The white substance may be a potential endoscopic marker for flat esophageal mucosal neoplastic lesions

A new endoscopic observation

Guodong Yang, PhD, Weiwei Du, MD, Xiaoying Zhang, PhD*, Tao Huang, MD, Jing Zhang, MD, Juan Liu, MD, Ying Ling, MD

Abstract

To determine whether the white substance can act as an endoscopic marker for flat esophageal mucosal neoplastic lesions.

Esophageal mucosal neoplastic lesions are mainly identified using white light endoscopy, because it is cost-effective; however, this method is limited for detecting early esophageal cancer and precancerous lesions, because these are typically flat mucosal neoplastic lesions. In our experience, a white substance surrounds or covers some flat esophageal mucosal lesions that are eventually diagnosed as neoplastic lesions by biopsy pathology.

After retrospective analysis of pathological and clinical data of 20,390 patients, we identified 352 patients with flat esophageal mucosal lesions on endoscopic images. Images were re-evaluated by 2 experienced endoscopists and the prevalence of the white substance recorded. Patients were divided into non-neoplastic and neoplastic groups, based on pathology.

The white substance was present in 3.5% (5/144) of non-neoplastic and 14.9% (31/208) of neoplastic cases ($P < .05$). The diagnostic sensitivity and specificity of the white substance for neoplastic lesions diagnosis were 14.9% and 96.5%, respectively. The presence of white substance was more common in males and in those aged 50 to 79 years. It was more commonly observed in the middle third of the esophagus, and its presence did not correlate with sex, age, or lesion location ($P > .05$).

The white substance, which is easily detected by white light endoscopy, may be an endoscopic marker facilitating detection of flat esophageal mucosal neoplastic lesions, irrespective of sex, age, and lesion location.

Abbreviations: CI = confidence interval, EC = esophageal cancer, EEC = early esophageal cancer, HIN = high-grade intraepithelial neoplasia, LIN = low-grade intraepithelial neoplasia, ME = magnifying endoscopy, NBI = narrow band imaging, NPV = negative predictive value, PPV = positive predictive value, WLE = white light endoscopy.

Keywords: early esophageal cancer, esophageal mucosal lesion, neoplastic lesion, precancerous lesions, white substance

1. Introduction

Esophageal cancer (EC) is a common malignant tumor with poor prognosis and reduced survival rate[1,2]; It is the cancer with the 8th highest incidence worldwide and is the 4th leading type of cancer in China.[3–5] When EC, in particular, is found at the advanced stage,

the best therapeutic opportunity may have been lost; the 5-year survival rate of this condition is only 54.9%.[6] However, if it is possible to identify early esophageal cancer (EEC) and precancerous lesions, minimally invasive treatment, such as endoscopic submucosal dissection, or regular monitoring may not only reduce mortality and morbidity, but also improve the long-term prognosis of such patients.[6–8] Therefore, the etiology and prevention of EEC and precancerous lesions require further study, particularly in those countries and regions with a high incidence, in which the EC-related burden of disease is particularly heavy.[2,9]

The clinical symptoms of EC are diverse, and may include poor swallowing, progressive dysphagia, abdominal discomfort, retrosternal discomfort, or may even be absent. The detection of EEC and precancerous lesions rely on clinical symptoms, which lack specificity.[10,11] Concurrent with the population's growing awareness of their health and the active education and management of this disease in high-incidence areas of EC, digestive endoscopic examination has become universal.[12] This facilitates detection of EEC and precancerous lesions with atypical symptoms, and greatly enriches the endoscopic data that can promote research on this disease. In addition to the endoscopist's skill, the endoscopic rate of detection of mucosal lesions of EEC and precancerous lesions also depends on the application of sophisticated endoscopic approaches, such as chromoendoscopy with iodine staining and narrow band imaging (NBI), as well as magnifying endoscopy (ME). However, these

high-grade endoscopic approaches are not available to all patients for economic reasons. Thus, the purpose of our study was to find an endoscopic feature under white light endoscopy (WLE) that is likely to be noticed by most endoscopists, to improve the rate of detection of EEC and precancerous lesions.

During our previous experience with endoscopic procedures, we encountered a peculiar white substance only around or above some flat esophageal mucosal lesions that were eventually mostly diagnosed as neoplastic lesions based on biopsy pathology. This substance can be directly observed by conventional endoscopy, and its morphology and distribution differs from the leukoplakia of esophageal mucosa and fungal plaques.

In this retrospective analysis of endoscopic images data obtained over the past 5 years, we investigated whether this phenomenon is universal or is valuable in cases with neoplastic lesions.

2. Materials and methods

2.1. Definitions

We used the following definitions in this study.

The white substance: a special white substance with clear boundaries, with a smooth or rough surface. This substance can have an isolated or patchy distribution, with cracks around esophageal lesions, and some may even completely obscure the lesion. Moreover, the white substance cannot be washed away by water (Fig. 1).

Flat esophageal mucosal lesion: for the purpose of this study, these lesions are described as an esophageal mucosal region that is rough, or less smooth, has an uneven color, occurring in an iodine-unstained area, with or without erosion, and vascular texture. Compared with the adjacent mucosa, such flat lesions can be slightly elevated, flat, or slightly depressed, but does not have obvious nodules, ulcers, or strictures.

Precancerous lesions: according to the World Health Organization classification of tumors of the digestive system, either low-grade intraepithelial neoplasia (LIN) or high-grade intraepithelial neoplasia (HIN) was classified as precancerous lesions.[13]

Esophageal mucosal neoplastic lesions: esophageal lesions with pathological findings indicating LIN, HIN, and carcinoma.

2.2. Research foundation

All endoscopic images were obtained from the Affiliated Hospital of North Sichuan Medical College Digestive Endoscopy Center, which is a medical center in the high EC-incidence area in China. Clinical information of the patients and endoscopic imaging data were recorded in the endoscopic database. All endoscopic procedures and diagnoses were completed by experienced endoscopists (with at least 2 years experience in upper gastrointestinal endoscopy). During the endoscopy procedure, a high-resolution white light imaging endoscope (EVIS LUCERA CLV-260; Olympus, Tokyo, Japan) and a video processor (EVIS LUCERA Olympus CV-260; Olympus) were used. The biopsy specimens and pathological results were evaluated by senior pathologist. The study was approved by an institutional review board, and the need for obtaining informed consent from patients was waived due to the retrospective nature of the study.

2.3. Patients

In the study, all patients who underwent upper gastrointestinal endoscopy were transferred from different outpatient doctors, without any special background or restriction (such as sex or age). These patients sought medical attention because of various gastrointestinal symptoms or due to findings of physical examination, and were free to choose topical pharyngeal or intravenous anesthesia during the endoscopic procedure.

2.4. Methods

We obtained endoscopic images and the relevant diagnosis of patients who underwent upper gastrointestinal endoscopic examination in our digestive endoscopy room from 2012 to 2017, and extracted the clinical data for those patients with an endoscopic description of a flat esophageal mucosal lesion. Patients who had no pathological data, for various reasons, were excluded. The patients finally enrolled in the study had complete clinical endoscopic data and pathological findings (Fig. 2). The endoscopic images of the patients included in the study were analyzed again by 2 experienced endoscopists according to the above definition of the white substance, and esophageal lesions with or without white substance were identified. According to the pathological results, the enrolled patients were divided into a neoplastic group (including a pathologic diagnosis of LIN, HIN, or carcinoma) and non-neoplastic (including chronic inflammation or squamous cell hyperplasia). All clinical data of the patients were comprehensively analyzed, and the endoscopic diagnosis, lesion location, pathological results, and presence or absence of the white substance were recorded.
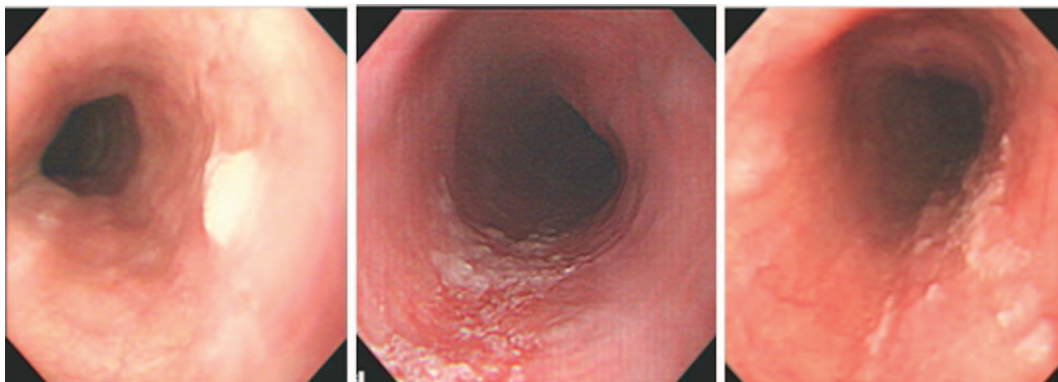

Figure 1. The peculiar white substance with clear boundaries can occur in isolation or have a patchy distribution, with cracks around lesions in the esophagus; in some cases, this substance even completely obscured the lesion. It cannot be washed away by water.
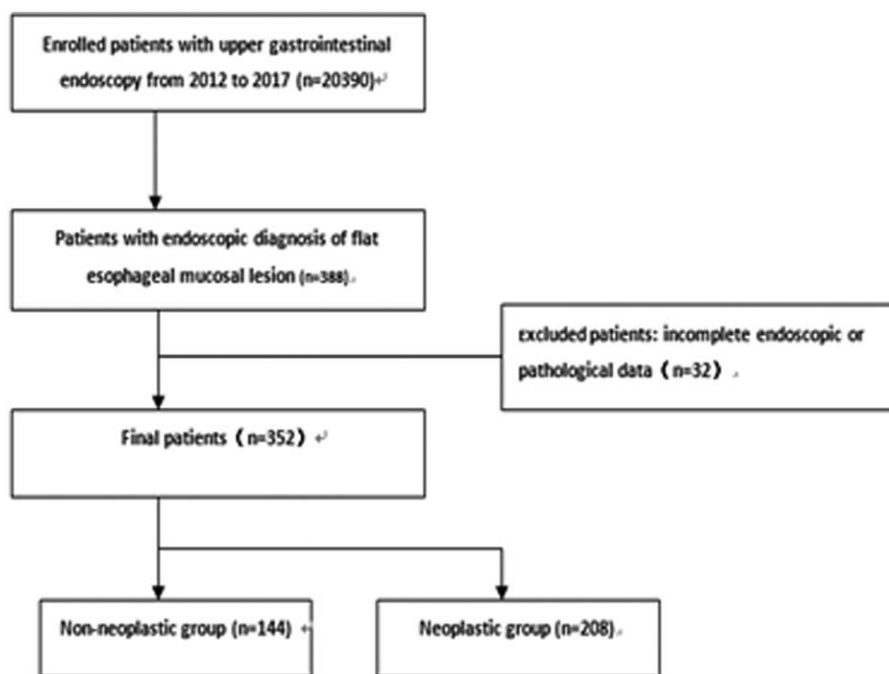
Figure 2. Flow diagram of patients enrolled in this study.

2.5. Statistical methods

Data were statistically analyzed using SPSS v.17.0 software. Categorical data were compared using the chi-squared test or Fisher exact test. The diagnostic values of the white substance, including sensitivity, specificity, and the corresponding 95% confidence intervals (CIs), were determined. The positive predictive value (PPV) and negative predictive value (NPV) were also calculated using standard formulas. A 2-tailed $P < .05$ was considered to indicate statistically significant differences.

3. Results

A total of 20,390 patients underwent upper gastrointestinal endoscopy from 2012 to 2017, and 388 cases had an endoscopic description of a flat esophageal mucosal lesion. Of these, 36 were excluded because of incomplete endoscopic or pathological data, for various reasons. Finally, data from 352 patients were analyzed. Patients' demographics and lesion characteristics are described in Table 1.

3.1. Clinicopathological characteristics

Of the patients included in the study, 220 were males, accounting for 62.5%. The mean age of these patients was 60 to 69 years. The endoscopic diagnosis of flat esophageal mucosal increased from 22.4% in patients 50 to 59 years old to 44.9% in patients 60 to 69 years old and 85.8% of patients were in the age range of 50 to 79 years (Fig. 3).

The lesions were located in the upper third of the esophagus in 59 cases (16.7%), in the middle third in 216 cases (61.4%), and in the lower third in 71 cases (20.2%), while the location was not described in 6 cases (1.7%). The final pathological diagnosis was esophageal neoplastic lesions in 208 patients, including LIN in 67 cases (32%), HIN in 106 cases (51%), and carcinoma in 35 cases (17%), while 144 patients were diagnosed with a non-neoplastic

lesion. In addition, the rate of identification of neoplastic lesions by WLE was 59%.

3.2. Prevalence of the white substance

The white substance was more prevalent in males (75%), in the middle third of the esophagus (66.7%), in patients aged 60 to 69

Table 1

Basic characteristics of the included patients with endoscopic diagnosis of flat esophageal mucosal lesions (n=352).

Sex, n (%)		
Males	220	(62.5)
Females	132	(37.5)
Lesion location, n (%)		
Upper third	59	(16.7)
Middle third	216	(61.4)
Lower third	71	(20.2)
No description	6	(1.7)
Age, n (%)		
≤29	2	(0.6)
30–39	4	(1.1)
40–49	43	(12.2)
50–59	79	(22.4
60–69	158	(44.9)
70–79	65	(18.5)
≥80	1	(0.3)
Pathological result, n (%)		
Neoplastic lesion		
LIN	67	(19.0)
HIN	106	(30.1)
Carcinoma	35	(9.9)
Non-neoplastic lesion	144	(40.9)
The white substance, n (%)		
Presence	36	(10.2)
Absence	316	(89.8)

HIN = high-grade intraepithelial neoplasia, LIN = low-grade intraepithelial neoplasia.
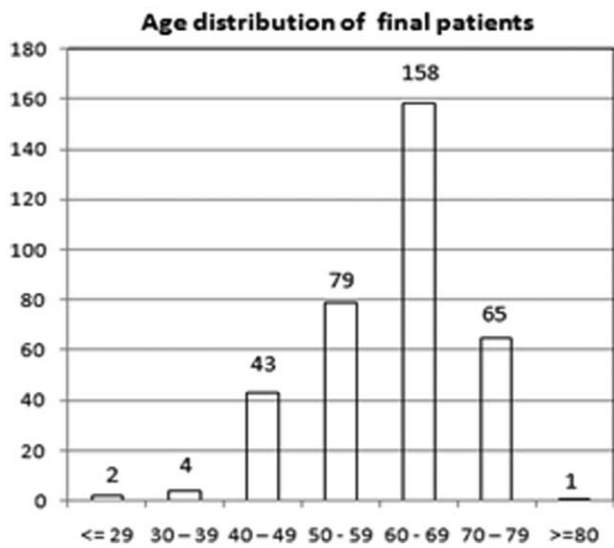
Figure 3. Age characteristics of the included patients with endoscopic diagnosis of flat esophageal mucosal lesions.

years (52.8%), and in those with a diagnosis of neoplastic lesion (86.1%, HIN accounted for 41.6%). It was rarer in individuals aged <40 years and in those over 80 years. In addition, there was no significant correlation between the presence of the white substance and sex, age, or lesion location ($P > .05$) (Table 2).

3.3. Correlation between white substance and neoplastic lesions

The prevalence of the white substance in the neoplastic group and non-neoplastic group was 14.9% (31/177) and 3.5% (5/144),

Table 2

Difference in clinicopathological characteristics between patients with and without the white substance.

	Presence (n = 36)		Absence (n = 316)		P
Sex					.102
Males	27	(75%)	193	(61.1%)	
Females	9	(25%)	123	(38.9%)	
Age					.927
≤29	0	(0%)	2	(0.6%)	
30–39	0	(0%)	4	(1.2%)	
40–49	3	(8.3%)	40	(12.7%)	
50–59	8	(22.2%)	71	(22.5%)	
60–69	19	(52.8%)	139	(44.0%)	
70–79	6	(16.7%)	59	(18.7%)	
≥80	0	(0%)	1	(0.3%)	
Lesion location					.290
Upper third	8	(22.2%)	51	(16.2%)	
Middle third	24	(66.7%)	192	(60.7%)	
Lower third	4	(11.1%)	67	(21.2%)	
Pathological result					.004
Neoplastic lesion					
LIN	9	(25.0%)	58	(18.3%)	
HIN	15	(41.6%)	91	(28.8%)	
Carcinoma	7	(19.4%)	28	(8.9%)	
Non-neoplastic lesion	5	(13.9%)	139	(44.0%)	

HIN = high-grade intraepithelial neoplasia, LIN = low-grade intraepithelial neoplasia.

Table 3

Diagnostic performance of the white substance for neoplastic lesion.

Prevalence (95% CI)	59.1% (53.7–64.2)
Sensitivity (95% CI)	14.9% (10.5–20.6)
Specificity (95% CI)	96.5% (91.7–98.7)
Positive predictive value	86.1% (69.7–94.8)
Negative predictive value	13.9% (5.2–30.3)

CI = confidence interval.

respectively (a = 0.01, $P < .05$). The diagnostic prevalence of the white substance for those diagnosed with an esophageal neoplastic lesion was 59.1% (95% CI, 53.7–64.2); its sensitivity was 14.9% (95% CI, 10.5–20.6); specificity was 96.5% (95% CI, 91.7–98.7); PPV was 86.1% (95% CI, 69.7–94.8); and NPV was 13.9% (95% CI, 5.2–30.3) (Table 3).

4. Discussion

At present, the diagnosis of EEC and precancerous lesions mainly depends on Dye Endoscopy, ME, NBI, and intrapapillary capillary loop patterns, and estimating the invasive depth by the ME classifications of Inoue and Arima, etc.[6,11,14–17] However, most of the high EC incidence areas, especially that of esophageal squamous cell carcinoma, are economically backward regions in which regional medical centers service a large number of patients.[5] It is therefore unrealistic that each patient would undergo high-grade endoscopic screening.[18–21] Thus, the combination of WLE and biopsy remains a highly cost-effective and primary means of detecting EEC and precancerous lesions.

In the study, we described a peculiar white substance that is found in some flat esophageal mucosal lesions, which cannot be washed away by water, and which may be an indicator of EC. Some earlier papers have reported that a white globe appearance[22] and white opaque substance,[23] which was associated with gastric diseases,[24–26] were observed in esophageal adenocarcinoma, and suggested that a white globe appearance may be a reliable endoscopic finding for esophageal adenocarcinoma.[26] However, most of these papers were case studies and only applied to adenocarcinoma of the esophagus, but not to squamous cell carcinoma, which is the main type of EC worldwide[6] and accounts for 90% of EC in China.[27] In the present study, most of the neoplastic lesions we collected were pathologically diagnosed squamous intraepithelial neoplasia and squamous cell carcinoma, and thus our results are representative. Moreover, the white substance can attract the attention of endoscopists and is easier to detect because it is obvious in esophageal lesions under WLE, without requiring the auxiliary use of NBI or ME.

In the present study, the patients with flat esophageal mucosal lesions were mostly 50 to 79 years old, with a peak at 60 to 69 years old. We retrospectively investigated the data of 20,390 patients, and found that upper gastrointestinal endoscopy was most commonly performed for people aged 40 to 49 years. Therefore, in patients older than 50 years, and particularly for those 60 to 69 years old, in whom a flat esophageal mucosal lesion is detected upon endoscopic examination, the possibility of a neoplastic lesion cannot be ignored. Epidemiologically, these lesions occur more commonly in males and in the middle third of the esophagus.

As described previously, the endoscopic characterization of EEC and precancerous lesions commonly appears completely

normal, or is flat and erythematous, but can also involve erosions and plaques, with little impact on the contour of the mucosal surface (Paris classification 0–IIa, IIb, IIc, also consistent with the flat esophageal mucosal lesion described above).[6,28] This can sometimes make these lesions difficult to identify, because the lesion may be small and atypical or covered with the white substance. Additionally, this type of mucosal lesion can also be found in normal/non-neoplastic lesions. However, unexpectedly, flat neoplastic lesions were specifically associated with the presence of white substance. In our study, the white substance coverage rate of neoplastic lesions was higher than that of non-neoplastic lesions (14.9% vs 3.5%). The diagnostic specificity and PPV of white substance for diagnosing neoplastic lesions was also high.

Furthermore, the presence of the white substance was not specific to any sex, different locations in the esophagus, or different types of neoplastic lesions; therefore, it allows differentiation between neoplastic and non-neoplastic lesions without confounding effects of these factors. Therefore, the diagnosis of EEC should also be considered when this white substance is found on the esophagus, even in the absence of a suspicious mucosal lesion, as the white substance can sometimes cover mucosal lesions. That is, we deem that the white substance presents a potential indicator for diagnosing EEC and precancerous lesions. However, the absence of white substance also cannot exclude a diagnosis of EEC and precancerous lesions because of its inadequate sensitivity.

Certainly, our observation of this special white substance also has several limitations. First, in the retrospective study, we could only obtain partial information about the white substance from previous endoscopic images and incomplete descriptions of the size, texture, properties, and microscopic changes of the corresponding esophageal lesion, its infiltration depth, tumor metastasis, etc. Thus, further prospective studies are required. Moreover, it is also necessary to take the white substance biopsy directly under endoscopy in order to distinguish its nature. Second, the endoscopic images included in this study were collected by different endoscopists. Some images were not clear and were excluded from our study and in others, the image may not have included white substance, and the prevalence of the white substance may actually be greater than determined in this retrospective study.

In conclusion, when a patient who is male, 60 to 69 years old, with a lesion located in the middle third of the esophagus, and with a white substance surrounding or covering a flat esophageal mucosal lesion under upper gastrointestinal endoscopy is encountered, it is important to search for a probable neoplastic lesion and to take a biopsy to avoid a missed diagnosis. This may facilitate early detection of EC and precancerous lesions. Nevertheless, further prospective studies are necessary to determine its accuracy.

Author contributions

Conceptualization: Jing Zhang, Tao Huang.
Data curation: Weiwei Du, Xiaoying Zhang, Jing Zhang, Tao Huang, Juan Liu, Ying Ling.
Formal analysis: Weiwei Du, Juan Liu, Ying Ling.
Funding acquisition: Guodong Yang, Xiaoying Zhang.
Project administration: Guodong Yang, Xiaoying Zhang.
Writing – original draft: Guodong Yang, Weiwei Du, Xiaoying Zhang.

References

[1] Zeng H, Zheng R, Guo Y, et al. Cancer survival in China, 2003–2005: a population-based study. Int J Cancer 2015;136:1921–30.

[2] Hua Z, Zheng X, Xue H, et al. Long-term trends and survival analysis of esophageal and gastric cancer in Yangzhong, 1991–2013. PLoS ONE 2017;12:e173896.

[3] Lin Y, Totsuka Y, Shan B, et al. Esophageal cancer in high-risk areas of China: research progress and challenges. Ann Epidemiol 2017;27:215–21.

[4] Tang WR, Fang JY, Wu KS, et al. Epidemiological characteristics and prediction of esophageal cancer mortality in China from 1991 to 2012. Asian Pac J Cancer Prev 2014;15:6929–34.

[5] Otterstatter MC, Brierley JD, De P, et al. Esophageal cancer in Canada: trends according to morphology and anatomical location. Can J Gastroenterol 2012;26:723–7.

[6] Kandiah K, Chedgy FJ, Subramaniam S, et al. Early squamous neoplasia of the esophagus: the endoscopic approach to diagnosis and management. Saudi J Gastroenterol 2017;23:75–81.

[7] Ning B, Abdelfatah MM, Othman MO. Endoscopic submucosal dissection and endoscopic mucosal resection for early stage esophageal cancer. Ann Cardiothorac Surg 2017;6:88–98.

[8] Kim SJ, Kim GH, Lee MW, et al. New magnifying endoscopic classification for superficial esophageal squamous cell carcinoma. World J Gastroenterol 2017;23:4416–21.

[9] Malhotra GK, Yanala U, Ravipati A, et al. Global trends in esophageal cancer. J Surg Oncol 2017;115:564–79.

[10] Vakil N, Moayyedi P, Fennerty MB, et al. Limited value of alarm features in the diagnosis of upper gastrointestinal malignancy: systematic review and meta-analysis. Gastroenterology 2006;131:390–401.

[11] Tentzeris V, Lake B, Cherian T, et al. Poor awareness of symptoms of oesophageal cancer. Interact Cardiovasc Thorac Surg 2011;12:32–4.

[12] Tan L, Feng J, Zhao Q, et al. Preoperative endoscopic titanium clip placement facilitates intraoperative localization of early-stage esophageal cancer or severe dysplasia. World J Surg Oncol 2017;15:145.

[13] Sarbia M, Wolfer S, Karimi D, et al. High-grade dysplasia, restricted to the basal cell layer involving the entire esophagus. World J Gastroenterol 2015;21:1663–5.

[14] Takahashi M, Shimizu Y, Ono M, et al. Endoscopic diagnosis of early neoplasia of the esophagus with narrow band imaging: correlations among background coloration and iodine staining findings. J Gastroenterol Hepatol 2014;29:762–8.

[15] Shimizu Y, Omori T, Yokoyama A, et al. Endoscopic diagnosis of early squamous neoplasia of the esophagus with iodine staining: high-grade intra-epithelial neoplasia turns pink within a few minutes. J Gastroenterol Hepatol 2008;23:546–50.

[16] Sato H, Inoue H, Ikeda H, et al. Utility of intrapapillary capillary loops seen on magnifying narrow-band imaging in estimating invasive depth of esophageal squamous cell carcinoma. Endoscopy 2015;47:122–8.

[17] Oyama T, Inoue H, Arima M, et al. Prediction of the invasion depth of superficial squamous cell carcinoma based on microvessel morphology: magnifying endoscopic classification of the Japan Esophageal Society. Esophagus 2017;14:105–12.

[18] di Pietro M, Canto MI, Fitzgerald RC. Endoscopic management of early adenocarcinoma and squamous cell carcinoma of the esophagus—screening, diagnosis, and therapy. Gastroenterology 2018;154:421–36.

[19] Liang H, Fan JH, Qiao YL. Epidemiology, etiology, and prevention of esophageal squamous cell carcinoma in China. Cancer Biol Med 2017;14:33–41.

[20] Roshandel G, Nourouzi A, Pourshams A, et al. Endoscopic screening for esophageal squamous cell carcinoma. Arch Iran Med 2013;16:351–7.

[21] Roshandel G, Semnani S, Malekzadeh R. None-endoscopic screening for esophageal squamous cell carcinoma—a review. Middle East J Dig Dis 2012;4:111–24.

[22] Tonai Y, Ishihara R, Yamasaki Y, et al. First reports of esophageal adenocarcinoma with white globe appearance in Japanese and Caucasian patients. Endosc Int Open 2016;4:E1075–7.

[23] Yoshii S, Kato M, Honma K, et al. Esophageal adenocarcinoma with white opaque substance observed by magnifying endoscopy with narrow band imaging. Dig Endosc 2015;27:392–6.

[24] Ueyama H, Matsumoto K, Nagahara A, et al. A white opaque substance-positive gastric hyperplastic polyp with dysplasia. World J Gastroenterol 2013;19:4262–6.

[25] Omura H, Yoshida N, Hayashi T, et al. Interobserver agreement in detection of "white globe appearance" and the ability of educational lectures to improve the diagnosis of gastric lesions. Gastric Cancer 2017;20:620–8.

[26] Yoshida N, Doyama H, Nakanishi H, et al. White globe appearance is a novel specific endoscopic marker for gastric cancer: a prospective study. Dig Endosc 2016;28:59–66.

[27] Chen S, Zhou K, Yang L, et al. Racial differences in esophageal squamous cell carcinoma: incidence and molecular features. Biomed Res Int 2017;2017:1204082.

[28] Participants in the Paris Workshop. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. Gastrointest Endosc. 2003; 58(suppl):S3–S43.