Clinical significance of esophagogastroduodenoscopy in patients with esophageal motility disorders

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Professor Takayuki Matsumoto
Editor
Digestive Endoscopy

26 August 2020

Dear Professor Takayuki Matsumoto,

We thank the editors and reviewers for their helpful comments on our manuscript. We are grateful for the opportunity to revise the manuscript and respond to the reviewers' comments.

We hope that our manuscript is now acceptable for publication in *Digestive Endoscopy*.

We look forward to hearing from you at your earliest convenience.

Yours sincerely,

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Responses to the Comments of a Reviewer

1) Authors used the normal values of the Sandhill system (Do Carmo GC, et al. NMO 2015). Did authors use a catheter with 32 circumferential sensors? Description about a catheter used in the present study in the previous version showed a different catheter. Therefore, I asked whether the UNI HRiM probe has been validated or not. However, authors did not answer about this question. I am not sure whether the same normal value indicated in do Carmo's study can be used if authors did not used the catheter with 32 circumferential sensors.

Response:

The manometric probe used in this study was the HRiM2 High Resolution Impedance Manometry Catheter with 32 circumferential pressure/16 impedance channels (model number UNI-ESO-WG1A1). This was the same probe used in Carmo's study, and it was validated. The description of the catheter used in the previous study was confusing; therefore, we deleted the reference to this article in our revised manuscript. Accordingly, we revised the Methods section as follows: ***"The manometric probe used in this study was the HRiM2 High Resolution Impedance Manometry Catheter with 32 circumferential pressure/16 impedance channels (model number UNI-ESO-WG1A1)."*** *(page 9, lines 3–5)*

2) Authors showed better sensitivity of endoscopic findings for esophageal motility disorders. Do authors recommend high-resolution manometry in all patients with abnormal endoscopic findings?

Response:

We do not recommend high-resolution manometry for all patients with dysphagia with these abnormal endoscopic findings. In Japan, both endoscopic specialists and non-specialists perform EGD; therefore, it is necessary to clarify the endoscopic parameters that allow non-specialists to treat patients with esophageal motility disorders. Therefore, if non-specialists find abnormal endoscopic results in patients with dysphagia, an additional barium esophagography will usually be performed. If the barium esophagography shows abnormalities, or if the dysphagia persists even if

the barium esophagography shows no abnormalities, the physician should refer the patient to a specialized facility that can perform high-resolution manometry.

3) Authors assert that non-occlusive contraction is an important finding for detecting esophageal motility disorders showing a study with FLIP. However, the study with FLIP cannot refer to this study since methodology for measuring esophageal motility is completely different. In addition, prevalence of non-occlusive contraction in patients with esophageal motility disorders should be compared with that in healthy subjects. Otherwise, I do not think that non-occlusive contraction is an important finding.

Response:

Thank you for your constructive comments. We have accordingly deleted the reference article on FLIP. In addition, we investigated the differences in the prevalence of nonocclusive contraction between 30 randomly selected patients with esophageal motility disorders (20 with esophageal achalasia, 2 with EGJ outflow obstruction, 5 with distal esophageal spasm, 2 with jackhammer esophagus and one with absent contractility) and 30 sex- and age-matched healthy subjects. The rate of nonocclusive contractions in patients with esophageal motility disorders was 60.0% (18/30), while that in healthy subjects was 20.0% (6/30). The rate of nonocclusive contractions in patients with esophageal motility disorders was significantly higher than that in healthy subjects (P=0.003). Accordingly, we added the following to the Discussion section: ***"To clarify the clinical significance of nonocclusive contraction, we additionally analyzed the differences in the prevalence of nonocclusive contraction between 30 randomly selected patients with esophageal motility disorders (20 with esophageal achalasia, 2 with EGJ outflow obstruction, 5 with distal esophageal spasm, 2 with jackhammer esophagus and one with absent contractility) and 30 sex- and age-matched healthy subjects. The rate of nonocclusive contractions in patients with esophageal motility disorders was significantly higher (60.0%, 18/30) than that in healthy subjects (20.0%, 6/30; P=0.003)."*** *(page 15, lines 4–11)*

4) Figures of high-resolution manometry showed double swallows. Double swallows could induce deglutitive inhibition; therefore, these figures are not appropriate if authors wanted to show a lack of peristalsis.

Response:

Per the reviewer's comment, we changed the figures to show high-resolution manometry without double swallows.

Clinical significance of esophagogastroduodenoscopy in patients with esophageal motility disorders

Short title: esophageal motility and endoscopy

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Authors' contributions: Masaki Matsubara analyzed the data, and drafted the manuscript; Noriaki Manabe made a study concept and design; analysis and interpretation of data; study supervision and analyzing; Maki Ayaki, Jun Nakamura, Takahisa Murao, Minoru Fujita, Masahiko Kuinose, Tomoki Yamatsuji, and Yoshio Naomoto participated in clinical data acquisition; Ken Haruma participated in clinical

data acquisition and evaluated biostatistical analysis; all authors participated in drafting or revising the article and approved the final version for submission.

Abstract

***Objectives*:** The first aim of this study was to elucidate the detection rate of esophagogastroduodenoscopy (EGD) in patients complaining of dysphagia with esophageal motility disorders; the second was to clarify the useful parameters of EGD associated with esophageal motility disorders.

***Methods*:** Participants included 380 patients who underwent EGD before high-resolution manometry (HRM) for dysphagia. EGD findings were investigated according to the following five parameters: resistance when passing through the esophagogastric junction (EGJ), residue in the esophageal lumen, esophageal dilation, and spastic and nonocclusive contractions. HRM diagnoses were based on the Chicago classification (v3.0).

***Results*:** The percentage of abnormal EGD findings was 64.4% among patients with esophageal motility disorders, and the results differed for each esophageal motility disorder. The rate of abnormal EGD for both EGJ outflow obstruction and major disorders of peristalsis was significantly higher than that for manometrically normal subjects. On multivariate analysis, resistance when passing through EGJ, residue in the esophageal lumen, spastic and nonocclusive contraction were significantly associated with esophageal motility disorders. The sensitivity, specificity, positive predictive value, and negative predictive value of these parameters for detection of esophageal motility disorders were 75.1%, 86.6%, 84.8% and 77.8%, respectively.

***Conclusion*:** EGJ outflow obstruction and major disorders of peristalsis can be screened with EGD. Among several endoscopic parameters, resistance when passing through EGJ, residue in the esophageal lumen, spastic and nonocclusive contraction are considered significantly useful indicators.

Key words: Chicago classification, dysphagia, esophageal motility disorder, esophagogastroduodenoscopy, high-resolution manometry

INTRODUCTION

Dysphagia, one of the most common complaints encountered in daily clinical practice, diminishes quality of life.[1,2] In treating patients with dysphagia, excluding malignant diseases is considered important because several studies have previously found a prevalence of cancer of 4%–15% in those referred with dysphagia.[3,4] Moreover, dysphagia resulting from functional diseases occurs not only for older but also for non-older patients.[5] Our previous study showed that 3.5% of patients presenting to the Digestive Centre of a University Hospital in Japan had dysphagia and that 11.3% of these patients had esophageal motility disorders.[6] Therefore, esophageal motility disorders are also considered to be an important cause of dysphagia. Currently, various types of esophageal motility disorders diagnosed by high-resolution manometry (HRM) have been reported.[5] It is well known that esophagogastroduodenoscopy (EGD) is clinically useful to screen out malignant diseases located in the esophagus and stomach.[7] However, to date, there have been only a few studies investigating the clinical significance of EGD in patients with esophageal motility disorders.[8] It is ideal to screen not only malignant diseases but also esophageal motility disorders by EGD at the same time. The first aim of this study was to elucidate the detection rate for patients complaining of dysphagia with esophageal motility disorders following EGD. The second aim was to clarify useful parameters of EGD associated with esophageal motility disorders.

METHODS

Patients

In this study, we enrolled 380 patients who visited our hospital from September 2011 through December 2018 with a primary complaint of dysphagia or with dysphagia as a symptom, and scoring ≥ 4 points on our previously validated 7-point Likert scale questionnaire for gastrointestinal symptoms.[6] All patients underwent EGD without receiving antispasmodic agents before undergoing HRM. In addition to the outpatient physicians' clinical assessments, blood tests and abdominal ultrasonography were performed before EGD, as necessary. We did not include patients with structural abnormalities found on either abdominal ultrasonography or EGD, those with eosinophilic infiltration confirmed by histology,[9] or those with systemic complications, namely metabolic or neurologic disease such as diabetes mellitus, myasthenia gravis, scleroderma, or parkinsonism. Patients who had a medical history of surgical treatment for upper gastrointestinal diseases were excluded. Patients with esophageal motility disorders who had a history of treatment by medications such as calcium-channel blockers, endoscopic balloon dilatation, or peroral endoscopic myotomy were also excluded. Medications that affect esophageal motility, such as acotiamide hydrochloride hydrate, domperidone, itopride hydrochloride, metoclopramide, and mosapride citrate hydrate, were discontinued 1 week before HRM; oral administration of proton pump

inhibitors and potassium-competitive acid blockers was allowed. Benzodiazepine sedation was allowed in this study when patients requested sedation for the EGD examination. The study was approved by the ethics committee of Kawasaki Medical School (No. 3664), and authorization for the use of medical records for research purposes was confirmed before access to the records was obtained.

Symptom assessment

Symptoms present before undergoing EGD were evaluated with a previously validated self-reported questionnaire.[5,6,10] The survey asked patients to rank the frequency of the symptom of dysphagia on a 7-point Likert scale. Symptoms graded 4 or higher were considered significant, according to our previous studies.[5,6,10] The question regarding the symptom of dysphagia was: ‘‘Does food get stuck in the throat/chest when you swallow?’’[5]

Endoscopic assessment

Two endoscopists (NM and KH), who are members of the Japan Gastroenterological Endoscopy Society and are qualified endoscopic specialists with more than 20 years of experience in EGD, conducted the procedure. The endoscope was introduced and the standard examination of the esophagus, stomach, and duodenum was completed. Thereafter, the endoscopists evaluated esophageal motility and documented

on a form their evaluation of the motility findings for each patient. After observing the middle and lower esophagus and lower esophageal sphincter (LES), the following five EGD findings were recorded as part of daily endoscopy in each report: (1) resistance to the endoscope when passing through the esophagogastric junction (EGJ); (2) residue in the esophageal lumen; (3) esophageal dilatation; (4) spastic contraction; and (5) nonocclusive contraction. Figures 1 and 2 show typical endoscopic images of EGD findings. The patient was diagnosed as having esophageal dilatation if we could not observe the entire circumference of the esophageal wall in one endoscopic visual field of the patient (Fig. 1c) according to the Japan Esophageal Society guidelines.[11] Spastic contractions were diagnosed when either spiral mucosal folds (Fig. 1d) or annular contraction rings were observed (Fig. 1e). Each endoscopic finding was considered positive when at least one of the aforementioned findings was observed during the examination. All endoscopic images were reviewed in random order (for blinding) by the other three authors (MM, MA, and MF) who were blinded to patients' names and clinical diagnoses. If the authors could not reach a consensus on diagnosis after scrutiny of the EGD findings, the patient in question was excluded. High-resolution white-light endoscopes used in this study were either the GIF-260 series, the GIF-290 series (both from Olympus Medical Systems, Tokyo, Japan), or the EG-L580NW (FUJIFILM Co., Tokyo, Japan).

Esophageal manometry

HRM was performed with a Sandhill Scientific INSIGHT G3 with HRiM2 Probe (Diversatek Healthcare, WI, USA). The manometric probe used in this study was the HRiM2 High Resolution Impedance Manometry Catheter with 32 circumferential pressure/16 impedance channels (model number UNI-ESO-WG1A1). The HRM diagnosis was made according to the Chicago classification (v3.0).[10] The interval between the EGD and HRM was 10 days at most. When diagnosing esophageal motility disorders with this HRM system, we used our own specific normal data, which are based on a previous study: the normal range (5–95th percentiles) for integrated relaxation pressure and distal contractile integral are 2.5–23.5 mmHg and 606–4998 mmHg·s·cm, respectively.[11]

Statistical analysis

Data are expressed as the mean ± standard deviation. Student's t test was used to compare the mean values of two independent groups. To compare categorical data, we used the chi-squared test with Yates' correction or Fisher's exact test. We calculated intra- and interobserver variations in the determination of the five endoscopic parameters. Kappa statistics with 95% confidence intervals (CIs) were calculated in accordance with Cohen's kappa calculation. Kappa values were evaluated as follows: ≤0.20, poor; 0.21—0.40, fair; 0.41—0.60, moderate; 0.61—0.80, substantial; and 0.81—

1.00, almost perfect. Logistic regression analysis was used to calculate odds ratios (ORs) and 95% CIs for the association of EGD with esophageal motility disorders. Multivariate logistic regression analysis included all factors determined by univariate analysis to be associated with esophageal motility disorders. In all analyses, $P<.05$ was considered significant. All statistical analyses were performed using the SPSS statistical package version 17.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Patients' characteristics

Among the 380 patients, 3 patients were excluded from the analysis because of poor quality endoscopic images. Furthermore, 6 patients for whom a consensus diagnosis could not be reached were excluded from the analysis. Finally, 253 patients with esophageal motility disorders, and 118 patients with normal HRM findings were included for investigation. Of the 371 patients, 352 (94.9%) received topical anaesthesia in the posterior pharynx, and 134 patients (36.1%) underwent EGD under benzodiazepine sedation: 90 of 253 (35.6%) patients with esophageal motility disorders and 44 of 118 (37.3%) patients with normal HRM findings. No other sedation such as ketamine or sevoflurane was given.

As shown in Table 1, the most prevalent esophageal motility disorder was esophageal achalasia, followed by ineffective esophageal motility and distal esophageal

spasm. Of the 127 patients with esophageal achalasia, 79 patients were diagnosed as having esophageal achalasia type 1, 34 patients as having esophageal achalasia type 2, and 14 patients as having esophageal achalasia type 3. When esophageal motility disorders were sub-classified into three categories, EGJ outflow obstruction accounted for 55.7%, major disorders of peristalsis accounted for 17.4%, and minor disorders of peristalsis accounted for 26.1%.

Endoscopic findings of each esophageal motility disorder

The percentage of abnormal EGD findings was 64.4% among patients complaining of dysphagia with esophageal motility disorders diagnosed by HRM, and these findings differed for each esophageal motility disorder, as detailed in Table 1 and 2. Among several endoscopic parameters related to esophageal motility disorders, nonocclusive contraction was the endoscopically abnormal finding observed most frequently. The rates of abnormal EGD for both EGJ outflow obstruction and major disorders of peristalsis were significantly higher than those for manometrically normal subjects (83.7% in EGJ outflow obstruction and major disorders of peristalsis vs. 11.9% in manometrically normal subjects, $P<.05$), whereas the rate for minor disorders of peristalsis was not significantly different from that of manometrically normal subjects.

The kappa value for intraobserver agreement in identifying the five endoscopic parameters was 0.80 (95% CI: 0.43–1.17), indicating substantial diagnostic agreement.

Furthermore, the kappa value for interobserver agreement between the two endoscopy specialists was 0.73 (95% CI: 0.42–1.05), indicating substantial diagnostic agreement. Agreement between one endoscopy specialist and one non-specialist physician was 0.67 (95% CI: 0.32–1.01), indicating moderate diagnostic agreement.

Endoscopic parameters related to each esophageal motility disorder

In addition to our aforementioned study results, a previous review article reported that minor disorders of peristalsis can be merged with normal motility because minor disorders of peristalsis can be seen in healthy individuals and do not always have management implications.[10] Therefore, we excluded minor disorders of peristalsis in our analysis. Table 3 shows the results of the multivariate logistic regression analysis for each esophageal motility disorder. All but two esophageal motility disorders, namely EGJ outflow obstruction and absent contractility, had one to three associated endoscopic parameters. Furthermore, the clinical importance of these characteristic abnormal endoscopic findings was different for each esophageal motility disorder. Interestingly, there were also different endoscopic parameters associated with each esophageal achalasia sub-type. Of the three types of esophageal achalasia, esophageal achalasia type 1 had the largest number of characteristic endoscopic abnormalities.

Endoscopic parameters related to esophageal motility disorders

If at least one of these five parameters are positive, the sensitivity, specificity, positive predictive value, and negative predictive value that a patient is diagnosed with esophageal motility disorder are 75.1% [95%CI: 70.9-78.6], 86.6% [95%CI: 82.4-90.0], 84.8% [95%CI: 80.0-88.7] and 77.8% [95%CI: 74.0-80.9], respectively.

Table 4 reveals that each endoscopic parameter was frequently observed in patients with esophageal dysmotility, by logistic regression analysis. Multivariate logistic regression analysis revealed that resistance when passing through EGJ, residue in the esophageal lumen, spastic and nonocclusive contraction were significant endoscopic parameters associated with esophageal motility disorders.

DISCUSSION

The present study revealed three novel findings. First, the proportion of patients with abnormal EGD findings was 64.4% among those complaining of dysphagia with esophageal motility disorders, and these characteristic EGD abnormal findings varied for each esophageal motility disorder. Second, EGJ outflow obstruction and major disorders of peristalsis can be screened with EGD. Third, among several endoscopic parameters related to esophageal motility disorders, resistance when passing through EGJ, residue in the esophageal lumen, spastic and nonocclusive contraction are considered significantly useful endoscopic parameters.

Multivariate logistic regression analysis for each esophageal motility disorder

revealed that all but two esophageal motility disorders, namely EGJ outflow obstruction and absent contractility, had one to three associated endoscopic parameters. Different endoscopic parameters were associated with each esophageal motility disorder. Although the five EGD parameters overlap with the descriptive rules for achalasia,[12] it remained unknown until now whether the weightings of these endoscopic parameters differed for different subtypes of esophageal achalasia and whether these parameters could be clinically applied to esophageal motility disorders other than esophageal achalasia. In this study, we confirmed that these parameters can be clinically applied to esophageal motility disorders other than esophageal achalasia and we clarified the weighting of each parameter for detecting different disorders. Therefore, we consider the results of this study to be clinically significant. In Japan, not only endoscopic specialists but also non-specialists perform EGD, so parameters must have sufficient sensitivity to detect patients with esophageal motility disorders in general practice. Our results indicate that this method is acceptable as a screening test for esophageal motility disorders in general practice.

Although primary peristaltic contractions of the esophagus are considered more forceful than secondary contraction, with longer duration and higher work output,[13] distension-evoked esophageal contractions (i.e., secondary peristaltic contractions) are also clinically important for esophageal clearance and movement of food to the stomach. Several studies have reported disturbed secondary peristalsis attributable to increased

esophageal stiffness and impaired muscle function in patients with achalasia, ineffective esophageal motility, and scleroderma.[14,15]

In this study, nonocclusive contraction was an important indicator in patients complaining of dysphagia with esophageal motility disorders. To clarify the clinical significance of nonocclusive contraction, we additionally analyzed the differences in the prevalence of nonocclusive contraction between 30 randomly selected patients with esophageal motility disorders (20 with esophageal achalasia, 2 with EGJ outflow obstruction, 5 with distal esophageal spasm, 2 with jackhammer esophagus and one with absent contractility) and 30 sex- and age-matched healthy subjects. The rate of nonocclusive contractions in patients with esophageal motility disorders was significantly higher (60.0%, 18/30) than that in healthy subjects (20.0%, 6/30; P=0.003). We have also observed contractile activity of the esophagus during EGD in some patients with types I and II achalasia and suspect that this may be an additional mechanism of panesophageal pressurization. Conventional manometry is not considered helpful for diagnosing nonocclusive contraction.[16] Contraction of the circular muscle causes occlusion of the esophageal lumen, whereas contraction of the longitudinal muscle does not cause occlusion. At present, the mechanism of nonocclusive contraction remains unknown; however, we consider abnormal coordination of circular and longitudinal contraction to be a possible mechanism, although further study is necessary.

There are six limitations to this study, the first of which concerns the possibility

of bias in the sub-classification of esophageal motility disorders in the enrolled patients. In the studies to date that have investigated the sub-classification of esophageal motility disorders in patients with dysphagia in Japan,[6,17,18] the results are consistent with those of our study cohort. Therefore, one would expect no major biases in registered patients with esophageal motility disorders. Second, we performed EGD without administering antispasmodic agents, although benzodiazepine sedation was allowed if necessary. However, previous manometric studies have shown that benzodiazepine sedation has only a small effect on esophageal motility.[19,20] In the current study, typical normal and abnormal motility profiles were observed in patients sedated with midazolam. However, because the effects of primary peristalsis induced by unconscious swallowing cannot be excluded, further studies are required. Third, the observation time, observation site in the esophagus, and volume of air insufflation may have influenced the results of this study. Because this was a retrospective study, we were not able to standardize these conditions in all cases. However, the two endoscopists who conducted the procedures in this study are members of the Japan Gastroenterological Endoscopy Society and are qualified endoscopic specialists with more than 20 years of experience in EGD. In all cases, the observation time was 10 to 15 seconds, and the observation site was from the middle to lower esophagus. Given the years of experience and expertise of those performing EGD, we assume that there was no large difference in observation time, observation site in the esophagus, or volume of air insufflation among patients; however, further prospective

study is required. Fourth, the last EGD diagnosis was made using both EGD reports and still EGD images of each patient. The EGD findings in this study were assessed from still images because moving images are not required except in cases of resistance to the endoscope when passing across the EGJ. Therefore, overall, we believe that these limitations do not affect our study results, although further larger studies using video endoscopy are necessary to confirm our results. Fifth, we could not confirm reproducibility of endoscopic findings because this was a retrospective study. The examination of esophageal fluoroscopy has reported the consistency of several abnormalities in esophageal motility disorders.[21] However, a recent study suggested that esophageal manometric findings may change in some patients with major disorders of peristalsis; endoscopic findings will change accordingly in these patients.[22] The consistency of EGD findings will be examined in the future to investigate this important clinical question. Finally, patients with normal esophageal motility in this study were not necessarily normal subjects because we did not perform provocative testing, such as multiple rapid swallows, rapid drink challenge, meal test, and abdominal compression. However, these provocative maneuvers appear to play a complementary role in the evaluation of esophageal motility; prospective studies are needed to determine the validity of these findings and whether they should lead to changes in clinical practice.[23]

In conclusion, 64.4% of patients complaining of dysphagia with esophageal motility disorders had abnormal EGD findings, and useful endoscopic parameters to

detect esophageal motility disorders were clearly shown in this study.

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Conflicts of interest: Authors declare no Conflict of Interests for this article.

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Figure Legends

Figure 1. Typical endoscopic image suggestive of esophageal motility disorders and corresponding HRM finding. (a) Resistance when passing through the esophagogastric junction. HRM diagnosis is esophageal achalasia. (b) Residue in the esophageal lumen. HRM diagnosis is absent contractility. (c) Esophageal dilatation. HRM diagnosis is esophageal achalasia. (d) Spastic contraction. HRM diagnosis is distal esophageal spasm. (e) annular contraction rings. HRM diagnosis is Jackhammer esophagus.

Figure 2. Typical endoscopic image suggestive of occlusive contraction (upper row) and nonocclusive contraction (lower row). Occlusive contraction was defined as one in which no gap in the esophageal lumen could be observed at maximum contraction (upper right), while nonocclusive contraction was defined as one in which a gap in the esophageal lumen could be observed at maximum contraction (lower right).

Video Legends

File name: Spastic_contraction. Videos of endoscopic findings of typical spastic contraction.

File name: NOC. Videos of endoscopic findings of typical nonocclusive contraction.

Clinical significance of esophagogastroduodenoscopy in patients with esophageal motility disorders

Short title: esophageal motility and endoscopy

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Authors' contributions: Masaki Matsubara analyzed the data, and drafted the manuscript; Noriaki Manabe made a study concept and design; analysis and interpretation of data; study supervision and analyzing; Maki Ayaki, Jun Nakamura, Takahisa Murao, Minoru Fujita, Masahiko Kuinose, Tomoki Yamatsuji, and Yoshio Naomoto participated in clinical data acquisition; Ken Haruma participated in clinical

data acquisition and evaluated biostatistical analysis; all authors participated in drafting or revising the article and approved the final version for submission.

Abstract

***Objectives*:** The first aim of this study was to elucidate the detection rate of esophagogastroduodenoscopy (EGD) in patients complaining of dysphagia with esophageal motility disorders; the second was to clarify the useful parameters of EGD associated with esophageal motility disorders.

***Methods*:** Participants included 380 patients who underwent EGD before high-resolution manometry (HRM) for dysphagia. EGD findings were investigated according to the following five parameters: resistance when passing through the esophagogastric junction (EGJ), residue in the esophageal lumen, esophageal dilation, and spastic and nonocclusive contractions. HRM diagnoses were based on the Chicago classification (v3.0).

***Results*:** The percentage of abnormal EGD findings was 64.4% among patients with esophageal motility disorders, and the results differed for each esophageal motility disorder. The rate of abnormal EGD for both EGJ outflow obstruction and major disorders of peristalsis was significantly higher than that for manometrically normal subjects. On multivariate analysis, resistance when passing through EGJ, residue in the esophageal lumen, spastic and nonocclusive contraction were significantly associated with esophageal motility disorders. The sensitivity, specificity, positive predictive value, and negative predictive value of these parameters for detection of esophageal motility disorders were 75.1%, 86.6%, 84.8% and 77.8%, respectively.

***Conclusion*:** EGJ outflow obstruction and major disorders of peristalsis can be screened with EGD. Among several endoscopic parameters, resistance when passing through EGJ, residue in the esophageal lumen, spastic and nonocclusive contraction are considered significantly useful indicators.

Key words: Chicago classification, dysphagia, esophageal motility disorder, esophagogastroduodenoscopy, high-resolution manometry

INTRODUCTION

Dysphagia, one of the most common complaints encountered in daily clinical practice, diminishes quality of life.[1,2] In treating patients with dysphagia, excluding malignant diseases is considered important because several studies have previously found a prevalence of cancer of 4%–15% in those referred with dysphagia.[3,4] Moreover, dysphagia resulting from functional diseases occurs not only for older but also for non-older patients.[5] Our previous study showed that 3.5% of patients presenting to the Digestive Centre of a University Hospital in Japan had dysphagia and that 11.3% of these patients had esophageal motility disorders.[6] Therefore, esophageal motility disorders are also considered to be an important cause of dysphagia. Currently, various types of esophageal motility disorders diagnosed by high-resolution manometry (HRM) have been reported.[5] It is well known that esophagogastroduodenoscopy (EGD) is clinically useful to screen out malignant diseases located in the esophagus and stomach.[7] However, to date, there have been only a few studies investigating the clinical significance of EGD in patients with esophageal motility disorders.[8] It is ideal to screen not only malignant diseases but also esophageal motility disorders by EGD at the same time. The first aim of this study was to elucidate the detection rate for patients complaining of dysphagia with esophageal motility disorders following EGD. The second aim was to clarify useful parameters of EGD associated with esophageal motility disorders.

METHODS

Patients

In this study, we enrolled 380 patients who visited our hospital from September 2011 through December 2018 with a primary complaint of dysphagia or with dysphagia as a symptom, and scoring ≥ 4 points on our previously validated 7-point Likert scale questionnaire for gastrointestinal symptoms.[6] All patients underwent EGD without receiving antispasmodic agents before undergoing HRM. In addition to the outpatient physicians' clinical assessments, blood tests and abdominal ultrasonography were performed before EGD, as necessary. We did not include patients with structural abnormalities found on either abdominal ultrasonography or EGD, those with eosinophilic infiltration confirmed by histology,[9] or those with systemic complications, namely metabolic or neurologic disease such as diabetes mellitus, myasthenia gravis, scleroderma, or parkinsonism. Patients who had a medical history of surgical treatment for upper gastrointestinal diseases were excluded. Patients with esophageal motility disorders who had a history of treatment by medications such as calcium-channel blockers, endoscopic balloon dilatation, or peroral endoscopic myotomy were also excluded. Medications that affect esophageal motility, such as acotiamide hydrochloride hydrate, domperidone, itopride hydrochloride, metoclopramide, and mosapride citrate hydrate, were discontinued 1 week before HRM; oral administration of proton pump

inhibitors and potassium-competitive acid blockers was allowed. Benzodiazepine sedation was allowed in this study when patients requested sedation for the EGD examination. The study was approved by the ethics committee of Kawasaki Medical School (No. 3664), and authorization for the use of medical records for research purposes was confirmed before access to the records was obtained.

Symptom assessment

Symptoms present before undergoing EGD were evaluated with a previously validated self-reported questionnaire.[5,6,10] The survey asked patients to rank the frequency of the symptom of dysphagia on a 7-point Likert scale. Symptoms graded 4 or higher were considered significant, according to our previous studies.[5,6,10] The question regarding the symptom of dysphagia was: ‘‘Does food get stuck in the throat/chest when you swallow?’’[5]

Endoscopic assessment

Two endoscopists (NM and KH), who are members of the Japan Gastroenterological Endoscopy Society and are qualified endoscopic specialists with more than 20 years of experience in EGD, conducted the procedure. The endoscope was introduced and the standard examination of the esophagus, stomach, and duodenum was completed. Thereafter, the endoscopists evaluated esophageal motility and documented

on a form their evaluation of the motility findings for each patient. After observing the middle and lower esophagus and lower esophageal sphincter (LES), the following five EGD findings were recorded as part of daily endoscopy in each report: (1) resistance to the endoscope when passing through the esophagogastric junction (EGJ); (2) residue in the esophageal lumen; (3) esophageal dilatation; (4) spastic contraction; and (5) nonocclusive contraction. Figures 1 and 2 show typical endoscopic images of EGD findings. The patient was diagnosed as having esophageal dilatation if we could not observe the entire circumference of the esophageal wall in one endoscopic visual field of the patient (Fig. 1c) according to the Japan Esophageal Society guidelines.[11] Spastic contractions were diagnosed when either spiral mucosal folds (Fig. 1d) or annular contraction rings were observed (Fig. 1e). Each endoscopic finding was considered positive when at least one of the aforementioned findings was observed during the examination. All endoscopic images were reviewed in random order (for blinding) by the other three authors (MM, MA, and MF) who were blinded to patients' names and clinical diagnoses. If the authors could not reach a consensus on diagnosis after scrutiny of the EGD findings, the patient in question was excluded. High-resolution white-light endoscopes used in this study were either the GIF-260 series, the GIF-290 series (both from Olympus Medical Systems, Tokyo, Japan), or the EG-L580NW (FUJIFILM Co., Tokyo, Japan).

Esophageal manometry

HRM was performed with a Sandhill Scientific INSIGHT G3 with HRiM2 Probe (Diversatek Healthcare, WI, USA). The manometric probe used in this study was the HRiM2 High Resolution Impedance Manometry Catheter with 32 circumferential pressure/16 impedance channels (model number UNI-ESO-WG1A1). The HRM diagnosis was made according to the Chicago classification (v3.0).[10] The interval between the EGD and HRM was 10 days at most. When diagnosing esophageal motility disorders with this HRM system, we used our own specific normal data, which are based on a previous study: the normal range (5–95th percentiles) for integrated relaxation pressure and distal contractile integral are 2.5–23.5 mmHg and 606–4998 mmHg·s·cm, respectively.[11]

Statistical analysis

Data are expressed as the mean ± standard deviation. Student's t test was used to compare the mean values of two independent groups. To compare categorical data, we used the chi-squared test with Yates' correction or Fisher's exact test. We calculated intra- and interobserver variations in the determination of the five endoscopic parameters. Kappa statistics with 95% confidence intervals (CIs) were calculated in accordance with Cohen's kappa calculation. Kappa values were evaluated as follows: ≤0.20, poor; 0.21—0.40, fair; 0.41—0.60, moderate; 0.61—0.80, substantial; and 0.81—

1.00, almost perfect. Logistic regression analysis was used to calculate odds ratios (ORs) and 95% CIs for the association of EGD with esophageal motility disorders. Multivariate logistic regression analysis included all factors determined by univariate analysis to be associated with esophageal motility disorders. In all analyses, $P<.05$ was considered significant. All statistical analyses were performed using the SPSS statistical package version 17.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Patients' characteristics

Among the 380 patients, 3 patients were excluded from the analysis because of poor quality endoscopic images. Furthermore, 6 patients for whom a consensus diagnosis could not be reached were excluded from the analysis. Finally, 253 patients with esophageal motility disorders, and 118 patients with normal HRM findings were included for investigation. Of the 371 patients, 352 (94.9%) received topical anaesthesia in the posterior pharynx, and 134 patients (36.1%) underwent EGD under benzodiazepine sedation: 90 of 253 (35.6%) patients with esophageal motility disorders and 44 of 118 (37.3%) patients with normal HRM findings. No other sedation such as ketamine or sevoflurane was given.

As shown in Table 1, the most prevalent esophageal motility disorder was esophageal achalasia, followed by ineffective esophageal motility and distal esophageal

spasm. Of the 127 patients with esophageal achalasia, 79 patients were diagnosed as having esophageal achalasia type 1, 34 patients as having esophageal achalasia type 2, and 14 patients as having esophageal achalasia type 3. When esophageal motility disorders were sub-classified into three categories, EGJ outflow obstruction accounted for 55.7%, major disorders of peristalsis accounted for 17.4%, and minor disorders of peristalsis accounted for 26.1%.

Endoscopic findings of each esophageal motility disorder

The percentage of abnormal EGD findings was 64.4% among patients complaining of dysphagia with esophageal motility disorders diagnosed by HRM, and these findings differed for each esophageal motility disorder, as detailed in Table 1 and 2. Among several endoscopic parameters related to esophageal motility disorders, nonocclusive contraction was the endoscopically abnormal finding observed most frequently. The rates of abnormal EGD for both EGJ outflow obstruction and major disorders of peristalsis were significantly higher than those for manometrically normal subjects (83.7% in EGJ outflow obstruction and major disorders of peristalsis vs. 11.9% in manometrically normal subjects, $P<.05$), whereas the rate for minor disorders of peristalsis was not significantly different from that of manometrically normal subjects.

The kappa value for intraobserver agreement in identifying the five endoscopic parameters was 0.80 (95% CI: 0.43–1.17), indicating substantial diagnostic agreement.

Furthermore, the kappa value for interobserver agreement between the two endoscopy specialists was 0.73 (95% CI: 0.42–1.05), indicating substantial diagnostic agreement. Agreement between one endoscopy specialist and one non-specialist physician was 0.67 (95% CI: 0.32–1.01), indicating moderate diagnostic agreement.

Endoscopic parameters related to each esophageal motility disorder

In addition to our aforementioned study results, a previous review article reported that minor disorders of peristalsis can be merged with normal motility because minor disorders of peristalsis can be seen in healthy individuals and do not always have management implications.[10] Therefore, we excluded minor disorders of peristalsis in our analysis. Table 3 shows the results of the multivariate logistic regression analysis for each esophageal motility disorder. All but two esophageal motility disorders, namely EGJ outflow obstruction and absent contractility, had one to three associated endoscopic parameters. Furthermore, the clinical importance of these characteristic abnormal endoscopic findings was different for each esophageal motility disorder. Interestingly, there were also different endoscopic parameters associated with each esophageal achalasia sub-type. Of the three types of esophageal achalasia, esophageal achalasia type 1 had the largest number of characteristic endoscopic abnormalities.

Endoscopic parameters related to esophageal motility disorders

If at least one of these five parameters are positive, the sensitivity, specificity, positive predictive value, and negative predictive value that a patient is diagnosed with esophageal motility disorder are 75.1% [95%CI: 70.9-78.6], 86.6% [95%CI: 82.4-90.0], 84.8% [95%CI: 80.0-88.7] and 77.8% [95%CI: 74.0-80.9], respectively.

Table 4 reveals that each endoscopic parameter was frequently observed in patients with esophageal dysmotility, by logistic regression analysis. Multivariate logistic regression analysis revealed that resistance when passing through EGJ, residue in the esophageal lumen, spastic and nonocclusive contraction were significant endoscopic parameters associated with esophageal motility disorders.

DISCUSSION

The present study revealed three novel findings. First, the proportion of patients with abnormal EGD findings was 64.4% among those complaining of dysphagia with esophageal motility disorders, and these characteristic EGD abnormal findings varied for each esophageal motility disorder. Second, EGJ outflow obstruction and major disorders of peristalsis can be screened with EGD. Third, among several endoscopic parameters related to esophageal motility disorders, resistance when passing through EGJ, residue in the esophageal lumen, spastic and nonocclusive contraction are considered significantly useful endoscopic parameters.

Multivariate logistic regression analysis for each esophageal motility disorder

revealed that all but two esophageal motility disorders, namely EGJ outflow obstruction and absent contractility, had one to three associated endoscopic parameters. Different endoscopic parameters were associated with each esophageal motility disorder. Although the five EGD parameters overlap with the descriptive rules for achalasia,[12] it remained unknown until now whether the weightings of these endoscopic parameters differed for different subtypes of esophageal achalasia and whether these parameters could be clinically applied to esophageal motility disorders other than esophageal achalasia. In this study, we confirmed that these parameters can be clinically applied to esophageal motility disorders other than esophageal achalasia and we clarified the weighting of each parameter for detecting different disorders. Therefore, we consider the results of this study to be clinically significant. In Japan, not only endoscopic specialists but also non-specialists perform EGD, so parameters must have sufficient sensitivity to detect patients with esophageal motility disorders in general practice. Our results indicate that this method is acceptable as a screening test for esophageal motility disorders in general practice.

Although primary peristaltic contractions of the esophagus are considered more forceful than secondary contraction, with longer duration and higher work output,[13] distension-evoked esophageal contractions (i.e., secondary peristaltic contractions) are also clinically important for esophageal clearance and movement of food to the stomach. Several studies have reported disturbed secondary peristalsis attributable to increased

esophageal stiffness and impaired muscle function in patients with achalasia, ineffective esophageal motility, and scleroderma.[14,15]

In this study, nonocclusive contraction was an important indicator in patients complaining of dysphagia with esophageal motility disorders. To clarify the clinical significance of nonocclusive contraction, we additionally analyzed the differences in the prevalence of nonocclusive contraction between 30 randomly selected patients with esophageal motility disorders (20 with esophageal achalasia, 2 with EGJ outflow obstruction, 5 with distal esophageal spasm, 2 with jackhammer esophagus and one with absent contractility) and 30 sex- and age-matched healthy subjects. The rate of nonocclusive contractions in patients with esophageal motility disorders was significantly higher (60.0%, 18/30) than that in healthy subjects (20.0%, 6/30; P=0.003). We have also observed contractile activity of the esophagus during EGD in some patients with types I and II achalasia and suspect that this may be an additional mechanism of panesophageal pressurization. Conventional manometry is not considered helpful for diagnosing nonocclusive contraction.[16] Contraction of the circular muscle causes occlusion of the esophageal lumen, whereas contraction of the longitudinal muscle does not cause occlusion. At present, the mechanism of nonocclusive contraction remains unknown; however, we consider abnormal coordination of circular and longitudinal contraction to be a possible mechanism, although further study is necessary.

There are six limitations to this study, the first of which concerns the possibility

of bias in the sub-classification of esophageal motility disorders in the enrolled patients. In the studies to date that have investigated the sub-classification of esophageal motility disorders in patients with dysphagia in Japan,[6,17,18] the results are consistent with those of our study cohort. Therefore, one would expect no major biases in registered patients with esophageal motility disorders. Second, we performed EGD without administering antispasmodic agents, although benzodiazepine sedation was allowed if necessary. However, previous manometric studies have shown that benzodiazepine sedation has only a small effect on esophageal motility.[19,20] In the current study, typical normal and abnormal motility profiles were observed in patients sedated with midazolam. However, because the effects of primary peristalsis induced by unconscious swallowing cannot be excluded, further studies are required. Third, the observation time, observation site in the esophagus, and volume of air insufflation may have influenced the results of this study. Because this was a retrospective study, we were not able to standardize these conditions in all cases. However, the two endoscopists who conducted the procedures in this study are members of the Japan Gastroenterological Endoscopy Society and are qualified endoscopic specialists with more than 20 years of experience in EGD. In all cases, the observation time was 10 to 15 seconds, and the observation site was from the middle to lower esophagus. Given the years of experience and expertise of those performing EGD, we assume that there was no large difference in observation time, observation site in the esophagus, or volume of air insufflation among patients; however, further prospective

study is required. Fourth, the last EGD diagnosis was made using both EGD reports and still EGD images of each patient. The EGD findings in this study were assessed from still images because moving images are not required except in cases of resistance to the endoscope when passing across the EGJ. Therefore, overall, we believe that these limitations do not affect our study results, although further larger studies using video endoscopy are necessary to confirm our results. Fifth, we could not confirm reproducibility of endoscopic findings because this was a retrospective study. The examination of esophageal fluoroscopy has reported the consistency of several abnormalities in esophageal motility disorders.[21] However, a recent study suggested that esophageal manometric findings may change in some patients with major disorders of peristalsis; endoscopic findings will change accordingly in these patients.[22] The consistency of EGD findings will be examined in the future to investigate this important clinical question. Finally, patients with normal esophageal motility in this study were not necessarily normal subjects because we did not perform provocative testing, such as multiple rapid swallows, rapid drink challenge, meal test, and abdominal compression. However, these provocative maneuvers appear to play a complementary role in the evaluation of esophageal motility; prospective studies are needed to determine the validity of these findings and whether they should lead to changes in clinical practice.[23]

In conclusion, 64.4% of patients complaining of dysphagia with esophageal motility disorders had abnormal EGD findings, and useful endoscopic parameters to

detect esophageal motility disorders were clearly shown in this study.

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Figure Legends

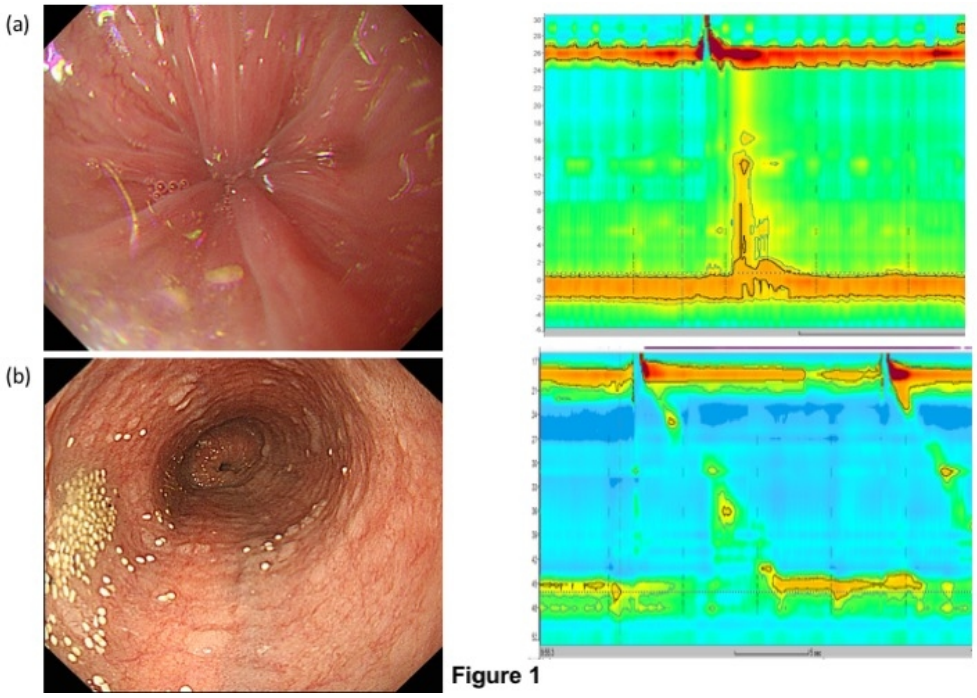
Figure 1. Typical endoscopic image suggestive of esophageal motility disorders and corresponding HRM finding. (a) Resistance when passing through the esophagogastric junction. HRM diagnosis is esophageal achalasia. (b) Residue in the esophageal lumen. HRM diagnosis is absent contractility. (c) Esophageal dilatation. HRM diagnosis is esophageal achalasia. (d) Spastic contraction. HRM diagnosis is distal esophageal spasm. (e) annular contraction rings. HRM diagnosis is Jackhammer esophagus.

Figure 2. Typical endoscopic image suggestive of occlusive contraction (upper row) and nonocclusive contraction (lower row). Occlusive contraction was defined as one in which no gap in the esophageal lumen could be observed at maximum contraction (upper right), while nonocclusive contraction was defined as one in which a gap in the esophageal lumen could be observed at maximum contraction (lower right).

Video Legends

File name: Spastic_contraction. Videos of endoscopic findings of typical spastic contraction.

File name: NOC. Videos of endoscopic findings of typical nonocclusive contraction.



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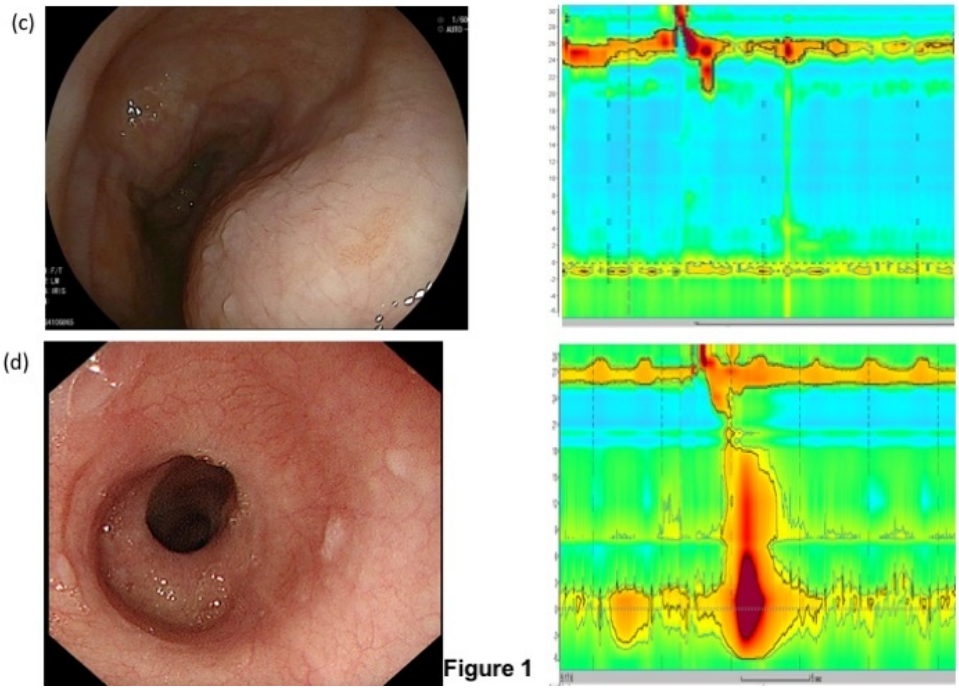
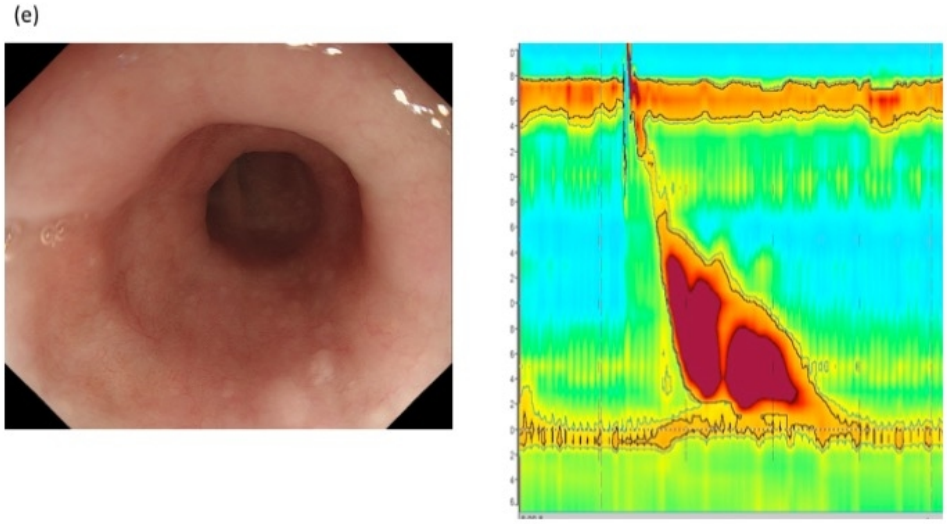


Figure 1. Typical endoscopic image suggestive of esophageal motility disorders and corresponding HRM finding. (c) Esophageal dilatation. HRM diagnosis is esophageal achalasia. (d) Spastic contraction. HRM diagnosis is distal esophageal spasm. (e) annular contraction rings. HRM diagnosis is Jackhammer esophagus.

277x191mm (66 x 66 DPI)



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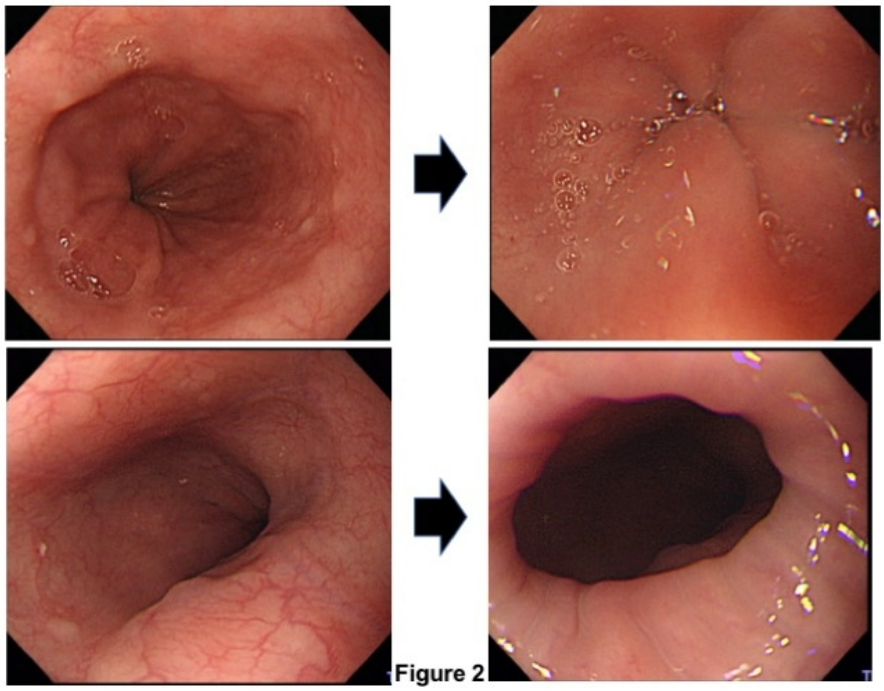
277x191mm (66 x 66 DPI)



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277x191mm (66 x 66 DPI)

Table 1. Proportion of abnormal EGD findings according to each type of esophageal motility disorder

Sub-classification	Manometric diagnosis	Total	Men/Women	Mean age	Abnormal EGD findings (%)
Disorders with EGJ outflow obstruction	Esophageal achalasia	127	58/69	51.7±16.0	116 (91.3%)
	EGJ outflow obstruction	14	6/8	70.7± 9.4	2 (14.3%)
Major disorders of peristalsis	Distal esophageal spasm	30	28/2	60.7±14.6	20 (66.7%)
	Jackhammer esophagus	10	10/0	72.0±2.7	6 (60.0%)
	Absent contractility	4	0/4	45.0±5.8	4 (100%)
Minor disorders of peristalsis	Ineffective esophageal motility	60	41/19	70.0±12.5	14 (23.3%)
	Fragmented peristalsis	6	2/4	69.3±19.2	1 (16.7%)
Unclassified motility abnormality		2	2/0	53.0	0 (0%)
Normal		118	77/41	66.1±11.0	14 (11.9%)

EGD, esophagogastroduodenoscopy; EGJ, esophagogastric junction. The EGD finding was positive when at least one EGD finding was detected.

Table 2. Detailed EGD findings in each esophageal motility disorder

Sub-classification	Manometric diagnosis	Total	Abnormal EGD findings				
			Resistance when passing through EGJ	Residue in the esophageal lumen	Esophageal dilation	Spastic contraction	Nonocclusive contraction
Disorders with EGJ outflow obstruction	Esohageal achalasia	127	48 (37.8%)	67 (52.8%)	44 (34.6%)	17 (13.4%)	105 (82.7%)
	EGJ outflow obstruction	14	1 (7.1%)	1 (7.1%)	0 (0%)	0 (0%)	1 (7.1%)
Major disorders of peristalsis	Distal esophageal spasm	30	3 (10.0%)	4 (13.3%)	0 (0%)	3 (30.0%)	6 (20.0%)
	Jackhammer esophagus	10	1 (10.0%)	1 (10.0%)	0 (0%)	3 (30.0%)	3 (30.0%)
	Absent contractility	4	0 (0%)	3 (75.0%)	0 (0%)	0 (0%)	3 (75%)
Minor disorders of peristalsis	Ineffective esophageal motility	60	0 (0%)	1 (1.7%)	0 (0%)	0 (0%)	11 (18.3%)
	Fragmented peristalsis	6	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (16.7%)
Unclassified motility abnormality		2	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Normal		118	1 (0.8%)	2 (1.7%)	0 (0%)	0 (0%)	13 (11.0%)

EGD, esophagogastroduodenoscopy; EGJ, esophagogastric junction. Among several endoscopic parameters related to esophageal motility disorders, nonocclusive contraction was the most frequently observed endoscopically abnormal finding.

Table 3. Multivariate logistic regression analysis for each esophageal motility disorder

Esophageal motility disorder		Endoscopic parameter	Multivariate OR (95% CI)
Esophageal achalasia	Type 1	Residue in the esophageal lumen	30.6 (3.8-248.0)
		Esophageal dilation	35.9 (2.6-505.3)
		Nonocclusive contraction	24.1 (9.4-61.8)
	Type 2	Residue in the esophageal lumen	56.8 (4.5-724.9)
		Nonocclusive contraction	71.4 (14.6-348.5)
	Type 3	Resistance when passing through EGJ	22.9 (1.4-375.0)
		Spastic contraction	23.9 (2.9-198.7)
EGJ outflow obstruction		No endoscopic parameters	
Distal esophageal spasm		Spastic contraction	7.8 (1.4-43.6)
		Residue in the esophageal lumen	9.6 (1.5-63.8)
		Nonocclusive contraction	2.86 (1.0-8.1)
Jackhammer esophagus		Spastic contraction	16.6 (2.0-136.7)
Absent contractility		No endoscopic parameters	

OR, odds ratio; CI, confidence interval; EGJ, esophagogastric junction

Table 4. Logistic regression analysis for esophageal motility disorders

Variable	Univariate OR (95% CI)	Multivariate OR (95% CI)
Resistance when passing through EGJ	36.9 (8.8-154.3)	7.1 (1.4-35.8)
Residue in the esophageal lumen	65.6 (15.8-272.4)	11.0 (2.3-53.6)
Esophageal dilation	57.7 (7.9-424.1)	5.1 (0.5-51.0)
Spastic contraction	9.09 (2.7-30.8)	4.7 (1.1-20.2)
Nonocclusive contraction	15.8 (9.0-27.8)	8.0 (4.3-214.9)

OR, Odds ratio; CI, confidence interval; EGJ, esophagogastric junction

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