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【 REVIEW ARTICLE 】

Endoscopy and Barrett's Esophagus: Current Perspectives in the US and Japan

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Abstract:
Barrett's esophagus (BE) is a precancerous disease that can lead to esophageal adenocarcinoma (EAC). Recently, the incidence of EAC arising from BE has been increasing, and EAC has now become a threat in many countries. However, there are many gaps among the various countries in terms of definitions and concepts and these gaps prevent discussing BE on the same footing. In order to eradicate BE, it is a global necessity to fill in these remaining gaps. We focused on the gaps and reviewed recent evidence and trends as well as the background of gaps between the US and Japan as two of the leading countries in the field of medical research. We also review the rapid advances in endoscopic techniques in relation to both diagnosis and therapy that are considered to be useful to eliminate the gaps between countries.

Key words: Barrett's esophagus, endoscopy, diagnosis, therapy, international perspectives

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Introduction

Barrett's esophagus (BE) is a premalignant condition that can lead to adenocarcinoma of the esophagus and esophagogastric junction (EGJ) (1). The incidence of esophageal adenocarcinoma (EAC) arising from BE has been increasing dramatically in the US since the 1980s, and EAC currently accounts for 60-70% of all esophageal cancers, thus surpassing squamous cell carcinoma (2). In Japan, the incidence rate remains considerably lower than in the US, however the frequency of EAC arising from BE is increasing [e.g., rising from 0.2% in 1995 to 2.3% in 2012 (3, 4)]. A Japanese tabulation and analysis of 1,794 EAC cases shows that the concomitant rate of reflux esophagitis was high at 70% and BE mucosa, as a background factor, was evaluated in 10% (5). Because BE is associated with chronic gastroesophageal reflux disease (GERD), the high incidence of reflux esophagitis, prompted by the decrease in *Helicobacter pylori* infection and the increase in obesity, can lead to BE (6-9). Although it is important to manage BE and to prevent malignant transformation, differences between countries can lead to many complications. This article reviews the gaps between the US and Japan, focusing on the use of endoscopy in BE.

The Diagnosis of Barrett's Esophagus

Endoscopic landmarks for BE diagnosis

In BE, the normal squamous mucosa of the distal esophagus is replaced by a columnar epithelium (1). Therefore, the endoscopic recognition of the EGJ is essential for the detection of BE. In 2006, the Prague C & M criteria, proposed by a subgroup of the International Working Group for the Classification of Oesophagitis (IWGCO) to standardize the objective diagnosis of endoscopic BE, stated that the EGJ landmark is the proximal end of gastric folds (10). Therefore, in the US, similar to other Western countries, the endoscopic EGJ landmark is the proximal limit of longitude gas-

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tric mucosal folds; however, in Japan, it is the lower margin of the small palisade vessels (11-14).

The lower margin of small palisade vessels was not chosen as the criteria because "discrimination between the true palisade vessels and other vascular patterns present in the mucosa below the EGJ was sometimes difficult and that the palisade vessels could not be seen adequately in all patients when standard endoscopic imaging methods were used (10)." Small palisade vessels are defined as veins with a diameter greater than 100 μm within the lamina propria mucosae (15). Therefore, the lower margin of small palisade vessels coincides anatomically with the boundary between the esophagus and stomach. These vessels can usually be easily found when the lower esophagus is adequately distended by air through endoscopy; however, in difficult cases, the patient must be forced to take a deep breath. In Western countries, endoscopic examination in an unconsciousness state is common; however, in Japan, mild sedation is recommended for frequent endoscopic examinations (16), and in such cases, patients can cooperate with requests from endoscopists. Japanese endoscopists report that the palisade vessels are visible in 98% of Japanese subjects (17).

Japanese endoscopists use palisade vessels as a landmark of EGJ because short segment BE (SSBE) is more common than long segment BE (LSBE) in Japan. The Japan Esophageal Society defines SSBE and LSBE as the presence of circular Barrett mucosa less than 3 cm in length or the presence of non-circular Barrett mucosa and as the presence of circular Barrett mucosa extending longitudinally for 3 cm or more, respectively (13). According to a report by Okita et al., among 5,338 patients, SSBE was endoscopically identified in 1,997 (37.4%) patients, whereas LSBE was identified in 10 (0.2%) patients (18). Moreover, according to a report by Sugimoto et al. among 135 patients, BE was identified in 116 (85.9%) by ultrathin transnasal endoscopy, and ultrashort-segment Barrett's esophagus (USBE, less than 1 cm) was 73%, that was higher ration than 13% of SSBE (among 1 cm and 3 cm), or none of LSBE. This results also indicated that the high incidence of detection of SSBE could be achieved by using an ultrathin transnasal endoscopy (19). In an investigation of the Prague C & M criteria, endoscopists were not able to reliably measure the shorter lengths of BE (<1 cm) (kappa values: any length, 0.49; ≥1 cm, 0.72; and < 1 cm, 0.21) (10). The American College of Gastroenterology (ACG) guideline recommends that a columnar-lined esophagus less than 1 cm should not be diagnosed as BE (20). On the other hand, in Japan, as there is no definition of the minimum length of a columnar-lined esophagus, Japanese reports regarding the prevalence of SSBE based on endoscopy findings vary widely from 1.2 to 59.0% and 85.9% with using ultrathin transnasal endoscopy (9, 13, 19).

In 2007, the Japan Esophageal Society added the oral margin of the longitudinal folds of the greater curvature of the stomach as an EGJ landmark; however, the use of this landmark is limited to situations where only small palisade vessels cannot be clearly identified (13). The factors that prevent the identification of palisade vessels include mucosal inflammation, dysplastic changes, the presence of a thick double muscularis mucosa, and insufficient extension and inadequate stretch of the esophagus. In contrast, the gastric fold-based landmark has the disadvantage of being ambiguous. The position of the proximal margin of the gastric fold can easily change by altering the degree of air deflation with endoscopy and changes in respiration (21). Moreover, in the presence of atrophic gastritis, which is very common in Japan because of *H. pylori* infection (22), the upper longitudinal end of the folds is difficult to detect. In recent decades, eradication therapy has dramatically reduced the *H. pylori* infection rate and reduced the incidence of atrophic gastritis, but it is reported that it takes more than five years for such existing atrophic gastritis to improve (6, 23, 24). Therefore, Japanese endoscopists prefer using palisade vessels that are more anatomically reliable and appropriate than vague gastric folds to detect SSBE.

Recently, new technologies have been developed to make palisade vessels more visible; among these technologies, narrow band imaging (NBI) is one of the most promising. In a study by Hamamoto et al., the EGJ detection rate was higher using NBI than using only white light imaging (25). Fig. 1 shows the endoscopic visualization of palisade vessels using NBI in both SSBE and LSBE.

Pathological definition

The Japan Esophageal Society defines BE as the presence of any of the following factors: esophageal glands or duct beneath the overlying columnar epithelium, squamous epithelial islands in the columnar epithelium, or double-layer muscularis mucosae beneath overlying epithelium, regardless of the presence of intestinal metaplasia (13). Similarly, the guidelines of the British Society of Gastroenterology state that "the presence of intestinal metaplasia is not prerequisite for the definition of Barrett's oesophagus (12)." However, in the US, pathological findings of intestinal metaplasia are needed to diagnose BE (11). It is widely accepted that intestinal metaplasia is the probable common precursor of adenocarcinoma. However, according to a report by Takubo et al., intestinal metaplasia was not observed anywhere in endoscopic mucosal resection specimens in 64 (56.6%) of 113 German cases with histological evidence of esophageal origin upon examination of both sides of a single histologic section (26). These authors reported a close relationship between EAC arising from BE and the cardiac mucosa rather than the intestinal mucosa (26, 27). Another study from the UK suggested that the presence of intestinal metaplasia is possibly less important for the diagnosis of BE (28). In this previous study, 712 patients were investigated retrospectively, and the cancer risks in the 379 (55.1%) patients with specialized intestinal metaplasia were similar to those of the remaining 309 (44.9%, p=NS) patients without intestinal metaplasia. On the other hand, American pathologists argue that "the frequent absence of residual intestinal metaplasia around an adenocarcinoma in an endoscopic mucosal resec-

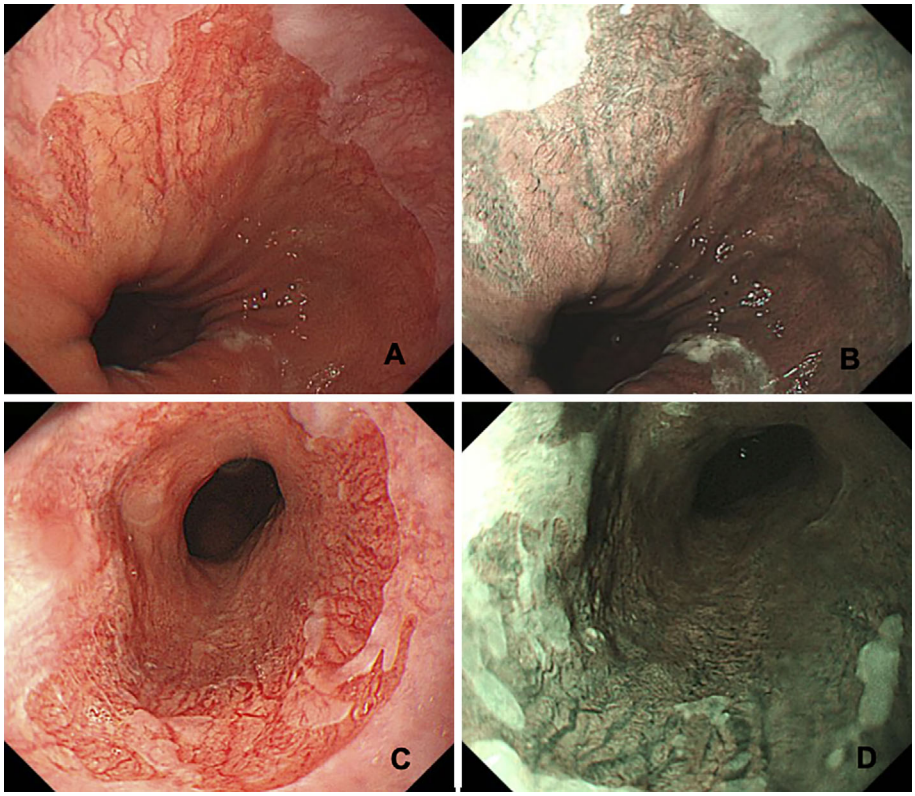

Figure 1. **Endoscopic visualization of the palisade vessels in the lower end of the esophagus. Conventional images of SSBE (A) and LSBE (C) are visualized with NBI (B, D), respectively.**

Table 1. **Correspondence between Modified Vienna Classification and Japanese Pathological Diagnosis.**

	Modified Vienna classification, Category	Japanese pathologists' diagnosis
3	Low grade dysplasia	Adenoma or well differentiated adenocarcinoma with low-grade atypia (noninvasive)*
4.1	High grade dysplasia	Adenocarcinoma with high-grade atypia (noninvasive)
4.2	Non-invasive carcinoma (Carcinoma in situ)	
4.3	Suspicion for invasive carcinoma	Intramucosal adenocarcinoma (suspicion of stromal invasion)
4.4	Intramucosal carcinoma	Intramucosal adenocarcinoma (with stromal invasion)
5	Submucosal carcinoma	Invasive adenocarcinoma (with submucosal invasion)

* It can be difficult to differentiate category 3 from inflammatory change. (Excerpts from the ESD/EMR guidelines for esophageal cancer by Japan Gastroenterological Endoscopy Society)

tion (EMR) specimen is the result of sampling errors (29)." Further studies and additional evidence are needed; however, the problem remains that precancerous lesions may evade surveillance in cases in which BE is limited to intestinal metaplasia.

The term "high-grade dysplasia" (intraepithelial neoplasia) that is often used in Western countries as a pathological diagnosis for BE is not used in Japan (30). Japanese pathologists diagnose the highly dysplastic lesion as well differentiated adenocarcinoma because it sometimes invades the mucosa or submucosa. Table 1 shows the correlation between the Modified Vienna classification and the Japanese pathological diagnosis (31).

Diagnostic method

In the US, there are guidelines suggesting who should be considered for BE screening: men with chronic (>5 years) and/or frequent (weekly or more) symptoms of gastroesophageal reflux (heartburn or acid regurgitation) and two or more risk factors (age >50 years, Caucasian race, presence of central obesity, current or past history of smoking, and confirmed family history of BE or EAC) (20). In Japan, al-

Table 2. Advanced Imaging Technologies for Detection of Dysplasia or Esophageal Adenocarcinoma Arising from Barrett's Esophagus.

Technique			Sensitivity/ Specificity (%)	NPV (%)
Image-Enhanced Endoscopy	Chromoendoscopy	Indigo carmine	67/99	96
		Methylene blue	64.2/95.9	69.8
		Acetic acid	96.6/84.6	98.3
	Optical-digital (Virtual Chromoendoscopy)	NBI	94.2/94.4	97.5
		AFI+NBI	80.6/46	88.7
Microscopic		Endomicroscopy (CLE)	90.4/89.9	96.2
		e-CLE	90.4/92.7	98.3
		p-CLE	90.3/77.3	95.1
Tomographic	Optical	OCT	70/60	47
		VLE	86/88	75

NPV: negative predictive value, NBI: narrow band imaging, AFI: autofluorescence imaging, CLE: confocal laser endomicroscopy, OCT: optical coherence tomography, VLE: volumetric laser endomicroscopy

though no screening standards for BE are currently established, endoscopic screening is recommended for patients who have certain abdominal symptoms, especially those with gastroesophageal reflux symptoms (9, 32). For patients who have no symptoms, gastric cancer screening is helpful for detecting BE. Since the Japanese government decided to introduce endoscopic screening for gastric cancer as a national program in 2016, the occasion of endoscopic screening has been increasing. In addition, esophagogastroduodenoscopy can be easily performed at a low cost in comparison to Western countries. Therefore, most EACs are detected at an early stage (5). Whereas, in the US, EAC patient' s prognosis remains poor with 19% five years survival, and ~40% of the patients have advanced stage at the time of diagnosis (33). Conventional endoscopy and a subsequent biopsy are the standards worldwide, including the US and Japan, for the diagnosis of BE related neoplasms (12, 13, 20, 34). However, because the dysplasia in BE only appears intermittently, it is very important to prevent sampling errors. Therefore, in the US, random four-quadrant biopsy sampling of every 1-2 cm of the columnar-lined esophagus, called the Seattle biopsy protocol, is recommended (11, 20). However, this protocol has problems related to safety and it is also time-consuming, labor-intensive, and expensive. To overcome these problems, several advanced imaging techniques, including chromoendoscopy, magnifying endoscopy, microscopic endoscopy, and tomographic endoscopy, have been developed. Table 2 shows the classification of these endoscopic imaging techniques and their sensitivity and specificity for the detection of dysplasia or EAC arising from BE (35-38). Regarding conventional endoscopy, high-resolution (HD) endoscopy was developed and has improved image quality; however, its dysplasia detection rate alone is reported to be 79% (39). Therefore, other advanced imaging techniques have been considered as combination modalities. In 2016, the American Society for Gastrointestinal Endoscopy (ASGE) Technology Committee reported a systematic review and meta-analysis of advanced imaging techniques (Table 2). The results indicated that targeted biopsies with acetic acid chromoendoscopy, NBI and confocal laser endomicroscopy (CLE) could replace the current random biopsy protocols (34). Volumetric laser endomicroscopy (VLE), a new generation of optical coherence tomography (OCT), has a higher sensitivity, specificity, and negative predictive value than traditional OCT in *ex vivo* EMR specimens (40). Based on its enhanced diagnostic performance, VLE is expected to be useful *in vivo* (41). Recently, the BING working group, composed of NBI experts from the US, Japan, and Europe, developed a system to identify dysplasia and EAC in patients with BE using NBI (42). In Japan, targeted biopsy with magnifying endoscopy and NBI is standard (43, 44). In order to identify areas of dysplasia more clearly and reduce the number of biopsies, the Japan Esophageal Society classification of BE was newly developed. This classification very simply categorizes most mucosal or vascular descriptors as "regular" for non-dysplastic and "irregular" for dysplastic BE (45).

The conventional gaps between the US and Japan in BE issues are summarized in Table 3.

Treatment

Endoscopic eradication therapy (EET) is the basis of the management of dysplasia and EAC arising from BE (11, 46). EET involves the resection of any visible neoplastic lesions, eradication of the remaining BE segment, management of adverse events, and enrollment in a surveillance program (46). According to the clinical guidelines recommended by the ACG, there are separate management strategies for nodular (Fig. 2) and nonnodular BE (Fig. 3) (20). Patients with nodularities are recommended to undergo initial endoscopic resection therapy. Subsequently, a histologic assessment of the resected specimen should guide the selection of further therapy. Regarding endoscopic resection therapy, EMR has been the gold standard; however,

Table 3. US-Japan Conventional Gaps in Barrett's Esophagus Issues.

	The US	Japan
Endoscopic landmarks of EGJ	The proximal end of gastric folds	·The lower margin of small palisade vessels ·The proximal end of gastric folds (Substitute, only when small palisade vessels are not clear)
Is the pathological existence of internal metaplasia required for the diagnosis of BE?	Yes	No
Diagnostic method of BE related neoplasm	Seattle biopsy protocol: random four-quadrant biopsy sampling of every 1-2 cm of the columnar lined esophagus	Targeted biopsy with magnifying endoscopy and NBI

EGJ: esophagogastric junction, BE: Barrett's esophagus, NBI: narrow band imaging, EAC: esophageal adenocarcinoma

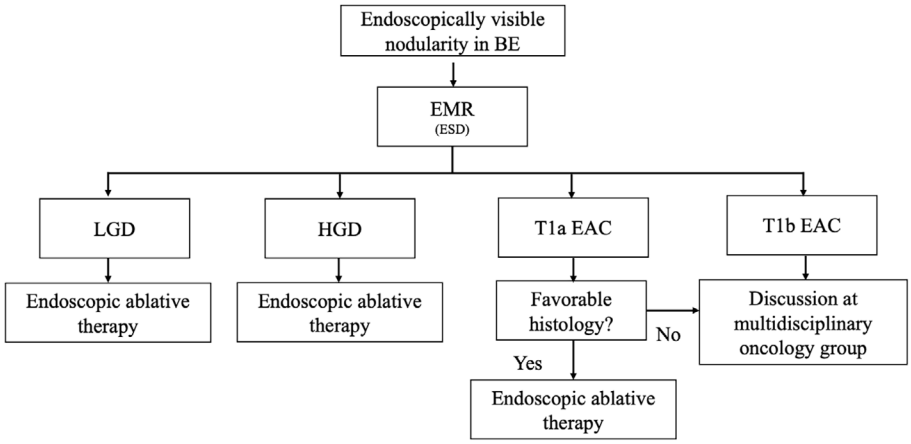

Figure 2. Management of nodular Barrett's esophagus (BE). Endoscopic resection therapy is recommended both for therapeutic benefits and to allow for the staging of the lesions. ESD, which can provide a more complete understanding of the margins but requires well trained team, is an alternative to EMR. A histologic assessment of the resected specimen guides further therapy. Excerpts from the ACG clinical guidelines. EMR: endoscopic mucosal resection, ESD: endoscopic submucosal dissection, LGD: low grade dysplasia, HGD: high grade dysplasia, EAC: esophageal adenocarcinoma

since its development, endoscopic submucosal dissection (ESD) has been considered as an alternative to EMR. Both EMR and ESD have therapeutic and diagnostic benefits. The resected lesion provides more information than does a biopsy, including the depth, lateral margins, and histological characteristics, all of which are important for clinical decision-making. Cap-assisted mucosectomy and multiband mucosectomy are the two main EMR techniques. In a randomized trial comparing these two techniques, multiband mucosectomy was faster and less expensive than cap-assisted mucosectomy, with no difference in the rate of adverse events or the quality of the resected specimens (47). Moreover, multiband mucosectomy was not inferior to ESD based on outcomes related to recurrence and complication rate and was considerably less time-consuming for the treatment of early BE or EGJ neoplasia (48). A randomized trial of ESD versus EMR for early Barrett's neoplasia showed that ESD achieved a higher R0 resection rate; however, it was more time-consuming and caused more severe adverse events (49). Despite this result, in Japan, ESD is preferred to piecemeal EMR for extensive lesions that cannot be resected at once with EMR, because the emphasis is placed on more accurately assessing the depth and lateral resection margins by providing an en bloc specimen, which is possible with ESD. Evidence obtained from Japanese endoscopists revealed that ESD was superior to EMR for endoscopic treatment of early squamous cell carcinoma of the esophagus with respect to R0 resection rate and local recurrence rate (50). There are also retrospective studies which indicate that ESD rather than EMR can archive complete resection with en bloc resection for endoscopic treatment of superficial adenocarcinoma of the esophagus in Japan (51, 52). These reports support the use of ESD for the treatment of superficial lesions. Another reason is that most Japanese therapeutic endoscopists are more familiar with ESD, as it was developed in Japan. Programs to master the ESD technique are being developed. Fig. 4 shows our successful ESD treatment for EAC arising from BE. The pathological diagnosis of this case was well differentiated tubular adenocarcinoma, pathological T1a-M without vascular invasion. There is Japanese flow chart about the treatment for esophageal superficial adenocarcinoma by Japan Gastroenterological En-

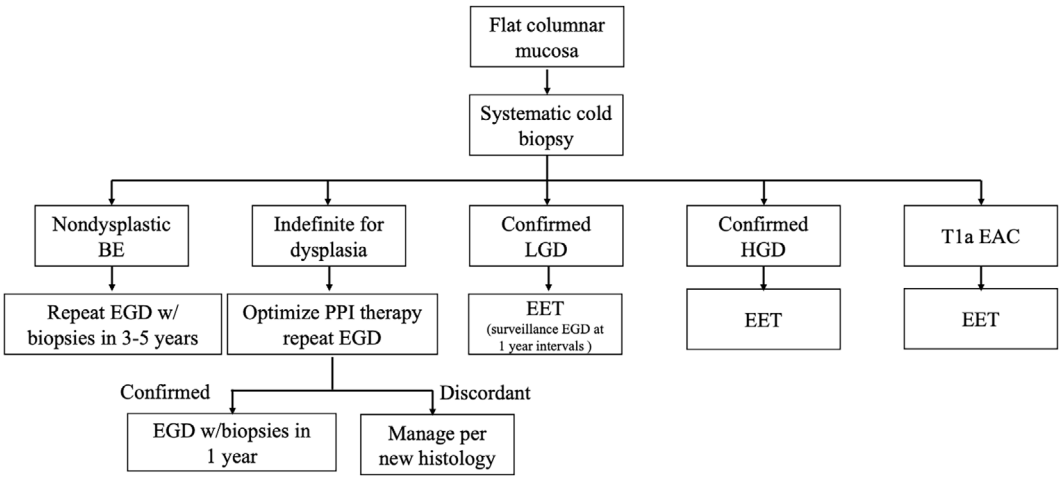

Figure 3. **Management of nonnodular Barrett's esophagus (BE). For BE patients without dysplasia, endoscopic surveillance should take place at intervals of 3 to 5 years. For patients with indefinite for dysplasia, repeat endoscopy after optimization of acid suppressive medications after 3-6 months should be performed. If the indefinite for the dysplasia reading is confirmed on the repeat examination, then a surveillance interval of 12 months is recommended. For the patients with confirmed LGD and without any life-limiting comorbidity, endoscopic therapy is considered to be the preferred treatment modality, although endoscopic surveillance every 12 months is an acceptable alternative. Patients with BE and confirmed HGD should be managed with endoscopic therapy unless they have a life-limiting comorbidity. Excerpts from the ACG clinical guidelines. LGD: low grade dysplasia, HGD: high grade dysplasia, EAC: esophageal adenocarcinoma, EGD: esophagogastroduodenoscopy, PPI: proton pump inhibitor, EET: endoscopic eradication therapy**

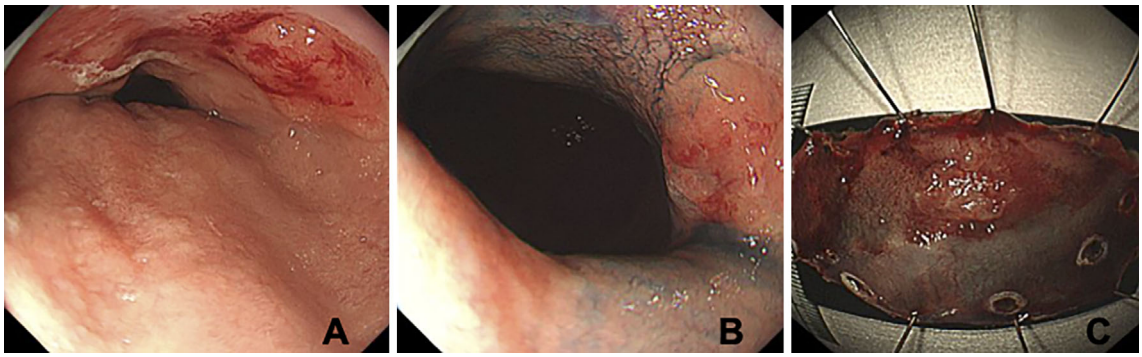

Figure 4. **ESD treatment for EAC arising from BE. A: Conventional image, B: Indigo carmine chromoendoscopy, C: Resection specimen**

doscopy Society, which recommends that endoscopic resection performed at once, and then a pathological diagnosis should be made to determine the treatment strategy thereafter (Fig. 5). Notably, both EMR and ESD have been proposed to be limited within three-quarters of the circumference of the esophagus to avoid stenosis associated with the ulcer healing process (53). Recently, several approaches for stenosis prevention after extensive esophageal ESD are proposed in Japan. Endoscopic balloon dilatation is the first choice and oral steroid combined with injection steroid is considered to be effective (54). Shibagaki et al. reported the effectiveness of the esophageal triamcinolone acetonide-filling method (55).

Endoscopic ablative therapy, performed for flat lesions, also plays an essential role in EET. In the US, there are three main ablation techniques used for BE: radiofrequency ablation (RFA), argon plasma coagulation (APC) and cryotherapy (11, 56). Among these techniques, only RFA has level 1 evidence, that is, the evidence obtained from at least one properly designed randomized controlled trial, for the prevention of cancer reported in the settings of both high-grade and low-grade dysplasia (57, 58). APC is a widely available technique commonly used to treat small residual or recurrent areas of flat lesions following endoscopic resection therapy or RFA. While RFA and APC cause immediate coagulation necrosis by heating, cryotherapy causes immediate and delayed tissue injury and necrosis by freezing (56). Although there is no level 1 evidence for cryotherapy, high rates of complete eradication of intestinal metaplasia and neoplasia have been reported (59, 60). In addition, this tech-

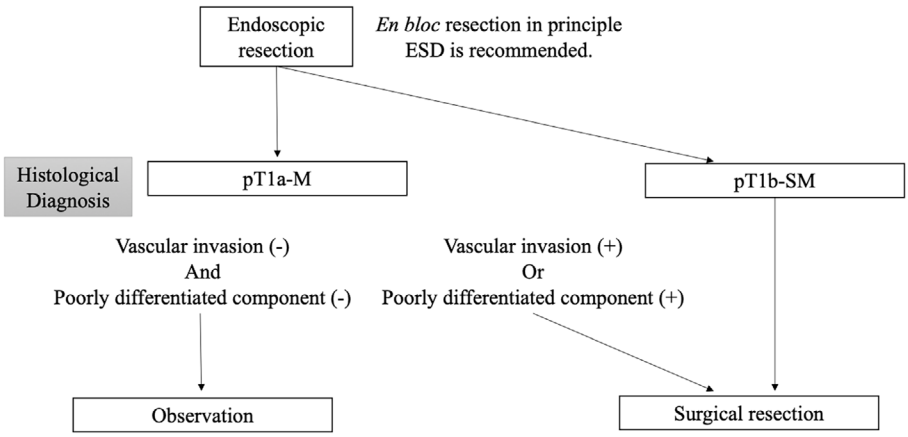

Figure 5. Treatment strategy for esophageal superficial adenocarcinoma. Excerpts and modifications from the ESD/EMR guidelines for esophageal cancer by the Japan Gastroenterological Endoscopy Society.

Table 4. The Main Endoscopic Ablation Therapies for Barrett's Esophagus in the US.

	RFA	APC	Cryotherapy
Mechanism of necrosis	heating	heating	freezing
Features	·level 1 evidence for the prevention of cancer	·Adequate for small area ·widely available technique including Japan	·high rates of complete eradication of intestinal metaplasia and neoplasia ·Can reach beyond the stricture ·Less pain after treatment than RFA

RFA: radiofrequency ablation

nique can be considered in patients who are refractory to RFA or in those requiring ablation of intestinal metaplasia beyond a stricture after EMR (46). Cryotherapy also has the advantage of being associaited with less pain after treatment compared to RFA (61, 62). The main endoscopic ablation therapies in the US are summarized in Table 4. Among these ablation therapies, only APC is currently available in Japan. It is common to obtain a precise diagnosis of the range of BE and then to perform the resection. APC can be considered only for removal of the remaining lesion after endoscopic resection therapy, because emphasis is placed on the pathological diagnosis of the irregular lesion; this is impossible with the ablation therapies. Moreover, most cases of BE in Japan are SSBE and it is rare that wide range of treatment is needed for such cases (32). According to a multicenter study from the US, the incidence rate of high-grade dysplasia or EAC is reported to be associated with the length of BE, and the annual incidence rate was 0.67%/year with mean BE length was 3.6 cm (63). In Japan, there is a multicenter prospective cohort study in cases with LSBE that estimates the incidence rate of EAC at 1.2%/year, which is similar to the values in reports from Western countries (64). Estimating from these reports, as SSBE cases accounts for the majority in Japan, the incidence rate can be estimated below 0.67~1.2%/year, suggesting that USBE has a particularly lower potential for malignancy. Therefore, SSBE, especially USBE, is not currently required to be strictly followed up.

Endoscopic surveillance should continue after successful endoscopic therapy. In the US, for patients with high-grade dysplasia or intramucosal carcinoma, endoscopic surveillance is recommended every 3 months for the first year, every 6 months for the second year, and annually thereafter. In patients with low-grade dysplasia, it is recommended every 6 months for the first year and annually thereafter (20). A new scoring system called the Progression in Barrett's Esophagus score was recently developed; it is based on male gender patients (9 points), cigarette smoking (5 points), BE length (1 point/cm) and confirmed low-grade dysplasia (11 points), and it identifies patients with BE at low (0-10 points, annual risk progression of 0.13%), intermediate (11-20 points, annual risk progression of 0.73%), or high risk (>20 points, annual risk progression of 2.1%) for high-grade dysplasia or EAC (65). In Japan, there are no guidelines for BE surveillance, however, it is common to perform endoscopic surveillance every 3 or 6 months for the first year after endoscopic treatment (32). Recent studies conducted in Japan show that the clinical and endoscopic characteristics of EAC arising from LSBE and SSBE are significantly different. These reports show that in LSBE, higher rate of hiatus hernia, smoking pack-years and statin use are observed and flat-type, accompanied-type 0-IIb, and

complex-type lesions are significantly more prevalent (66, 67). These features can be very useful in establishing the optimal surveillance strategy for BE patients.

Conclusion

We reviewed the endoscopic field concerning BE from the perspective of the US and Japan. In Japan, the incidence of BE and associated neoplasms is low. However, based on recent trends, it can be predicted that the incidence of this disease will increase in the near future, and thus, BE must not be overlooked. The fact that the frequency of SSBE is higher than that of LSBE in Japan highlights several gaps in our understanding of the pathophysiology of BE. Further studies comparing patients from Western countries and Eastern countries may help to elucidate these differences.

The authors state that they have no Conflict of Interest (COI).

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