and pH monitoring alone cannot evaluate the bile reflux, they have a limited role for investigating the bile-induced epithelial alterations at the GOJ.

CQ 13

What is the role of high-resolution manometry (HRM) and functional luminal imaging probe (EndoFLIP) planimetry in the evaluation of GOJ pathophysiology?

Statement 13

HRM is useful for evaluating the motor function of the GOJ, whereas functional luminal imaging probe (EndoFLIP) planimetry is useful for evaluating the distensibility of the GOJ.

Agreement

Strongly agree 86%.
Agree with minor reservation 14%.
Disagree with major reservation 0%.
Strongly disagree 0%.

Quality of evidence

High 69%.
Moderate 24%.
Low 7%.
Very low 0%.

Strength of recommendation

Strong 62%.
Weak 38%.
Not applicable 0%.

Textual explanation

Studies have reported techniques and usefulness of HRM in evaluating pathophysiology of oesophageal motor disorders.[140–150] A recently introduced functional lumen imaging probe (EndoFLIP) allowed three-dimensional imaging of lumen distensibility in real time and clarified functional and anatomical abnormalities of GOJ in cases with GORD, eosinophilic esophagitis, achalasia and other gastrointestinal motor diseases.[151–158] Due to limited availability and suboptimal resolution, however, no detailed study looking into the changes of histologic phenotype at the GOJ mucosa with this instrument has been published.

CQ 14

How can we define a GOJZ to clarify junctional pathologies?

Statement 14

A GOJZ can be defined endoscopically as a transitional segment extending 1 cm either side of GOJ.

Agreement

Strongly agree 69%.
Agree with minor reservation 17%.
Disagree with major reservation 7%.
Strongly disagree 7%.

Quality of evidence

High 21%.
Moderate 45%.

Low 24%.
Very low 10%.

Strength of recommendation

Strong 45%.
Weak 48%.
Not applicable 7%.

Textual explanation

The GOJ is defined as a border between the abdominal oesophagus and the gastric cardia. The GOJ is radiologically recognised by barium swallow as a sharp angulation between the tubular oesophagus and the sac-shaped stomach. This incisura is called angle of His. Angle of His is anatomically created by the collar-sling muscle of the stomach. The collar-sling muscle is the most inner muscle layer of the gastric cardia. The upper margin of the collar-sling muscle is considered as GOJ anatomically in muscle level.[91 159–161]

The SCJ is an epithelial landmark, which is clearly recognisable by endoscopy as a border of white oesophageal squamous mucosa and salmon pink gastric mucosa. Thus, SCJ seems to be a simple and endoscopically clear landmark of GOJ, but it quite often shifts proximally in pathological conditions like erosive oesophagitis and BO.[10 56]

The DEPV is an independent and anatomically fixed marker of GOJ (refer to CQ2). Without BO, DEPV corresponds accurately to SCJ.[45 53]

In most Asian populations, PV are clearly observed during endoscopic examination, but it is not uncommonly obscured in Western populations. In such a situation the PEGF is an alternative visually recognisable indicator. DEPV and PEGF are mostly in the same location, but PEGF is often affected by insufflated air volume at endoscopy (refer to CQ3–5 for detailed explanation).

In the submucosal layer, spindle veins are one of the specific markers of gastric cardia (online supplemental figure 2). When the spindle veins appear in the submucosal tunnel, they mark the beginning of the gastric submucosa.[47 48] Spindle veins run vertically and connect both branched vessel (at the level of muscularis mucosae (CM)) and submucosal drainage veins in the gastric cardia. Spindle veins are regarded as a characteristic anatomical landmark during submucosal endoscopy such as POEM (per-oral endoscopic myotomy).

The length of cardiac-type mucosa varies from a few millimetres to a few centimetres in the literature, but as explained in the previous sections above, the extent of this type of mucosa is very limited. Cardiac-type mucosa has its specific histological and immunohistochemical features (refer to CQ 7 to CQ 9).[72–75 86 93 94]

DEPV and PEGF at mucosal level, spindle veins at submucosal level and upper margin of oblique muscle at muscle level are not exactly at the same position but close to the DEPV (same position to SCJ without BO) with a few centimetre discrepancies. Therefore, GOJ is practically and theoretically recognised as a 'junctional zone' including these gaps and variations (refer to CQ 25).

Although metaplastic changes of the squamous epithelium exceeding 1 cm from the GOJ as defined in CQ 2 can reproducibly be recognisable as BO, which are supported by several consensus documents, the issue of the cardiac-type mucosa found within 1 cm from the GOJ has been left unsettled. In this consensus, we agreed that all the cardiac-type mucosa found above the GOJ should be considered as BO (refer to CQ 1). However, considering the discrepancies between the various guidelines, the area residing within 1 cm proximal to the GOJ is included in the GOJZ. Thus, oesophageal side of GOJZ includes so-called USSBO.

As for the range on the gastric side, we set the mucosal area within 1 cm from the GOJ (as defined by DEPV) based on the maximum extent of distribution of the cardiac-type gland mucosa in adults to reduce inclusion of pathologies of the gastric fundic mucosa (refer to CQ 9). This new definition of GOJZ is narrower by 1 cm in the gastric side than the well-known Sievert type II definition[162] but will substantially eliminate the inclusion of gastric pathology. To estimate the length of GOZ during routine endoscopic examinations, currently available endoscopes have a diameter of approximately 1 cm, which can be used as a reference.

CQ 15

What are the principal causes of inflammation in the GOJZ?

Statement 15

H. pylori infection and GOR are the principal causes of inflammation in the GOJZ.

Agreement

Strongly agree 90%.
Agree with minor reservation 3%.
Disagree with major reservation 7%.
Strongly disagree 0%.

Quality of evidence

High 80%.
Moderate 17%.
Low 3%.
Very low 0%.

Strength of recommendation

Strong 83%.
Weak 17%.
Not applicable 0%.

Textual explanation

H. pylori

Infection causes inflammation in all the gastric mucosa from the gastric cardia, corpus and antrum.[104 106 163–169] Inflammation tends to be more intense in the cardia as compared with gastric corpus.[104 106 163] *H. pylori* colonisation in the oesophageal mucosa, which correlated with inflammatory changes, was also reported.[170] However, inflammation in the cardia occurs even without *H. pylori* infection and has been shown to be associated with GOR.[44 79 169 171–173] Chronic inflammation of the GOJ mucosa appears to be the immediate consequence of GORD, correlating with endoscopic diagnosis,[169] and occurs without *H. pylori* infection.[44 79 169 171]

The inflammatory changes can be induced by bile reflux. Indeed, bile reflux gastritis and IM at the cardia are correlated.[174 175] Bile acids in low pH milieu are harmful in inducing oxidative and nitrosative stress in oesophageal epithelial cells, leading to DNA damage.[176 177]

Luminal nitrosative stress derived from dietary components (such as leafy vegetables containing a high amount of nitrates) could be a potential chemical insult to the human GOJ area.[178–181] The oesophageal microbiota other than *H. pylori* may also be involved in the inflammation in the GOJZ.[182–189] As Gram-negative microbiota are predominant in the reflux

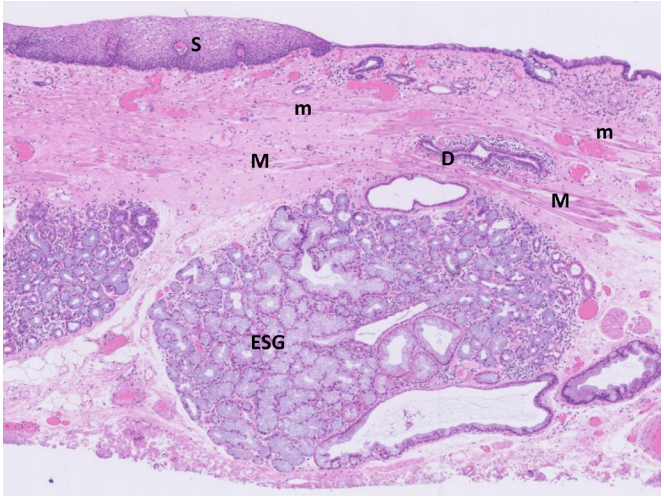

Figure 3 Histological features of oesophagus at the gastro-oesophageal junction. In this specimen, histological features unique to the oesophagus are depicted; namely double muscularis mucosa consisting of the superficial muscularis mucosae (m) and the deep muscularis mucosae (M), squamous epithelium (S) and the duct (D) connected to the oesophageal submucosal gland (oesophageal gland proper; ESG). Note the right side of the epithelium is covered by columnar epithelium containing goblet cells. Presence of double muscularis mucosae, and the oesophageal submucosal gland underneath the epithelium indicate that the columnar epithelium is not gastric mucosa but metaplastic oesophageal mucosa. (This histology photo was provided by professor KM.).

oesophagitis and BO, lipopolysaccharide derived from them may mediate inflammation and metaplasia via activation of Toll-like receptors in the epithelium and inflammatory cells at the GOJZ.[190] A number of studies also showed that obesity-induced adipocytokine abnormalities are associated with BO.[191–198] The role of these chemical, bacterial and endocrine factors in causing inflammation in the GOJZ should be further investigated.

CQ 16

What is the mechanism and clinical relevance of formation of double MM in the oesophagus?

Statement 16

Double MM is likely the result of inflammation and will guide the pathological staging and clinical management of lesions in the oesophagus.

Agreement

Strongly agree 73%.
Agree with minor reservation 21%.
Disagree with major reservation 3%.
Strongly disagree 3%.

Quality of evidence

High 63%.
Moderate 34%.
Low 3%.
Very low 0%.

Strength of recommendation

Strong 72%.
Weak 28%.
Not applicable 0%.

Textual explanation

Histologically, double MM is a specific feature of BO noted by Takubo *et al*[199] and has been observed in 71% of 66 histological sections.[51 198] Therefore, double MM is considered to be one of the most frequent features specific for BO.[200] The lamina propria of the original oesophagus lies within the double MM.[201 202] The deep MM is continuous with that of the gastric mucosa and lies beneath the oesophageal squamous epithelium. Smooth muscle fibres of the superficial MM of the columnar epithelial mucosa spread into the lamina propria. The proximal end of the thin MM becomes indistinct and disappears in fibrous tissue deep to the transition zone between the metaplastic columnar epithelium and the original squamous epithelium. The distal end of the superficial MM connects with the deep MM in the GOJZ. Thus, BO should be understood as comprehensive changes that involve the epithelium, lamina propria and MM, rather than a change limited to the epithelium (figure 3). However, no previous studies have investigated whether the columnar epithelium induces the stroma (lamina propria, MM) or vice versa. Although we can see double MM in cases of reflux oesophagitis, invasion by early squamous cell carcinoma, and sclerotherapy in the oesophagus, unlike the MM-associated BO, however, these double MM are seen in a very limited area. Therefore, we can consider that double MM is the result of reactive changes, likely to inflammation.[203]

CQ 17

Can metaplastic cardiac-type mucosa progress into IM?

Statement 17

Metaplastic cardiac-type mucosa shows molecular evidence of intestinal differentiation and appears to be the precursor of IM.

Agreement

Strongly agree 71%.
Agree with minor reservation 25%.
Disagree with major reservation 4%.
Strongly disagree 0%.

Quality of evidence

High 64%.
Moderate 29%.
Low 7%.
Very low 0%.

Strength of recommendation

Strong 71%.
Weak 25%.
Not applicable 4%.

Textual explanation

Many hypotheses have been reported regarding the cellular origin of BO with IM. These include (1) the columnar epithelium being directly generated from the oesophageal squamous epithelium,[204–206] (2) a gastric mucosa creeping theory,[207 208] (3) development from the oesophageal glands,[209] (4) development from the transitional mucosa at the GOJ,[210] (5) a foetal remnant[211] and (6) development from bone marrow cells.[212] Hattori's group had shown a sequence of morphological changes of squamous epithelium leading to BO, found a peculiar metaplastic change common to other parts of the gut, and proposed the concept

of a 'gut regenerative cell lineage' (GRCL).[204] The GRCL is characterised by pyloric-foveolar metaplasia with goblet cell metaplasia, which occurs in the regenerative process in response to chronic inflammation.[204 213] Columnar metaplasia without goblet cells reportedly has the potential to involve intestinal phenotypes.[204 207 214–216] The earliest form of columnar metaplasia resembles gastric mucosal epithelium.[204 207 214 217–219] The finding suggests that the cellular origin of the columnar metaplasia in the GOJZ might be similar to BO with IM. A recent report with sophisticated genetic analyses supports that BO originates from gastric cardia.[220] It is, therefore, presumed that with time, and ongoing injury and inflammation, the metaplasia then undergoes additional reprogramming, which ultimately results in the development of intestinal differentiation.

CQ 18

Which is the more common metaplastic mucosa in the GOJZ, cardiac or intestinal type?

Statement 18

Metaplastic cardiac-type mucosa is more frequent in the GOJZ.

Agreement

Strongly agree 79%.
Agree with minor reservation 21%.
Disagree with major reservation 0%.
Strongly disagree 0%.

Quality of evidence

High 68%.
Moderate 32%.
Low 0%.
Very low 0%.

Strength of recommendation

Strong 71%.
Weak 29%.
Not applicable 0%.

Textual explanation

From data obtained mainly from biopsy specimens, Barrett's mucosa has been classified into fundic, cardiac and intestinal types, in what was thought to be the order of arrangement from the distal end.[221] However, biopsies in this study were blindly taken by suction method and might have been obtained from the gastric mucosa in hiatus hernia. Therefore, it is questionable that the cellular phenotypes reported in this study truly represented those of BO. Observations of resected specimens have indicated that these types tend to be arranged in an intricate mosaic pattern, especially in SSBO.[222] However, it is difficult to judge the mucosal phenotypes as precise proportion of respective metaplasia was not reported, and inclusion of gastric fundic mucosa was suspected in this study. In a more recent study with a large number of biopsy samples taken under direct endoscopic examinations, cardiac-type mucosa without IM was most frequent (45.9%) as compared with IM (14.8%) within 1 cm from the GOJ as judged by PEGF.[223] There are a few studies which examined mucin phenotype in the columnar epithelium-lined oesophagus. A study with specimens obtained by endoscopic submucosal dissection showed that the cardiac-type mucosa, the intestinal-type mucosa and a mixture of both types were present in 34.3%, 14.3% and 51.4%, respectively.[224] The three epithelial types of columnar metaplastic mucosa were arranged as stated: cardiac in the distal, both cardiac and intestinal type in the middle and intestinal (when present) at the top. Another study from Japan reported that the SSBO predominantly had gastric-type mucin phenotype.[225] In a large multicentre study (*hisot*GERD trial), patients with cardiac-type mucosa at the GOJ were much higher than those with IM.[226] It should be noted that columnar, non-IM is a salient feature of paediatric or young patients with Barrett' epithelium or GOJ.[219 227–230] Age-dependent increase in the intestinal metaplastic changes indicates that cardiac-type metaplasia represents the early metaplastic change before IM arises.

Below the GOJ, genuine cardiac mucosa is present in the majority, if not all, of normal subjects. In a Chinese cohort, cardiac-type mucosa was more frequent than IIM in biopsy samples taken just below the GOJ.[231] Similarly, IM in the gastric cardia was present in only a minority of patients with or without BO.[232] In sum, we can conclude that the cardiac-type mucosa is the predominant metaplasia observed in the GOJZ, although the cellular origins of the metaplastic cardiac-type mucosa might be different depending on the location.

CQ 19

What factors are associated with IM in the GOJZ?

Statement 19

Gastric acid, pepsin, bile, nitrosative stress and *H. pylori* are associated with IM in the GOJZ.

Agreement

Strongly agree 72%.
Agree with minor reservation 21%.
Disagree with major reservation 7%.
Strongly disagree 0%.

Quality of evidence

High 47%.
Moderate 39%.
Low 14%.
Very low 0%.

Strength of recommendation

Strong 50%.
Weak 50%.
Not applicable 0%.

Textual explanation

Association of mixed acid and bile reflux with BO with the metaplastic mucosal length of over 1 cm has been well documented.[130 134 233] Mechanistically, involvement of gastric acid and bile in the development of metaplastic changes were also indicated by experimental studies.[234–238] It can be presumed that similar mechanisms are involved in the intestinal metaplastic changes in the GOJZ. In addition, reactive nitrogen species imposed at human GOJZ[178 179] could be involved in the development of BO, which was shown in basic experimental studies[239 240] although the association in the clinical settings remains to be proved. Since Barrett's metaplasia is accompanied and preceded by cardiac-type metaplasia, and gene expression and immunohistological patterns between the metaplasia at both sites are similar,[99 241] cardiac-type metaplasia may be the precursor of Barrett's metaplasia with IM. In a longitudinal observational cohort study, progression to macroscopically visible BO was observed in about a quarter of patients with IM at the SCJ, supporting this notion.[242] Thus, causative factors for Barrett's

metaplasia (eg, gastric acid, bile, nitrosative stress) could also act as stimuli for development of cardiac-type columnar metaplasia (see also CQ 20 for the risk of neoplasia in the columnar metaplasia).

In subjects with *H. pylori* infection, but without reflux, however, chronic inflammation due to *H. pylori* can be a major causative factor for IM in the GOJZ.[104 106 243–247] In a large autopsy series, IM at the GOJZ was localised in the gastric side (namely, distal to the PEGF) in more than 90% cases. These cases also had more IM in the distal stomach, indicating a link with *H. pylori* gastritis.[248]

As mentioned in CQ14, dysbiosis of the oesophageal microbiota and alterations of adipocytokines might also play a role in the IM.

CQ 20

Do we have useful molecular markers to predict the progression of metaplastic cardiac-type mucosa to IM?

Statement 20

Although several markers have been proposed, there is no established marker ready for clinical application.

Agreement

Strongly agree 76%.
Agree with minor reservation 24%.
Disagree with major reservation 0%.
Strongly disagree 0%.

Quality of evidence

High 38%.
Moderate 62%.
Low 0%.
Very low 0%.

Strength of recommendation

Strong 52%.
Weak 48%.
Not applicable 0%.

Textual explanation

Although many hypotheses concerning the pathogenesis of GOJ mucosal metaplasia have been proposed, the precise molecular mechanisms of metaplastic change at the GOJ mucosa and the origin of cells from which GOJ metaplastic mucosa forms are not clear. The elevated expression of CDX2, EpCam and villin have been reported at the human GOJ metaplastic mucosa.[213 214 249–252] However, increases in these markers were shown in the cardiac-type columnar metaplasia and may be used as predictors for the future development of IM. Trefoil factor 3 (TFF3) is another marker for detecting BO[253] employed for non-invasive screening. Unfortunately, TFF3 may not be suitable for identifying the IM at the GOJZ as it was expressed in the cardiac-type mucosa as well as oesophageal submucosal gland.[254 255] More recently, gene methylation profile has been explored as diagnostic biomarkers.[256–261] Furthermore, microRNA (miR) profiles in the oesophageal mucosa as well as blood unique to BO have been extensively investigated.[262–266] Although these newer biomarker panels have advantages of providing more objective measures and several promising results have been reported, their diagnostic performance on differentiating BO with IM from pure columnar metaplasia and on the intestinal metaplastic changes at the GOJZ requires further verification.

CQ 21

Does metaplastic cardiac-type mucosa in the absence of IM in the GOJZ predispose to adenocarcinoma?

Statement 21

Metaplastic cardiac-type mucosa in the absence of IM in the GOJZ appears to have a risk of progression to malignancy.

Agreement

Strongly agree 49%.
Agree with minor reservation 45%.
Disagree with major reservation 3%.
Strongly disagree 3%.

Quality of evidence

High 17%.
Moderate 59%.
Low 21%.
Very low 3%.

Strength of recommendation

Strong 31%.
Weak 66%.
Not applicable 3%.

Textual explanation

The criteria used in the USA suggest that metaplastic columnar epithelium with goblet cells is the main precursor of dysplasia and cancer, and as such, represents the specific subgroup of patients with columnar lined oesophagus at highest risk for neoplastic progression[2 267–269] (see also textural explanation for CQ 1). While it is true that most cancers arise in the columnar lined oesophagus with goblet cells, there is indisputable evidence that metaplastic non-goblet columnar mucosa is at risk for cancer.[31–35 221] In a recent study by Lavery *et al*, development of adenocarcinoma from premalignant columnar epithelium without goblet cells was convincingly demonstrated by tracing the clonal origin of cancer across an entire Barrett's segment via a combination of histopathologic spatial mapping and clonal ordering.[36] The non-goblet columnar epithelium, mainly cardiac-type mucosa, shows molecular abnormalities and the potential for neoplastic progression.[28–36 218 224 270] A small prospective study also showed that development of adenocarcinoma in patients with the columnar metaplastic mucosa without IM.[271] Therefore, metaplastic cardiac-type mucosa without IM is deemed to be an 'at risk' condition predisposing to neoplastic transformation.

CQ 22

Can IEE improve the diagnosis of IM in the GOJZ?

Statement 22

IEE with or without magnification can enhance the detection of IM in the GOJZ.

Agreement

Strongly agree 83%.
Agree with minor reservation 17%.
Disagree with major reservation 0%.
Strongly disagree 0%.

Quality of evidence
High 37%.
Moderate 60%.
Low 3%.
Very low 0%.

Strength of recommendation
Strong 53%.
Weak 47%.
Not applicable 0%.

Textual explanation
It has been reported that magnification endoscopy with chromostaining (methylene blue, indigo-carmine, and acetic acid) and IEE such as NBI with magnification or LCI without magnification achieved high degree of accuracy for detection of the IM in BO.[60 68 69 272–283] Although evidence is limited, improved diagnostic performance of IEE with or without magnification on the diagnosis of IM in the GOJZ has also been reported.[273 283]

CQ 23
What should adenocarcinoma arising from the 'GOJZ' be named?

Statement 23
We propose to name it 'GOJZ adenocarcinoma'.

Agreement
Strongly agree 90%.
Agree with minor reservation 10%.
Disagree with major reservation 0%.
Strongly disagree 0%.

Quality of evidence
High 44%.
Moderate 43%.
Low 10%.
Very low 3%.

Strength of recommendation
Strong 67%.
Weak 33%.
Not applicable 0%.
Textual explanation for CQ 23 (see CQ 24).

CQ 24
How is a GOJZ adenocarcinoma defined?

Statement 24
A GOJZ adenocarcinoma is one with its epicentre lying within 10 mm either side of the GOJ.

Agreement
Strongly agree 93%.
Agree with minor reservation 7%.
Disagree with major reservation 0%.
Strongly disagree 0%.

Quality of evidence
High 47%.
Moderate 50%.
Low 3%.
Very low 0%.

Strength of recommendation
Strong 70%
Weak 30%.
Not applicable 0%.

Textual explanation for CQ 23 and CQ 24
A short segment (GOJZ) straddling 1 cm proximal and distal to the GOJ has different spectra of the mucosa (see CQ 14 for the definition of GOJZ). However, the adenocarcinoma is assumed to develop only from the columnar epithelial cells such as the cardiac-type mucosa, specialised metaplastic mucosa, oesophageal cardiac glands (superficial oesophageal glands) and oesophageal submucosal glands, but not from the stratified oesophageal squamous cells. As it is difficult to exactly identify the cellular origin of the epithelium from which the adenocarcinomas in this area originate, an umbrella term 'GOJZ adenocarcinoma' is proposed for encompassing them in this meeting.

This new definition of GOJZ adenocarcinoma is distinct from the previous definitions on the adenocarcinoma of the GOJ, often called 'cardiac cancer' or 'cancer in the gastric cardia'. For instance, Misumi *et al* proposed the definition of cardiac cancers as the tumours having its epicentre residing between 1 cm proximal and 2 cm distal to the GOJ area.[284] The justification for his definition was derived from meticulous histological examinations on resected specimens where he showed that the distribution of 'cardiac glands' was 2.6 mm above and 6.7 mm below the SCJ on average. In his later report,[285] the distribution of the cardiac glands ranged 7.5 mm proximal and 13 mm distal to the SCJ with the mean distance 0.8 mm for the proximal margin and 2.7 mm for the distal margin from the SCJ. Unfortunately, however, the landmark used for judging the GOJ in these studies was the SCJ which was located 0.5 cm to 1 cm proximal to the angle of His. Indeed, the submucosal oesophageal gland, a hallmark of the oesophageal tissue, was depicted in the 'gastric' side and several squamous cell carcinomas occurred in the 'gastric' side of the junction in these reports, implying the true GOJ lies below the reference line (SCJ) employed for these studies. If the angle of His had been used as the reference line, the distribution of cardiac gland should be less than 5 mm from the true GOJ in the majority of cases, which corroborates well with the ranges described by other anatomical studies (see CQ 7 and 8).

In Europe, Siewert proposed to classify the adenocarcinomas arising in the lower oesophagus to upper stomach into three subclasses (designated as I, II and III according to the location of tumour epicentre) based on his extensive surgical experience[162 286] in order to guide to selection of surgical operation. In this Siewert classification, 'true cardia cancer', designated as Siewert type II, was defined as a tumour with the epicentre located from 1 cm above to 2 cm below the GOJ, that is, similar to Misumi's definition. Again, SCJ (Schleimhautgrenze: Z-line) was used as the GOJ in his report, and, hence, the range of the true cardiac-type mucosa of Siewert type II likely was overestimated in the gastric side. Furthermore, as has been discussed in the previous sections (CQ 8 and 9), the cardia mucosa consisted with pure mucous glands (excluding oxyntocardiac glands), if present, is confined within several millimetres distal to the GOJ. Thus, by adopting the concept of GOJZ adenocarcinoma, which narrows the mucosal area by 1 cm in the distal gastric side than the well-recognised Siewert type II adenocarcinoma,[162] inclusion of gastric cancer should be reduced (see CQ 25 and CQ 26). Indeed, Ichikura *et al* proposed a new definition of 'true

cardia carcinoma' arising within 1 cm from the GOJ (type IIA) as their nodal involvement pattern was different from the subcardia cancer (type IIB, more than 1 cm distal to GOJ).[287] Therefore, GOJZ adenocarcinomas corresponding to true cardia carcinoma (type IIA) by Ichikura *et al* would better reflect clinical features of adenocarcinomas regarding lymphatic spread and provide clearer guidance for selecting surgical management. This new definition pertinent to the histologic evidence on the distribution of the cardia mucosa may offer a practical clinical benefit.

However, this concept would still include adenocarcinomas of heterogeneous origins; those originating from the USSBO, those from the oesophageal submucosal glands, and those from the metaplastic cardiac or oxyntocardiac epithelium and so forth. Nevertheless, this concept will provide a category for the adenocarcinomas arising from the ultrashort segment (<1 cm) columnar epithelium which many guidelines have precluded from the diagnosis of BO due to the length rule of 1 cm. As proposed in CQ 1, however, if lifting the length rule of 1 cm for the diagnosis of BO is internationally agreed on, adenocarcinomas located in the proximal half of the GOJZ should be unified as adenocarcinoma of the oesophagus arising from the Barrett's epithelium (as defined in CQ 1) in the future.

CQ 25

Are there two distinctive aetiologies of cancer in the GOJZ?

Statement 25

There are two major distinctive aetiologies for GOJZ adenocarcinoma: GORD-related and *H. pylori* infection.

Agreement

Strongly agree 100%.
Agree with minor reservation 0%.
Disagree with major reservation 0%.
Strongly disagree 0%.

Quality of evidence

High 97%.
Moderate 3%.
Low 0%.
Very low 0%.

Strength of recommendation

Strong 100%.
Weak 0%.
Not applicable 0%.

Textual explanation

(see CQ 26).

CQ 26

Should cancers arising in the GOJZ be classified separately from cancers arising in the rest of the stomach?

Statement 26

Cancer arising in the GOJZ has a mixed aetiology and should be classified separately from cancers arising in the rest of the stomach that are largely due to *H. pylori* infection.

Agreement

Strongly agree 90%.
Agree with minor reservation 7%.
Disagree with major reservation 3%.
Strongly disagree 0%.

Quality of evidence

High 53%.
Moderate 40%.
Low 7%.
Very low 0%.

Strength of recommendation

Strong 80%.
Weak 20%.
Not applicable 0%.

Textual explanation for CQ25 and CQ26

Several studies have consistently documented the distinct pathways leading to the GOJ adenocarcinoma as defined by Siewert type II,[162] based on the differences in several pathophysiological factors such as gastric acid secretion,[288] reflux esophagitis or columnar metaplasia of the oesophagus,[289 290] *H. pylori* infection,[289–291] gastric atrophy[288–293] and IM.[291 294] Furthermore, different biological and oncogenic alterations have been observed among these tumours.[295 296] This evidence strongly suggests that the adenocarcinomas arising in the GOJ have two distinct aetiologies, one associated with hypersecretion of gastric acid and reflux oesophagitis, and another with gastric acid hyposecretion and advanced gastric atrophy. It has to be remembered, however, that a subset of patients with the Siewert's type II adenocarcinomas retained acid hypersecretion despite of *H. pylori* infection.[297]

Considering the tumour locations, it was reported that superficial adenocarcinomas located above the GOJ judged by the DEPV associated with reflux oesophagitis with lower grade of gastric atrophy while those below the junction had less reflux oesophagitis with more advanced gastric atrophy.[298] This observation was supported by Uedo *et al* who reported that Siewert-type II adenocarcinomas at T1 stage could be separated according to the tumour location: those above the GOJ were more associated with GORD while those below the GOJ were associated with *H. pylori* infection and atrophy.[299] Thus, adenocarcinomas arising in the proximal segment of the GOJZ had similar aetiology with OAC. In contrast, the majority of GOJZ adenocarcinomas arising from the distal segment below GOJ had more mucosal background akin to gastric adenocarcinomas caused mainly by *H. pylori* infection, at least in East Asia. However, simple aetiological dichotomy of the adenocarcinoma may not be appropriate. In Yamada's report,[293] 81% of gastritis positive group had reflux oesophagitis, which was similar to the non-gastritis group, although SSBO in gastritis-positive group was 36%, significantly less than that of non-gastritis group (72%). In Uedo's data, 31% of patients classified into 'atrophy' group were of closed types (CII and CIII), according to Kimura and Takemoto's classification[300] without endoscopic atrophy in the vicinity of GOJ. Moreover, GORD symptoms and SSBO were present in 52% and 41%, respectively, in the 'atrophy' group,[299] indicating the reflux-induced mucosal changes occurred in a substantial proportion of the 'atrophy' subgroup. These findings corroborated well with the report by Inomata *et al*.[297]

Collectively, adenocarcinomas arising in the GOJ are assumed to have at least three aetiological subgroups, the first one with high gastric acid secretion accompanied with reflux in the absence of *H. pylori* infection, the second with high gastric acid secretion, positive reflux, mild atrophy with *H. pylori* infection

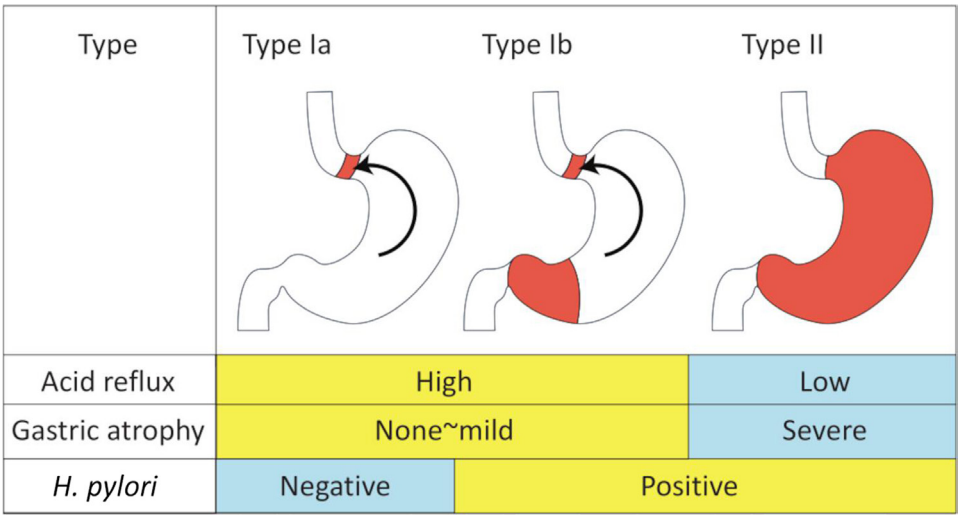

Figure 4 Pathophysiological mechanisms of columnar metaplasia at the gastro-oesophageal junction zone (GOJZ). Two independent mechanisms, gastroduodenal reflux in high gastric acidity (type I) and hypo- or achlorhydria due to advanced atrophy caused by *H. pylori* infection (type II) were postulated for causing columnar metaplasia at the GOJZ. Type I may be subdivided further into two subtypes, gastroduodenal reflux in *H. pylori*-negative patients without gastric atrophy (type Ia), and gastroduodenal reflux in *H. pylori*-positive patients with mild gastritis limited in the antrum (type Ib). Nitrosative and oxidative stress occurring at the GOJ may also contribute the inflammation. In *H. pylori*-positive subjects, inflammation around the GOJ may be higher than the gastric corpus and can be a cause of atrophic and/or intestinal metaplastic change. However, more frequent pattern of gastric atrophy is pangastritis progressing from the distal stomach toward proximal direction. Theoretically autoimmune gastritis (AIG) may involve GOJZ. However, detailed investigation on histological changes at the GOJZ in AIG is scarce, and hence this hypothetical subtype is not depicted in this figure. Curved black arrows indicate reflux (gastric acid and bile acid). Vermillion areas indicate inflammations and/or metaplasia caused by these factors.

(similar to those with duodenal ulcer) and the third with low gastric acid secretion, negative reflux and extensive gastric atrophy with positive *H. pylori* infection (figure 4). In patients with autoimmune gastritis with extensive corpus atrophy may be an additional subgroup belonging to the third type, but data for the neoplastic changes at GOJZ in AIG are scarce and, thus, require further study.

Although Siewert defined the adenocarcinoma arising from the mucosa between 1 cm above and 2 cm below the GOJ as 'true cardia adenocarcinoma' (Siewert type II), true cardiac mucosa was shown to span only a much narrower area than that defined by Siewert type II cancer (see CQ 8 and CQ 9). Therefore, the distal mucosa beyond this narrow area of the true cardia mucosa should be considered as the gastric fundic mucosa. Logically, the adenocarcinoma arising from the gastric mucosa should be classified as gastric cancer, not junctional adenocarcinoma nor carcinoma of the cardia. By adopting more strict definition for the adenocarcinoma arising in the GOJ (CQ 23 and CQ24), we would better delineate the aetiology of the junctional adenocarcinomas by excluding proximal gastric cancers.

CQ 27

What molecular events lead to neoplasia arising in the GOJZ?

Statement 27

Many genetic and epigenetic abnormalities have been described in GOJZ neoplasia, but the exact mechanisms remain unclear.

Agreement

Strongly agree 93%.
Agree with minor reservation 7%.
Disagree with major reservation 0%.
Strongly disagree 0%.

Quality of evidence

High 62%.
Moderate 38%.
Low 0%.
Very low 0%.

Strength of recommendation

Strong 69%.
Weak 31%.
Not applicable 0%.

Textual explanation

As described in the previous CQs, adenocarcinomas arising in GOJZ have different aetiologies and likely originate from various cancer stem cells. For this reason, no simple account on the molecular pathogenesis of the neoplasia arising in the GOJZ would be possible. However, with the advent of rapid advancement of sequencing technology, substantial data have been accumulated to analyse the molecular abnormalities of the OAC.[301–310] These reports verified that alterations of *p53* and $p16^{INK4a}$ as the most frequent early genetic events as documented earlier.[311–316] Importantly, such genetic changes were shown to be present in the Barrett's stem cells.[317] Between the two, *p53* may play a more important role in the progression to cancer by underpinning the generation of clonal diversity,[307 317] a significant factor for this transition. A longitudinal study also demonstrated that *p53* lesions increased the risk of progression to cancer (OR=13.8 with 95% CI 3.2 to 61.0, p<0.001)), whereas $p16^{INK4a}$ lesions did not.[318] Interestingly, these new data revealed the presence of multiple clones with different molecular alterations in the precancerous Barrett's epithelium[303 304] even in the same patients, not to mention among the different

patients, suggesting a complexity of molecular pathways leading to cancer.

Since adenocarcinomas arising from USSBO were included in some of these studies,[301 305 306 310 318] we may assume that the molecular events leading to neoplasia should resemble with OAC in this subset of GOJZ adenocarcinomas. Although some differences between OAC and cancer in the cardia were noted in earlier studies,[319–322] a number of genetic changes observed in the adenocarcinoma in the cardia have also been shared with OAC.[304 305] Furthermore, a large-scale comparative genomic analysis of OAC revealed a similarity not only with the adenocarcinoma in the GOJ area but also with the chromosome instable subset of gastric adenocarcinoma, predominantly located in the proximal stomach.[308] Another report also demonstrated similar transcriptome profiles of intestinal type of the three subtypes of GOJ adenocarcinomas defined by Siewert, in which Asian cohort was also included.[309]

Except for some particular chromosomal sites susceptible to DNA damages (fragile sites such as *FHIT* or *WWOX* locus),[323 324] chromosomal instability occurs in a late stage of oesophageal carcinogenesis, often accompanied with gene amplification of growth factor receptors such as *ERBB2* (*HER2*) and *EGFR*.[303–305 324] In some cases, massive catastrophic chromosomal aberrations, such as chromothripsis and breakage-fusion-bridge events, precipitate cancerous changes.[304 324 325] Similar major chromosomal aberrations were shown in the cardia cancer and associated high-grade dysplasia as well.[306 308] Collectively, we may assume that the overall genetic landscape of GOJZ adenocarcinomas defined in this consensus would remain similar to that of the OAC.[310]

In addition to these genetic mutations and chromosomal changes, epigenetic abnormalities such as methylations have been shown in BO and OAC.[308 310 326–331] Recent comprehensive methylome analyses identified multiple subtypes with distinctive relations to transcriptional and chromosomal changes,[327–331] implying the presence of diverse carcinogenic routes with complex interactions between genetic and epigenetic changes. Other epigenetic changes occurring in non-coding RNA, such as miR and long non-coding RNAs, have been documented as early as the mucosa with reflux oesophagitis, which are progressively diversified from Barrett's mucosa, dysplasia to adenocarcinoma by methylation and chromosomal number variation,[332–339] adding further layer of complexity in the genetic changes leading to neoplasia.

Further investigations are required for unravelling the precise temporal relationship and causal mechanisms involved in the alterations between genetic alterations and neoplastic progression with a careful consideration on tumour localisation.

It should be of note that the role of *H. pylori* infection, one of the major culprits assumed to invoke inflammatory changes in the GOJZ, has not been linked to the serial genetic pathways leading to the GOJZ adenocarcinomas. Despite being a major aetiologic factor in gastric carcinogenesis, the role of *H. pylori* in genetic changes was ill defined across the major genetically classified subsets of gastric cancers,[340] likely due to the lack of information on the infection status. Future studies on genetic changes in the GOJZ adenocarcinoma should incorporate this important aetiological factor.

CQ 28

Can IEE improve diagnostic yields of early adenocarcinoma arising in the GOJZ?

Statement 28

IEE with or without magnification is likely to improve diagnostic yields of early adenocarcinoma arising in the GOJZ.

Agreement

Strongly agree 86%.
Agree with minor reservation 14%.
Disagree with major reservation 0%.
Strongly disagree 0%.

Quality of evidence

High 59%.
Moderate 38%.
Low 3%.
Very low 0%.

Strength of recommendation

Strong 69%.
Weak 31%.
Not applicable 0%.

Textual explanation

There is no study focusing on endoscopic diagnosis of early adenocarcinoma arising in the GOJZ alone. Because GOJ is located between the distal oesophagus and the proximal stomach, the evidence obtained in the Barrett's neoplasia and early gastric cancer would be inferred for early adenocarcinoma arising in the GOJZ. Regarding the Barrett's neoplasia, early studies did not provide evidence for increased interobserver agreement or increased yield to identifying early neoplasia,[341] a more recent meta-analysis, however, revealed IEE (both chromoendoscopy and equipment-based IEE) with or without magnification increased the diagnostic yield for detection of neoplasia by 34% in comparison with WLI.[342] There was no significant difference between chromoendoscopy and equipment-based IEE in the subanalysis. The American Society for Gastrointestinal Endoscopy (ASGE) recommended acetic acid chromoendoscopy and NBI, which met the thresholds (per-patient sensitivity of >90%, negative predictive value of >98%, specificity of >80%) set by the ASGE preservation and incorporation of valuable endoscopic innovations (PIVI).[343] To further enhance diagnostic reproducibility among different endoscopists, endoscopic classifications of Barrett's neoplasia by using NBI with magnification have been established.[344 345] However, the PIVI thresholds achieved by these techniques were on the diagnostic performance on detected lesions, but their capability of detecting neoplastic lesions in surveillance endoscopy was not confirmed. Indeed, Boerwinkel *et al* concluded that these advanced imaging techniques did not significantly increase the number of patient with a diagnosis of early neoplasia compared with high-definition white light endoscopy.[346] Other IEE modalities, iScan Optical Enhancement system, BLI and LCI also demonstrated improved visualisation of neoplasia in BO,[67 68 347–349] but their utility in neoplasia surveillance in BO requires further validation. In an attempt to achieve more stable, higher diagnostic performance in detecting neoplasia in patients with BO, artificial intelligence (AI) technologies have been reported,[350 351] which is expected to be introduced in clinical practice in the near future.

In terms of early gastric cancer, a meta-analysis for the characterisation of early gastric cancer revealed advantages of NBI with magnification over WLI with pooled sensitivity and specificity of 0.83 versus 0.48 and 0.96 versus 0.67, respectively.[352] The classification system based on surface mucosal and vessel

pattern is well established.[353] In recent well-designed controlled studies, however, the second-generation NBI was not superior to high-definition WL endoscopy in detecting early GC.[354 355] In contrast, considerably higher performance in detecting gastric neoplasia with another IEE modality, LCI has been reported from different institutions and countries,[356–358] indicating promising role of this IEE in early gastric cancer surveillance.

As shown in the detection of Barrett's neoplasia, a number of studies have reported highly accurate diagnostic capability in the diagnosis of early gastric cancer with AI technologies,[359–363] and their introduction to real clinical practice to assist endoscopists will be available soon.

Considering the limitation and difficulty in adhering to the current Seattle protocol for detecting neoplasia even in patients with a shorter length of BO,[364] these AI technologies coupled with IEE are expected to facilitate the detection of neoplastic lesions arising not only in the GOJZ but also in the long-segment BO.

DISCUSSION

A number of controversial issues regarding the GOJ area have been left unresolved until today. These include the definition of BO in terms of length criteria and of the requirement for SCE (IM), the definition of GOJ and the question on the existence of the cardia mucosa as an innate epithelium. In order to resolve these issues, a critical starting point should be the definition of the GOJ applicable to our clinical practice with endoscopic diagnosis, as we cannot determine the exact length of BO nor the extent of the cardia mucosa unless we decide the point to separate oesophagus from stomach.

Two criteria, PEGF and DEPV, have been utilised so far for the definition of the GOJ. Although these definitions have inherent shortcomings, in this consensus meeting we adopted DEPV as a more appropriate landmark for defining GOJ, since it has a more valid anatomical basis as the landmark. It has to be remembered, however, that a proper observation method with appropriate air insufflation is required to identify this landmark, often neglected in the past. Recent advanced endoscopic image enhanced technology may also facilitate the identification of this landmark. In order to facilitate the adoption of DEPV as the landmark for GOJ, an illustrative manual showing the technical details for proper observation method is planned. We hope that the feasibility of DEPV as the standard landmark of the GOJ is verified by international multicentre prospective studies with or without IEE.

Regarding the definition of BO that has been discrepant among international guidelines, we adopted a new definition in which both length definition and requirement of specialised columnar metaplasia (ie, IM) were abolished. The length threshold for diagnosis of BO has historically been changed, and the 1 cm of length threshold adopted in some of the current guidelines is set not on explicit scientific basis but on technical reasons such as poor reproducibility of the endoscopic diagnosis and dubious clinical significance. However, adenocarcinomas arising from the USSBO and/or GOJZ are increasing in Japan.[365] These adenocarcinomas arising from USSBO are designated as Barrett's adenocarcinomas in Japan and possibly in the USA (according to the AGA guidelines when IM is coexisted in the short (less than 1 cm) segment of columnar metaplasia). However, adenocarcinomas occurring in the GOJZ have been classified under GOJ adenocarcinomas separate from OAC (Barrett's adenocarcinoma) according to the ICD-11 classification[366] or IARC's classification of digestive tract tumours.[367] In this consensus meeting, we still have retained the concept of GOJZ adenocarcinoma considering internationally accepted clinical practice and disease classification systems, but theoretically adenocarcinomas arising from the USSBO should be classified under OAC in the future. As for the requirement of IM for defining BO, recent evidence indicates that columnar metaplasia without IM entails elevated risk of neoplastic changes. Problems of sampling error and inconvenience of random sampling are another reason to lift this requirement. Indeed, a very recent provocative study with sophisticated genetic analyses presented evidence that BO may originate from gastric cardia,[220] a step forward to unify the proximal segment of GOJZ as BO.

In close relation to the issue of columnar metaplasia of the oesophagus is the controversy on the nature of cardiac mucosa, whether it is an innate mucosa or a metaplastic changes of oesophageal squamous epithelium. In this consensus, we agreed that cardiac epithelium with pure mucous glands does exist as an innate mucosa between squamous epithelium of the oesophagus and gastric oxyntic mucosa based on a detailed review of the literature. However, the genuine cardiac mucosa, thus defined, only spans less than 10 mm, and may not be circumferential in some cases. Therefore, the cardia cancer, most widely adopted definition by Siewert type II, which included adenocarcinomas located 2 cm distal to the SCJ, need to be redefined in order to avoid inclusion of the proximal gastric cancers in this category. Therefore, the distal range from the GOJ (defined as DEPV) of adenocarcinomas arising from the subjunctional mucosa was decreased to 1 cm. In clinical practice, however, it is often difficult to identify the precise mucosal origin of the adenocarcinomas of the GOJ, we propose the concept of GOJZ spanning 1 cm proximal and 1 cm distal to the GOJ and adenocarcinomas arising from the GOJZ as GOJZ adenocarcinomas. As mentioned previously, this GOJZ adenocarcinoma can develop from several cellular origins, such as metaplastic oesophageal mucosa, oesophageal cardiac glands, oesophageal submucosal glands, genuine cardia glands, transitional oxyntocardiac glands and metaplastic oxyntic mucosa. Further refined definition of GOJZ adenocarcinomas, in particular, separation of Barrett's adenocarcinomas from this concept should be addressed to avoid duplication. Nevertheless, this new definition of GOJZ adenocarcinomas will better serve to clarify aetiological factors contributing to neoplasia arising at this particular zone, by principally eliminating proximal gastric cancers due to *H. pylori* infection. At present, we admit that adoption of new concept of GOJZ requires wider recognition and practice implementation. For which, it is planned that this concept is discussed at the consensus meeting held at the 15th international gastric cancer congress 2023. As for the major pathoaetiological factors, gastroduodenal reflux, nitrosative stresses and microbiota including *H. pylori* infections have been proposed. Although advanced atrophy caused by *H. pylori* can contribute to proximal gastric cancer, a majority of them may be excluded by this new concept. However, two lines of evidence showing that the metaplastic changes can take place in the cardia region independent from the distal stomach, and *H. pylori* can infect metaplastic oesophageal mucosa suggest that three major pathoaetiologies, hyperacidity with reflux and/or oxy- and nitrogen-radicals, hyperacidity and *H. pylori* infection and hypoacidity due to advanced atrophy caused by *H. pylori* infection. Thus, the conventional idea that *H. pylori* infection might be protective in the development of BO is too simplistic, since acid hypersecretion similar to the situation seen in duodenal ulcer can take place in *H. pylori* infection and damage the GOJ mucosa. It is also possible that other microbiota may contribute to the inflammation and progression to neoplastic transformation of this zone.

Considering the remarkable advancement of imaging technology combined with AI, this will facilitate identification of dysplastic changes or early cancers arising from the GOJZ which can be managed with minimally invasive endoscopic therapy. It is important for all the endoscopists to describe the exact location of the neoplasms in relation to GOJ, presence or absence of BO, and aetiological factors such as GORD, gastric mucosal atrophy, and *H. pylori* as described above.

Although major issues have been resolved by this interdisciplinary expert consensus, the concepts adopted, and their usefulness, await further validation in the real world. In other words, we recognised a huge area of interesting research themes regarding the issues surrounding the GOJZ are wide open to us. Thus, we do hope this consensus document will play a role in promoting our understanding of the complex pathophysiology of the GOJZ, thorough which better prevention and management on the diseases in the GOJZ can be offered.

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Acknowledgements Authors are indebted to Drs Junichi Akiyama, Chika Kusano, Sachiyo Nomura, Yuto Shimamura and Shizuki Takemura for their excellent clerkship for recording the documents at the consensus meeting. We also thank Ms. Emiko Dan and Mr. Hiroyuki Yasui, of the Organization of Japan Digestive Disease Week for their business support, and Mr. Masayoshi Umemura and Mr. Kenya Morimoto of Omura Printing Co. Ltd for developing the internet-based voting system. Excellent secretarial and operation support given by Ms. Hiroko Eto, Ms. Aki Iiyama and Mr Tadashi Komada from Japan Convention Services Inc. is greatly appreciated.

Contributors KS and MK planned and organised the meeting. PM, KELM, EME-O rearranged the CQ and statements prepared by the Japanese faculty members. Japanese faculty members did literature search and wrote the draft the statements for their allocated CQs. KS finalised the whole manuscript from the drafts prepared by the Japanese faculty members and updated the literature except textural explanation for CQ1, which was jointly written with SJS. All the authors contributed to develop consensus document by voting and providing their comments. They also contributed to revise the manuscript prepared by KS by constructive proposals. SJS and EME-O did editing of the manuscript.

Funding The cost of this meeting was provided by the fund from the APDW meeting in Kobe 2016 deposited to the account of the Organization of JDDW. We also thank Professor Daniel Sifrim, The London School of Medicine and Dentistry Queen Mary, University of London, Professor Nicholas J Shaheen, University of North Caroline School of Medicine and Professor Parakrama Chandrasoma, University of Southern California Medical Center for their contributions during the consensus development.

Competing interests KS serves as an advisor for Fujifilm Medical Co. and received a lecture fee from Fujifilm Medical Co. MF received lecture fee from Olympus Medical Systems Co. and Fujifilm Medical Co. He also received research grant from Olympus Medical Systems Co, Fujifilm Medical Co. and HOYA Pentax Co. HI serves as an advisor for Olympus Medical Systems Co. HM received a lecture fee from Fujifilm Medical Co. GT and HT received lecture fees from Olympus Medical Co. and Fujifilm Medical Co. Other authors have declared no competing interests regarding this manuscript

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

1 Sugano K, Tack J, Kuipers EJ, *et al*. Kyoto global consensus report on *Helicobacter pylori* gastritis. *Gut* 2015;64:1353–67.

2 American Gastroenterological Association, Spechler SJ, Sharma P, *et al*. American gastroenterological association medical position statement on the management of Barrett's esophagus. *Gastroenterology* 2011;140:1084–91.
3 Fitzgerald RC, di Pietro M, Ragunath K, *et al*. British Society of gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. *Gut* 2014;63:7–42.
4 Kuwano H, Nishimura Y, Oyama T, *et al*. Guidelines for diagnosis and treatment of carcinoma of the esophagus April 2012 edited by the Japan esophageal Society. *Esophagus* 2015;12:1–30.
5 Shaheen NJ, Falk GW, Iyer PG, *et al*. ACG clinical guideline: diagnosis and management of Barrett's esophagus. *Am J Gastroenterol* 2016;111:30–50.
6 Fock KM, Talley N, Goh KL, *et al*. Asia-Pacific consensus on the management of gastro-oesophageal reflux disease: an update focusing on refractory reflux disease and Barrett's oesophagus. *Gut* 2016;65:1402–15.
7 Weusten B, Bisschops R, Coron E, *et al*. Endoscopic management of Barrett's esophagus: European Society of gastrointestinal endoscopy (ESGE) position statement. *Endoscopy* 2017;49:191–8.
8 Atkins D, Best D, Briss PA, *et al*. Grading quality of evidence and strength of recommendations. *BMJ* 2004;328:1490.
9 Guyatt GH, Oxman AD, Vist GE, *et al*. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.
10 Sharma P, Dent J, Armstrong D, *et al*. The development and validation of an endoscopic grading system for Barrett's esophagus: the Prague C & M criteria. *Gastroenterology* 2006;131:1392–9.
11 Lee Y, Cook M, Bhatia S, *et al*. Interobserver reliability in the endoscopic diagnosis and grading of Barrett's esophagus: an Asian multinational study. *Endoscopy* 2010;42:699–704.
12 Dekel R, Wakelin DE, Wendel C, *et al*. Progression or regression of Barrett's esophagus--is it all in the eye of the beholder? *Am J Gastroenterol* 2003;98:2612–5.
13 Guda NM, Partington S, Vakil N. Inter- and intra-observer variability in the measurement of length at endoscopy: implications for the measurement of Barrett's esophagus. *Gastrointest Endosc* 2004;59:655–8.
14 Hirota WK, Loughney TM, Lazas DJ, *et al*. Specialized intestinal metaplasia, dysplasia, and cancer of the esophagus and esophagogastric junction: prevalence and clinical data. *Gastroenterology* 1999;116:277–85.
15 Sharma P, Weston AP, Morales T, *et al*. Relative risk of dysplasia for patients with intestinal metaplasia in the distal oesophagus and in the gastric cardia. *Gut* 2000;46:9–13.
16 Morales TG, Camargo E, Bhattacharyya A, *et al*. Long-term follow-up of intestinal metaplasia of the gastric cardia. *Am J Gastroenterol* 2000;95:1677–80.
17 Pohl H, Pech O, Arash H, *et al*. Length of Barrett's oesophagus and cancer risk: implications from a large sample of patients with early oesophageal adenocarcinoma. *Gut* 2016;65:196–201.
18 Harrison R, Perry I, Haddadin W, *et al*. Detection of intestinal metaplasia in Barrett's esophagus: an observational comparator study suggests the need for a minimum of eight biopsies. *Am J Gastroenterol* 2007;102:1154–61.
19 Kim SL, Waring JP, Spechler SJ, *et al*. Diagnostic inconsistencies in Barrett's esophagus. *Gastroenterology* 1994;107:945–9.
20 Naini BV, Souza RF, Odze RD. Barrett's esophagus: a comprehensive and contemporary review for pathologists. *Am J Surg Pathol* 2016;40:e45–66.
21 McDonald SAC, Graham TA, Lavery DL, *et al*. The Barrett's gland in phenotype space. *Cell Mol Gastroenterol Hepatol* 2015;1:41–54.
22 Nicholson AM, Graham TA, Simpson A, *et al*. Barrett's metaplasia glands are clonal, contain multiple stem cells and share a common squamous progenitor. *Gut* 2012;61:1380–9.
23 Lavery DL, Nicholson AM, Poulsom R, *et al*. The stem cell organisation, and the proliferative and gene expression profile of Barrett's epithelium, replicates pyloric-type gastric glands. *Gut* 2014;63:1854–63.
24 Glickman JN, Wang H, Das KM, *et al*. Phenotype of Barrett's Esophagus and Intestinal Metaplasia of the Distal Esophagus and Gastroesophageal Junction. *Am J Surg Pathol* 2001;25:87–94.
25 Oh DS, DeMeester SR, Tanaka K, *et al*. The gene expression profile of cardia intestinal metaplasia is similar to that of Barrett's esophagus, not gastric intestinal metaplasia. *Dis Esophagus* 2011;24:516–22.
26 Gulizia JM, Wang H, Antonioli D, *et al*. Proliferative characteristics of intestinalized mucosa in the distal esophagus and gastroesophageal junction (short-segment Barrett's esophagus): a case control study. *Hum Pathol* 1999;30:412–8.
27 Meining A, Ott R, Becker I, *et al*. The Munich Barrett follow up study: suspicion of Barrett's oesophagus based on either endoscopy or histology only--what is the clinical significance? *Gut* 2004;53:1402–7.
28 Romagnoli S, Roncalli M, Graziani D, *et al*. Molecular alterations of Barrett's esophagus on microdissected endoscopic biopsies. *Lab Invest* 2001;81:241–7.
29 Chaves P, Crespo M, Ribeiro C, *et al*. Chromosomal analysis of Barrett's cells: demonstration of instability and detection of the metaplastic lineage involved. *Mod Pathol* 2007;20:788–96.
30 Liu W, Hahn H, Odze RD, *et al*. Metaplastic esophageal columnar epithelium without goblet cells shows DNA content abnormalities similar to goblet cell-containing epithelium. *Am J Gastroenterol* 2009;104:816–24.
31 Kelty CJ, Gough MD, Van Wyk Q, *et al*. Barrett's oesophagus: intestinal metaplasia is not essential for cancer risk. *Scand J Gastroenterol* 2007;42:1271–4.
32 Gatenby PAC, Ramus JR, Caygill CPJ, *et al*. Relevance of the detection of intestinal metaplasia in non-dysplastic columnar-lined oesophagus. *Scand J Gastroenterol* 2008;43:524–30.
33 Takubo K, Aida J, Naomoto Y, *et al*. Cardiac rather than intestinal-type background in endoscopic resection specimens of minute Barrett adenocarcinoma. *Hum Pathol* 2009;40:65–74.
34 Demicco EG, Farris AB, Baba Y, *et al*. The dichotomy in carcinogenesis of the distal esophagus and esophagogastric junction: intestinal-type vs cardiac-type mucosa-associated adenocarcinoma. *Mod Pathol* 2011;24:1177–90.
35 Watanabe G, Ajioka Y, Takeuchi M, *et al*. Intestinal metaplasia in Barrett's oesophagus may be an epiphenomenon rather than a preneoplastic condition, and CDX2-positive cardiac-type epithelium is associated with minute Barrett's tumour. *Histopathology* 2015;66:201–14.
36 Lavery DL, Martinez P, Gay LJ, *et al*. Evolution of oesophageal adenocarcinoma from metaplastic columnar epithelium without goblet cells in Barrett's oesophagus. *Gut* 2016;65:907–13.
37 Fukuda S, Watanabe K, Yoshida T, *et al*. Low risk of esophageal adenocarcinoma among patients with ultrashort-segment Barrett's esophagus in Japan. *Dig Endosc* 2022;34:757–65.
38 Boyce HW. Endoscopic definitions of esophagogastric junction regional anatomy. *Gastrointest Endosc* 2000;51:586–92.
39 McClave SA, Boyce HW, Gottfried MR. Early diagnosis of columnar-lined esophagus: a new endoscopic diagnostic criterion. *Gastrointest Endosc* 1987;33:413–6.
40 Csendes A, Maluenda F, Braghetto I, *et al*. Location of the lower oesophageal sphincter and the squamous columnar mucosal junction in 109 healthy controls and 778 patients with different degrees of endoscopic oesophagitis. *Gut* 1993;34:21–7.
41 Derakhshan MH, Crumley A, Forshaw M, *et al*. An unexpected mucosal metaplasia at the gastric cardia in longstanding pernicious anemia. *Am J Gastroenterol* 2015;110:1505–6.
42 Bombeck CT, Dillard DH, Nyhus LM. Muscular anatomy of the gastroesophageal junction and role of phrenoesophageal ligament; autopsy study of sphincter mechanism. *Ann Surg* 1966;164:643–54.
43 Chandrasoma P, Makarewicz K, Wickramasinghe K, *et al*. A proposal for a new validated histological definition of the gastroesophageal junction. *Hum Pathol* 2006;37:40–7.
44 Pinto D, Plieschnegger W, Schneider NI, *et al*. Carditis: a relevant marker of gastroesophageal reflux disease. data from a prospective central European multicenter study on histological and endoscopic diagnosis of esophagitis (histoGERD trial). *Dis Esophagus* 2019;32. doi:10.1093/dote/doy073. [Epub ahead of print: 01 Jan 2019].
45 De Carvalho CAF. Sur l'angio-architecture veineuse de la zone de transition oesophago-gastrique et son interprétation fonctionnelle. *Cells Tissues Organs* 1966;64:125–62.
46 Vianna A, Hayes PC, Moscoso G, *et al*. Normal venous circulation of the gastroesophageal junction. A route to understanding varices. *Gastroenterology* 1987;93:876–89.
47 Maselli R, Inoue H, Ikeda H, *et al*. Microvasculature of the esophagus and gastroesophageal junction: lesson learned from submucosal endoscopy. *World J Gastrointest Endosc* 2016;8:690–6.
48 Inoue H, Shiwaku H, Iwakiri K, *et al*. Clinical practice guidelines for peroral endoscopic myotomy. *Dig Endosc* 2018;30:563–79.
49 Sato T, Kato Y. Palisading longitudinal esophagus vessels at esophago-gastric junction. *Hepatogastroenterology* 2008;55:305–7.
50 Sato T, Kato Y, Matsuura M, *et al*. Significance of palisading longitudinal esophagus vessels: identification of the true esophagogastric junction has histopathological and oncological considerations. *Dig Dis Sci* 2010;55:3095–101.
51 Aida J, Vieth M, Ell C, *et al*. Palisade vessels as a new histologic marker of esophageal origin in ER specimens from columnar-lined esophagus. *Am J Surg Pathol* 2011;35:1140–5.
52 Huang Q. Definition of the esophagogastric junction. *Arch Pathol Lab Med* 2011;135:384–9.
53 Hoshihara Y, Kogure T. What are longitudinal vessels? endoscopic observation and clinical significance of longitudinal vessels in the lower esophagus. *Esophagus* 2006;3:145–50.
54 Amano Y, Ishimura N, Furuta K, *et al*. Which landmark results in a more consistent diagnosis of Barrett's esophagus, the gastric folds or the palisade vessels? *Gastrointest Endosc* 2006;64:206–11.
55 Boyce HW. The normal anatomy around the oesophagogastric junction: an endoscopic view. *Best Pract Res Clin Gastroenterol* 2008;22:553–67.
56 Ishimura N, Amano Y, Kinoshita Y. Endoscopic definition of esophagogastric junction for diagnosis of Barrett's esophagus: importance of systematic education and training. *Dig Endosc* 2009;21:213–8.
57 Kusano C, Kaltenbach T, Shimazu T, *et al*. Can Western endoscopists identify the end of the lower esophageal palisade vessels as a landmark of esophagogastric junction? *J Gastroenterol* 2009;44:842–6.

58 Schölvinck DW, Goto O, Seldenrijk CA, *et al*. Detection of palisade vessels as a landmark for Barrett's esophagus in a Western population. *J Gastroenterol* 2016;51:682–90.
59 Osawa H, Yamamoto H, Yamada N, *et al*. Diagnosis of endoscopic Barrett's esophagus by transnasal flexible spectral imaging color enhancement. *J Gastroenterol* 2009;44:1125–32.
60 Takeda T, Nagahara A, Ishizuka K, *et al*. Improved visibility of Barrett's esophagus with linked color imaging: inter- and intra-rater reliability and quantitative analysis. *Digestion* 2018;97:183–94.
61 Hanna S, Rastogi A, Weston AP, *et al*. Detection of Barrett's esophagus after endoscopic healing of erosive esophagitis. *Am J Gastroenterol* 2006;101:1416–20.
62 Vieth M, Kulig M, Leodolter A, *et al*. Histological effects of esomeprazole therapy on the squamous epithelium of the distal oesophagus. *Aliment Pharmacol Ther* 2006;23:313–9.
63 Sharma P, Morales TG, Sampliner RE. Short segment Barrett's esophagus--the need for standardization of the definition and of endoscopic criteria. *Am J Gastroenterol* 1998;93:1033–6.
64 Chandrasoma P, Wijetunge S, Ma Y, *et al*. The dilated distal esophagus: a new entity that is the pathologic basis of early gastroesophageal reflux disease. *Am J Surg Pathol* 2011;35:1873–81.
65 Takubo K, Vieth M, Aida J, *et al*. Differences in the definitions used for esophageal and gastric diseases in different countries: endoscopic definition of the esophagogastric junction, the precursor of Barrett's adenocarcinoma, the definition of Barrett's esophagus, and histologic criteria for mucosal adenocarcinoma or high-grade dysplasia. *Digestion* 2009;80:248–57.
66 Kumagai Y, Yagi M, Aida J, *et al*. Detailed features of palisade vessels as a marker of the esophageal mucosa revealed by magnifying endoscopy with narrow band imaging. *Dis Esophagus* 2012;25:484–90.
67 Bratlie SO, Johnsson E, Jönsson C, *et al*. Multiple-Band Imaging Provides Better Value Than White-light Endoscopy in Detection of Dysplasia in Patients With Barrett's Esophagus. *Clin Gastroenterol Hepatol* 2015;13:1068–74.
68 Tokunaga M, Matsumura T, Ishikawa K, *et al*. The efficacy of linked color imaging in the endoscopic diagnosis of Barrett's esophagus and esophageal adenocarcinoma. *Gastroenterol Res Pract* 2020;2020:1–8.
69 Adachi K, Ishimura N, Kishi K, *et al*. Prevalence of Barrett's Epithelium Shown by Endoscopic Observations with Linked Color Imaging in Subjects with Different H. pylori Infection Statuses. *Intern Med* 2021;60:667–74.
70 Johns BAE. Developmental changes in the oesophageal epithelium in man. *J Anat* 1952;86:431–42.
71 Ellison E, Hassall E, Dimmick JE. Mucin histochemistry of the developing gastroesophageal junction. *Pediatr Pathol Lab Med* 1996;16:195–206.
72 Zhou H, Greco MA, Daum F, *et al*. Origin of cardiac mucosa: ontogenic consideration. *Pediatr Dev Pathol* 2001;4:358–63.
73 Park YS, Park HJ, Kang GH, *et al*. Histology of gastroesophageal junction in fetal and pediatric autopsy. *Arch Pathol Lab Med* 2003;127:451–5.
74 De Hertogh G, Van Eyken P, Ectors N, *et al*. On the existence and location of cardiac mucosa: an autopsy study in embryos, fetuses, and infants. *Gut* 2003;52:791–6.
75 Kilgore SP, Ormsby AH, Gramlich TL, *et al*. The gastric cardia: fact or fiction? *Am J Gastroenterol* 2000;95:921–4.
76 Sato T, Kato Y, Matsuura M, *et al*. Significance of palisading longitudinal esophagus vessels: identification of the true esophagogastric junction has histopathological and oncological considerations. *Dig Dis Sci* 2010;55:3095–101.
77 Huang Q. Controversies of cardiac glands in the proximal stomach: a critical review. *J Gastroenterol Hepatol* 2011;26:450–5.
78 Spechler SJ. Follow cardiac metaplasia: treat or ignore? *Dig Dis Sci* 2018;63:2052–8.
79 Oberg S, Peters JH, DeMeester TR, *et al*. Inflammation and specialized intestinal metaplasia of cardiac mucosa is a manifestation of gastroesophageal reflux disease. *Ann Surg* 1997;226:522–32.
80 Chandrasoma PT, Lokuhetty DM, Demeester TR, *et al*. Definition of histopathologic changes in gastroesophageal reflux disease. *Am J Surg Pathol* 2000;24:344–51.
81 Chandrasoma PT, Der R, Ma Y, *et al*. Histology of the gastroesophageal junction: an autopsy study. *Am J Surg Pathol* 2000;24:402–9.
82 Chandrasoma P. Pathophysiology of Barrett's esophagus. *Semin Thorac Cardiovasc Surg* 1997;9:270–8.
83 Chandrasoma P. Pathological basis of gastroesophageal reflux disease. *World J Surg* 2003;27:986–93.
84 Chandrasoma P. Controversies of the cardiac mucosa and Barrett's oesophagus. *Histopathology* 2005;46:361–73.
85 Chandrasoma PT. Fetal "cardiac mucosa" is not adult cardiac mucosa. *Gut* 1798;2003:52.
86 De Hertogh G, Van Eyken P, Ectors N, *et al*. On the origin of cardiac mucosa: a histological and immunohistochemical study of cytokeratin expression patterns in the developing esophagogastric junction region and stomach. *World J Gastroenterol* 2005;11:4490–6.
87 Derdoy JJ, Bergwerk A, Cohen H, *et al*. The gastric cardia. *Am J Surg Pathol* 2003;27:499–504.
88 Bensley RR. The cardiac glands of mammals. *Am J Anat* 1902;2:105–56.
89 Krause WJ, Ivey KJ, Baskin WN, *et al*. Morphological observations on the normal human cardiac glands. *Anat Rec* 1978;192:59–71.
90 Van Zanten SJ, Dixon MF, Lee A. The gastric transitional zones: neglected links between gastroduodenal pathology and *Helicobacter* ecology. *Gastroenterology* 1999;116:1217–29.
91 Hayward J. The lower end of the oesophagus. *Thorax* 1961;16:36–41.
92 Miyagawa Y. The exact distribution of the gastric glands in man and in certain animals. *J. Anat* 1921;55:56–67.
93 Sarbia M, Donner A, Gabbert HE. Histopathology of the gastroesophageal junction. *Am J Surg Pathol* 2002;26:1207–12.
94 Nakanishi Y, Saka M, Eguchi T, *et al*. Distribution and significance of the oesophageal and gastric cardiac mucosae: a study of 131 operation specimens. *Histopathology* 2007;51:515–9.
95 Stojsic ZM, Stevanovic RM, Stojanovic MM, *et al*. Histological features of gastric cardia in adults: an autopsy study. *J Gastrointestin Liver Dis* 2011;20:13–18.
96 Odze RD. Unraveling the mystery of the gastroesophageal junction: a pathologist's perspective. *Am J Gastroenterol* 2005;100:1853–67.
97 Robertson EV, Derakhshan MH, Wirz AA, *et al*. Central obesity in asymptomatic volunteers is associated with increased intrasphincteric acid reflux and lengthening of the cardiac mucosa. *Gastroenterology* 2013;145:730–9.
98 Robertson EV, Derakhshan MH, Wirz AA, *et al*. Hiatus hernia in healthy volunteers is associated with intrasphincteric reflux and cardiac mucosal lengthening without traditional reflux. *Gut* 2017;66:1208–15.
99 Derakhshan MH, Robertson EV, Yeh Lee Y, *et al*. In healthy volunteers, immunohistochemistry supports squamous to columnar metaplasia as mechanism of expansion of cardia, aggravated by central obesity. *Gut* 2015;64:1705–14.
100 Kimura K. Chronological transition of the fundic-pyloric border determined by stepwise biopsy of the lesser and greater curvatures of the stomach. *Gastroenterology* 1972;63:584–92.
101 Tatsuta M, Saegusa T, Okuda S. Studies on gastritis in the upper portion of the stomach by Congo-red test. *Jpn J Gastroenterol* 1972;69:459–73.
102 Tatsuta M. Development and extension of atrophic gastritis and intestinal metaplasia in the upper portion of the stomach. *Gastroenterol Endosc* 1982;24:1381–90.
103 Tatsuta M, Iishi H, Ichii M, *et al*. Chromoendoscopic observations on extension and development of fundal gastritis and intestinal metaplasia. *Gastroenterology* 1985;88:70–4.
104 Genta RM, Huberman RM, Graham DY. The gastric cardia in *Helicobacter pylori* infection. *Hum Pathol* 1994;25:915–9.
105 Nakamura M, Kawano T, Endo M, *et al*. Intestinal metaplasia at the esophagogastric junction in Japanese patients without clinical Barrett's esophagus. *Am J Gastroenterol* 1999;94:3145–9.
106 Hackelsberger A, Günther T, Schultze V, *et al*. Role of aging in the expression of *Helicobacter pylori* gastritis in the antrum, corpus, and cardia. *Scand J Gastroenterol* 1999;34:138–43.
107 Yung E, Li X, Chandrasoma P. Intestinal Metaplasia of the "Cardia": Accurate Differentiation of Gastric or Esophageal Origin With an Expanded Biopsy Protocol. *Am J Surg Pathol* 2021;45:945–50.
108 Andrici J, Tio M, Cox MR, *et al*. Hiatal hernia and the risk of Barrett's esophagus. *J Gastroenterol Hepatol* 2013;28:415–31.
109 Eusebi LH, Telese A, Cirota GG, *et al*. Systematic review with meta-analysis: risk factors for Barrett's oesophagus in individuals with gastro-oesophageal reflux symptoms. *Aliment Pharmacol Ther* 2021;53:968–76.
110 Sifrim D, Holloway R, Silny J, *et al*. Acid, nonacid, and gas reflux in patients with gastroesophageal reflux disease during ambulatory 24-hour pH-impedance recordings. *Gastroenterology* 2001;120:1588–98.
111 Streets CG, DeMeester TR. Ambulatory 24-hour esophageal pH monitoring: why, when, and what to do. *J Clin Gastroenterol* 2003;37:14–22.
112 Zerbib F, Roman S, Ropert A, *et al*. Esophageal pH-impedance monitoring and symptom analysis in GERD: a study in patients off and on therapy. *Am J Gastroenterol* 2006;101:1956–63.
113 Mainie I, Tutuian R, Shay S, *et al*. Acid and non-acid reflux in patients with persistent symptoms despite acid suppressive therapy: a multicentre study using combined ambulatory impedance-pH monitoring. *Gut* 2006;55:1398–402.
114 Sifrim D, Castell D, Dent J, *et al*. Gastro-oesophageal reflux monitoring: review and consensus report on detection and definitions of acid, non-acid, and gas reflux. *Gut* 2004;53:1024–31.
115 Lundell LR, Dent J, Bennett JR, *et al*. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut* 1999;45:172–80.
116 Miwa H, Kondo T, Oshima T. Gastroesophageal reflux disease-related and functional heartburn: pathophysiology and treatment. *Curr Opin Gastroenterol* 2016;32:344–52.
117 Smout AJPM, Bredenoord AJ. GERD: a challenge to our view of reflux oesophagitis pathogenesis. *Nat Rev Gastroenterol Hepatol* 2016;13:504–5.
118 Pandolfino JE, Lee TJ, Schreiner MA, *et al*. Comparison of esophageal acid exposure at 1 cm and 6 cm above the squamocolumnar junction using the Bravo pH monitoring system. *Dis Esophagus* 2006;19:177–82.

119 Wenner J, Johnsson F, Johansson J, *et al*. Acid reflux immediately above the squamocolumnar junction and in the distal esophagus: simultaneous pH monitoring using the wireless capsule pH system. *Am J Gastroenterol* 2006;101:1734–41.
120 Appelman HD, Umar A, Orlando RC, *et al*. Barrett's esophagus: natural history. *Ann N Y Acad Sci* 2011;1232:292–308.
121 Oberg S, DeMeester TR, Peters JH, *et al*. The extent of Barrett's esophagus depends on the status of the lower esophageal sphincter and the degree of esophageal acid exposure. *J Thorac Cardiovasc Surg* 1999;117:572–80.
122 Fass R, Hell RW, Garewal HS, *et al*. Correlation of oesophageal acid exposure with Barrett's oesophagus length. *Gut* 2001;48:310–3.
123 Csendes A, Smok G, Quiroz J, *et al*. Clinical, endoscopic, and functional studies in 408 patients with Barrett's esophagus, compared to 174 cases of intestinal metaplasia of the cardia. *Am J Gastroenterol* 2002;97:554–60.
124 Farré R, Fornari F, Blondeau K, *et al*. Acid and weakly acidic solutions impair mucosal integrity of distal exposed and proximal non-exposed human oesophagus. *Gut* 2010;59:164–9.
125 Farré R, van Malenstein H, De Vos R, *et al*. Short exposure of oesophageal mucosa to bile acids, both in acidic and weakly acidic conditions, can impair mucosal integrity and provoke dilated intercellular spaces. *Gut* 2008;57:1366–74.
126 Wu L, Oshima T, Shan J, *et al*. PAR-2 activation enhances weak acid-induced ATP release through TRPV1 and ASIC sensitization in human esophageal epithelial cells. *Am J Physiol Gastrointest Liver Physiol* 2015;309:G695–702.
127 Farré R, Blondeau K, Clement D, *et al*. Evaluation of oesophageal mucosa integrity by the intraluminal impedance technique. *Gut* 2011;60:885–92.
128 Farré R. Pathophysiology of gastro-esophageal reflux disease: a role for mucosa integrity? *Neurogastroenterol Motil* 2013;25:783–99.
129 Zhong C, Duan L, Wang K, *et al*. Esophageal intraluminal baseline impedance is associated with severity of acid reflux and epithelial structural abnormalities in patients with gastroesophageal reflux disease. *J Gastroenterol* 2013;48:601–10.
130 Xie C, Sifrim D, Li Y, *et al*. Esophageal baseline impedance reflects mucosal integrity and predicts symptomatic outcome with proton pump inhibitor treatment. *J Neurogastroenterol Motil* 2018;24:43–50.
131 Champion G, Richter JE, Vaezi MF, *et al*. Duodenogastroesophageal reflux: relationship to pH and importance in Barrett's esophagus. *Gastroenterology* 1994;107:747–54.
132 Kauer WK, Peters JH, DeMeester TR, *et al*. Mixed reflux of gastric and duodenal juices is more harmful to the esophagus than gastric juice alone. The need for surgical therapy re-emphasized. *Ann Surg* 1995;222:525–33.
133 Caldwell MT, Lawlor P, Byrne PJ, *et al*. Ambulatory oesophageal bile reflux monitoring in Barrett's oesophagus. *Br J Surg* 1995;82:657–60.
134 Vaezi MF, Richter JE. Role of acid and duodenogastroesophageal reflux in gastroesophageal reflux disease. *Gastroenterology* 1996;111:1192–9.
135 Cuomo R, Koek G, Sifrim D, *et al*. Analysis of ambulatory duodenogastroesophageal reflux monitoring. *Dig Dis Sci* 2000;45:2463–9.
136 Oh DS, Hagen JA, Fein M, *et al*. The impact of reflux composition on mucosal injury and esophageal function. *J Gastrointest Surg* 2006;10:787–96.
137 Vaezi MF, Richter JE. Synergism of acid and duodenogastroesophageal reflux in complicated Barrett's esophagus. *Surgery* 1995;117:699–704.
138 Nehra D, Howell P, Williams CP, *et al*. Toxic bile acids in gastro-oesophageal reflux disease: influence of gastric acidity. *Gut* 1999;44:598–602.
139 Takahashi Y, Amano Y, Yuki T, *et al*. Impact of the composition of gastric reflux bile acids on Barrett's oesophagus. *Dig Liver Dis* 2011;43:692–7.
140 Zhang XJ, Xiang XL, Tu L, *et al*. The effect of position on esophageal structure and function determined with solid-state high-resolution manometry. *J Dig Dis* 2015;16:350–6.
141 Choi YJ, Park MI, Park SJ, *et al*. The effect of water bolus temperature on esophageal motor function as measured by high-resolution manometry. *Neurogastroenterol Motil* 2014;26:1628–34.
142 Besanko LK, Burgstad CM, Cock C, *et al*. Changes in esophageal and lower esophageal sphincter motility with healthy aging. *J Gastrointestin Liver Dis* 2014;23:243–8.
143 Gyawali CP, Patel A. Esophageal motor function: technical aspects of manometry. *Gastrointest Endosc Clin N Am* 2014;24:527–43.
144 Holloway RH, Boeckxstaens GEE, Penagini R, *et al*. Objective definition and detection of transient lower esophageal sphincter relaxation revisited: is there room for improvement? *Neurogastroenterol Motil* 2012;24:54–60.
145 Mittal RK, Karstens A, Leslie E, *et al*. Ambulatory high-resolution manometry, lower esophageal sphincter lift and transient lower esophageal sphincter relaxation. *Neurogastroenterol Motil* 2012;24:40–2.
146 Kwiatek MA, Pandolfino JE, Kahrilas PJ. 3D-high resolution manometry of the esophagogastric junction. *Neurogastroenterol Motil* 2011;23:e461–9.
147 de Leon A, Thörn S-E, Ottosson J, *et al*. Body positions and esophageal sphincter pressures in obese patients during anesthesia. *Acta Anaesthesiol Scand* 2010;54:458–63.
148 Pandolfino JE, Ghosh SK, Zhang Q, *et al*. Quantifying EGJ morphology and relaxation with high-resolution manometry: a study of 75 asymptomatic volunteers. *Am J Physiol Gastrointest Liver Physiol* 2006;290:G1033–40.
149 Pandolfino JE, Shi G, Zhang Q, *et al*. Measuring EGJ opening patterns using high resolution intraluminal impedance. *Neurogastroenterol Motil* 2005;17:200–6.
150 McCray WH, Chung C, Parkman HP, *et al*. Use of simultaneous high-resolution endoluminal sonography (HRES) and manometry to characterize high pressure zone of distal esophagus. *Dig Dis Sci* 2000;45:1660–6.
151 Ata-Lawenko RM, Lee YY. Emerging roles of the endoluminal functional lumen imaging probe in gastrointestinal motility disorders. *J Neurogastroenterol Motil* 2017;23:164–70.
152 Kwiatek MA, Pandolfino JE, Hirano I, *et al*. Esophagogastric junction distensibility assessed with an endoscopic functional luminal imaging probe (EndoFLIP). *Gastrointest Endosc* 2010;72:272–8.
153 Nathanson LK, Brunott N, Cavallucci D. Adult esophagogastric junction distensibility during general anesthesia assessed with an endoscopic functional luminal imaging probe (EndoFLIP®). *Surg Endosc* 2012;26:1051–5.
154 Perretta S, McAnena O, Botha A, *et al*. Acta from the EndoFLIP® symposium. *Surg Innov* 2013;20:545–52.
155 Carlson DA, Lin Z, Kahrilas PJ, *et al*. The Functional Lumen Imaging Probe Detects Esophageal Contractility Not Observed With Manometry in Patients With Achalasia. *Gastroenterology* 2015;149:1742–51.
156 Lottrup C, McMahon BP, Ejstrud P, *et al*. Esophagogastric junction distensibility in hiatus hernia. *Dis Esophagus* 2016;29:463–71.
157 Hirano I, Pandolfino JE, Boeckxstaens GE. Functional lumen imaging probe for the management of esophageal disorders: expert review from the clinical practice updates Committee of the AGA Institute. *Clin Gastroenterol Hepatol* 2017;15:325–34.
158 Desprez C, Roman S, Leroi AM, *et al*. The use of impedance planimetry (Endoscopic Functional Lumen Imaging Probe, EndoFLIP®) in the gastrointestinal tract: A systematic review. *Neurogastroenterol Motil* 2020;32:e13980.
159 Brasseur JG, Ulerich R, Dai Q, *et al*. Pharmacological dissection of the human gastro-oesophageal segment into three sphincteric components. *J Physiol* 2007;580:961–75.
160 Balakrishna P, Parshad R, Rohila J, *et al*. Symptomatic outcome following laparoscopic Heller's cardiomyotomy with DOR fundoplication versus laparoscopic Heller's cardiomyotomy with angle of his accentuation: results of a randomized controlled trial. *Surg Endosc* 2015;29:2344–51.
161 Tanaka S, Kawara F, Toyonaga T, *et al*. Two penetrating vessels as a novel indicator of the appropriate distal end of peroral endoscopic myotomy. *Dig Endosc* 2018;30:206–11.
162 Siewert JR, Stein HJ. Carcinoma of the cardia: carcinoma of the gastroesophageal junction-classification, pathology and extent of resection. *Dis Esophagus* 1996;9:173–82.
163 Hackelsberger A, Günther T, Schultze V. Prevalence and pattern of *Helicobacter pylori* gastritis in the gastric cardia. *Am J Gastroenterol* 1997;92:2220–4.
164 Egi Y, Kim S, Ito M, *et al*. *Helicobacter pylori* infection is the major risk factor for gastric inflammation in the cardia. *Dig Dis Sci* 2006;51:1582–8.
165 Carelli AP, Patrício FRS, Kawakami E. Carditis is related to *Helicobacter pylori* infection in dyspeptic children and adolescents. *Dig Liver Dis* 2007;39:117–21.
166 Petersson F, Franzén LE, Borch K. Characterization of the gastric cardia in volunteers from the general population. Type of mucosa, *Helicobacter pylori* infection, inflammation, mucosal proliferative activity, p53 and p21 expression, and relations to gastritis. *Dig Dis Sci* 2010;55:46–53.
167 Wang Y, Liu S, Zhang Y, *et al*. *Helicobacter pylori* infection and gastric cardia cancer in Chaoshan region. *Microbes Infect* 2014;16:840–4.
168 Goldblum JR, Vicari JJ, Falk GW, *et al*. Inflammation and intestinal metaplasia of the gastric cardia: the role of gastroesophageal reflux and *H. pylori* infection. *Gastroenterology* 1998;114:633–9.
169 Voutilainen M, Färkkilä M, Mecklin JP, *et al*. Chronic inflammation at the gastroesophageal junction (carditis) appears to be a specific finding related to *Helicobacter pylori* infection and gastroesophageal reflux disease. The Central Finland Endoscopy Study Group. *Am J Gastroenterol* 1999;94:3175–80.
170 Contreras M, Salazar V, García-Amado MA, *et al*. High frequency of *Helicobacter pylori* in the esophageal mucosa of dyspeptic patients and its possible association with histopathological alterations. *Int J Infect Dis* 2012;16:e364–70.
171 Lembo T, Ippoliti AF, Ramers C, *et al*. Inflammation of the gastro-oesophageal junction (carditis) in patients with symptomatic gastro-oesophageal reflux disease: a prospective study. *Gut* 1999;45:484–8.
172 Peitz U, Vieth M, Malfertheiner P. Carditis at the interface between GERD and *Helicobacter pylori* infection. *Dig Dis* 2004;22:120–5.
173 Malfertheiner P, Peitz U. The interplay between Helicobacter pylori, gastro-oesophageal reflux disease, and intestinal metaplasia. *Gut* 2005;54 Suppl 1:i13–20.
174 Dixon MF, Mapstone NP, Neville PM, *et al*. Bile reflux gastritis and intestinal metaplasia at the cardia. *Gut* 2002;51:351–5.
175 Mukaisho K-I, Nakayama T, Hagiwara T, *et al*. Two distinct etiologies of gastric cardia adenocarcinoma: interactions among pH, *Helicobacter pylori*, and bile acids. *Front Microbiol* 2015;6:412.
176 Dvorak K, Payne CM, Chavarria M, *et al*. Bile acids in combination with low pH induce oxidative stress and oxidative DNA damage: relevance to the pathogenesis of Barrett's oesophagus. *Gut* 2007;56:763–71.

177 Goldman A, Shahidullah M, Goldman D, *et al*. A novel mechanism of acid and bile acid-induced DNA damage involving Na+/H+ exchanger: implication for Barrett's oesophagus. *Gut* 2010;59:1606–16.
178 Iijima K, Henry E, Moriya A, *et al*. Dietary nitrate generates potentially mutagenic concentrations of nitric oxide at the gastroesophageal junction. *Gastroenterology* 2002;122:1248–57.
179 McColl KEL. When saliva meets acid: chemical warfare at the oesophagogastric junction. *Gut* 2005;54:1–3.
180 Suzuki H, Iijima K, Scobie G, *et al*. Nitrate and nitrosative chemistry within Barrett's oesophagus during acid reflux. *Gut* 2005;54:1527–35.
181 Ara N, Iijima K, Asanuma K, *et al*. Disruption of gastric barrier function by luminal nitrosative stress: a potential chemical insult to the human gastro-oesophageal junction. *Gut* 2008;57:306–13.
182 Yang L, Lu X, Nossa CW, *et al*. Inflammation and intestinal metaplasia of the distal esophagus are associated with alterations in the microbiome. *Gastroenterology* 2009;137:588–97.
183 Liu N, Ando T, Ishiguro K, *et al*. Characterization of bacterial biota in the distal esophagus of Japanese patients with reflux esophagitis and Barrett's esophagus. *BMC Infect Dis* 2013;13:130.
184 Blackett KL, Siddhi SS, Cleary S, *et al*. Oesophageal bacterial biofilm changes in gastro-oesophageal reflux disease, Barrett's and oesophageal carcinoma: association or causality? *Aliment Pharmacol Ther* 2013;37:1084–92.
185 Gall A, Fero J, McCoy C, *et al*. Bacterial composition of the human upper gastrointestinal tract microbiome is dynamic and associated with genomic instability in a Barrett's esophagus cohort. *PLoS One* 2015;10:e0129055.
186 Kaakoush NO, Castaño-Rodríguez N, Man SM, *et al*. Is Campylobacter to esophageal adenocarcinoma as Helicobacter is to gastric adenocarcinoma? *Trends Microbiol* 2015;23:455–62.
187 Yu Y, Gao F, Chen X, *et al*. Changes in the distal esophageal microbiota in Chinese patients with reflux esophagitis. *J Dig Dis* 2019;20:18–24.
188 Snider EJ, Compres G, Freedberg DE, *et al*. Alterations to the esophageal microbiome associated with progression from Barrett's esophagus to esophageal adenocarcinoma. *Cancer Epidemiol Biomarkers Prev* 2019;28:1687–93.
189 Peter S, Pendergraft A, VanDerPol W, *et al*. Mucosa-associated microbiota in Barrett's esophagus, dysplasia, and esophageal adenocarcinoma differ similarly compared with healthy controls. *Clin Transl Gastroenterol* 2020;11:e00199.
190 Nadatani Y, Huo X, Zhang X, *et al*. NOD-like receptor protein 3 inflammasome priming and activation in Barrett's epithelial cells. *Cell Mol Gastroenterol Hepatol* 2016;2:439–53.
191 Francois F, Roper J, Goodman AJ, *et al*. The association of gastric leptin with oesophageal inflammation and metaplasia. *Gut* 2008;57:16–24.
192 Kendall BJ, Macdonald GA, Hayward NK, *et al*. Leptin and the risk of Barrett's oesophagus. *Gut* 2008;57:448–54.
193 Thompson OM, Beresford SAA, Kirk EA, *et al*. Serum leptin and adiponectin levels and risk of Barrett's esophagus and intestinal metaplasia of the gastroesophageal junction. *Obesity* 2010;18:2204–11.
194 Rubenstein JH, Morgenstern H, McConell D, *et al*. Associations of diabetes mellitus, insulin, leptin, and ghrelin with gastroesophageal reflux and Barrett's esophagus. *Gastroenterology* 2013;145:1237–44.
195 Greer KB, Falk GW, Bednarchik B, *et al*. Associations of serum adiponectin and leptin with Barrett's esophagus. *Clin Gastroenterol Hepatol* 2015;13:2265–72.
196 Tseng P-H, Yang W-S, Liou J-M, *et al*. Associations of circulating gut hormone and adipocytokine levels with the spectrum of gastroesophageal reflux disease. *PLoS One* 2015;10:e014141.
197 Chandar AK, Devanna S, Lu C, *et al*. Association of serum levels of adipokines and insulin with risk of Barrett's esophagus: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2015;13:2241–55.
198 Thomas SJ, Almers L, Schneider J, *et al*. Ghrelin and leptin have a complex relationship with risk of Barrett's esophagus. *Dig Dis Sci* 2016;61:70–9.
199 Takubo K, Sasajima K, Yamashita K, *et al*. Double muscularis mucosae in Barrett's esophagus. *Hum Pathol* 1991;22:1158–61.
200 Takubo K, Vieth M, Aryal G, *et al*. Islands of squamous epithelium and their surrounding mucosa in columnar-lined esophagus: a Pathognomonic feature of Barrett's esophagus? *Hum Pathol* 2005;36:269–74.
201 Takubo K, Vieth M, Aida J, *et al*. Histopathological diagnosis of adenocarcinoma in Barrett's esophagus. *Dig Endosc* 2014;26:322–30.
202 Abraham SC, Krasinskas AM, Correa AM, *et al*. Duplication of the muscularis mucosae in Barrett esophagus: an underrecognized feature and its implication for staging of adenocarcinoma. *Am J Surg Pathol* 2007;31:1719–25.
203 Takubo K. Double Muscularis Mocosae in Barrett's Esophagus. In: *Pathology of the esophagus*. 3rd ed. Tokyo, Japan: Wiley Publishing Japan K.K., 2017: 216–7.
204 Tatsuta T, Mukaisho K-I, Sugihara H, *et al*. Expression of Cdx2 in early GRCL of Barrett's esophagus induced in rats by duodenal reflux. *Dig Dis Sci* 2005;50:425–31.
205 Milano F, van Baal JWPM, Buttar NS, *et al*. Bone morphogenetic protein 4 expressed in esophagitis induces a columnar phenotype in esophageal squamous cells. *Gastroenterology* 2007;132:2412–21.
206 Kazumori H, Ishihara S, Kinoshita Y. Roles of caudal-related homeobox gene Cdx1 in oesophageal epithelial cells in Barrett's epithelium development. *Gut* 2009;58:620–8.
207 Kushima R, Mukaisho K-I, Takemura S, *et al*. [Barrett's esophagus: analyses from human and experimental animal studies]. *Pathologe* 2013;34:138–47.
208 Quante M, Bhagat G, Abrams JA, *et al*. Bile acid and inflammation activate gastric cardia stem cells in a mouse model of Barrett-like metaplasia. *Cancer Cell* 2012;21:36–51.
209 Leedham SJ, Preston SL, McDonald SAC, *et al*. Individual crypt genetic heterogeneity and the origin of metaplastic glandular epithelium in human Barrett's oesophagus. *Gut* 2008;57:1041–8.
210 Jiang M, Li H, Zhang Y, *et al*. Transitional basal cells at the squamous-columnar junction generate Barrett's oesophagus. *Nature* 2017;550:529–33.
211 Wang X, Ouyang H, Yamamoto Y, *et al*. Residual embryonic cells as precursors of a Barrett's-like metaplasia. *Cell* 2011;145:1023–35.
212 Sarosi G, Brown G, Jaiswal K, *et al*. Bone marrow progenitor cells contribute to esophageal regeneration and metaplasia in a rat model of Barrett's esophagus. *Dis Esophagus* 2008;21:43–50.
213 Mukaisho K-I, Miwa K, Kumagai H, *et al*. Gastric carcinogenesis by duodenal reflux through gut regenerative cell lineage. *Dig Dis Sci* 2003;48:2153–8.
214 Hahn HP, Blount PL, Ayub K, *et al*. Intestinal differentiation in metaplastic, nongoblet columnar epithelium in the esophagus. *Am J Surg Pathol* 2009;33:1006–15.
215 Groisman GM, Amar M, Meir A. Expression of the intestinal marker Cdx2 in the columnar-lined esophagus with and without intestinal (Barrett's) metaplasia. *Mod Pathol* 2004;17:1282–8.
216 Mari L, Milano F, Parikh K, *et al*. A pSMAD/CDX2 complex is essential for the intestinalization of epithelial metaplasia. *Cell Rep* 2014;7:1197–210.
217 Chaves P, Pereira AD, Cruz C, *et al*. Recurrent columnar-lined esophageal segments--study of the phenotypic characteristics using intestinal markers. *Dis Esophagus* 2002;15:282–6.
218 Chaves P, Cruz C, Dias Pereira A, *et al*. Gastric and intestinal differentiation in Barrett's metaplasia and associated adenocarcinoma. *Dis Esophagus* 2005;18:383–7.
219 Dias Pereira A, Chaves P. Columnar-lined oesophagus without intestinal metaplasia: results from a cohort with a mean follow-up of 7 years. *Aliment Pharmacol Ther* 2012;36:282–9.
220 Nowicki-Osuch K, Zhuang L, Jammula S, *et al*. Molecular phenotyping reveals the identity of Barrett's esophagus and its malignant transition. *Science* 2021;373:760–7.
221 Paull A, Trier JS, Dalton MD, *et al*. The histologic spectrum of Barrett's esophagus. *N Engl J Med* 1976;295:476–80.
222 Thompson JJ, Zinsser KR, Enterline HT. Barrett's metaplasia and adenocarcinoma of the esophagus and gastroesophageal junction. *Hum Pathol* 1983;14:42–61.
223 Chandrasoma PT, Der R, Ma Y, *et al*. Histologic classification of patients based on mapping biopsies of the gastroesophageal junction. *Am J Surg Pathol* 2003;27:929–36.
224 Aida J, Vieth M, Shepherd NA, *et al*. Is carcinoma in columnar-lined esophagus always located adjacent to intestinal metaplasia?: a histopathologic assessment. *Am J Surg Pathol* 2015;39:188–96.
225 Azuma N, Endo T, Arimura Y, *et al*. Prevalence of Barrett's esophagus and expression of mucin antigens detected by a panel of monoclonal antibodies in Barrett's esophagus and esophageal adenocarcinoma in Japan. *J Gastroenterol* 2000;35:583–92.
226 Langner C, Schneider NI, Plieschnegger W, *et al*. Cardiac mucosa at the gastro-oesophageal junction: indicator of gastro-oesophageal reflux disease? data from a prospective central European multicentre study on histological and endoscopic diagnosis of oesophagitis (histoGERD trial). *Histopathology* 2014;65:81–9.
227 Dahms BB, Rothstein FC. Barrett's esophagus in children: a consequence of chronic gastroesophageal reflux. *Gastroenterology* 1984;86:318–23.
228 Qualman SJ, Murray RD, McClung HJ, *et al*. Intestinal metaplasia is age related in Barrett's esophagus. *Arch Pathol Lab Med* 1990;114:1236–40.
229 Hassall E. Cardia-type mucosa as an esophageal metaplastic condition in children: "Barrett esophagus, intestinal metaplasia-negative?". [corrected]. *J Pediatr Gastroenterol Nutr* 2008;47:102–6.
230 Dias Pereira A, Ramalho PM, Chaves P. Characteristics of cardiac epithelium at the esophagogastric junction of a pediatric population with gastroesophageal reflux. *Dis Esophagus* 2014;27:709–14.
231 Law S, Lam KY, Chu K-M, *et al*. Specialized intestinal metaplasia and carditis at the gastroesophageal junction in Chinese patients undergoing endoscopy. *Am J Gastroenterol* 2002;97:1924–9.
232 Siddiki HA, Lam-Himlin DM, Kahn A, *et al*. Intestinal metaplasia of the gastric cardia: findings in patients with versus without Barrett's esophagus. *Gastrointest Endosc* 2019;89:759–68.
233 Koek GH, Sifrim D, Lerut T, *et al*. Multivariate analysis of the association of acid and duodeno-gastro-oesophageal reflux exposure with the presence of oesophagitis, the severity of oesophagitis and Barrett's oesophagus. *Gut* 2008;57:1056–64.

234 Marchetti M, Caliot E, Pringault E. Chronic acid exposure leads to activation of the cdx2 intestinal homeobox gene in a long-term culture of mouse esophageal keratinocytes. *J Cell Sci* 2003;116:1429–36.
235 Kazumori H, Ishihara S, Rumi MAK, *et al*. Bile acids directly augment caudal related homeobox gene Cdx2 expression in oesophageal keratinocytes in Barrett's epithelium. *Gut* 2006;55:16–25.
236 Huo X, Zhang HY, Zhang XI, *et al*. Acid and bile salt-induced CDX2 expression differs in esophageal squamous cells from patients with and without Barrett's esophagus. *Gastroenterology* 2010;139:194–203.
237 Sun D, Wang X, Gai Z, *et al*. Bile acids but not acidic acids induce Barrett's esophagus. *Int J Clin Exp Pathol* 2015;8:1384–92.
238 Huo X, Zhang X, Yu C, *et al*. Aspirin prevents NF-κB activation and CDX2 expression stimulated by acid and bile salts in oesophageal squamous cells of patients with Barrett's oesophagus. *Gut* 2018;67:606–15.
239 Endo H, Iijima K, Asanuma K, *et al*. Exogenous luminal nitric oxide exposure accelerates columnar transformation of rat esophagus. *Int J Cancer* 2010;127:2009–19.
240 Asanuma K, Huo X, Agoston A, *et al*. In oesophageal squamous cells, nitric oxide causes S-nitrosylation of Akt and blocks Sox2 (sex determining region Y-box 2) expression. *Gut* 2016;65:1416–26.
241 DeMeester SR, Wickramasinghe KS, Lord RVN, *et al*. Cytokeratin and DAS-1 immunostaining reveal similarities among cardiac mucosa, CIM, and Barrett's esophagus. *Am J Gastroenterol* 2002;97:2514–23.
242 Leodolter A, Nocon M, Vieth M, *et al*. Progression of specialized intestinal metaplasia at the cardia to macroscopically evident Barrett's esophagus: an entity of concern in the ProGERD study. *Scand J Gastroenterol* 2012;47:1429–35.
243 Hackelsberger A, Günther T, Schultze V, *et al*. Intestinal metaplasia at the gastro-oesophageal junction: *Helicobacter pylori* gastritis or gastro-oesophageal reflux disease? *Gut* 1998;43:17–21.
244 Günther T, Hackelsberger A, Malfertheiner P, *et al*. Is typing of metaplasia at the squamocolumnar junction revealing its aetiology? *Virchows Arch* 2000;436:6–11.
245 Goldblum JR, Richter JE, Vaezi M, *et al*. *Helicobacter pylori* infection, not gastroesophageal reflux, is the major cause of inflammation and intestinal metaplasia of gastric cardiac mucosa. *Am J Gastroenterol* 2002;97:302–11.
246 Yagi K, Nakamura A, Sekine A. Intestinal metaplasia of gastric cardia and carditis in Japanese patients with *Helicobacter pylori* infection. *Digestion* 2004;70:103–8.
247 Xie S, Wang S, Xue L, *et al*. *Helicobacter pylori* Is Associated With Precancerous and Cancerous Lesions of the Gastric Cardia Mucosa: Results of a Large Population-Based Study in China. *Front Oncol* 2020;10:205.
248 Ormsby AH, Kilgore SP, Goldblum JR, *et al*. The location and frequency of intestinal metaplasia at the esophagogastric junction in 223 consecutive autopsies: implications for patient treatment and preventive strategies in Barrett's esophagus. *Mod Pathol* 2000;13:614–20.
249 Tamagawa Y, Ishimura N, Uno G, *et al*. Notch signaling pathway and Cdx2 expression in the development of Barrett's esophagus. *Lab Invest* 2012;92:896–909.
250 Tamagawa Y, Ishimura N, Uno G, *et al*. Bile acids induce delta-like 1 expression via Cdx2-dependent pathway in the development of Barrett's esophagus. *Lab Invest* 2016;96:325–37.
251 Saller J, Al Diffalha S, Neill K, *et al*. Cdx-2 expression in esophageal biopsies without goblet cell intestinal metaplasia may be predictive of Barrett's esophagus. *Dig Dis Sci* 2020;65:1992–8.
252 Anders M, Sarbia M, Grotzinger C, *et al*. Expression of EpCAM and villin in Barrett's esophagus and in gastric cardia. *Dis Markers* 2008;24:287–92.
253 Lao-Sirieix P, Boussioutas A, Kadri SR, *et al*. Non-endoscopic screening biomarkers for Barrett's oesophagus: from microarray analysis to the clinic. *Gut* 2009;58:1451–9.
254 Peitz U, Kouznetsova I, Wex T, *et al*. TFF3 expression at the esophagogastric junction is increased in gastro-esophageal reflux disease (GERD). *Peptides* 2004;25:771–7.
255 Kouznetsova I, Kalinski T, Peitz U, *et al*. Localization of TFF3 peptide in human esophageal submucosal glands and gastric cardia: differentiation of two types of gastric pit cells along the rostro-caudal axis. *Cell Tissue Res* 2007;328:365–74.
256 Chettouh H, Mowforth O, Galeano-Dalmau N, *et al*. Methylation panel is a diagnostic biomarker for Barrett's oesophagus in endoscopic biopsies and non-endoscopic cytology specimens. *Gut* 2018;67:1942–9.
257 Moinova HR, LaFramboise T, Lutterbaugh JD, *et al*. Identifying DNA methylation biomarkers for non-endoscopic detection of Barrett's esophagus. *Sci Transl Med* 2018;10:eaaso5840.
258 Iyer PG, Taylor WR, Johnson ML, *et al*. Highly discriminant methylated DNA markers for the non-endoscopic detection of Barrett's esophagus. *Am J Gastroenterol* 2018;113:1156–66.
259 Wang Z, Kambhampati S, Cheng Y, *et al*. Methylation biomarker panel performance in EsophaCap cytology samples for diagnosing Barrett's esophagus: a prospective validation study. *Clin Cancer Res* 2019;25:2127–35.
260 Iyer PG, Taylor WR, Johnson ML, *et al*. Accurate nonendoscopic detection of Barrett's esophagus by methylated DNA markers: a multisite case control study. *Am J Gastroenterol* 2020;115:1201–9.
261 Lin R, Li C, Liu Z, *et al*. Genome-wide DNA methylation profiling identifies epigenetic signatures of gastric cardiac intestinal metaplasia. *J Transl Med* 2020;18:292.
262 Mallick R, Patnaik SK, Wani S, *et al*. A systematic review of esophageal microRNA markers for diagnosis and monitoring of Barrett's esophagus. *Dig Dis Sci* 2016;61:1039–50.
263 Cabibi D, Caruso S, Bazan V, *et al*. Analysis of tissue and circulating microRNA expression during metaplastic transformation of the esophagus. *Oncotarget* 2016;7:47821–30.
264 Bus P, Kestens C, Ten Kate FJW, *et al*. Profiling of circulating microRNAs in patients with Barrett's esophagus and esophageal adenocarcinoma. *J Gastroenterol* 2016;51:560–70.
265 Li X, Kleeman S, Coburn SB, *et al*. Selection and application of tissue microRNAs for nonendoscopic diagnosis of Barrett's esophagus. *Gastroenterology* 2018;155:771–83.
266 Craig MP, Rajakaruna S, Paliy O, *et al*. Differential MicroRNA Signatures in the Pathogenesis of Barrett's Esophagus. *Clin Transl Gastroenterol* 2020;11:e00125.
267 Bhat S, Coleman HG, Yousef F, *et al*. Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study. *J Natl Cancer Inst* 2011;103:1049–57.
268 Chandrasoma P, Wijetunge S, DeMeester S, *et al*. Columnar-lined esophagus without intestinal metaplasia has no proven risk of adenocarcinoma. *Am J Surg Pathol* 2012;36:1–7.
269 Bandla S, Peters JH, Ruff D, *et al*. Comparison of cancer-associated genetic abnormalities in columnar-lined esophagus tissues with and without goblet cells. *Ann Surg* 2014;260:72–80.
270 Ishikawa K, Okimoto K, Matsumura T, *et al*. Comprehensive analysis of Barrett's esophagus: focused on carcinogenic potential for Barrett's cancer in Japanese patients. *Dig Dis Sci* 2021;66:2674–81.
271 Norita K, Koike T, Saito M, *et al*. Long-term endoscopic surveillance for Barrett's esophagus in Japan: multicenter prospective cohort study. *Dig Endosc* 2021;33:1085–92.
272 Sharma P, Weston AP, Topalovski M, *et al*. Magnification chromoendoscopy for the detection of intestinal metaplasia and dysplasia in Barrett's oesophagus. *Gut* 2003;52:24–7.
273 Toyoda H, Rubio C, Befrits R, *et al*. Detection of intestinal metaplasia in distal esophagus and esophagogastric junction by enhanced-magnification endoscopy. *Gastrointest Endosc* 2004;59:15–21.
274 Guelrud M, Herrera I. Acetic acid improves identification of remnant islands of Barrett's epithelium after endoscopic therapy. *Gastrointest Endosc* 1998;47:512–5.
275 Canto MI, Setrakian S, Willis J, *et al*. Methylene blue-directed biopsies improve detection of intestinal metaplasia and dysplasia in Barrett's esophagus. *Gastrointest Endosc* 2000;51:560–8.
276 Breyer HP, Silva De Barros SG, Maguilnik I, *et al*. Does methylene blue detect intestinal metaplasia in Barrett's esophagus? *Gastrointest Endosc* 2003;57:505–9.
277 Ngamruengphong S, Sharma VK, Das A. Diagnostic yield of methylene blue chromoendoscopy for detecting specialized intestinal metaplasia and dysplasia in Barrett's esophagus: a meta-analysis. *Gastrointest Endosc* 2009;69:1021–8.
278 Hamamoto Y, Endo T, Nosho K, *et al*. Usefulness of narrow-band imaging endoscopy for diagnosis of Barrett's esophagus. *J Gastroenterol* 2004;39:14–20.
279 Kara MA, Ennahachi M, Fockens P, *et al*. Detection and classification of the mucosal and vascular patterns (mucosal morphology) in Barrett's esophagus by using narrow band imaging. *Gastrointest Endosc* 2006;64:155–66.
280 Sharma P, Bansal A, Mathur S, *et al*. The utility of a novel narrow band imaging endoscopy system in patients with Barrett's esophagus. *Gastrointest Endosc* 2006;64:167–75.
281 Goda K-ichi, Tajiri H, Ikegami M, *et al*. Usefulness of magnifying endoscopy with narrow band imaging for the detection of specialized intestinal metaplasia in columnar-lined esophagus and Barrett's adenocarcinoma. *Gastrointest Endosc* 2007;65:36–46.
282 Singh R, Anagnostopoulos GK, Yao K, *et al*. Narrow-band imaging with magnification in Barrett's esophagus: validation of a simplified grading system of mucosal morphology patterns against histology. *Endoscopy* 2008;40:457–63.
283 Sugimoto H, Kawai T, Naito S, *et al*. Surveillance of short-segment Barrett's esophagus using ultrathin transnasal endoscopy. *J Gastroenterol Hepatol* 2015;30 Suppl 1:41–5.
284 Misumi A, Baba K, Shojima K. Definition of cardiac cancer. *Stomach and Intestine* 1982;17:573–9.
285 Misumi A, Murakami A, Harada K, *et al*. Definition of carcinoma of the gastric cardia. *Langenbecks Arch Chir* 1989;374:221–6.
286 Siewert JR, Hölscher AH, Becker K, *et al*. [Cardia cancer: attempt at a therapeutically relevant classification]. *Chirurg* 1987;58:25–32.
287 Ichikura T, Chochi K, Sugasawa H, *et al*. Proposal for a new definition of true cardia carcinoma. *J Surg Oncol* 2007;95:561–6.
288 Horii T, Koike T, Abe Y, *et al*. Two distinct types of cancer of different origin may be mixed in gastroesophageal junction adenocarcinomas in Japan: evidence from direct evaluation of gastric acid secretion. *Scand J Gastroenterol* 2011;46:710–9.
289 Hansen S, Vollset SE, Derakhshan MH, *et al*. Two distinct aetiologies of cardia cancer; evidence from premorbid serological markers of gastric atrophy and *Helicobacter pylori* status. *Gut* 2007;56:918–25.

290 Derakhshan MH, Malekzadeh R, Watabe H, *et al*. Combination of gastric atrophy, reflux symptoms and histological subtype indicates two distinct aetiologies of gastric cardia cancer. *Gut* 2008;57:298–305.
291 Kamada T, Kurose H, Yamanaka Y, *et al*. Relationship between gastroesophageal junction adenocarcinoma and *Helicobacter pylori* infection in Japan. *Digestion* 2012;85:256–60.
292 Urabe M, Ushiku T, Shinozaki-Ushiku A, *et al*. Adenocarcinoma of the esophagogastric junction and its background mucosal pathology: a comparative analysis according to Siewert classification in a Japanese cohort. *Cancer Med* 2018;7:5145–54.
293 Yamada M, Kushima R, Oda I, *et al*. Different histological status of gastritis in superficial adenocarcinoma of the esophagogastric junction. *Jpn J Clin Oncol* 2014;44:65–71.
294 Nunobe S, Nakanishi Y, Taniguchi H, *et al*. Two distinct pathways of tumorigenesis of adenocarcinomas of the esophagogastric junction, related or unrelated to intestinal metaplasia. *Pathol Int* 2007;57:315–21.
295 Demicco EG, Farris AB, Baba Y, *et al*. The dichotomy in carcinogenesis of the distal esophagus and esophagogastric junction: intestinal-type vs cardiac-type mucosa-associated adenocarcinoma. *Mod Pathol* 2011;24:1177–90.
296 Katai H, Ishida M, Yamashita H, *et al*. HER2 expression in carcinomas of the true cardia (Siewert type II esophagogastric junction carcinoma). *World J Surg* 2014;38:426–30.
297 Inomata Y, Koike T, Ohara S, *et al*. Preservation of gastric acid secretion may be important for the development of gastroesophageal junction adenocarcinoma in Japanese people, irrespective of the *H. pylori* infection status. *Am J Gastroenterol* 2006;101:926–33.
298 Jin L, Yoshida M, Kitagawa Y, *et al*. Subclassification of superficial cardia cancer in relation to the endoscopic esophagogastric junction. *J Gastroenterol Hepatol* 2008;23 Suppl 2:S273–7.
299 Uedo N, Yoshio T, Yoshinaga S, *et al*. Endoscopic gastric mucosal atrophy distinguishes the characteristics of superficial esophagogastric junction adenocarcinoma. *Dig Endosc* 2017;29 Suppl 2:26–36.
300 Kimura K, Takemoto T. An endoscopic recognition of the atrophic border and its significance in chronic gastritis. *Endoscopy* 1969;1:87–97.
301 Dulak AM, Stojanov P, Peng S, *et al*. Exome and whole-genome sequencing of esophageal adenocarcinoma identifies recurrent driver events and mutational complexity. *Nat Genet* 2013;45:478–86.
302 Weaver JMJ, Ross-Innes CS, Shannon N, *et al*. Ordering of mutations in preinvasive disease stages of esophageal carcinogenesis. *Nat Genet* 2014;46:837–43.
303 Ross-Innes CS, Becq J, Warren A, *et al*. Whole-Genome sequencing provides new insights into the clonal architecture of Barrett's esophagus and esophageal adenocarcinoma. *Nat Genet* 2015;47:1038–46.
304 Stachler MD, Taylor-Weiner A, Peng S, *et al*. Paired exome analysis of Barrett's esophagus and adenocarcinoma. *Nat Genet* 2015;47:1047–55.
305 Secrier M, Li X, de Silva N, *et al*. Mutational signatures in esophageal adenocarcinoma define etiologically distinct subgroups with therapeutic relevance. *Nat Genet* 2016;48:1131–41.
306 Ferrer-Torres D, Nancarrow DJ, Kuick R, *et al*. Genomic similarity between gastroesophageal junction and esophageal Barrett's adenocarcinomas. *Oncotarget* 2016;7:54867–82.
307 Yamamoto Y, Wang X, Bertrand D, *et al*. Mutational spectrum of Barrett's stem cells suggests paths to initiation of a precancerous lesion. *Nat Commun* 2016;7:10380.
308 Cancer Genome Atlas Research Network, Analysis Working Group: Asan University, BC Cancer Agency, *et al*. Integrated genomic characterization of oesophageal carcinoma. *Nature* 2017;541:169–75.
309 Bornschein J, Wernisch L, Secrier M, *et al*. Transcriptomic profiling reveals three molecular phenotypes of adenocarcinoma at the gastroesophageal junction. *Int J Cancer* 2019;145:3389–401.
310 Frankell AM, Jammula S, Li X, *et al*. The landscape of selection in 551 esophageal adenocarcinomas defines genomic biomarkers for the clinic. *Nat Genet* 2019;51:506–16.
311 Prevo LJ, Sanchez CA, Galipeau PC, *et al*. P53-Mutant clones and field effects in Barrett's esophagus. *Cancer Res* 1999;59:4784–7.
312 Galipeau PC, Prevo LJ, Sanchez CA, *et al*. Clonal expansion and loss of heterozygosity at chromosomes 9p and 17p in premalignant esophageal (Barrett's) tissue. *J Natl Cancer Inst* 1999;91:2087–95.
313 Wong DJ, Paulson TG, Prevo LJ. $p16^{(INK4a)}$ lesions are common, early abnormalities that undergo clonal expansion in Barrett's metaplastic epithelium. *Cancer Res* 2001;61:8284–9.
314 Bian Y-S, Osterheld M-C, Fontolliet C, *et al*. P16 inactivation by methylation of the CDKN2A promoter occurs early during neoplastic progression in Barrett's esophagus. *Gastroenterology* 2002;122:1113–21.
315 Segal F, Kaspary APB, Prolla JC, *et al*. P53 protein overexpression and *p53* mutation analysis in patients with intestinal metaplasia of the cardia and Barrett's esophagus. *Cancer Lett* 2004;210:213–8.
316 Maley CC, Galipeau PC, Li X, *et al*. Selectively advantageous mutations and hitchhikers in neoplasms: p16 lesions are selected in Barrett's esophagus. *Cancer Res* 2004;64:3414–27.
317 Maley CC, Galipeau PC, Finley JC, *et al*. Genetic clonal diversity predicts progression to esophageal adenocarcinoma. *Nat Genet* 2006;38:468–73.
318 Stachler MD, Camarda ND, Deitrick C, *et al*. Detection of mutations in Barrett's esophagus before progression to high-grade dysplasia or adenocarcinoma. *Gastroenterology* 2018;155:156–67.
319 Ireland AP, Shibata DK, Chandrasoma P, *et al*. Clinical significance of p53 mutations in adenocarcinoma of the esophagus and cardia. *Ann Surg* 2000;231:179–87.
320 Tanière P, Martel-Planche G, Maurici D, *et al*. Molecular and clinical differences between adenocarcinomas of the esophagus and of the gastric cardia. *Am J Pathol* 2001;158:33–40.
321 van Dekken H, Alers JC, Riegman PH, *et al*. Molecular cytogenetic evaluation of gastric cardia adenocarcinoma and precursor lesions. *Am J Pathol* 2001;158:1961–7.
322 Marsman WA, Birjmohun RS, van Rees BP, *et al*. Loss of heterozygosity and immunohistochemistry of adenocarcinomas of the esophagus and gastric cardia. *Clin Cancer Res* 2004;10:8479–85.
323 Lai LA, Kostadinov R, Barrett MT, *et al*. Deletion at fragile sites is a common and early event in Barrett's esophagus. *Mol Cancer Res* 2010;8:1084–94.
324 Li X, Galipeau PC, Paulson TG, *et al*. Temporal and Spatial Evolution of Somatic Chromosomal Alterations: A Case-Cohort Study of Barrett's Esophagus. *Cancer Prev Res* 2014;7:114–27.
325 Nones K, Waddell N, Wayte N, *et al*. Genomic catastrophes frequently arise in esophageal adenocarcinoma and drive tumorigenesis. *Nat Commun* 2014;5:5224.
326 Contino G, Vaughan TL, Whiteman D, *et al*. The evolving genomic landscape of Barrett's esophagus and esophageal adenocarcinoma. *Gastroenterology* 2017;153:657–73.
327 Wu W, Bhagat TD, Yang X, *et al*. Hypomethylation of noncoding DNA regions and overexpression of the long noncoding RNA, *AFAP1-AS1*, in Barrett's esophagus and esophageal adenocarcinoma. *Gastroenterology* 2013;144:956–66.
328 Xu E, Gu J, Hawk ET, *et al*. Genome-wide methylation analysis shows similar patterns in Barrett's esophagus and esophageal adenocarcinoma. *Carcinogenesis* 2013;34:2750–6.
329 Krause L, Nones K, Loffler KA, *et al*. Identification of the CIMP-like subtype and aberrant methylation of members of the chromosomal segregation and spindle assembly pathways in esophageal adenocarcinoma. *Carcinogenesis* 2016;37:356–65.
330 Yu M, Maden SK, Stachler M, *et al*. Subtypes of Barrett's oesophagus and oesophageal adenocarcinoma based on genome-wide methylation analysis. *Gut* 2019;68:389–99.
331 Jammula S, Katz-Summercom AG, Li X. Identification of subtypes of Barrett's esophagus and esophageal adenocarcinoma based on DNA methylation profiles and integration of transcriptome and genome data. *Gastroenterology* 2020;156:1682–97.
332 Fassan M, Volinia S, Palatini J, *et al*. Microrna expression profiling in the histological subtypes of Barrett's metaplasia. *Clin Transl Gastroenterol* 2013;4:e34.
333 Garman KS, Owzar K, Hauser ER, *et al*. MicroRNA expression differentiates squamous epithelium from Barrett's esophagus and esophageal cancer. *Dig Dis Sci* 2013;58:3178–88.
334 Slaby O, Srovnal J, Radova L, *et al*. Dynamic changes in microRNA expression profiles reflect progression of Barrett's esophagus to esophageal adenocarcinoma. *Carcinogenesis* 2015;36:521–7.
335 Abraham JM, Meltzer SJ. Long noncoding RNAs in the pathogenesis of Barrett's esophagus and esophageal carcinoma. *Gastroenterology* 2017;153:27–34.
336 Maag JLV, Fisher OM, Levert-Mignon A, *et al*. Novel aberrations uncovered in Barrett's esophagus and esophageal adenocarcinoma using whole transcriptome sequencing. *Mol Cancer Res* 2017;15:1558–69.
337 Clark RJ, Craig MP, Agrawal S, *et al*. microRNA involvement in the onset and progression of Barrett's esophagus: a systematic review. *Oncotarget* 2018;9:8179–96.
338 Craig MP, Rajakaruna S, Paliy O, *et al*. Differential microRNA signatures in the pathogenesis of Barrett's esophagus. *Clin Transl Gastroenterol* 2020;11:e00125.
339 Song JH, Tieu AH, Cheng Y, *et al*. Novel long noncoding RNA miR205HG functions as an esophageal tumor-suppressive hedgehog inhibitor. *Cancers* 2021;13. doi:10.3390/cancers13071707. [Epub ahead of print: 03 04 2021].
340 Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature* 2014;513:202–9.
341 Curvers WL, Bohmer CJ, Mallant-Hent RC, *et al*. Mucosal morphology in Barrett's esophagus: interobserver agreement and role of narrow band imaging. *Endoscopy* 2008;40:799–805.
342 Qumseya BJ, Wang H, Badie N, *et al*. Advanced imaging technologies increase detection of dysplasia and neoplasia in patients with Barrett's esophagus: a meta-analysis and systematic review. *Clin Gastroenterol Hepatol* 2013;11:1562–70.
343 , Thosani N, Abu Dayyeh BK, *et al*, ASGE Technology Committee. ASGE technology Committee systematic review and meta-analysis assessing the ASGE preservation and incorporation of valuable endoscopic innovations thresholds for adopting real-time imaging-assisted endoscopic targeted biopsy during endoscopic surveillance of Barrett's esophagus. *Gastrointest Endosc* 2016;83:684–98.

344 Sharma P, Bergman JJGHM, Goda K, *et al*. Development and validation of a classification system to identify high-grade dysplasia and esophageal adenocarcinoma in Barrett's esophagus using narrow-band imaging. *Gastroenterology* 2016;150:591–8.
345 Goda K, Fujisaki J, Ishihara R, *et al*. Newly developed magnifying endoscopic classification of the Japan Esophageal Society to identify superficial Barrett's esophagus-related neoplasms. *Esophagus* 2018;15:153–9.
346 Boerwinkel DF, Swager A-F, Curvers WL, *et al*. The clinical consequences of advanced imaging techniques in Barrett's esophagus. *Gastroenterology* 2014;146:622–9.
347 Everson MA, Lovat LB, Graham DG, *et al*. Virtual chromoendoscopy by using optical enhancement improves the detection of Barrett's esophagus-associated neoplasia. *Gastrointest Endosc* 2019;89:247–56.
348 de Groof AJ, Swager A-F, Pouw RE, *et al*. Blue-light imaging has an additional value to white-light endoscopy in visualization of early Barrett's neoplasia: an international multicenter cohort study. *Gastrointest Endosc* 2019;89:749–58.
349 de Groof AJ, Fockens KN, Struyvenberg MR, *et al*. Blue-light imaging and linked-color imaging improve visualization of Barrett's neoplasia by nonexpert endoscopists. *Gastrointest Endosc* 2020;91:1050–7.
350 Ebigbo A, Mendel R, Probst A, *et al*. Real-time use of artificial intelligence in the evaluation of cancer in Barrett's oesophagus. *Gut* 2020;69:615–6.
351 de Groof AJ, Struyvenberg MR, van der Putten J. Deep-learning system detects neioplasia in patients with Barrett's esophagus with higher accuracy than endoscopists in a multistep training and validation study with benchmarking. *Gastroenterology* 2020;156:915–29.
352 Zhang Q, Wang F, Chen Z-Y, *et al*. Comparison of the diagnostic efficacy of white light endoscopy and magnifying endoscopy with narrow band imaging for early gastric cancer: a meta-analysis. *Gastric Cancer* 2016;19:543–52.
353 Muto M, Yao K, Kaise M, *et al*. Magnifying endoscopy simple diagnostic algorithm for early gastric cancer (MESD A-G). *Dig Endosc* 2016;28:379–93.
354 Kakushima N, Yoshida N, Doyama H, *et al*. Near-focus magnification and second-generation narrow-band imaging for early gastric cancer in a randomized trial. *J Gastroenterol* 2020;55:1127–37.
355 Yoshida N, Doyama H, Yano T, *et al*. Early gastric cancer detection in high-risk patients: a multicentre randomised controlled trial on the effect of second-generation narrow band imaging. *Gut* 2021;70:67–75.
356 Fukuda H, Miura Y, Osawa H, *et al*. Linked color imaging can enhance recognition of early gastric cancer by high color contrast to surrounding gastric intestinal metaplasia. *J Gastroenterol* 2019;54:396–406.
357 Ono S, Kawada K, Dohi O, *et al*. Linked color imaging focused on neoplasm detection in the upper gastrointestinal tract: a randomized trial. *Ann Intern Med* 2021;174:18–24.
358 Gao J, Zhang X, Meng Q, *et al*. Linked color imaging can improve detection rate of early gastric cancer in a high-risk population: a multi-center randomized controlled clinical trial. *Dig Dis Sci* 2021;66:1212–9.
359 Horiuchi Y, Aoyama K, Tokai Y, *et al*. Convolutional neural network for differentiating gastric cancer from gastritis using magnified endoscopy with narrow band imaging. *Dig Dis Sci* 2020;65:1355–63.
360 Horiuchi Y, Hirasawa T, Ishizuka N, *et al*. Performance of a computer-aided diagnosis system in diagnosing early gastric cancer using magnifying endoscopy videos with narrow-band imaging (with videos). *Gastrointest Endosc* 2020;92:856–65.
361 Hu H, Gong L, Dong D, *et al*. Identifying early gastric cancer under magnifying narrow-band images with deep learning: a multicenter study. *Gastrointest Endosc* 2021;93:1333–41.
362 Ikenoyama Y, Hirasawa T, Ishioka M, *et al*. Detecting early gastric cancer: comparison between the diagnostic ability of convolutional neural networks and endoscopists. *Dig Endosc* 2021;33:141–50.
363 Ling T, Wu L, Fu Y, *et al*. A deep learning-based system for identifying differentiation status and delineating the margins of early gastric cancer in magnifying narrow-band imaging endoscopy. *Endoscopy* 2021;53:469–77.
364 Wani S, Williams JL, Komanduri S, *et al*. Endoscopists systematically undersample patients with long-segment Barrett's esophagus: an analysis of biopsy sampling practices from a quality improvement registry. *Gastrointest Endosc* 2019;90:732–41.
365 Matsuno K, Ishihara R, Ohmori M, *et al*. Time trends in the incidence of esophageal adenocarcinoma, gastric adenocarcinoma, and superficial esophagogastric junction adenocarcinoma. *J Gastroenterol* 2019;54:784–91.
366 World Health Organization. Icd-11 for mortality and morbidity statistics. Available: https://icd.who.int/browse11/en [Accessed Dec 2021].
367 International Agency for Research on Cancer. *Who classification of tumours of the digestive system*. 5th edn. Lyon France, 2019.