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Narrow-band Imaging for the Head and Neck Region and the Upper Gastrointestinal Tract

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Endoscopy is essential for the diagnosis and treatment of cancers derived from the gastrointestinal tract. However, a conventional white-light image has technical limitations in detecting small or superficial lesions. Narrow-band imaging, especially with magnification, allows visualization of microstructure patterns and microvascular patterns on the mucosal surface. These technical breakthroughs enable endoscopists to easily detect small pre-neoplastic and neoplastic lesions and to make a differential diagnosis of these lesions. Appropriate diagnosis with narrow-band imaging contributes to minimally invasive endoscopic resection.

Key words: endoscopy – narrow-band imaging – early detection – differential diagnosis

NARROW-BAND IMAGING

Narrow-band imaging (NBI) is an innovative optical technology that allows distinct visualization of microsurface patterns and microvascular patterns on the mucosal surface (1–3). The NBI system uses narrow-band illumination created with optical interference filters that generate 415 and 540 nm wavelengths, corresponding to the peaks of absorption of hemoglobin. Therefore, thin blood vessels, such as capillaries, in the epithelium or mucosal layer can be seen more distinctly than in a conventional white-light image (Fig. 1).

Currently, two types of image reconstruction systems are used for endoscopic imaging: a red–green–blue (RGB) time sequential illumination system with a monochrome charge-coupled device (CCD) and white-light illumination with a colour-chip CCD. The NBI system is applicable to both systems by placing the narrow-band light filter in front of the light source. NBI can provide the same clinical benefits with both illumination systems (Table 1), although the colour reproduction and the image resolution are somewhat different in the two systems (4).

HEAD AND NECK REGION

Head and Neck Cancer

Lugol chromoendoscopy is the standard method for detecting early squamous cell carcinoma (SCC) of the esophagus. However, Lugol dye solution cannot be applied to the oropharynx or hypopharynx because of the risk of aspiration. Moreover, the image resolution of rhinolaryngoscopy does not effectively identify superficial neoplastic lesions in the head and neck region. Therefore, early detection of cancers in the oropharynx and the hypopharynx has been difficult. This is partly attributable to the technological limitations in mounting a high-resolution CCD on the tip of a rhinolaryngoscope.

Muto et al. (5) first reported the utility of NBI combined with magnifying endoscopy (Q240Z, Olympus Medical Systems, Tokyo, Japan) in the identification of superficial SCCs in the head and neck region. Compared with white-light imaging (WLI), NBI significantly improved the visualization of the cancerous lesions by enhancing the contrast between the cancerous lesion and the background non-neoplastic epithelium and by the clear magnification of the

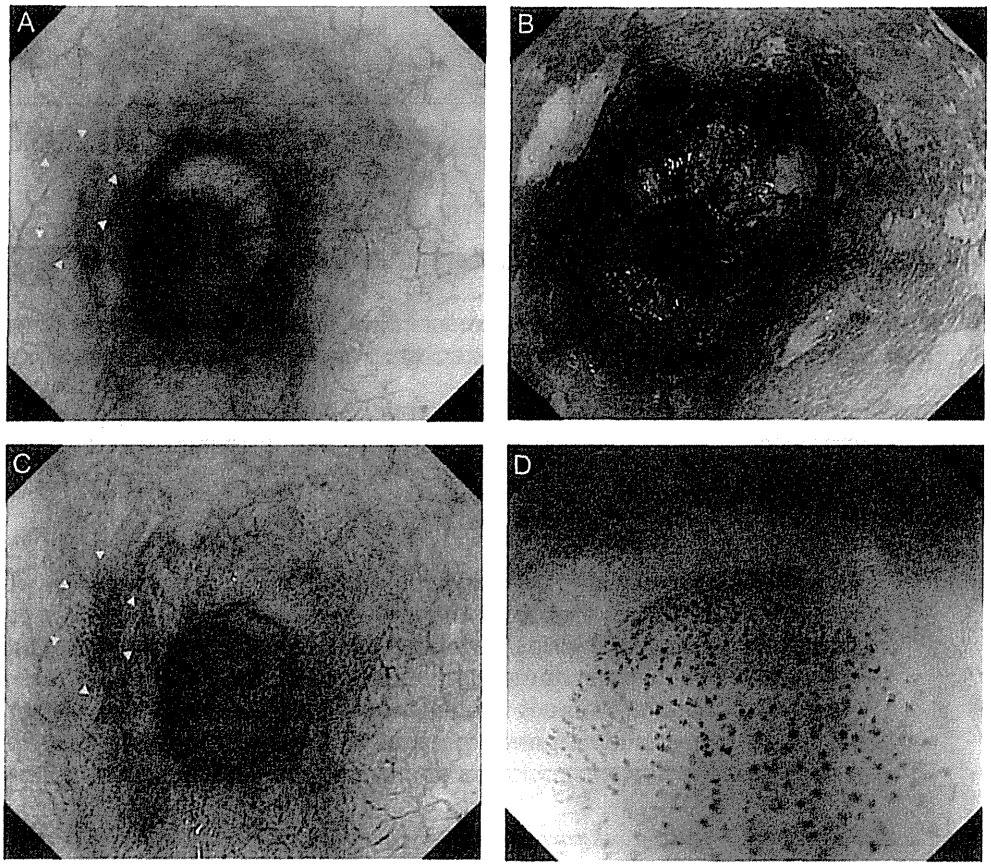

Figure 1. Superficial squamous cell carcinoma in the lower thoracic esophagus. (A) WLI shows scattered reddish spots in the slightly reddish area. (B) Lugol chromoendoscopy shows unstained area. (C) and (D) NBI shows clearly defined brownish spots indicating dilated intrapapillary capillary loops.

microvascular architecture (6). Muto et al. (1) reported that the well-demarcated brownish areas observed under NBI and the microvascular irregularities visible under magnification with NBI are useful indicators of cancerous lesions in the head and neck region. In the multicenter prospective randomized study, NBI is revealed to be superior to WLI in the detection and differential diagnosis of superficial head and neck cancer (7).

Watanabe et al. (8, 9) reported that the NBI rhinolaryngoscope (ENF-V2, Olympus Medical Systems) with a colour-chip light source (CLV-160B, Olympus Medical Systems) improved the diagnostic accuracy, and the negative predictive values for superficial lesions in the oropharynx and hypopharynx compared with those of conventional WLI. However, there is still a critical difference in the image qualities of CCDs between gastrointestinal endoscopy and rhinolaryngoscopy.

Ugumori et al. (10) prospectively compared the images taken with a colour-chip-based rhinolaryngoscope and those taken with an RGB-sequential-system-based high-resolution gastrointestinal endoscope. Whereas the conventional white-light rhinolaryngoscope identified a well-demarcated line between the neoplastic and non-neoplastic lesions in only 10% (5/51) of cases and microvascular irregularities in only 27% (14/51), the NBI rhinolaryngoscope identified these in 63% (32/51) and 94% (49/51) of cases, respectively. These results indicate that even with a rhinolaryngoscope, NBI can improve the visualization of epithelial neoplasms of the head and neck region. When combined with a high-definition television camera, the effectiveness of NBI is improved in terms of both its sensitivity and specificity (11).

NBI is also reportedly useful in detecting metachronous SCC after treatment for esophageal SCC (chemoradiotherapy, radiation therapy or surgery), unknown primary SCC of the neck and adenoid hypertrophy (12–18) (Table 1).

The early detection of cancer in this region increases the possibility of minimally invasive surgery, including endoscopic mucosal resection and endoscopic submucosal dissection methods (19, 20). The potential advantages to patients resulting from an early diagnosis, with the preservation of organ and tissue functions, are obvious.

ESOPHAGUS

Esophageal SCC

Although early detection of cancer offers the best prognosis, many esophageal SCCs (ESCCs) are still detected at a late stage, with a consequently poor prognosis. One reason is that early detection of ESCC is difficult using conventional WLI

es of NBI in contrast to WLI or CE in clinical practice in the head and neck region and the upper gastrointestinal tract

egory	Study aim	Evidence	Magnification	Study design	Diagnosis
ıamous cell :inoma	Detection	NBI >WLI (accuracy: 86.7 vs. 62.9%)	+	Prospective RCT	On site
	Differential diagnosis	NBI > WLI	+	Prospective RCT	On site
ıamous cell :inoma	Detection	NBI > WLI (accuracy: 88.9 vs. 56.5%)	+	Prospective RCT	On site
		NBI = iodine CE (accuracy: 95.1 vs. 85.9 %)	+	Prospective non-RCT	On site
	Differential diagnosis	NBI > WLI	+	Prospective RCT	On site
:nocarcinoma	Detection of HGD/early cancer	NBI = WLI + indicocalmine CE	+	Prospective non-RCT	On site
	Differential diagnosis	M-NBI > M-WLI	+	Prospective non-RCT	Review
	Grade of dysplasia	NBI > WLI	−	Prospective non-RCT	On site
rett's esophagus	Detection of SIM	NBI = indigocalmine CE > WLI (Sn.: 56 vs. 55 vs. 24%, Sp.: 90 vs. 100 vs. 40%)	+	Prospective non-RCT	Review
:nocarcinoma	Detection	No literature			
	Differential diagnosis of small depressive lesions	C-WLI + M-NBI > M-NBI > C-WLI (accuracy: 96.6 vs. 90.4 vs. 64.8%)	+	Prospective RCT	On site
	Differential diagnosis of superficial elevated lesions	M-NBI > C-WLI (accuracy: 92 vs. 74%)	+	Retrospective	Review
	Detection of lateral extent of early gastric cancer	M-NBI > indigocalmine CE	+	Prospective RCT	On site
	Diagnosis of tumour depth	No pivotal study			
:noma	Detection	No pivotal study			
:nocarcinoma	Detection	No pivotal study			
	Differential diagnosis	No pivotal study			
pullary tumour	Visualization of tumour margin	NBI > indigocalmine CE	−	Prospective non-RCT	Review

maging; WLI, white-light imaging; PPV, positive predictive value; NPV, negative predictive value; SIM, specialized intestinal metaplasia; HGD, high-grade dysplasia; Sn., se
NBI, magnifying NBI; M-WLI, magnifying WLI; CE, chromoendoscopy; C-WLI, conventional non-magnifying WLI.

endoscopy because it cannot identify the morphological changes of superficial ESCC. Although Lugol chromoendoscopy is a sensitive method for the detection of early superficial ESCC (Fig. 1A and B), iodine is an irritant and causes unpleasant reactions, such as pain, discomfort and sometimes allergic reaction. In contrast, NBI is less invasive than Lugol chromoendoscopy and enhances the clarity of the intrapapillary capillary loop (IPCL) patterns beneath the epithelium (5, 21, 22) and so it is expected to replace Lugol chromoendoscopy in this role (Fig. 1C and D).

Using an ultrathin endoscope (5 mm in diameter at the distal end; XP260N, Olympus Medical Systems), Lee et al. (23) reported the utility of NBI in the detection and accurate diagnosis of ESCC. The sensitivity of NBI was significantly better than that of conventional WLI. The specificity and positive predictive value of NBI were also better than those of Lugol chromoendoscopy, whereas their diagnostic accuracy and negative predictive value were similar. These results suggest that, even when an ultrathin endoscope is used, NBI is the best tool for screening for superficial esophageal neoplasms, as in the head and neck region.

In a multicentre prospective randomized study (7), NBI with a standard-diameter endoscope showed ~2-fold greater sensitivity than WLI. Furthermore, most of the Lugol-voiding lesions overlooked by NBI endoscopy were low-grade intraepithelial neoplasia or lesions without atypical findings (24).

In 2011, a new classification of magnified endoscopy for superficial ESCC was proposed by the Japan Esophageal Society (25), which allows differential diagnosis of ESCC, intraepithelial neoplasia and inflammation. This classification is expected to simplify the diagnosis and evaluation of the depth of invasion of superficial ESCCs.

Gastroesophageal Reflux Disease

GERD is defined by the presence of reflux esophagitis. When it causes reflux symptoms (chest pain, heartburn, discomfort, etc.), the patient's quality of life is adversely affected (26). Moreover, a significant number of patients with GERD symptoms show no endoscopic signs of esophagitis. This condition is described as 'non-erosive reflux disease' (NERD). Many NERD patients show minimal endoscopic findings, such as a whitish or reddish edematous change or erosion that is not regarded as a mucosal break (27). These minimal changes are potentially related to various GERD symptoms (28). However, the interobserver agreement when NERD is diagnosed with conventional WLI is reportedly too low to support the clinical significance of this technique (29). In contrast, NBI is expected to overcome this limitation, because it allows visualization of the superficial and slight findings attributable to NERD, which cannot be seen with conventional WLI.

Lee et al. (30) reported that the intraobserver and interobserver consistencies in grading esophagitis improved when NBI was used instead of WLI. Sharma et al. (31) reported a feasibility study of magnified endoscopy with NBI in patients with GERD. They showed that increased numbers and the dilatation of IPCLs were the best predictors of a diagnosis of GERD, with moderate-to-high interobserver agreement.

Barrett's Esophagus and Cancer

The incidence of esophageal adenocarcinoma is increasing in Western countries (32) and Barrett's esophagus (BE) is a precursor lesion of this malignancy. Surveillance of BE using WLI with random four-quadrant biopsies is the accepted practice and is recommended by the American Gastroenterological Association statement (33). Sharma et al. (34) showed in a randomized, controlled, international, crossover trial that the success of NBI in detecting intestinal metaplasia did not differ from that of the currently accepted practice of random biopsies, but required significantly fewer biopsies.

Because esophageal adenocarcinoma has a poor prognosis when detected at an advanced stage, endoscopic surveillance is recommended to detect high-grade dysplasia and mucosal neoplasia in patients with BE. However, it is difficult to identify these lesions with conventional WLI. NBI with magnifying endoscopy allows us to visualize the details of the mucosal microsurface pattern and the microvascular pattern without additional equipment or dye solutions (35).

Hamamoto et al. (36) first reported that NBI could better visualize the esophagogastric junction, net-like capillary vessels and columnar-lined esophagus (seen in BE) than conventional WLI. Kara et al. (37) reported that indigo carmine chromoendoscopy and NBI were similarly effective in the diagnosis of high-grade dysplasia or early cancer in BE. Wolfsen et al. (38) reported that high-resolution NBI can detect dysplastic lesions more efficiently, with fewer biopsy samples, than standard-resolution WLI. Singh et al. (39) reported that NBI with magnification is superior to WLI with magnification in the prediction of histology in BE.

A recent meta-analysis (40) that included 446 patients with 2194 lesions reported that NBI with magnification shows high diagnostic precision in detecting high-grade dysplasia, with a sensitivity and specificity of 96 and 94%, respectively.

STOMACH

Detection of Gastric Neoplasm by NBI

In the stomach, NBI has been considered to be used with magnification for detailed examinations. Because the light intensity under the NBI filter is low, a non-magnified image becomes dark compared with that produced under WLI. Furthermore, because the image becomes noisy with the electrical enhancement used to keep the endoscopic image bright, it is insufficient to observe the wide area of the stomach. There is also, as yet, no evidence that NBI is

superior to WLI in detecting early gastric neoplasms. To overcome these limitations, a much brighter NBI system with higher resolution will be commercially available when this review is published. Then, the evidence of other clinical benefits of NBI such as detection will be expected in future.

Differential Diagnosis of Gastric Cancer

Yao et al. (41) originally reported unique magnifying endoscopic findings of gastric cancer in 2002. This marked the beginning of the era of using magnifying endoscopy for the diagnosis of gastric cancer. The utility of magnifying endoscopic observations combined with WLI for the differential diagnosis of flat or slightly depressed gastric cancers and non-neoplastic lesions, such as gastritis, has been reported. NBI combined with magnifying endoscopy (magnifying NBI) provides better visualization of the mucosal surface and microvascular architecture than magnifying WLI (42). Several reports have compared the diagnostic yield of magnifying NBI with that of magnifying or non-magnifying WLI in distinguishing small gastric cancers from the flat or depressed benign lesions caused by chronic gastritis (43–45). However, all those reports had some limitations: they were performed at only one institution, evaluated stored images and did not involve real-time assessment or included gastric lesions with a definite pathological diagnosis. To overcome these limitations, Ezoe et al. performed a multicenter, prospective, randomized, controlled trial that targeted newly detected, undiagnosed lesions to compare and evaluate the diagnostic yields of magnifying NBI and conventional WLI. The trial revealed that magnifying NBI, especially after non-magnifying WLI, showed an extremely high diagnostic performance (46).

These lines of evidence suggest that magnifying NBI is currently one of the standard endoscopic modalities in the differential diagnosis of gastric cancers.

Determination of the Lateral Extent of Gastric Cancer

To achieve a complete resection of a mucosal gastric cancer with endoscopic resection, an accurate diagnosis of the extent of the tumour is required. By clearly visualizing the microvascular architecture and the microsurface structure inside and outside the lesion, magnifying NBI can distinguish the cancer margins from the surrounding benign mucosa, so it is expected to be useful for delineating the extent of a gastric tumour. In 2004, Sumiyama et al. (47) retrospectively described the feasibility of NBI for the guidance of *en bloc* endoscopic resection when combined with a multibending endoscope, but did not perform a formal evaluation. Kadowaki et al. compared the utility of magnifying NBI and magnifying WLI in recognizing gastric cancer demarcation. They also reported that magnifying NBI is more useful when it is combined with acetic acid (48). Kiyotoki et al. (49) and Nagahama et al. (50) reported the superiority of magnifying NBI to chromoendoscopy for determining the lateral extent of early gastric cancer. These lines of evidence suggest that magnifying NBI can be a useful modality for determining the lateral extent of gastric cancer. However, it must be emphasized that it is still difficult to accurately define the tumour margin in undifferentiated gastric cancers; the successful delineation rate was 0% for undifferentiated cancers in one study (50). Because undifferentiated gastric cancers often spread subepithelially and are covered with the non-neoplastic foveolar epithelium, observation of the mucosal surface by NBI is not useful for determining the tumour margin of this type of gastric cancer. Therefore, it is necessary to take biopsy specimens of the surrounding mucosa to define the extent of an otherwise undetectable tumour in undifferentiated gastric cancers.

Prediction of the Histological Type of Gastric Cancer

Nakayoshi et al. (51) reported that the different microvascular patterns detected with magnifying NBI images are useful in predicting the histological type of a superficial gastric cancer. Differentiated adenocarcinomas display a 'fine network pattern,' and undifferentiated adenocarcinomas display a 'corkscrew pattern' in their microvascular structures (Fig. 2). Yoshida et al. (52) reported that a 'non-

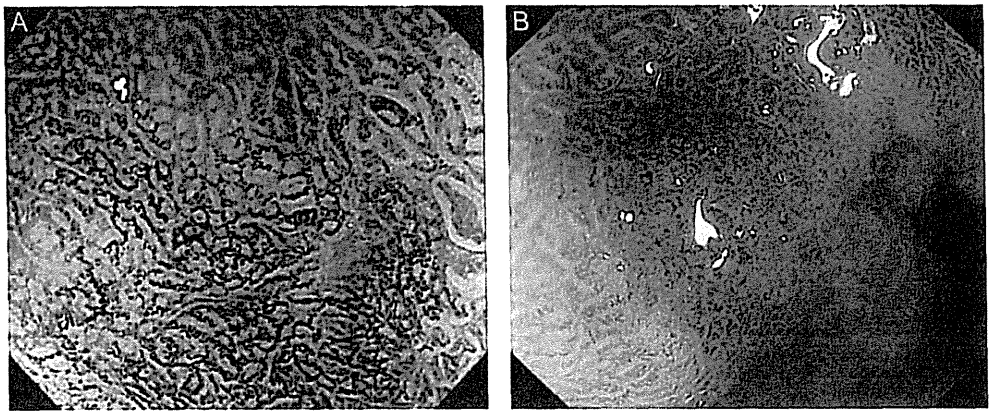

Figure 2. Microvascular patterns of gastric cancer. (A) Fine network pattern indicates differentiated adenocarcinoma. (B) Corkscrew pattern indicates undifferentiated adenocarcinoma.

structural pattern' appeared to be a useful marker of undifferentiated superficial gastric cancers.

Although these studies have indicated the utility of magnifying NBI in the prediction of the histopathological type of a gastric cancer, its reliability must be validated in a large-scale prospective study. Moreover, even if magnifying NBI can predict the histological type of a cancerous lesion, histological confirmation by biopsy is required at this time. However, the prediction of histological type could be useful to the endoscopists when selecting the site of a biopsy in a lesion because gastric cancers are usually heterogeneous.

Diagnosis of the Tumour Depth of Gastric Cancer

In contrast to ESCC, there is no evidence that NBI, with or without magnifying endoscopy, can predict the depth of tumour invasion in a patient with gastric cancer.

Diagnosis of Gastric Adenoma

Because most gastric adenomas form protruded lesions, the differential diagnosis of protruded gastric cancer and protruded adenoma is sometimes difficult (53, 54). Yao et al. reported that the characteristic finding of magnifying NBI, a white opaque substance (Fig. 3), is a relevant sign for differentiating protruded adenomas from protruded cancers (55). Tsuji et al. (56) also reported that the presence of an irregular microvascular pattern or irregular microsurface pattern with a demarcation line between the lesion and the surrounding area under magnifying NBI is useful in distinguishing cancers from adenomas. Maki et al. (57) reported that magnifying NBI appears to be useful in differentiating between cancerous and adenomatous superficial elevated lesions of the stomach with significantly higher sensitivity and accuracy. In contrast, depressed-type adenoma is rare, although it is clinically important because it has greater malignant potential than protruded adenoma (58). Tamai et al. (59) reported that depressed-type adenomas display a regular ultrafine pattern, in which the network of microvessels is composed of small and regular circles, which differs from the irregular fine network pattern of well-differentiated gastric cancers.

These reports indicate that magnifying NBI should be a useful modality for the accurate diagnosis of gastric adenoma.

DUODENUM

Small duodenal ampullary tumours are treated by surgical resection or endoscopic resection. However, the lateral margin must be precisely assessed before curative endoscopic resection. Uchiyama et al. (60) reported that magnifying NBI with a direct frontal-view magnifying endoscope can predict the histological characteristics of ampullary lesions by detecting abnormal vessels and microsurface patterns. Itoi et al. (61) reported that NBI with a conventional duodenoscope, with no magnifying capacity, allowed better visualization of the tumour margin than indigo carmine chromoendoscopy. However, these studies included only a small number of cases, so further studies with a sufficient number of patients are required to evaluate the usefulness of NBI for duodenal tumours.

CONCLUSION

NBI is now a useful endoscopic modality for the head and neck region and the upper gastrointestinal tract. It helps the endoscopists to do early detection and accurate diagnosis for the head and neck neoplasia and disease in the upper gastrointestinal diseases. Furthermore, it enables minimally invasive treatment and improves the patients' survival and quality of life. Then, standard education programme of NBI in clinical practice will be needed.

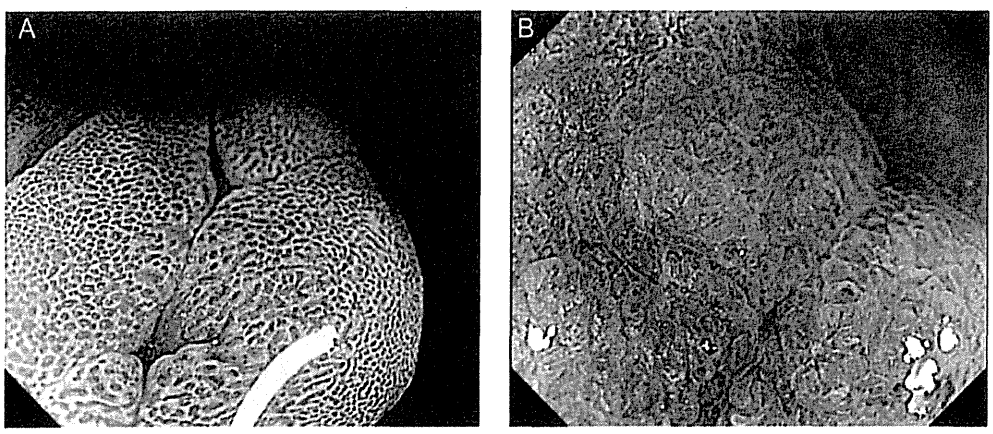

Figure 3. White opaque substance (WOS) within an elevated adenoma and well-differentiated adenocarcinoma. (A) The regular distribution of WOS indicates adenoma. (B) The irregular distribution of WOS indicates adenocarcinoma.

Conflict of interest statement

None declared.

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Review

Endoscopic diagnostic strategy of superficial esophageal squamous cell carcinoma

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The prognosis of the esophageal squamous cell carcinoma is still poor. Early detection is ideal to improve patient survival. In particular, superficial cancer limited within the mucosal layer is a good candidate for minimally invasive treatment by endoscopic resection with curative intent. However, an effective endoscopic diagnostic strategy is not established worldwide. Herein, we review the published papers on this subject.

Key words: endoscopic ultrasonography (EUS), esophagus, image-enhanced endoscopy (IEE), Lugol chromoendoscopy, narrow-band imaging (NBI), esophageal squamous cell carcinoma (ESCC)

INTRODUCTION

SQUAMOUS CELL CARCINOMA (SCC) is the predominant histological type of esophageal cancer worldwide.[1] Asia (China, Kazakhstan, Taiwan and Japan) and Eastern Africa are the areas with the highest incidence. Smoking, ethanol in alcoholic beverages and acetaldehyde associated with alcoholic beverages are definite risk factors for esophageal SCC (ESCC).[2] Because these definite risk factors are recognized, early detection of ESCC can be expected for those at risk.

Endoscopy plays an important role in the early detection of cancer in the gastrointestinal tract, which includes the esophagus. However, detection is not always easy for endoscopists, because endoscopic findings of superficial esophageal cancers are slight and minimal. Therefore, an ideal strategy for the early detection of ESCC is required.

According to the depth of the invasion, superficial ESCC is classified into Tis (carcinoma in situ/high-grade dysplasia), T1a (tumor invades the lamina propria or muscularis mucosae) or T1b (tumor invades the submucosa) by the International Union Against Cancer Classification of Malignant Tumours (7th edition) (Fig. 1).[3] Because more than half of the patients with superficial ESCC have no symptoms associated with cancer, effective screening is important for early detection. Early detection enables us to use minimally invasive treatment, such as endoscopic resection (EMR: endoscopic mucosal resection, ESD: endoscopic submucosal dissection), and those with superficial ESCC can expect to be cured.

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IDEAL DIAGNOSTIC STRATEGY

(i) Identification of subject at risk:
1. drinkers;
2. smokers;
3. aldehyde dehydrogenase type 2 (ALDH2) deficiency;[4]
4. inadequate intake of green-yellow vegetables and fruits.

(ii) Detection:
1. conventional white light imaging (WLI);
2. Lugol chromoendoscopy;
3. equipment-based image-enhanced endoscopy (IEE).[5]

(iii) Differential diagnosis:
1. conventional WLI;
2. Lugol chromoendoscopy;[6–8]
3. equipment-based IEE.

(iv) Estimation of the depth of invasion:
1. conventional WLI;
2. equipment-based IEE;
3. endoscopic ultrasound (EUS).

(v) Histological confirmation by biopsy.

WHITE LIGHT IMAGING

SUPERFICIAL ESCC, ESPECIALLY Tis and T1a ESCC, sometimes lacks any changes in appearance. In these cases, early detection of superficial ESCC by

conventional WLI is difficult. Disappearance of the vascular network in the mucosa (Fig. 2), uneven surface and tiny white coating are indications of the possible presence of superficial ESCC (Fig. 3).

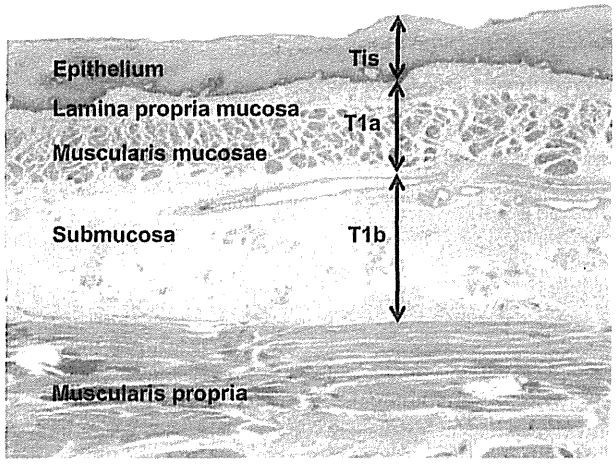

Figure 1 Histological structure of the esophageal wall. From the surface of the lumen, the esophagus comprises squamous epithelium, lamina propria mucosa, muscularis mucosae, submucosa, muscularis propria and adventitia. According to the 7th Classification of Malignant Tumors (TNM), superficial esophageal squamous cell carcinoma is classified into Tis (carcinoma in situ/high-grade dysplasia), T1a (tumor invades the lamina propria or muscularis mucosae) or T1b (tumor invades the submucosa).

LUGOL CHROMOENDOSCOPY

LUGOL CHROMOENDOSCOPY IS the standard method for detecting and identifying the margin of the lateral extension of ESCC.[6] However, it causes unpleasant reactions, such as chest pain and discomfort, in those who undergo endoscopic examination, and occasionally causes allergic reactions including flushing, asthma and iodine shock. Sodium thiosulfate solution is useful in reducing these adverse symptoms.[9] Giving i.v. steroids before examination is sometimes effective in preventing allergic reactions.

After staining with Lugol solution, a pink color change indicates ESCC (Fig. 4). The pink color change is clearly revealed after 2–3 min after Lugol staining. Shimizu *et al.* reported that when used as a diagnostic index for high-grade intraepithelial squamous neoplasia and SCC, the pink color sign shows sensitivity and specificity of 91.9% and 94.0%, respectively.[10] Ishihara *et al.* also reported that sensitivity and specificity of diagnosis of high-grade intraepithelial neoplasia or invasive cancer were 88% and 95%, respectively.[11]

The so-called 'Tatami-no-me' sign[12] is a useful indicator of the depth of invasion of ESCC (Fig. 5). 'Tatami' means traditional Japanese-style flooring and the endoscopic appearance of the 'Tatami-no-me' sign is similar to the surface pattern of Tatami (Japanese traditional floor). If the Tatami-no-me sign is not seen in a cancerous lesion, the neoplasia might have invaded the deep layer of the lamina propria. If the Tatami-no-me sign is seen, the lesion will not have invaded the deep layer of the lamina propria.

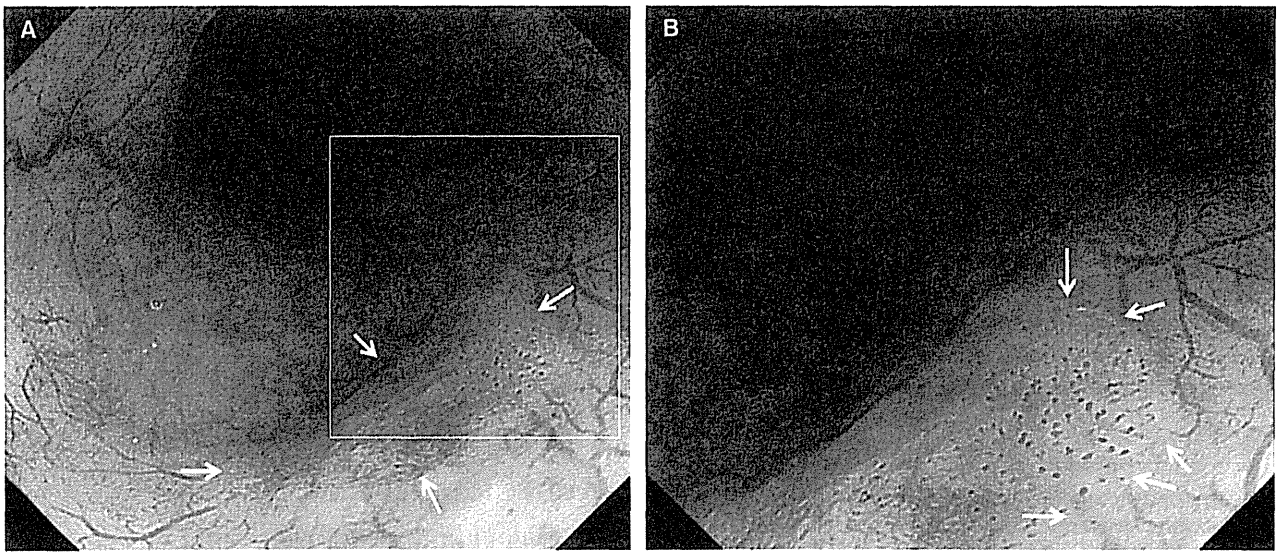

Figure 2 *Superficial esophageal squamous cell carcinoma. The margin of the light reddish area (arrows in [A]) shows disappearance of the vascular network in the mucosa (arrows in B).*

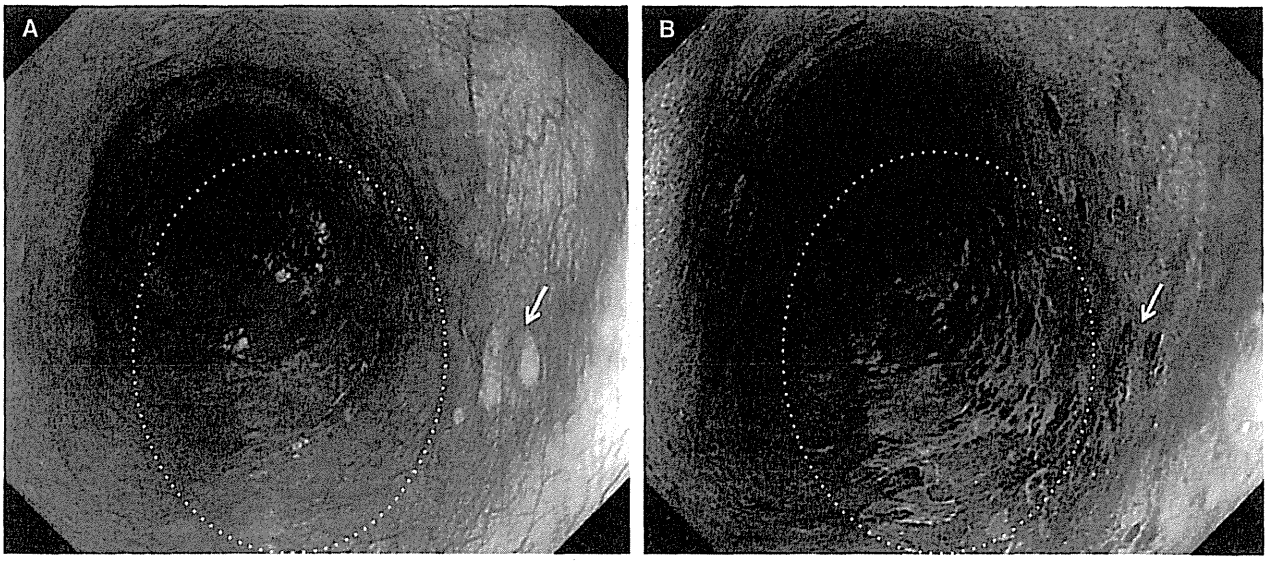

Figure 3 Superficial esophageal squamous cell carcinoma. (A) White light imaging shows uneven surface and tiny white coating in the esophageal wall. Arrow indicates glycogenic acanthosis as a landmark. (B) Lugol chromoendoscopy shows wide Lugol-voiding lesion with irregular margin. Arrow indicates glycogenic acanthosis as a landmark.

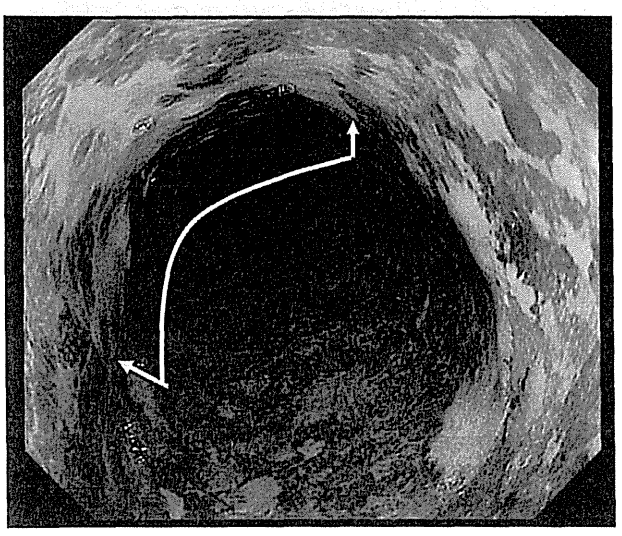

Figure 4 Lugol chromoendoscopy shows a superficial esophageal cancer: the suspicious lesion shows pink color change (arrow).

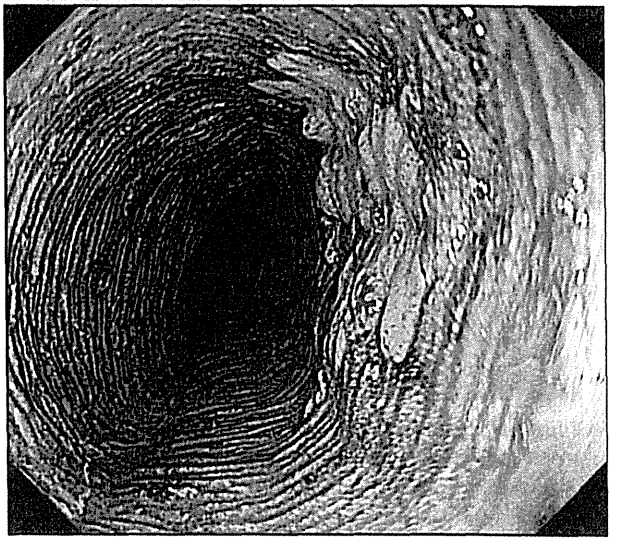

Figure 5 Lugol chromoendoscopy shows 'Tatami-no-me' sign. 'Tatami' means traditional Japanese-style flooring.

EQUIPMENT-BASED IMAGE-ENHANCED ENDOSCOPY

IMAGE-ENHANCED ENDOSCOPY[5] is expected to accurately diagnose high-grade intraepithelial neoplasia and SCC with minimal invasion of the esophagus. IEE combined with magnification is a powerful tool to characterize the lesion.

Among the IEE types, narrow-band imaging (NBI)[13,14] has been found to provide a highly accurate diagnosis of superficial ESCC. The NBI endoscopy system uses two narrow-band illuminations of 415 nm and 540 nm by the NBI filter, corresponding to the peaks of absorption of hemoglobin. Therefore, thin blood vessels, such as capillaries, in the epithelium or mucosal layer can be seen more distinctly than in conventional WLI. Under NBI observation, most of the

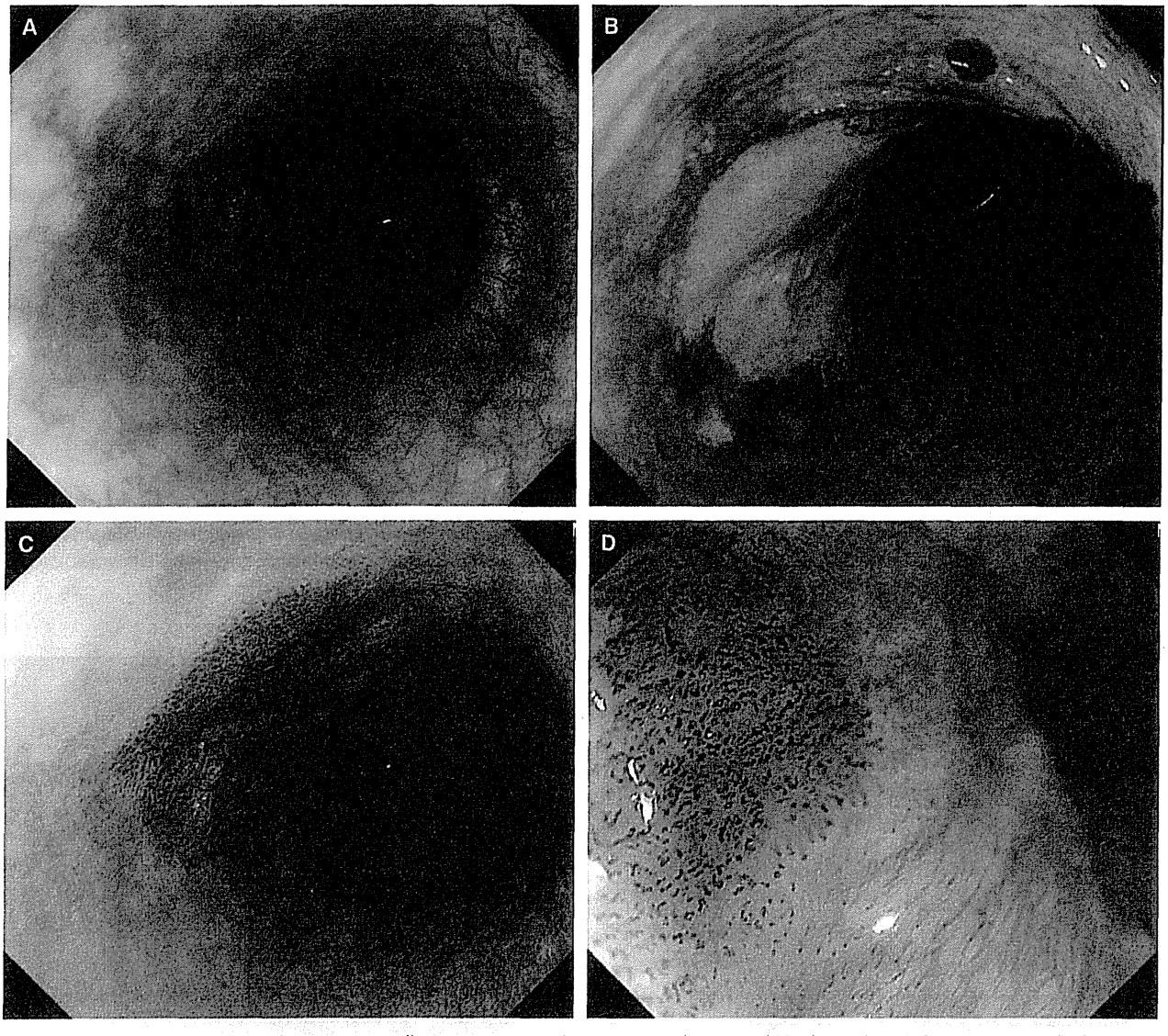

Figure 6 Superficial esophageal squamous cell carcinoma. (A) The cancerous lesion is difficult to identify by conventional white light imaging. (B) Lugol chromoendoscopy clearly reveals the cancerous lesion as a Lugol-voiding lesion. (C) Narrow-band imaging (NBI) shows the cancerous lesion as a well-demarcated brownish area. (D) Magnified NBI shows irregularity of the microvessels in the brownish area while the surrounding background mucosa does not show dilation and tortuous change of the intraepithelial papillary capillary loop (IPCL).

superficial cancer is seen as a brownish area (Fig. 6).[15,16] With magnification, irregularity of the intraepithelial papillary capillary loop (IPCL) is also seen (Fig. 6).[17]

In a prospective multicenter randomized controlled study, Muto *et al.* reported that NBI detected superficial ESCC more frequently than did WLI (97% *vs* 55%, $P < 0.001$).[18] The sensitivity and accuracy of NBI for the diagnosis of superficial ESCC were 97.2% and 88.9%, respectively. Furthermore, even small lesions (<10 mm) were more effectively detected by NBI with magnification than with WLI (94% *vs* 39%, $P = 0.03$).

The screening of second primary ESCC in patients with head and neck cancer is important, and Lugol chromoendoscopy has been used for its detection.[19] In a study reported by Takenaka *et al.*,[20] the specificity of NBI was significantly superior to conventional WLI (95.4% *vs* 84.7%, $P < 0.001$), whereas the sensitivity of NBI and Lugol chromoendoscopy was equivalent (90.9% *vs* 100%, not significant). Further-

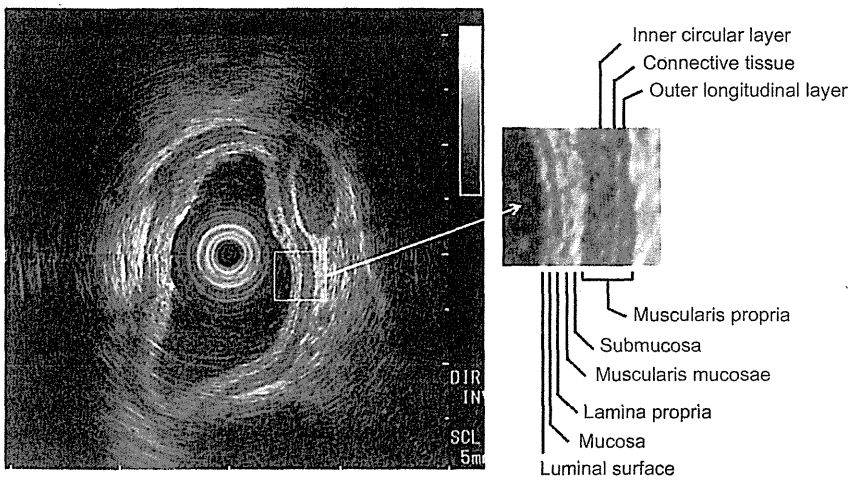

Figure 7 Endoscopic ultrasonography (EUS) image of the normal esophageal wall by 20 MHz miniprobe demonstrates a nine-layered structure (arrow). The first five layers correspond to the echogenic luminal surface (high echo), mucosa (low echo), lamina propria (high echo), muscularis mucosae (low echo), submucosa (high echo). Next are inner circular (low echo) and outer longitudinal layers (low echo) of muscularis propria. They are separated by a thin hyperechoic layer of the connective tissue (high echo).

more, most of the Lugol-voiding lesions overlooked by NBI were low-grade intraepithelial neoplasia or lesions with atypical findings. These results indicate that NBI is a useful and less invasive screening method for ESCC.

In contrast, when NBI is used without magnification, the false-positive rate is high.[21] Therefore, NBI is recommended for use with magnification to provide both higher sensitivity and higher specificity.[20,22]

ENDOSCOPIC ULTRASONOGRAPHY

THE DEPTH OF ESCC invasion into the esophageal wall is closely associated with metastasis to lymph nodes.[23] The frequency of metastasis in the lymph nodes in ESCC that is confined to the mucosa is 3%. The risk increases to 12% for cancer invading the muscularis mucosae, and increases markedly to 26–46% in those with submucosal invasion. Because ESCC confined to the mucosal layer is correlated with a low frequency of metastasis, and because surgery confers a high risk of morbidity and mortality, these patients are considered to be appropriate candidates for minimally invasive treatment by EMR or ESD. ESCC invading the muscularis mucosae is indicated for surgical resection, but may still be treated by ESD. ESCC with submucosal invasion necessitates surgical resection and/or chemoradiotherapy.[24,25]

To estimate the depth of ESCC invasion for superficial ESCC, standard endoscopy with image enhancement and EUS are currently considered the best methods. Other methods, such as the barium meal, computed tomography (CT) and positron emission tomography (PET), are considered less appropriate for superficial ESCC because of their resolution limitations.

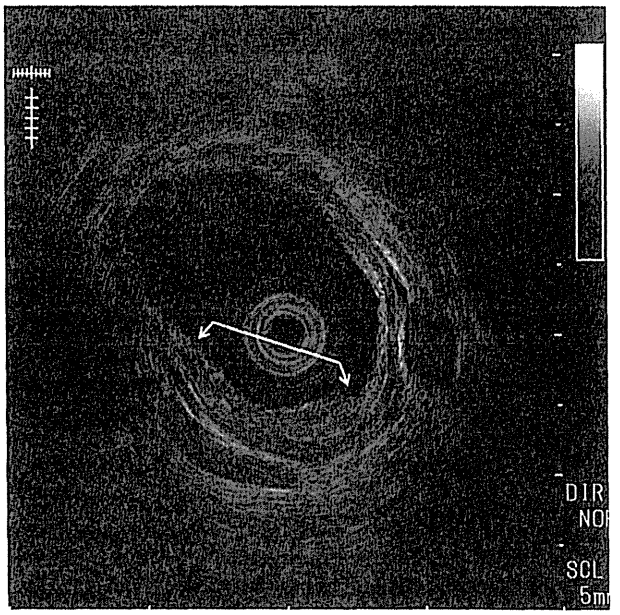

Figure 8 Endoscopic ultrasonography (EUS) image demonstrates a low echoic mass located in the submucosal layer (arrow).

To estimate the depth of invasion, the distinct tissue layers of the esophageal wall should be identified. To visualize them, 20 MHz or 30 MHz miniature probes should be used. These high-resolution probes provide nine-layered echostructures (Fig. 7). Generally, a tumor can be seen as a low echoic mass by EUS (Fig. 8). If the cancerous lesion invades the submucosal layer, EUS delivers a low-echo mass in the high-echo layer and corresponding submucosal layer. A balloon should be attached to the tip of the endoscope to keep deaerated water in the esophageal lumen and prevent

regurgitation to the pharynx. An endoscope with a water jet function is desirable to keep the esophageal lumen wider and to obtain clear images.

CONFLICT OF INTERESTS

AUTHORS DECLARE NO conflict of interests for this article.

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Clinical Trial Notes

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A Phase II Clinical Trial of Endoscopic Submucosal Dissection for Early Gastric Cancer of Undifferentiated Type: Japan Clinical Oncology Group Study JCOG1009/1010

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A Phase II clinical trial has been initiated to evaluate the efficacy and safety of endoscopic submucosal dissection for intramucosal (cT1a) gastric cancer of undifferentiated type. Patients with cT1a gastric cancer with undifferentiated-type adenocarcinoma are eligible for the study. The tumor size should be 2 cm or less without ulceration. The study will enroll a total of 325 patients from 51 institutions over a 4-year period. The primary endpoint is proportion of 5-year overall survival (% 5-year overall survival) in patients with undifferentiated dominant type. The secondary endpoints are overall survival, relapse-free survival, distant metastasis-free survival, % 5-year overall survival without either recurrence or gastrectomy, % en-bloc resection with endoscopic submucosal dissection, % pathological curative resection with endoscopic submucosal dissection, % 5-year overall survival in patients with differentiated dominant type, % 5-year overall survival in patients with pathologically curative resection with endoscopic submucosal dissection and adverse events. This trial was registered at the UMIN Clinical Trials Registry as UMIN000004995.

Key words: clinical trial-trial design – clinical trials – endoscopy-upper GI

INTRODUCTION

Gastrectomy with lymph node dissection has been the standard treatment in patients with early gastric cancer (EGC) in Japan, because complete cure can almost always be achieved (1). On the other hand, endoscopic resection (ER) is an attractive alternative for some EGC because it is a minimally invasive, stomach-conserving procedure and postoperative quality of life is better.

The indications for ER are limited to EGC without lymph node metastasis because the treatment involves only local resection without lymph node dissection. As per the Japanese Gastric Cancer Treatment Guidelines 2010 (ver.3) set forth by the Japan Gastric Cancer Association, the indication for ER is

limited to intramucosal (cT1a) lesions of differentiated (intestinal) type 2 cm or less in diameter, based on the potential for lymph node metastasis and technique for en-bloc resection.

A large retrospective study of surgically resected cases showed that some cT1a (i.e. mucosal cancer without ulceration (UL) regardless of its size and intramucosal cancer with UL 3 cm or less) demonstrated no lymph node metastasis (2). Moreover, recent technical advances in ER, including endoscopic submucosal dissection (ESD) (3), have enabled en-bloc resection of cT1a tumors larger than 2 cm (4). Thus, it is speculated that ER using ESD techniques may cure some patients with differentiated type of EGC beyond the indications described in the current practice guidelines. A multi-institutional clinical trial, by Japan Clinical Oncology Group (JCOG0607), is currently in progress to examine these indications, as previously reported (5).

With regard to EGC of undifferentiated (diffuse) type, a consensus could not be reached as to which lesions present a negligible risk of lymph node metastasis in the above-mentioned retrospective analysis because of the small sample size (2). Hirasawa et al. (6) recently reviewed additional surgical data 9 years after the initial publication. They concluded that intramucosal EGC of undifferentiated that are 2 cm or less in size, without lymphovascular invasion and UL, presented a negligible risk of lymph node metastasis. In addition, Yamamoto et al. (7) reported excellent results with regard to ESD for undifferentiated-type EGC, with a high proportion of curative resection. From the results of these two reports, we speculated that ER using ESD techniques would be an appropriate indication for certain EGC of undifferentiated type. A multi-institutional Phase II trial (JCOG1009/1010) was therefore initiated to evaluate the efficacy and safety of ESD for EGC of undifferentiated type beyond currently accepted indications (Fig. 1). JCOG1009/1010 is a collaborative study between the two JCOG study subgroups: JCOG1009 is a part of the study by the Gastrointestinal Endoscopy Study Group (GIESG) and JCOG1010 is a part of the study by Stomach Cancer Study Group (SCSG) of the JCOG. JCOG1009/1010 has one common protocol and one primary analysis.

The JCOG Protocol Review Committee approved the protocol in December 2010. The study was registered in the UMIN Clinical Trial Registry [www.umin.ac.jp/ctr/] as UMIN000004995, and activated in February 2011.

JCOG1009/1010 PROTOCOL

Purpose

The aim of this study is to evaluate the efficacy and safety of ESD for intramucosal gastric cancer of undifferentiated type, clinically diagnosed as intramucosal cancer 2 cm or less in size without ulceration.

Study Setting

Multi-institutional (51 centers), single-arm, Phase II trial.

Resources

This study is supported by the Grants-in-Aid for Cancer Research (20S-3 and 20S-6), the National Cancer Center Research and Development Fund (23-A-16 and 23-A-19) and Health and Labour Sciences Research Grant for Clinical Cancer Research (22–021) from the Ministry of Health, Labour and Welfare, Japan.

Endpoints

The primary endpoint is proportion of 5-year overall survival (% 5-year OS) in patients with undifferentiated dominant-type EGC diagnosed in the ESD specimen (Fig. 1). The secondary endpoints are OS, relapse-free survival (RFS), distant metastasis-free survival, % 5-year survival without either recurrence or gastrectomy, % en-bloc resection with ESD, % pathologically curative resection with ESD, % 5-year OS in patients with differentiated dominant-type EGC diagnosed in the ESD specimen, % 5-year OS in patients with pathologically curative resection with ESD and adverse events.

In this trial, OS is defined as the time from registration to death from any cause, and it is censored at the last contact day for a living patient. RFS is defined as the time from registration to either the first event of recurrence or death from any cause, and it is censored at the last day when the patient is alive without recurrence. Adverse events are evaluated according to Common Terminology Criteria for Adverse Events version 4.0—JCOG. The criteria for pathologically curative resection are described in 'Decision criteria after ESD' section.

Inclusion Criteria

Patients are eligible for inclusion in the study if they meet all of the following criteria: (i) histologically proven components of undifferentiated (diffuse)-type adenocarcinoma (*por or sig*) of the stomach in biopsy specimen; (ii) confirmation of the horizontal margin by cancer-free endoscopic biopsy around the lesion, which should be examined at each participating institution; (iii) non-recurrent single tumor; (iv) clinical T1a (intramucosal); (v) tumor size 2 cm or less; (vi) absence of ulcer findings endoscopically; (vii) low likelihood for luminal stenosis after ESD; (viii) clinical N0/M0 by abdominal CT scan; (ix) age 20–80 years old; (x) performance status (ECOG) of 0 or 1; (xi) no prior gastrectomy and no reconstructive surgery involving the stomach for esophageal cancer; (xii) no prior chemotherapy (including hormone therapy) or radiation therapy for any other malignancies; (xiii) sufficient organ function and (xiv) written informed consent.

Exclusion Criteria

Patients are excluded from the study if they meet any of the following criteria: (i) simultaneous or metachronous (within

	cT1a (mucosa)			
	UL (–)		UL (+)	
	≤20 mm	>20 mm	≤30 mm	>30 mm
Differentiated (intestinal)	Absolute indication by the guideline	Expanded indication, being evaluated in JCOG0607	expanded indication being evaluated in JCOG0607	No indication, requiring surgery
Undifferentiated (diffuse)	No indication, being evaluated in this study, JCOG1009/1010	No indication, requiring surgery	No indication, requiring surgery	No indication, requiring surgery

Figure 1. Indications for endoscopic resection of early gastric cancer.

5 years) multiple cancers, except intramucosal tumor curable with local therapy; (ii) infectious disease requiring systemic therapy; (iii) body temperature higher than 38°C; (iv) pregnant or breast-feeding woman; (v) psychosis; (vi) use of systemic steroids; (vii) history of myocardial infarction within 6 months or unstable angina pectoris within 3 weeks; (viii) uncontrolled hypertension; (ix) severe respiratory disease requiring continuous oxygen therapy; (x) inability to hold anticoagulant or antiplatelet medications and (xi) uncontrolled diabetes mellitus or administration of insulin.

Registration

Patients are registered into the JCOG1009/1010 trial after confirming the inclusion/exclusion criteria by telephone or fax to the JCOG Data Center. Online website registration is also available.

Quality Control of ESD

Thirty institutions among the GIESG and 21 institutions among the SCSG of the JCOG are participating in this trial (Table 1). All participating endoscopists have agreed to the technical details for ESD. To control the quality of the ESD technique and endoscopic diagnosis, central review of photographs and videotapes in arbitrarily selected patients will be performed at the semi-annual investigators' meeting. All ESD procedures are done or directly supervised endoscopists certified by study chair. The minimum criterion for certification in this study is having experience with 50 or more ESD for gastric cancer.

Treatment Methods

Endoscopic Submucosal Dissection

ESD of EGC is performed within 30 days after patient registration. Tumors should be resected en-bloc with ESD, and ESD should be performed by certified endoscopists or other staff members under the supervision of certified endoscopists. There are no specific criteria regarding devices used for ESD.

Decision Criteria after ESD

After ESD, patients are categorized into two groups: undifferentiated type group and differentiated-type group, according to the dominant histopathology diagnosed in the resected specimens. In both groups, ESD is deemed 'non-curative' if any of the following criteria is met in the histological diagnosis of resected specimens;

(A) undifferentiated type group:
  (i) pT1b (submucosa, SM),
  (ii) with UL,
  (iii) size of tumor >2 cm;
(B) differentiated type group:
  (i) pT1a (M) with UL and size of tumor ≥3 cm,
  (ii) pT1b (SM1; tumor invasion is within 0.5 mm beyond the muscularis mucosae) with a component of undifferentiated type adenocarcinoma in the most advanced area,
  (iii) pT1b (SM1) and size of tumor 3 cm or more,
  (iv) depth of tumor invasion is pT1b (SM2, tumor invasion is 0.5 mm or deeper beyond the muscularis mucosae) or more,
  (v) pT1a (M) without UL and size of undifferentiated type histology component 2 cm or more;
(C) both groups:
  (i) vascular or lymphatic invasion present,
  (ii) histological vertical margin positive or non-evaluable,
  (iii) histological horizontal margin positive or non-evaluable,
  (iv) tumors not treated in en-bloc resection,
  (v) intratumor resection found pathologically,
  (vi) presence of component of muc (mucinous adenocarcinoma).

'Non-curative' cases must undergo gastrectomy according to the Japanese Gastric Cancer Treatment Guidelines.

ESD is deemed 'curative' if none of the above criteria are met. 'Curative' cases receive no additional treatment after ESD.

Table 1. Participating institutions

GIESG (30 institutions)
1. Iwate Prefectural Central Hospital, Iwate
2. Iwate Medical University Hospital, Iwate
3. Yamagata Prefectural Central Hospital, Yamagata
4. Ibaraki Prefectural Central Hospital, Ibaraki
5. Tochigi Cancer Center, Tochigi
6. National Cancer Center Hospital East, Chiba
7. Asahi Hospital, Chiba
8. Chiba Cancer Center, Chiba
9. National Cancer Center Hospital, Tokyo
10. Showa University Hospital, Tokyo
11. Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo
12. Toranomon Hospital, Tokyo
13. Kanagawa Cancer Center, Kanagawa
14. Yokohama Municipal Citizen's Hospital, Kanagawa
15. Kitasato University East Hospital, Kanagawa
16. Yokohama City University Medical Center, Kanagawa
17. Ishikawa Prefectural Central Hospital, Ishikawa
18. Saku Central Hospital, Nagano
19. Shizuoka Cancer Center Hospital, Shizuoka
20. Aichi Cancer Center, Aichi
21. Aichi Cancer Center Aichi Hospital, Aichi
22. Kyoto University Graduate School of Medicine, Kyoto
23. Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka
24. Osaka City General Hospital, Osaka
25. Kobe University Hospital, Hyogo
26. Hyogo Cancer Center, Hyogo
27. Shikoku Cancer Center, Ehime
28. Kochi Health Sciences Center, Kochi
29. Sano Hospital, Hyogo
30. Hiroshima City Hospital, Hiroshima
SCSG (21 institutions)
1. Sendai Medical Center
2. Miyagi Cancer Center
3. Tokyo Metropolitan Bokutoh Hospital
4. Niigata Cancer Center Hospital
5. Tsubame Rosai Hospital
6. Toyama Prefectural Central Hospital
7. Gifu Municipal Hospital
8. Shizuoka General Hospital
9. Kyoto Medical Center
10. Japanese Red Cross Kyoto Daini Hospital
11. Osaka University
12. Kinki University
13. Osaka National Hospital
14. Osaka Medical College
15. Sakai Municipal Hospital
16. Hyogo College of Medicine, Hyogo
17. Itami City Hospital, Hyogo
18. Tenri Hospital, Nara
19. Wakayama Medical University
20. Hiroshima City Asa Hospital, Hiroshima
21. Oita University Hospital, Oita

Follow-up

All enrolled patients are followed for at least 5 years. Follow-up includes serum tumor markers (CEA and CA19-9), upper GI endoscopy, chest X-ray (or CT) and abdominal CT at least every 6 months for the first 3 years, and then annually.

Central Pathology Review

To reduce the institutional variation in pathological diagnosis, central pathology review of all resected specimens by ESD will be performed. Prior to initiation of this study, pathologists from participating institutions attended the investigators' meeting to share the consensus in pathological assessment for the ESD specimens.

Study Design and Statistical Methods

This trial is designed as a confirmatory trial to determine the efficacy and safety of ESD for cT1a undifferentiated-type early gastric cancer in terms of 5-year OS. Primary analysis will be carried out for the patients with undifferentiated dominant-type diagnosed in ESD specimen (Fig. 2). The sample size for undifferentiated type is planned to be 193 (anticipated total number of registered patients, 276) with 5 years of follow-up and an accrual period of 4 years. This sample size provided 70% power under the hypothesis of primary endpoint as the expected value of 93.2% and threshold value of 88.2% using one-sided testing at 5% significance level. However, because the accrual rate was higher than expected, the sample size was re-evaluated. By the protocol revision, the final sample size based on registered patients was 325 (259 with undifferentiated type), provided 80% power under the hypothesis of primary endpoint as the expected value 94.7% and threshold value of 89.7% using one-sided alpha of 0.025. To test the hypothesis, 5-year OS estimated by the Kaplan–Meier method and its confidence interval based on Greenwood's formula are used.

Interim Analysis and Monitoring

Interim analysis is not planned. If the number of cases with treatment-related death, severe (grade 3 or 4) bleeding or

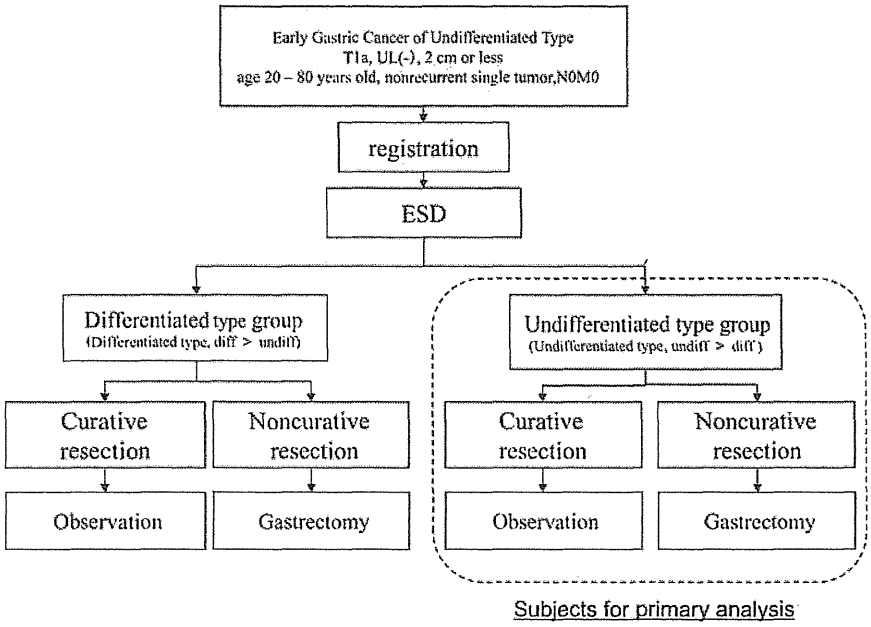

Figure 2. Study schema.

severe (grade 3 or 4) perforation reaches 2, 8 or 19, respectively, the registration will be suspended unless the JCOG Data and Safety Monitoring Committee approves continuation of the trial. The JCOG Data Center is responsible for data management, central monitoring and statistical analysis. JCOG Data Center also provides semi-annual monitoring reports, submitted to and reviewed by the JCOG Data and Safety Monitoring Committee. None of the physicians performing the interventions will be involved in the data analysis. For quality assurance, site-visit audits, not for a specific study basis but for the study group basis, will be performed by the JCOG Audit Committee.

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Conflict of interest statement

None declared.

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Review

Surveillance after endoscopic mucosal resection or endoscopic submucosal dissection for esophageal squamous cell carcinoma

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The objectives of surveillance after endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) for esophageal squamous cell carcinoma are: (i) early detection and treatment of recurrence; and (ii) early detection and treatment of metachronous esophageal squamous cell carcinoma and second primary cancers. Protocols for follow up after EMR or ESD for esophageal squamous cell carcinoma should be based on the risks of lymph node metastasis and distant metastasis as assessed on the basis of tumor staging at initial treatment. Early detection of recurrence or metachronous carcinomas often allows curative or less invasive treatment. Particular attention should be paid to the development of metachronous esophageal squamous cell carcinomas and second primary cancers (in particular, head and neck cancer and gastric cancer because of their high incidence).

Key words: endoscopic mucosal resection, endoscopic submucosal dissection, esophageal squamous cell carcinoma, Japan Esophageal Cohort Study (JEC Study), surveillance

INTRODUCTION

RECENTLY, THE INDICATION range of endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) for esophageal squamous cell carcinoma has been extended, thereby potentially increasing future risks of local recurrence, nodal recurrence, and distant recurrence.[1] Esophageal squamous cell carcinoma carries an appreciable risk of metachronous esophageal squamous cell carcinoma and second primary cancers such as head and neck cancer and gastric cancer. A previous study reported that a second primary cancer was the most common cause of death in patients who underwent surgery for esophageal cancer without lymph node metastasis.[2] Therefore, regular follow up of the head and neck, esophagus, and stomach by upper gastrointestinal endoscopy is essential.[3,4] Caution is also required for the development of tumors in the colorectum and other organs.[5] However, standardized protocols for follow up after EMR or ESD have yet to be established.

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LOCAL RECURRENCE AFTER EMR OR ESD

BECAUSE LOCAL RECURRENCE after EMR or ESD usually occurs within 1 year after initial treatment and may develop after 2 to 3 years, long-term follow up is required.[6,7] Lugol chromoendoscopy is mainly used to detect local recurrence. Follow-up examinations are usually carried out at 6-month intervals or at 3-month intervals for up to 6 months to 1 year after resection.[6–11] A trend towards a higher risk of local recurrence is associated with piecemeal resection, multiple Lugol-voiding lesions (LVL), and EMR as compared with ESD, necessitating stricter follow-up examination by upper gastrointestinal endoscopy.[6–9]