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Kyoto International Consensus Report on Anatomy, Pathophysiology and Clinical Significance of the Gastroesophageal Junction

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Aim: to present the main statements of Kyoto International Consensus report on anatomy, pathophysiology, and clinical significance of the gastroesophageal junction.
Key points. The experts reviewed and adopted 28 statements concerning (1) the definition of the gastroesophageal junction (GEJ); (2) the definition of the GEJ zone, covering the area located 1 cm proximal and 1 cm distal in relation to gastroesophageal junction; (3) the assessment of chemical and bacterial (*Helicobacter pylori*) factors leading to the development of inflammation, metaplasia and neoplasia of the mucosa of the GEJ; and (4) a new definition of Barrett's esophagus.
Conclusion. The new definitions of GEJ, GEJ zone and Barrett's esophagus adopted by the International Consensus will be used in subsequent studies, which will contribute to improving the results of treatment of diseases of this area.
Keywords: gastroesophageal junction, gastroesophageal reflux disease, Barrett's esophagus, *Helicobacter pylori*
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Киотское международное согласительное совещание, посвященное анатомии, патофизиологии и клиническому значению пищеводно-желудочного перехода

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Цель: представить основные положения Киотского международного согласительного совещания, посвященного анатомии, патофизиологии и клиническому значению пищеводно-желудочного перехода.
Основные положения. Экспертами были рассмотрены и приняты 28 положений, касающихся: 1) определения пищеводно-желудочного перехода (ПЖП); 2) определения зоны ПЖП, охватывающей участок, расположенный на 1 см проксимально и 1 см дистально по отношению к ПЖП; 3) оценки химических и бактериальных (*Helicobacter pylori*) факторов, ведущих к развитию воспаления, метаплазии и неоплазии слизистой оболочки зоны ПЖП; и 4) нового определения пищевода Баррета.
Заключение. Принятые Киотским международным согласительным совещанием новые определения ПЖП, зоны ПЖП и пищевода Баррета будут использоваться при проведении последующих исследований, что будет способствовать улучшению результатов лечения заболеваний данной области.
Ключевые слова: желудочно-пищеводный переход, гастроэзофагеальная рефлюксная болезнь, пищевод Баррета, *Helicobacter pylori*
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In 2022, the Gut journal published the proceedings of the Kyoto International Consensus Meeting on the anatomy, pathophysiology, and clinical significance of the gastroesophageal junction [1]. The necessity for such a meeting was dictated by the presence of different approaches to defining the gastroesophageal junction (GEJ), the GEJ zone, and Barrett's esophagus (BE).

Thirty-seven experts took part in the voting. The statement was considered adopted if the level of approval — "strongly agree" or "agree" — with minor reservation totaled more than 80 %. In addition, response options such as "disagree with major reservation" and "strongly disagree" were used for voting. The level of evidence was graded as "high", "moderate", "low", and "very low"; and the strength of recommendation was graded as "strong", "weak", or "not applicable". First, a clinical question (CQ) was formulated, followed by a Statement containing the answer to it.

CQ 1. *How can we define BE conceptually?*

Statement 1. *BE is the condition in which a metaplastic columnar mucosa predisposed to neoplasia replaces the squamous mucosa of the distal esophagus (agreement: strongly agree — 97 %, agree with minor reservation — 3 %; quality of evidence: high — 72 %, moderate — 28 %; strength of recommendation: strong — 90 %, weak — 10 %).*

In a commentary on this statement, experts emphasized that the new definition of BE does not provide a need for a certain extent of intestinal metaplasia of the esophageal mucosa (> 1 cm). At the same time, they do not recommend dynamic endoscopic monitoring of patients with an ultrashort segment of BE (< 1 cm), considering that risk of developing esophageal adenocarcinoma is very low.

CQ 2. *Which of the two — the distal end of the palisade vessels of the esophagus or proximal end of gastric folds (PEGF) — is more appropriate anatomical landmark of the GEJ?*

Statement 2. *Anatomically, the distal end of the palisade vessels of the esophagus is more appropriate than the PEGF for defining the GEJ (agreement: strongly agree — 71 %, agree with minor reservation — 11 %, agree 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 %).*

The comment notes that the distal end of the palisade vessels of the esophagus retains its value for definition of GEJ even with the development of esophagus intestinal metaplasia, as well as with the occurrence of atrophy and intestinal metaplasia of the epithelium of the gastric mucosa.

CQ 3. *Which of the two landmarks — the distal end of the palisade vessels of the esophagus or PEGF — is more appropriate for clinically defining the GEJ?*

Statement 3. *Clinically, if the distal end of the palisade vessels of the esophagus is clearly identifiable, it should be used for defining the GEJ. In case the palisade vessels are not identifiable, the PEGF should be used as a landmark of the GEJ (agreement: strongly agree — 78 %, agree with minor reservation — 11 %, agree with major reservation — 11 %; quality of evidence: high — 57 %, moderate — 29 %, low — 14 %; strength of recommendation: strong — 68 %, weak — 32 %).*

The comment notes that due to mucous inflammation of the distal esophagus it may be hard to identify the palisade vessels of the esophagus. In such cases, PEGF can be applied as a surrogate guide to finding GEJ.

CQ 4. *What is the most appropriate endoscopic method to identify the distal end of the palisade vessels?*

Statement 4. *White light imaging with/without image-enhanced endoscopy in both forward and retroflexed views with air insufflation is the most appropriate method for identifying the distal end of the palisade vessels (agreement: strongly agree — 71 %; agree with minor reservation — 29 %; quality of evidence: high — 57 %, moderate — 36 %, low — 7 %; strength of recommendation: strong — 79 %, weak — 21 %).*

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 %; quality of evidence: high — 78 %, moderate — 18 %, low — 4 %; strength of recommendation: strong — 93 %, weak — 7 %).*

CQ 6. *Can image-enhanced endoscopy improve visibility of the palisade vessels?*

Statement 6. *Image-enhanced endoscopy can improve the visibility of palisade vessels (agreement: strongly agree — 72 %, agree with minor reservation — 21 %, agree with major reservation — 7 %; quality of evidence: high — 21, moderate — 57 %, low — 18 %, very low — 4 %; strength of recommendation: strong — 39 %, weak — 61 %).*

Comments on Statements 4–6. Experts emphasize that in the presence of reflux esophagitis or BE, endoscopic identification of the palisade vessels of the esophagus may be difficult due to mucous inflammation or dysplastic changes. Insufficient air insufflation may also make them difficult to be visualized. For this reason, PEGF can be used to determine GEJ.

CQ 7. *What is the location of the squamocolumnar junction in the fully developed fetus?*

Statement 7. *In the fully developed fetus, the squamocolumnar junction is located at the terminal end of the esophagus. There is no congenital columnar metaplastic change (agreement: strongly agree — 75 %, agree with minor reservation — 21 %, agree with major reservation — 4 %; quality of evidence: high — 47 %, moderate — 39 %, low — 14 %; strength of recommendation: strong — 68, weak — 32 %).*

The commentary states that the fetal esophagus is initially lined with tubular epithelium, then ciliated epithelial cells appear. By the end of pregnancy, they disappear, turning into stratified squamous epithelium.

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 %; quality of evidence: high — 43 %, moderate — 50 %, low — 7 %; strength of recommendation: strong — 50 %, weak — 50 %).*

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 %; quality of evidence: high — 48 %, moderate — 45 %, low — 7 %; strength of recommendation: strong — 55 %, weak — 45 %.*

Comments on Statements 8–9. Experts noted that there are conflicting views on whether cardiac-type mucosa is a normal parent component or the result of metaplasia of the stratified squamous epithelium of the esophagus. Experts agreed that true cardiac-type mucosa exists in fetuses, newborns, and young children as the original intrinsic structural component, but its extent does not exceed 1 mm. As for adults, the extent of the cardiac-type mucosa in them significantly exceeds that one in newborns and young children, and such a significant extent of the cardiac-type mucosa may be due to either metaplastic changes in the adjacent stratified squamous epithelium of the esophagus or the epithelium of the gastric mucosa.

CQ 10. *Which direction does the cardiac-type mucosa lengthen?*

Statement 10. *Cardiac-type mucosa expands proximally due to gastro-esophageal reflux disease (GERD) (agreement: strongly agree — 71 %, agree with minor reservation — 29 %; quality of evidence: high — 68 %, moderate — 32 %; strength of recommendation: strong — 82 %, weak — 18 %).*

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 %; quality of evidence: high — 68 %, moderate — 32 %, strength of recommendation: strong — 79, weak — 21 %).*

Comments on Statements 10–11. Experts noted that the presence of a hiatus hernia predisposes to gastroesophageal reflux and promotes proximal extension of the cardiac-type mucosa due to columnar cell metaplasia of the most distal portions of the esophageal 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 esophageal junctional mucosal pathophysiology (agreement: strongly agree — 66 %, agree with minor reservation — 31 %, agree with major reservation — 3 %; quality of evidence: high — 38 %, moderate — 55 %, low — 7 %; strength of recommendation: strong — 55 %, weak — 45 %).*

In their commentary the experts noted that luminal esophageal pH monitoring may be useful for assessing the pathophysiological mechanisms of changes in GEJ mucosa. It is assumed that not only an acidic (pH < 4), but also a faintly acidic (pH > 4) medium disrupts the permeability of GEJ mucosa. As the permeability of the mucous membrane increases, impedance measurements decrease, which allows this method to be used to assess the integrity of the esophagus mucosa.

CQ 13. *What is the role of high-resolution manometry (HRM) and functional luminal imaging probe (EndoFLIP) planimetry in the evaluation of GEJ pathophysiology?*

Statement 13. *HRM is useful for evaluating the motor function of the GEJ, whereas functional luminal imaging probe (EndoFLIP) planimetry is useful for evaluating the distensibility of the GEJ (agreement: strongly agree — 86 %, agree with minor reservation — 14 %,*

quality of evidence: high — 69 %, moderate — 24 %, low — 7 %; strength of recommendation: strong — 62 %, weak — 38 %).

The commentary points to the utility of using HRM to evaluate the pathophysiologic mechanisms of esophageal motility disorders. Luminal imaging probe planimetry (functional lumen imaging probe, FLIP), recently introduced into clinical practice, provides real-time 3D-imaging of luminal distensibility and the identification of functional and anatomical changes GEJ.

CQ 14. *How can we define a GEJ zone to clarify junctional pathologies?*

Statement 14. *A GEJ zone can be defined endoscopically as a transitional segment extending 1 cm either side of GEJ (agreement: strongly agree — 69 %, agree with minor reservation — 17 %, agree 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 %).*

The commentary notes that metaplastic changes in stratified squamous epithelium localized at a distance of more than 1 cm from the GEJ can be regarded as BE, which is confirmed by several consensus meetings. At the same time, the mucous area of the cardiac type, located within 1 cm of GEJ didn't get designation. In this consensus meeting, the experts came to the general conclusion that areas of the cardiac-type mucosa of any extent located proximal to GEJ should be considered as BE. At the same time, areas sizes less than 1 cm are included in the GEJ zone and are called the ultra-short segment of the BE.

CQ 15. *What are the principal causes of inflammation in the GEJ zone?*

Statement 15. *H. pylori infection and gastroesophageal reflux are the principal causes of inflammation in the GEJ zone (agreement: strongly agree — 90 %, agree with minor reservation — 3 %, agree with major reservation — 7 %; quality of evidence: high — 80 %, moderate — 17 %, low — 3 %; strength of recommendation: strong — 83 %, weak — 17 %).*

The commentary to this statement notes, that *H. pylori* infection causes inflammation of the mucous membrane of any part of the stomach, including in the cardia area; however, inflammation here can occur without the participation of *H. pylori* due to gastroesophageal reflux, including bile reflux, can lead to the development of intestinal metaplasia. Other microorganisms found in the lumen of the esophagus (in particular, gram-negative bacteria) can also contribute to the occurrence of reflux esophagitis and BE.

CQ 16. *What is the mechanism and clinical relevance of formation of double muscularis mucosae in the esophagus?*

Statement 16. *The double muscularis mucosae of the esophagus is most likely formed as a result of inflammation and is a specific stage of the pathological process requiring clinical evaluation (agreement: strongly agree — 73 %, agree with minor reservation — 21 %, agree with major reservation — 3 %, strongly disagree — 3 %; quality of evidence: high — 63 %, moderate — 34 %, low — 3 %; strength of recommendation: strong — 72 %, weak — 28 %).*

The commentary indicates that the double muscularis mucosae is one of the most common features characteristics of BE. It can also occur with reflux esophagitis, in the initial stage of squamous cell carcinoma, but it occupies a very small area.

CQ 17. *Can metaplastic cardiac-type mucosa progress into intestinal metaplasia?*

Statement 17. *Metaplastic cardiac-type mucosa shows molecular evidence of intestinal differentiation and appears to be the precursor of intestinal metaplasia (agreement: strongly agree — 71 %, agree with minor reservation — 25 %, agree with major reservation — 4 %; quality of evidence: high — 64 %, moderate — 29 %, low — 7 %; strength of recommendation: strong — 71 %; weak — 25 %, not applicable — 4 %).*

As stated in the commentary, experts now believe that over time, against the background of ongoing inflammation, columnar cell metaplasia of the esophageal mucosa undergoes additional reprogramming, which ultimately results in the development of intestinal metaplasia.

CQ 18. *Which is the more common metaplastic mucosa in the GEJ zone — cardiac or intestinal type?*

Statement 18. *Metaplastic cardiac-type mucosa is more frequent in the GEJ zone (agreement: strongly agree — 79 %; agree with minor reservation — 21 %; quality of evidence: high — 68 %, moderate — 32 %; strength of recommendation: strong — 71 %, weak — 29 %).*

The commentary notes that the increase in the frequency of intestinal metaplasia due to age of patients indicates that metaplasia in the GEJ zone precedes the development of intestinal metaplasia.

CQ 19. *What factors are associated with intestinal metaplasia in the GEJ zone?*

Statement 19. *Gastric acid, pepsin, bile, nitrosative stress and H. pylori are associated with intestinal metaplasia in the GEJ zone*

(agreement: strongly agree — 72 %, agree with minor reservation — 21 %, agree with major reservation — 7 %; quality of evidence: high — 47 %, moderate — 39 %; strength of recommendation: strong — 50 %, weak — 50 %).

The commentary emphasized that the association of mixed (acid and bile) gastroesophageal reflux with BE, which has a length of intestinal metaplasia of more than 1 cm, is currently considered well proven. Active forms of nitrogenous compounds located in the GEJ zone may also be involved in the development of BE. In patients with *H. pylori* infection who do not have gastroesophageal reflux, chronic inflammation caused by these bacteria becomes the main cause of the development of intestinal metaplasia in the GEJ zone.

CQ 20. *Do we have useful molecular markers to predict the progression of metaplastic cardiac-type mucosa to intestinal metaplasia?*

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 %; quality of evidence: high — 38 %, moderate — 62 %; strength of recommendation: strong — 52, weak — 48 %).*

The commentary states that despite numerous hypotheses, the molecular mechanisms of GEJ mucosa metaplasia remain unclear. Although a number of markers have been proposed to determine metaplasia of the GEJ mucosa (increased expression of CDX2, EpCam and villin), their diagnostic value in differentiating BE from purely columnar cell metaplasia of the GEJ zone requires further research.

CQ 21. *Does metaplastic cardiac-type mucosa in the absence of intestinal metaplasia in the GEJ zone predispose to adenocarcinoma?*

Statement 21. *Metaplastic cardiac-type mucosa in the absence of intestinal metaplasia in the GEJ zone appears to have a risk of progression to malignancy (agreement: strongly agree — 49 %, agree with minor reservation — 45 %, agree 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 %).*

The commentary notes that the criteria adopted in the United States indicate that metaplasia of columnar epithelium with the presence of goblet cells is a precursor of dysplasia and cancer. But molecular abnormalities that contribute to the progression of neoplastic changes have been identified even with mucous metaplasia of the cardiac type. Thus, cardiac-type mucosal metaplasia in the absence of intestinal metaplasia is considered a condition predisposing to neoplastic transformation.

CQ 22. *Can image-enhanced endoscopy improve the diagnosis of intestinal metaplasia in the GEJ zone?*

Statement 22. *Image-enhanced endoscopy with or without magnification can enhance the detection of intestinal metaplasia in the GEJ zone (agreement: strongly agree — 83 %, agree with minor reservation — 17 %; quality of evidence: high — 37 %, moderate — 60 %, low — 3 %; strength of recommendation: strong — 53 %, weak — 47 %).*

The commentary concludes that magnification chromoendoscopy (with methylene blue, indigo carmine, and acetic acid) and narrow-band magnification endoscopy or associated color enhancement imaging improve the accuracy of detection of intestinal mucosal metaplasia in the GEJ zone.

CQ 23. *What should adenocarcinoma arising from the 'GEJ zone' be named?*

Statement 23. *We propose to name it "GEJ zone adenocarcinoma" (agreement: strongly agree — 90 %, agree with minor reservation — 10 %; quality of evidence: high — 44 %, moderate — 43 %, low — 10 %, very low — 3 %; strength of* recommendation: strong — 67 %, weak — 33 %).

CQ 24. *How is a GEJ zone adenocarcinoma defined?*

Statement 24. *A GEJ zone adenocarcinoma is one with its epicentre lying within 10 mm either side of the GEJ (agreement: strongly agree — 93 %, agree with minor reservation — 7 %; quality of evidence: high — 47 %, moderate — 50 %, low — 3 %; strength of recommendation: strong — 70 %, weak — 30 %).*

Commentary on Statements 23–24. It was emphasized that the new name "GEJ zone adenocarcinoma" differs from the previously existing terms "cardiac gastric cancer" and "gastric cardia cancer". But this term will continue to include adenocarcinomas of various origins: from the ultrashort segment of the esophagus, submucosal glands of the esophagus, metaplastic epithelium of the cardia. In the future adenocarcinomas localized in the proximal part of the GEJ zone should be unified as esophageal adenocarcinomas arising from metaplastic intestinal epithelium.

CQ 25. *Are there two distinctive etiologies of cancer in the GEJ zone?*

Statement 25. *There are two major distinctive etiologies for GEJ zone adenocarcinoma: GERD-related and H. pylori infection (agreement: strongly agree — 100 %; quality*

of evidence: high — 97 %, moderate — 3 %; strength of recommendation: strong — 100 %).

CQ 26. *Should cancers arising in the GEJ zone be classified separately from cancers arising in the rest of the stomach?*

Statement 26. *Cancer arising in the GEJ zone has a mixed etiology 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 %, agree with major reservation — 3 %; quality of evidence: high — 53 %, moderate — 40 %, low — 7 %; strength of recommendation: strong — 80 %, weak — 20 %).*

Comments on Statements 25–26. Adenocarcinomas arising in the GEJ zone, depending on the etiology, can be divided into three subgroups: the first one is characterized by high secretion of hydrochloric acid, accompanied by its reflux in the absence of *H. pylori* infection; the second one is characterized by high secretion of hydrochloric acid, the presence of reflux and weak atrophy of the antral mucosa caused by *H. pylori*; the third one is characterized by low secretion of hydrochloric acid, absence of reflux and diffuse atrophy of the gastric mucosa associated with *H. pylori* infection.

CQ 27. *What molecular events lead to neoplasia arising in the GEJ zone?*

Statement 27. *Many genetic and epigenetic abnormalities have been described in GEJ zone neoplasia, but the exact mechanisms remain unclear (agreement: strongly agree — 93 %, agree with minor reservation — 7 %; quality of evidence: high — 62 %, moderate — 38 %; strength of recommendation: strong — 69 %, weak — 31 %).*

The commentary suggested that the molecular changes (primarily genetic) in GEJ zone adenocarcinoma will be similar to those in esophageal adenocarcinoma, but the causal mechanisms involved in the relationship between genetic abnormalities and progression of neoplastic changes require careful evaluation of tumor location. In addition, future studies of genetic disorders in adenocarcinoma in the GEJ zone should consider such an important etiological factor as *H. pylori* infection.

CQ 28. *Can image-enhanced endoscopy improve diagnostic yields of early adenocarcinoma arising in the GEJ zone?*

Statement 28. *Image-enhanced endoscopy with or without magnification is likely to improve diagnostic yields of early adenocarcinoma arising in the GEJ zone (agreement: strongly agree — 86 %; agree with minor reservation — 14 %; quality of evidence: high — 59 %, moderate — 38 %, low — 3 %; strength of recommendation: strong — 69 %, weak — 31 %).*

The commentary notes that currently there are no studies specifically devoted to the diagnosis of early-stage adenocarcinoma in the GEJ zone. Since the GEJ is located between the distal portion of the esophagus and the proximal stomach, we can conclude that the results of studies of the effectiveness of high-resolution endoscopy in the diagnosis of neoplastic changes in BE and early-stage gastric cancer are also applicable to the diagnosis of early-stage adenocarcinoma in the GEJ zone.

Thus, the consensus meeting approved the following new approaches regarding the anatomical and clinical features of the GEJ:

– a new definition of BE has been proposed that does not require taking into account the extent of the area of intestinal metaplasia, which can serve as a new platform for future research;

– the use of a unified endoscopic landmark (the distal end of the palisade vessels of the esophagus) will avoid inaccuracies in the diagnosis of short BE;

– for practical purposes, a new definition of the GEJ zone has been proposed, which includes an area of the mucous membrane located within 1 cm proximally and 1 cm distally relative to the GEJ;

There is no doubt that the provisions adopted by the consensus meeting and their implementation in clinical practice will help improve the diagnosis of BE and early stages of adenocarcinoma in the GEJ zone.

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