

FIGURE 3. Comparison of endoscopic images of the pyriform sinus mucosal lesion. (A) On conventional laryngoscopy, the irregular microvascular pattern and demarcation line of the mucosa are unclear. (B) Compared with conventional laryngoscopy, the irregular mucosal microvascular pattern and demarcation line of the mucosa are well visualized by narrowband imaging (NBI) laryngoscopy.

tified in 12 patients (41%). Given previous reports that the rate of developing synchronous and metachronous carcinomas in patients with carcinomas of the head and neck mucosal sites ranges from 8% to 19%,⁷⁻⁹ the present subjects should be considered a high-risk group, and the patients with multiple Lugol-voiding lesions were thus at risk of development of multiple cancers in the head and neck region.

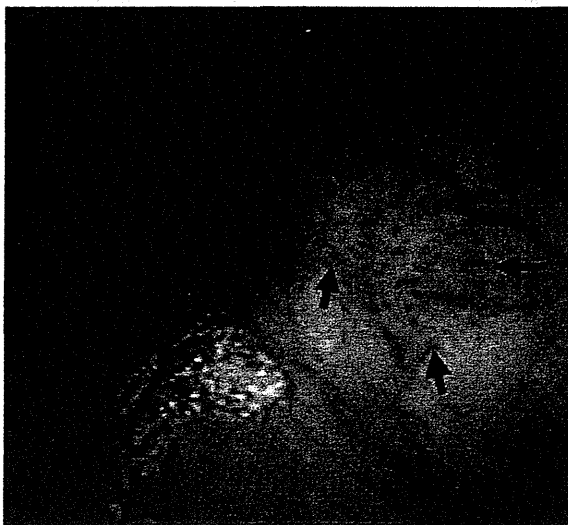


FIGURE 4. Squamous cell carcinoma in situ of the hypopharynx. A close-up view with narrowband imaging shows both a clearly irregular microvascular pattern and demarcation line of the mucosa.

The wide adoption of Lugol chromoendoscopy in the esophagus in high-risk populations, notably heavy drinkers and heavy smokers, has resulted in a dramatic increase in the detection of superficial cancers.¹⁰ Endoscopic mucosal resection is used as a minimally invasive treatment in these patients and yields better survival than surgery.¹¹ However, Lugol staining cannot be used in the head and neck region because of the unpleasant reactions it produces, including severe chest pain and even allergic shock and aspiration into the airway. The introduction of noninvasive NBI GI endoscopic screening has allowed the detection of SCC in situ in the oropharynx and hypopharynx,² greatly facilitating effective screening and surveillance in high-risk populations. Confirmation that the NBI laryngoscope system, which is equipped with a conventional laryngoscope system routinely used by otolaryngologists, is useful in detecting early cancer and should be of considerable benefit to patients.

Here, we showed that the NBI laryngoscope is significantly better than the conventional laryngoscope in detecting the irregular microvascular pattern and distinguishing the demarcation line of these cancers, in turn indicating the ability of this system to clinically recognize SCC in situ at oropharyngeal and hypopharyngeal mucosal sites. Its high detection rate and comparable examination time indicate that the NBI laryngoscope represents an alternative to the conventional laryngoscope. Median time to the completion of examination by conventional and NBI was

75 and 121 seconds, respectively, confirming the suitability of NBI for daily clinical practice.

Regarding the treatment of these lesions, endoscopic mucosal resection is indicated for superficial cancer in the oropharynx and hypopharynx detected by NBI laryngoscopy, as is it for superficial cancer in the esophagus, on the basis that carcinoma in situ and microinvasive cancer have no or a low risk of lymph node or organ metastasis. Nevertheless, long-term follow-up is required to determine whether endoscopic mucosal resection is suitable as a standard treatment for such lesions.

Introduction of the NBI system to routine otolaryngologist practice may drastically change diagnostic strategies for the early detection of carcinomas in head and neck lesions and may lead to minimally invasive treatment of head and neck lesions at an earlier stage than is presently possible. Although a surveillance standard has not been established, in consideration of the risk of multiple cancers, follow-up at 6 months to 1 year is considered necessary.

Of note, several of our cases which could not be detected with the NBI laryngoscope, because of the pooling of saliva on the mucosa of the oropharynx and hypopharynx and concealment within tissue folds like the pyriform sinus and the inferior resolution of the charge-coupled device of the endoscope, were detected by NBI GI endoscopy. Further improvements in charge-coupled device resolution and saliva removal, and the combined use of the NBI and rigid endoscope for the detection of hidden lesions, for example in the pyriform sinus, will overcome this disadvantage of the laryngoscope.

CONCLUSION

The NBI laryngoscope may play an important role in the diagnosis and treatment of superficial carcinoma in the oropharynx and hypopharynx.

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Review

Narrow-band imaging of the gastrointestinal tract

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Introduction

A narrow-band imaging (NBI) system is now commercially available worldwide from Olympus Medical Systems as an endoscopic diagnostic tool for the gastrointestinal (GI) tract. The most important strengths of the NBI system are enhancements in endoscopic visualization of superficial neoplastic lesions and the microvascular architecture.^{1–5} As endoscopic magnification maximizes the latter strength, NBI is expected to yield breakthroughs in endoscopic diagnosis. Angiogenesis is critical in the transition from the premalignant to the malignant phenotype, so detection and diagnosis based in part on morphologic changes to the microvessels are ideal. These advantages will potentially allow us to easily identify and accurately diagnose superficial neoplasms of the GI tract.

In contrast, conventional endoscopic diagnosis using white light is based on subtle morphological changes such as superficially elevated, flat, or depressed lesions and on minimal changes in color such as reddish discoloration. However, these findings are difficult to recognize, especially for inexperienced endoscopists, who require much skill training. As a result, the diagnosis may be inaccurate or a precancerous lesion or superficial cancer in the GI tract may be overlooked. From the point of view of the effective cancer screening, these disadvantages must be overcome.

When combined with magnifying endoscopy, NBI can clearly demarcate the margin between a nonneoplastic lesion and a cancerous lesion and can increase the con-

trast of morphological changes of the mucosal surface and microvessels. Inoue and colleagues^{6,7} and Yao and colleagues^{8,9} have already reported the importance of findings of microvascular irregularities in cancer of the esophagus and stomach, respectively. However, in images magnified while using white light, these changes have been difficult to identify. With NBI, these changes are easily recognized, thus renewing our awareness of the importance of microvascular irregularities in cancerous lesions.

Herein, we review publications on use of an NBI system in the GI tract.

Technical background of NBI

The NBI system was developed through collaboration between Japanese National Cancer Center Hospital East and Olympus Medical Systems (Tokyo, Japan) with support since 1999 by a Grant for Scientific Research Expenses for Health and Welfare Programs. Sano et al.¹⁰ first reported the clinical utility of NBI in the GI tract in 2001. After respective approval by the U.S. Food and Drug Administration and the Japanese Ministry of Health, Labour and Welfare, Olympus Medical Systems introduced the NBI system commercially in the United States, in December 2005, and Japan, in May 2006.

There are two types of videoendoscope system: a red-green-blue (RGB) sequential illumination type and a color chip type. An RGB sequential illumination system uses three broadband optical filters that cover all wavelengths of the visible spectrum, approximately from 400 to 800 nm (Fig. 1A). A color chip system uses a color charge-coupled device (CCD) chip with tiny color filters in each pixel (Fig. 2A). Both systems use a xenon lamp as the light source. The difference between these two systems is in how the color image is created. The NBI system uses an NBI filter to create two narrow-band

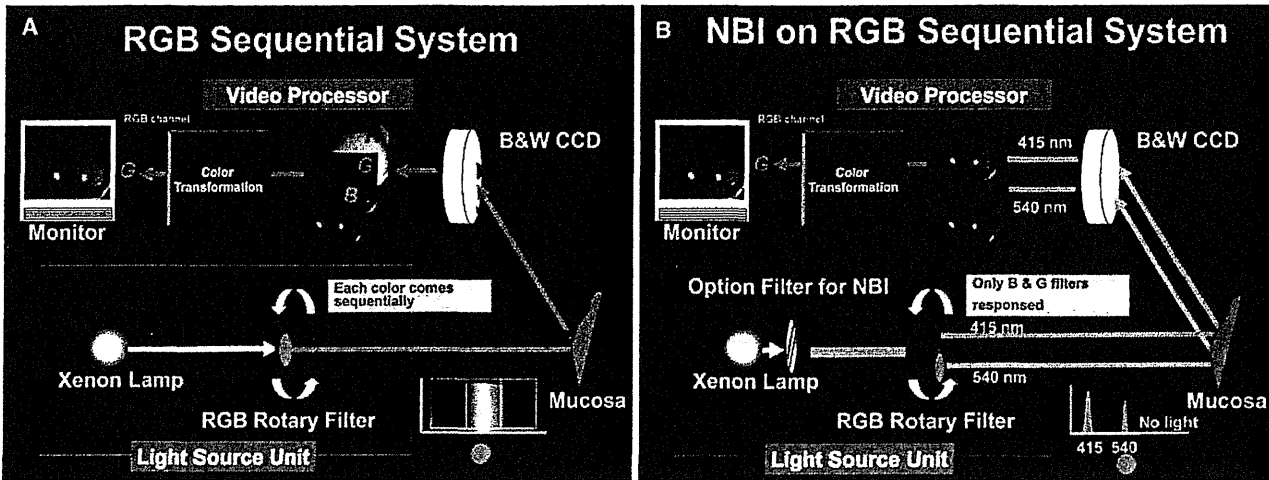


Fig. 1. **A** The red-green-blue (*RGB*) sequential illumination system. **B** A narrow-band imaging (*NBI*) system based on the *RGB* sequential illumination system. The *NBI* system uses two narrow-band illumination beams of 415 and 540 nm produced by an *NBI* filter

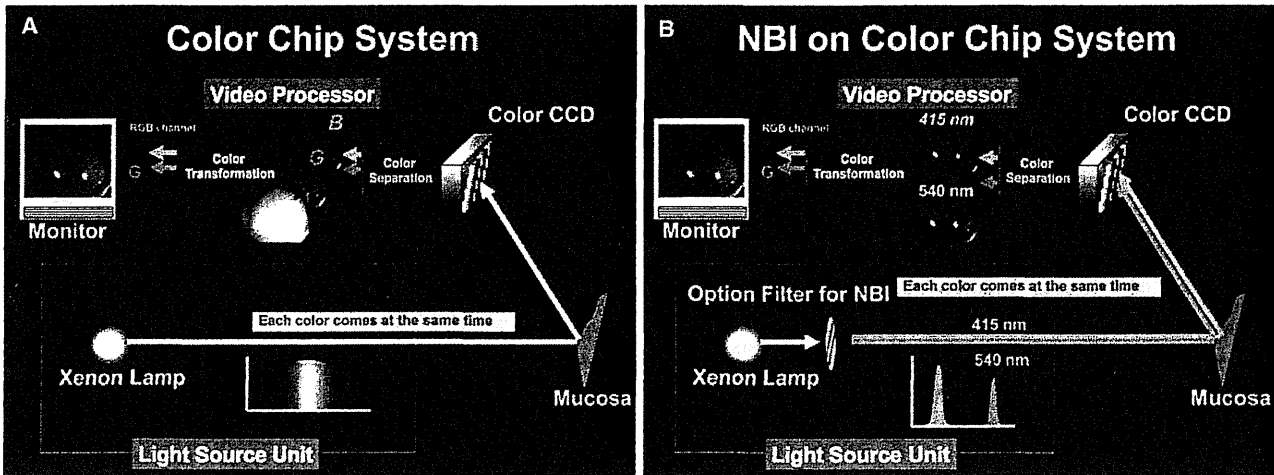


Fig. 2. **A** The color chip system uses a color charge-coupled device (*CCD*) chip. **B** The *NBI* system based on color chip system. The *NBI* system uses two narrow-band illumination beams of 415 and 540 nm produce by an *NBI* filter

illumination beams at 415 and 540 nm (Figs. 1B, 2B). Under *NBI* observation, the broadband white light derived from the xenon lamp is split into two bands (wavelengths, 415 and 540 nm), which illuminate the surface of the mucosa.

In *NBI* with the *RGB* sequential illumination system, the *NBI* filter is placed in the light path in front of an *RGB* rotary filter (Fig. 1B). In observations with the *NBI* filter, the illumination passes only the *B* and *G* filters to obtain images at 415 and 540 nm. For *NBI* observation with the color chip system (Fig. 2B), the *NBI* filter is placed in the light path, whereas this filter is not used for conventional white light observation. Two narrow-band images at 415 and 540 nm should be

produced when the *NBI* filter is used. However, to create a color image on a CRT or liquid crystal monitor, three images are needed to be output to its *R*, *B*, and *G* channels. Thus, the 415-nm beam is allocated to the *B* and *G* channels so that the blood vessels on the mucosal surface are reproduced with a brownish color, and the 540-nm beam is allocated to the *R* channel so that the vessels in the deeper layer are indicated by cyan.

Combination with magnifying endoscopy

NBI performance is maximized, increasing the accuracy of the diagnosis, when it is combined with magnifica-

tion. However, the capabilities of the RGB sequential illumination system and those of the color CCD system to utilize magnification differ. While the RGB sequential illumination system allows for optical magnification of the image by up to 80 times, the color CCD system has a digital zoom for $1.2 \times$ and $1.5 \times$ magnification. Thus, the diagnostic power of these two systems is likely to differ. In addition, NBI observation without magnification has a potential disadvantage because the image may be too dark to identify morphological and color changes.

Image-enhanced endoscopy

Recently, the American Gastroenterological Association proposed the term "image enhanced endoscopy" (IEE),¹¹ which encompasses various means of enhancing contrast during endoscopy, by using dye, optical, or electronic methods. IEE includes both dye-based and equipment-based methods, and the NBI system is classified as optical equipment-based IEE.

Squamous cell carcinoma (oropharynx, hypopharynx, and esophagus)

Major histological types of esophageal cancer are squamous cell carcinoma (SCC) and adenocarcinoma. The former is mainly associated with alcohol and tobacco abuse, and the latter is associated with acid reflux. Lugol chromoendoscopy is the standard technique for detecting early SCC in the esophagus.¹² While normal epithelium is stained dark brown by the Lugol solution, a cancerous lesion remains unstained and is pink under white light observation.¹³ However, Lugol solution is irritating and causes unpleasant reactions such as chest pain and discomfort and sometimes allergic shock. In addition, Lugol dye solution cannot be applied to the oropharyngeal or hypopharyngeal mucosa because of aspiration risk. Therefore, early detection of SCC in this region is quite difficult, and most SCCs are diagnosed at an advanced stage, leading to a poor prognosis.

Morphological changes to an intrapapillary capillary loop (IPCL) have been recognized as a new target for diagnosis of SCC in the esophagus.^{6,7} However, evaluation of IPCLs under white light observation requires high levels of proficiency. Yoshida et al.¹⁴ compared the ability of experienced endoscopists and novices to identify and evaluate IPCLs by NBI and white light observation. Both experienced and novice assessors reported that image contrast was superior and identification and evaluation of IPCLs were easier with NBI than with white light observation. Furthermore, NBI with magni-

fication improved the diagnostic accuracy of depth of invasion based on IPCL findings, especially for inexperienced endoscopists. Clinically, it is very important to shorten the learning curve of the inexperienced endoscopist.

Muto et al.^{4,15} reported that NBI combined with magnifying endoscopy is very useful for identifying superficial SCC in the head and neck region. They also reported that visualization of cancerous lesions and abnormal microvessels is significantly improved by NBI compared with white light observation because of enhancement of microvascular architecture.^{3,4} This finding is clinically significant because no cases of superficial cancer in the oropharynx or hypopharynx were reported before the advent of NBI.

Early detection enables us to apply endoscopic mucosal resection (EMR) and endoscopic subepithelial dissection (ESD) methods in the head and neck region as well as in the GI tract.¹⁵ This benefits the patient greatly because organs and functions can be preserved by a less-invasive treatment, and it may even save the patient's life.

The usefulness of NBI has also been confirmed in the ear-nose-throat (ENT) field. Watanabe et al.^{16,17} reported that an NBI rhinolaryngoscope (ENF-V2, Olympus Medical Systems) with a light source (CLV-160B, Olympus Medical Systems) improved the diagnostic accuracy and negative predictive value of superficial lesions in the oropharynx and hypopharynx. According to the concept of "field cancerization," patients with head and neck cancer or esophageal SCC have a high risk of development of synchronous or metachronous SCC in these regions. Because NBI is expected to detect cancer at an earlier stage, it will contribute to the improved survival of patients with multiple SCCs.

Preliminary results of a Japanese multicenter prospective randomized controlled study comparing detection and diagnostic accuracy of superficial SCC in the head and neck region and the esophagus between NBI and conventional white light observation, conducted in a back-to-back fashion, showed a significantly higher detection rate and accuracy with NBI.¹⁸ This result suggests that NBI should be a standard examination in screening for cancer of the squamous epithelium.

Table 1 summarizes data for NBI for the esophagus and the head and neck region. All of the studies in the GI field were performed using an RGB sequential illumination endoscopy system. In contrast, endoscopy of the ENT field was conducted using the color CCD chip system. However, the results obtained using both systems demonstrated that NBI could detect early cancer both in the esophagus and in the head and neck region.

Table 1. NBI of lesions in the squamous epithelium of the head and neck region and the esophagus

Year	First author	Objective	NBI system	Endoscope	Magnification	NBI findings	Ref. no
2004	Muto	Diagnosis of superficial cancer in the oropharynx and hypopharynx	RGB sequential illumination system	Gastrointestinal endoscope	+	1. Well-demarcated brownish area; 2. microvascular proliferation pattern	15
2004	Yoshida	Diagnosis of superficial esophageal lesions	RGB sequential illumination system	Gastrointestinal endoscope	+	RGB band value of IPCL and background mucosa	14
2005	Muto	Diagnosis of superficial cancer in the oropharynx and hypopharynx	RGB sequential illumination system	Gastrointestinal endoscope	+	NBI improved identification of brownish area and microvascular irregularity	4
2006	Watanabe	Diagnosis of superficial cancer in the oropharynx and hypopharynx	Color CCD chip system	Rhinolaryngoscope	-	NBI laryngoscope can detect carcinoma in situ	16
2007	Lee	Grading of esophagitis	RGB sequential illumination system	Gastrointestinal endoscope	-	NBI improved intraobserver and interobserver consistency	21
2007	Sharma	Diagnosis of GERD	RGB sequential illumination system	Gastrointestinal endoscope	+	Increased number and dilation of IPCLs are the best predictors	20
2008	Watanabe	Diagnosis of superficial cancer in the oropharynx and hypopharynx	Color CCD chip system	Rhinolaryngoscope	-	NBI improved accuracy, sensitivity, and negative predictive value	17

NBI, narrow-band imaging; IPCL, intrapapillary capillary loop; GERD, gastroesophageal reflux disease; RGB, red-green-blue; CCD, charge-coupled device

Gastroesophageal reflux disease

Gastroesophageal reflux disease (GERD) is a common disorder causing heartburn in Western countries. Patients are endoscopically classified as having non-erosive reflux disease (NERD), erosive esophagitis, or Barrett's esophagus. Because more than 60% of patients with GERD show no signs of esophagitis, NERD is also described as endoscopy-negative reflux disease. In some ways, conventional endoscopy is a rather insensitive test for the diagnosis of GERD in patients with NERD. Kiesslich et al.¹⁹ reported that patients with NERD show a prominent vasculature pattern above the Z-line, although they found no significant difference between NERD patients and the control group. NBI is expected to overcome the limitations of conventional endoscopy and allow the visualization of superficial and small esophageal lesions in GERD patients that cannot be seen by conventional white light endoscopy.

Sharma et al.²⁰ conducted a feasibility study of NBI with a magnifying endoscope (GIF-Q240Z, Olympus Medical Systems) in patients with GERD. GERD symptoms were evaluated by two validated questionnaires. The features seen only by NBI were compared between GERD patients and controls. Patients with GERD had increased numbers, dilation, and tortuosity of IPCLs compared with controls. Multivariate analysis showed that increased numbers and dilation of IPCLs were the best predictors of a diagnosis of GERD. Therefore, they concluded that NBI endoscopy might improve the diagnosis of GERD, particularly in patients with NERD. The results of this pilot study indicate that NERD should be reevaluated by novel technologies in a prospective controlled trial.

Using high-resolution endoscopy (GIF-H260, Olympus Medical Systems), Lee et al.²¹ reported that NBI improved intraobserver and interobserver reproducibilities in grading esophagitis compared with conventional white light imaging. In this study, the Los Angeles classification was used for evaluation of esophagitis. The Los Angeles classification was originally established to improve intraobserver and interobserver agreement. However, evaluation of mucosal breaks depends on the observer's experience in performing upper endoscopy and thus often results in poor to fair agreement. NBI is useful for overcoming these difficulties in grading esophagitis.

Interobserver and intraobserver consistency are important for standardization of accurate diagnoses. In the Kansas study,²⁰ intraobserver agreement was modest, while interobserver agreement was very good, perhaps because of the limited number of investigators (only two) and the time required to learn to recognize novel IPCL findings in GERD. Thus, the problem of interobserver and intraobserver variability might be solved

by shortening the learning curve with the use of magnifying endoscopy.

Barrett's esophagus

Barrett's esophagus is defined as the presence of columnar epithelium in the distal esophagus with histological evidence of specialized intestinal metaplasia (SIM). The most important risk factor for development of Barrett's esophagus is chronic acid reflux disease, which stimulates the replacement of the distal esophageal squamous epithelium with SIM. Barrett's esophagus is a precursor of esophageal adenocarcinoma, and endoscopic surveillance has therefore been recommended to detect intraepithelial neoplasia or adenocarcinoma at an early stage such as mucosal cancer. Table 2 summarizes published data about Barrett's esophagus.

However, with conventional white light endoscopy it is difficult to identify dysplastic and early neoplastic changes in SIM. In Western countries, use of four-quadrant random biopsies is widely accepted, but they are prone to sampling error because it is a "blind approach." Improvement of visualization of Barrett's columnar epithelium and distinguishing metaplasia from dysplasia or neoplasia is expected to result in more accurate biopsies and more effective screening.

Hamamoto et al.²² were the first to report that NBI is able to provide better visualization of the esophago-gastric junction, net-like capillary vessels, and the columnar-lined esophagus than conventional white light endoscopy. Using high-resolution endoscopy, Kara et al.²³ conducted a prospective randomized crossover study comparing indigo carmine chromoendoscopy to NBI for the detection of high-grade dysplasia or early cancer in patients with Barrett's esophagus. Among 28 patients with known or suspected high-grade dysplasia or early cancer, 14 were histologically confirmed by targeted or random biopsies. The overall sensitivity for diagnosis of high-grade dysplasia and early cancer was comparable between indigo carmine chromoendoscopy (93%) and NBI (86%). Most lesions could be identified by high-resolution endoscopy alone (79%), suggesting that NBI might replace indigo carmine chromoendoscopy as an adjunct to high-resolution endoscopy.

NBI with magnifying endoscopy enables visualization of the details of the mucosal surface and capillary networks without using dyes. Characteristics of SIM observed by high-resolution endoscopy with NBI are a regular villous/gyrus-forming pattern and a regular vascular pattern.^{24,25} High-grade intraepithelial neoplasia is characterized by three abnormalities: an irregular/disrupted mucosal pattern, an irregular vascular pattern, and abnormal blood vessels. All high-grade intraepithe-

lial neoplasia have at least one abnormality, and 85% have two or more abnormalities.²⁴ These criteria are quite accurate for the diagnosis of SIM and high-grade intraepithelial neoplasia, respectively. Goda et al.²⁶ reported that the addition of a capillary pattern to fine mucosal patterns improved the diagnostic value of observations by magnifying endoscopy with NBI for detecting SIM and superficial adenocarcinoma. Kara et al.²⁴ also reported the importance of the vascular pattern for recognizing dysplastic and cancerous lesions in Barrett's esophagus.

Most studies evaluate the mucosal pattern and capillary pattern separately.²⁴⁻²⁶ Each type of data is very important for understanding the details of both subtle mucosal changes and irregular microvascular changes, in particular their clinical significance. However, these classifications are difficult to apply in routine clinical practice. To reduce interobserver variability, a simple classification system is important.

Anagnostopoulos et al.²⁷ reported the diagnostic power of using both mucosal and capillary patterns for detection of SIM and high-grade dysplasia. Sensitivity, specificity, and positive and negative predictive values for the combination of a regular microstructure pattern (tubular/villous/linear) and no microstructural pattern to detect SIM were 100%, 78.8%, 93.5%, and 100%, respectively, and those for the combination of an irregular microstructure pattern and the presence of a microvascular pattern for prediction of high-grade dysplasia were 90%, 100%, 99.2%, and 100% respectively.

Singh et al.²⁸ simplified the grading system for mucosal morphology patterns in relation to histology as follows: type A, round pits with regular microvasculature (columnar mucosa without intestinal mucosa); type B, villous/ridge pits with regular microvasculature (intestinal metaplasia); type C, absent pits with regular microvasculature (intestinal metaplasia); and type D, distorted pits with irregular microvasculature (high-grade dysplasia). The positive and negative predictive values were 100% and 97%, respectively, for type A (columnar mucosa without intestinal mucosa); 88% and 91%, respectively, for types B and C (intestinal metaplasia); and 81% and 99%, respectively, for type D (high-grade dysplasia). This classification showed reproducibility and repeatability both by endoscopists experienced in the use of NBI and those unfamiliar with NBI, suggesting a rapid learning curve. Therefore, NBI combined with high-resolution magnifying endoscopy allows both expert and nonexpert endoscopists to perform targeted biopsies for SIM and high-grade dysplasia with high success.

In contrast, Curvers et al.²⁹ reported that the addition of enhancement techniques, including indigo carmine chromoendoscopy, acetic acid chromoendoscopy, and NBI to white light imaging did not improve

Table 2. NBI for Barrett's esophagus

Year	First author	NBI system	Magnification	Study aim and evaluation	Results	Ref No
2004	Hamamoto	RGB sequential illumination system	+	Visualization of Barrett's esophagus	NBI > WLI	22
2005	Kara	RGB sequential illumination system	+	Detection of high-grade dysplasia and early cancer	Indigo carmine chromoendoscopy = NBI	23
2006	Sharma	RGB sequential illumination system	+	Ridge/villous pattern for diagnosis of intestinal metaplasia	Sensitivity (93.5%), specificity (86.7%), positive predictive value (94.7%)	25
2006	Kara	RGB sequential illumination system	+	Ridge/villous pattern for diagnosis of high-grade dysplasia Characterization and classification of mucosal morphology	Sensitivity (100%), specificity (98.7%), positive predictive value (95.3%) SIM: 80% = villous/gyrus-forming pattern with regular vascular pattern 20% = flat mucosa with normal-appearing long branching vessels High-grade intraepithelial neoplasia: irregular/disrupted mucosal pattern, irregular vascular pattern, abnormal vessels	24
2007	Anagnostopoulos	RGB sequential illumination system	+	Irregular microvascular/ microstructural pattern for the prediction of high-grade dysplasia	Sensitivity (90%), specificity (100%), negative predictive value (99.2%), negative predictive value (100%)	27
2007	Goda	RGB sequential illumination system	+	Comparison of mucosal pattern and capillary pattern	SIM: cerebriform fine mucosal pattern, ivy- or deoxyribonucleic acid-like capillary pattern mucosal pattern + capillary pattern improve the diagnostic accuracy of SIM	26
2008	Wolfsen	Color CCD chip system	-	Detection of high-grade dysplasia Grade of dysplasia Number of biopsy sample	NBI > WLI NBI > WLI NBI < WLI	30
2008	Curvers	RGB sequential illumination system	+	Interobserver agreement for the mucosal morphology (indigo carmine chromoendoscopy vs. acetic acid chromoendoscopy vs. NBI)	No difference	29
2008	Singh	RGB sequential illumination system	+	Identification of early neoplasia (indigo carmine chromoendoscopy vs. acetic acid chromoendoscopy vs. NBI) Type A (round pits with regular microvasculature) Type B (villous/ridge pits with regular microvasculature) Type C (absent pits with regular microvasculature) Type D (distorted pits with regular microvasculature)	No difference Positive predictive value (100%), negative predictive value (97%) Positive predictive value (88%), negative predictive value (91%) Positive predictive value (88%), negative predictive value (91%) Positive predictive value (81%), negative predictive value (99%)	28

SIM, specialized intestinal metaplasia; WLI, white light imaging

interobserver agreement with regard to neoplasia in Barrett's esophagus. Interpretation of their study has some limitations because they used a smaller number of the photos than other studies, and they used only the best still photos that they obtained, selected on the basis of image quality and similarity. These still photos were a set comprising indigo carmine chromoendoscopy, acetic acid chromoendoscopy, NBI, and white light imaging photos. During routine endoscopic observation, it is sometime difficult to obtain high-quality images because of, for example, excess dye, unevenly spread dye, or contact bleeding. As a result, it may be difficult to make a real-time or on-site endoscopic diagnosis. Therefore, their negative results might have been caused by selection bias. In other words, this study reveals the importance of image quality and comparability among images for accurate diagnosis and good interobserver agreement. In the near future, we should ascertain the actual and real-time yield of enhancement techniques for identifying neoplasia to improve the clinical practice.

All of these endoscopic studies of Barrett's esophagus except one used an RGB sequential illumination system, and most studies were carried out in Western countries. This may suggest that RGB sequential illumination system is superior to the color chip system when NBI and magnifying endoscopy are combined. Using a color chip system, Wolfsen et al.³⁰ compared

high-resolution NBI endoscopy with conventional resolution white light endoscopy. They showed an increased yield with the use of high-resolution NBI compared with the use of conventional resolution white light endoscopy, as well as a need for fewer biopsies.³⁰ In addition, high-resolution NBI detected higher grades of dysplasia in individual patients and detected dysplasia in more patients compared than conventional resolution endoscopy. These findings suggest that a difference in the videoendoscopy system may not be very important in terms of diagnostic power and that NBI is no longer the standard for detecting high-grade dysplasia and superficial cancer in Barrett's esophagus.

Stomach

In the stomach, NBI should be used during magnifying endoscopy observation. Because light intensity under the NBI filter is low, the nonmagnified image is darker than the white light image. Furthermore, if electronic enhancement is used to brighten the endoscopic image, the image becomes noisy. Thus, nonmagnifying endoscopy is insufficient to observe the wide space of the stomach. In inexperienced hands, the endoscopic diagnosis might be misleading and lesions might be overlooked. Table 3 summarizes the published data on

Table 3. NBI for gastric lesions

Year	Author	NBI system	Magnification	Evaluated lesions	NBI findings	Ref. No
2004	Nakayoshi	RGB sequential illumination system	+	Differentiated adenocarcinoma Undifferentiated adenocarcinoma	Fine network pattern Corkscrew pattern	34
2004	Sumiyama	RGB sequential illumination system	+	Gastric cancer	Irregular fine network capillary structure Border of lesion recognized by differences in capillary structure	35
2006	Tamai	RGB sequential illumination system	+	Depressed gastric adenoma	Regular ultrafine network pattern	36
2006	Uedo	RGB sequential illumination system	+	Gastric intestinal metaplasia	Light blue crest	31
2007	Yao	RGB sequential illumination system	+	Differentiated adenocarcinoma	Demarcation line Disappearance of regular subepithelial capillary network pattern Irregular microvascular pattern	33
2008	Bansal	RGB sequential illumination system	+	Normal epithelium/ mild-moderate gastritis <i>H. pylori</i> gastritis Intestinal metaplasia	Regular mucosal and capillary pattern Irregular mucosal pattern and decreased capillary density Ridge/villous mucosal pattern	32

gastric lesions. All studies but one were reported by Japanese researchers.

Identification of intestinal metaplasia by NBI

Helicobacter pylori-associated gastritis induces atrophic gastritis and intestinal metaplasia (IM) and is a risk factor for dysplasia and gastric cancer. Gastric IM is associated with a risk for the development of differentiated adenocarcinoma. However, conventional white light imaging has a high rate of interobserver variability and correlates poorly with histological findings. Uedo et al.³¹ first found that in magnifying NBI, the appearance of a light blue crest in the gastric mucosa is a highly accurate indicator of the presence of histological metaplasia. Bansal et al.³² also reported that the sensitivity and specificity of a ridge/villous pattern for the diagnosis of intestinal metaplasia are 80% and 100%, respectively.

Differential diagnosis of superficial gastric cancer

To date, there is no evidence that magnifying NBI is superior for the detection of an early gastric neoplasm compared with magnifying white light imaging. Conventionally, an endoscopic diagnosis of a superficial gastric neoplasm is made on the basis of mucosal surface structural and color changes. However, there is high interobserver variability in the identification of these changes, so accurate diagnosis of superficial gastric cancer is quite difficult, especially for nonexpert endoscopists.

Yao et al.³³ reported unique magnifying endoscopy findings in intestinal-type gastric cancer as follows: (1) presence of a demarcation line between the reddish lesion and the surrounding mucosa; (2) disappearance of the regular subepithelial capillary network (SECN); and (3) presence of an irregular microvascular pattern within the flat lesions. They prospectively studied the diagnostic accuracy of these magnifying endoscopy findings for differentiating between gastritis and flat, reddish gastric cancer. All of the gastric cancer lesions showed both the demarcation line and the disappearance of the regular SECN, whereas only 25.3% and 22.9% of gastritis lesions showed these findings. The sensitivity and negative predictive value of the demarcation line and the disappearance of the regular SECN for distinguishing flat gastric cancer were both 100%. The diagnostic accuracy of an irregular microvascular pattern was 98.7%. Therefore, magnifying endoscopy findings based on microsurface and microvascular architecture are quite useful for making a differential diagnosis between flat reddish gastric cancer and gastritis.

As a next step, we should investigate the reproducibility of the results and compare the yield of gastric

cancer between magnifying NBI and magnifying white light imaging in a randomized controlled study, because NBI is known to strongly enhance visualization of microsurface and microvascular architecture.

Nakayoshi et al.³⁴ classified the microvascular pattern of superficial gastric cancer in magnifying NBI images into three groups: A, fine network, B, corkscrew, and C, unclassified patterns. They also compared endoscopic patterns with histological findings. Among 109 cases of differentiated early gastric adenocarcinoma, microvascular patterns A, B, and C were observed in 66%, 3.7%, and 30.3% of cases, respectively. In contrast, among 56 cases of undifferentiated early gastric adenocarcinoma, pattern B was observed in 85.7% of cases, whereas patterns A and C were observed in 3.6% and 10.7%, respectively. Thus, the microvascular pattern in magnifying NBI images is useful for predicting the histologic type of superficial gastric cancer: differentiated adenocarcinomas display a fine network pattern, whereas undifferentiated adenocarcinomas display a corkscrew pattern in their microvascular structure.

Magnifying NBI is also useful for identifying the lateral extent of superficial gastric cancer.³⁵ This capability is very important for accurate assessment of the safety margin, to ensure complete resection by EMR or ESD.

Gastric adenoma

Most gastric adenomas are the protruded type. While depressed-type adenomas are rare, they are clinically important because they have higher malignant potential than protruded adenomas. However, detection of depressed-type adenomas has been difficult because endoscopic findings have not been clearly defined. Tamai et al.³⁶ reported that depressed-type adenomas display a regular ultrafine pattern, in which the network of microvessels is composed of small, regular circles. This pattern differs from the irregular fine network pattern of well-differentiated adenocarcinomas.

Duodenum

Ampullary tumor is a relatively rare neoplasm and is an indication for endoscopic or surgical resection. However, the selection of treatment remains controversial, because the differential diagnosis between adenoma and adenocarcinoma is difficult. Therefore, an accurate diagnosis is needed so that the appropriate management for the patient can be selected. Uchiyama et al.³⁷ reported that inflammatory changes result in oval-shaped villi, whereas all adenomas and adenocarcinomas display pinecone/leaf-shaped villi, or an irregular, nonstructured pattern. Similar to superficial cancer of

Table 4. Comparison of diagnostic performance for neoplastic and nonneoplastic lesions between conventional colonoscopy, chromoendoscopy, and NBI

Year	First author	Evaluation methods	n (lesions)	Endoscopy system	Magnification	Modality	Sensitivity	Specificity	Accuracy	Ref. No
2004	Machida	Real-time diagnosis	43	RGB sequential illumination system	+	Conventional WLI Chromoendoscopy NBI	85.3 100 100	44.4 75 75	79.1 93.4 93.4	5
2007	Su	Blinded review of recorded DVD	110	RGB sequential illumination system	-	Conventional WLI Chromoendoscopy NBI	82.9 95.7 95.7	80 87.5 87.5	72.7 92.1 92.1	44
2007	Chiu	Blinded review of selected images with best quality	180	RGB sequential illumination system	-	Conventional WLI Chromoendoscopy NBI	62.1-65.2 78.7-85.1 82.3-86.5 91.3-97.2 87.0-95.0	74.4-85.4 79.5-84.6 59-82.7 74.4-90.5 71.8-88.1	67.2-68.3 78.9-85.0 80.6-82.4 92.2-91.1 87.2-90.0	45

the esophagus, magnifying NBI can be used to predict the histological characteristics of an ampullary lesion. Abnormal vessels are seen only in adenocarcinomas and not in adenomas.

Colon

Most colorectal cancers (CRCs) arise from adenomas, according to the adenoma-carcinoma sequence concept.³⁸ Therefore, early detection and subsequent removal of adenomas are very important to reduce the incidence of CRC and the consequent mortality. However, it is sometimes difficult to distinguish neoplastic (adenoma with dysplasia and adenocarcinoma) from nonneoplastic polyps (e.g., hyperplastic polyps) by conventional white light imaging. Nonneoplastic lesions, which do not require removal, account for 10%–30% of removed polyps.³⁹ Furthermore, a systematic review of published data reported that 22%–28% of adenomas may be missed during colonoscopic screening.^{40–42} Chromoendoscopy using a dye such as indigo carmine (dye-based image enhanced endoscopy) increases the detection rate of small flat or depressed lesions, which have a higher malignant potential than protruding ones. Fu et al.⁴³ reported that magnifying chromoendoscopy is significantly better than chromoendoscopy alone or white light imaging alone for the diagnosis of neoplastic lesions. NBI has the potential to decrease the number of overlooked lesions and the number of lesions unnecessarily removed.

Distinguishing neoplastic from nonneoplastic lesions with conventional colonoscopy, chromoendoscopy, and NBI

Machida et al.⁵ first evaluated the clinical feasibility of the NBI system for colorectal lesions. In their pilot study, NBI with a magnifying endoscope achieved better visualization of the mucosal vascular network pattern than conventional white light imaging. They found that the diagnostic accuracy of NBI for neoplastic polyps was equivalent to that of chromoendoscopy. Furthermore, and of clinical relevance, their data were obtained by real-time image processing during colonoscopy, whereas most other studies used have used recorded images and, what is more, only selected excellent images. Su et al.⁴⁴ reported similar results with NBI but without the use of a magnifying endoscope. Chiu et al.⁴⁵ demonstrated that both low- and high-magnification NBI is capable of distinguishing neoplastic from nonneoplastic lesions, and that its diagnostic accuracy is better than that of conventional white light imaging and equivalent to that of chromoendoscopy (Table 4).

All three studies used an NBI endoscopy system based on RGB sequential illumination (CF-Q240ZI, Olympus Medical Systems) and showed that NBI could distinguish neoplastic from nonneoplastic colorectal lesions, indicating that NBI, with either magnifying or nonmagnifying endoscopy, has the potential to replace dye-based chromoendoscopy for this purpose.

NBI for detection of colorectal adenoma

Rex et al.⁴⁶ compared white light imaging and NBI in a prospective randomized controlled trial of colonoscopy withdrawal for colorectal adenoma detection. In their study, a single endoscopist used a high-definition but nonmagnifying colonoscope based on the color CCD system (Olympus 180 series, Olympus America, Center Valley, PA, USA). They found that NBI did not result in a high adenoma detection rate. Using same model of nonmagnifying colonoscope, Adler et al.⁴⁷ also reported negative results for adenoma detection by NBI compared with conventional white light imaging.

In colonoscopic screening, overlooking of the colon polyp is one of the major problems to be solved, because it can lead to the development of colon cancer within a few years after a complete colonoscopy. Rastogi et al.⁴⁸ demonstrated in their back-to-back study that a second NBI pass detected more adenomas than the first pass with white light colonoscopy. However, their study has several limitations. Patients were not randomized to either the conventional and NBI colonoscope, and 40% of the additional polyps could be detected by a second white light colonoscopy. Furthermore, the study was a pilot feasibility study so the results are not definitive.

In hereditary nonpolyposis colorectal cancer (HNPCC), colonic adenoma appears to show accelerated progression to carcinoma.⁴⁹ Thus, colonoscopic surveillance is very important to reduce the death rate.⁵⁰ In a back-to-back study, East et al.⁵¹ reported that a second pass with NBI of the proximal colon of HNPCC patients detected significantly more adenomas than the first pass with white light colonoscopy. In addition, the proportion of flat adenomas detected was higher in the NBI pass than in the white light pass. These results indicate that NBI can help reduce interval cancer rates.

In a recent prospective randomized controlled study in Japan, Inoue et al.⁵² detected significantly more adenomas and more diminutive (<5 mm) lesions with a pancolonic NBI system than with conventional white light imaging. They used an endoscope based on the RGB sequential illumination system, but it is not clear whether they used a magnifying endoscope.

Flat and depressed colorectal neoplasia are difficult to identify with conventional white light colonoscopy. Uraoka et al.⁵³ conducted a pilot single-center study and

reported that NBI improved the detection of flat and diminutive lesions over conventional white light imaging.

At present, NBI has been shown to be useful for detection of colonic adenoma only by studies using magnifying NBI and the RGB sequential illumination system (Table 5).

Identification of pit patterns and vascular patterns by NBI

Kudo et al.⁵⁴ proposed a pit pattern classification system using chromoendoscopy that has been widely accepted by experienced endoscopists. This classification system shows excellent sensitivity of more than 90% relative to histologic diagnosis. Interobserver and intraobserver variabilities are also low. Magnifying NBI can enhance the mucosal surface pit pattern without dye staining or spraying.⁵ East et al.⁵⁵ reported that pit patterns are not always identical between NBI and conventional chromoendoscopy, as assessed by two experienced endoscopists, one Japanese trained and the other European trained. They proposed that the classification system of Kudo et al.⁵⁴ should be modified and validated before it is used. In contrast, Hirata et al.⁵⁶ reported that determination of the pit pattern by NBI with magnification was nearly the same as that obtained by standard magnification with chromoendoscopy. However, their study was a retrospective analysis, and, furthermore, the image assessment method used is unclear.

With regard to the vascular pattern, Katagiri et al.⁵⁷ demonstrated that the capillary pattern detected by magnifying NBI can be used to assess the degree of atypia in early colorectal neoplasia. This pilot study was performed by a single endoscopist who was familiar with magnifying NBI. Hirata et al.⁵⁸ reported that microvascular features such as thickness and irregularity are associated with the histologic grade as well as with the depth of submucosal invasion. However, the image assessment method that they used is unclear.

Conclusions

NBI is a promising endoscopic technology that may improve detection and diagnostic accuracy for precancerous lesions and early cancer in the head and neck region, esophagus, stomach, duodenum, and colon. To date, many positive clinical data have been published. This brand-new technology enables us to detect early cancer or premalignant lesions in the GI tract, which will enable minimally invasive treatment or intensive surveillance of the patients.

However, most studies were conducted at a single institute and performed by a one or a few observers.

Table 5. Comparison of adenoma detection ability between conventional colonoscopy and NBI

Year	First author	Evaluation methods	n (patients)	Endoscopy system	Magnification	Modality	Results	P value	Ref. No
2007	Rex	Prospective RCT (WLI vs. NBI)	434	Color CCD chip system	-	WLI NBI	Percentage of patients with >1 adenoma (all sizes) 67% 65%	NS	46
2007	Adler	Prospective RCT (WLI vs. NBI)	401	Color CCD chip system	-	WLI NBI	Adenoma per patient, mean \pm SD 0.26 (0.66) 0.33 (0.73)	NS	47
2007	East	Back-to-back (WLI followed by NBI)	62	RGB sequential illumination system	+	WLI NBI	Percentage of patients with >1 adenoma (>5 mm) 27% 42%	0.004	51
2008	Inoue	Prospective RCT (WLI vs. NBI)	243	RGB sequential illumination system	+/-	WLI NBI	Percentage of patients with >1 adenoma (>5 mm) 17% 30%	0.011	52
2008	Rastogi	Back-to-back after polypectomy (WLI followed by NBI)	40	Color CCD chip system	-	WLI NBI	Number of detected adenomas 43 29 additional adenomas		48

RCT, randomized controlled trial

Then, we should confirm these data by a large-scale prospective randomized trial to standardize the diagnostic criteria.

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外科治療 Vol. 101 No. 5 (2009:11)

今日の食道癌診療

食道癌内視鏡診断の新しい動向

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食道癌内視鏡診断の新しい動向

At the dawn of a new endoscopic diagnosis for esophageal cancer

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食道癌の内視鏡診断学は、拡大内視鏡や NBI (narrow band imaging) の登場により新たな展開を迎えた。AFI (Autofluorescence Imaging) や ECS (Endocytoscopy), 共焦点内視鏡 (Confocal Endomicroscopy), EG (real time tissue elastography), OCT (optical coherence tomography) といった新しい診断技術も臨床応用されつつあり、これらを使いこなし高精度で低侵襲的な診断を目指すことが重要である。

はじめに

食道癌の最大の危険因子は飲酒・喫煙であり、なかでもアルデヒド脱水素酵素 2 型 (ALDH2: aldehyde dehydrogenase 2) の欠損者がハイリスクとされる¹⁾。ALDH2 欠損者は、エタノールの代謝産物であるアセトアルデヒドの蓄積により、顔面紅潮や動悸等の症状が出現するため、問診でも多くの場合予測可能である²⁾。

ALDH2 のホモ欠損者は、飲酒に適さないが、ヘテロ欠損者では、アセトアルデヒド耐性により飲酒ができるようになるため、食道癌のハイリスク群になると考えられている³⁾。また、食道癌は異時性多発癌に加え、頭頸部や胃、大腸の他臓器重複癌が多いことから⁴⁾⁵⁾、食道のみならず多角的なスクリーニングやサーベイランスが必要であ

ることは知っておくべきである。

I. 食道癌の内視鏡診断

1. 従来の内視鏡診断法

これまで、食道癌の内視鏡診断は白色光による観察が基本であったが、表在癌の内視鏡所見は乏しく、その発見は困難であった(図 1)。ヨード染色法は腫瘍部が不染を呈するため容易に診断できるが(図 2)、刺激が強く胸痛や違和感、時にはアレルギー反応をきたすため被検者への負担は大きい⁶⁾。また、強い刺激性により表層粘膜が脱落するため、上皮化を惹起し、その後の診断や治療の妨げになることもある。

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Key words: NBI/拡大内視鏡/AFI/ECS/共焦点内視鏡

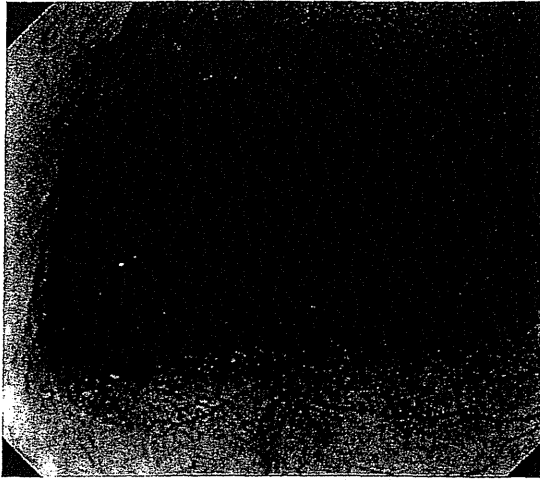


図1 食道表在癌 0-IIc 白色光
中部食道左壁を中心に半周に及ぶ発赤をした浅い陥凹性病変を認める。

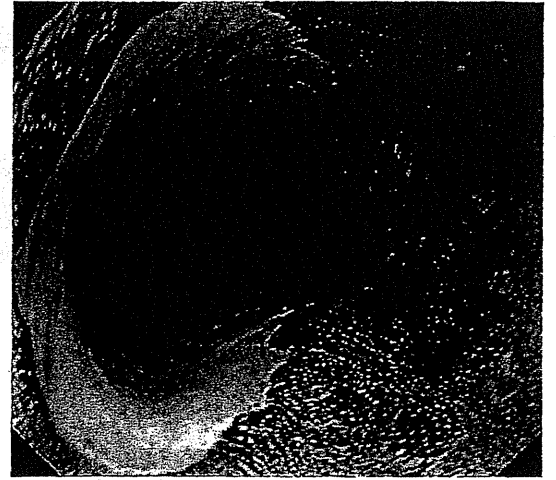


図2 食道表在癌 0-IIc ヨード染色
発赤陥凹性病変に一致してヨード不染像を呈する。

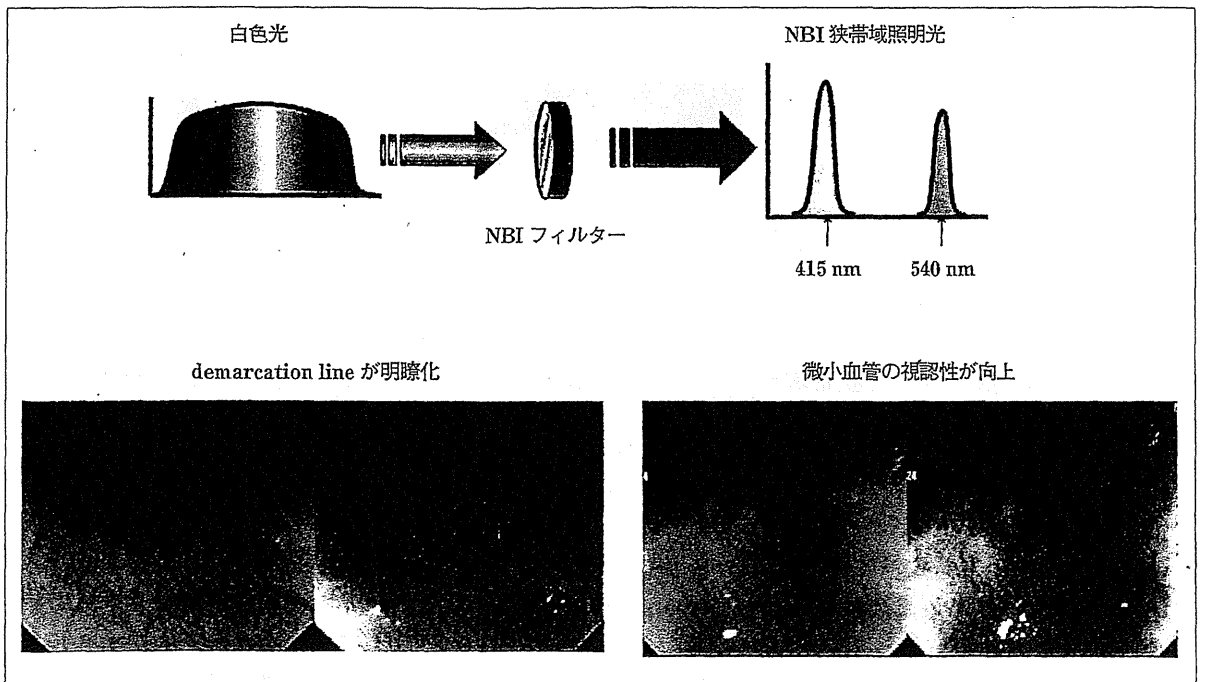


図3 NBIフィルター特性

2. 新しい内視鏡診断

1) 画像強調内視鏡

i) Narrow band imaging (NBI)

NBI は観察光の分光特性を利用して粘膜表層の微細血管構像の視認性を向上させる光学的画像強調機能である。光は、生体組織に照射されると、

一部は表面で反射され、残りの光は組織に吸収される。ヘモグロビンが415 nm と540 nm の波長を強く吸収することを利用し(図3)、NBI システムでは415 nm と540 nm を狭帯域照明光として採用している。キセノンランプと Red-Green-Blue (RGB) 回転フィルタとの間に NBI 用光学フ

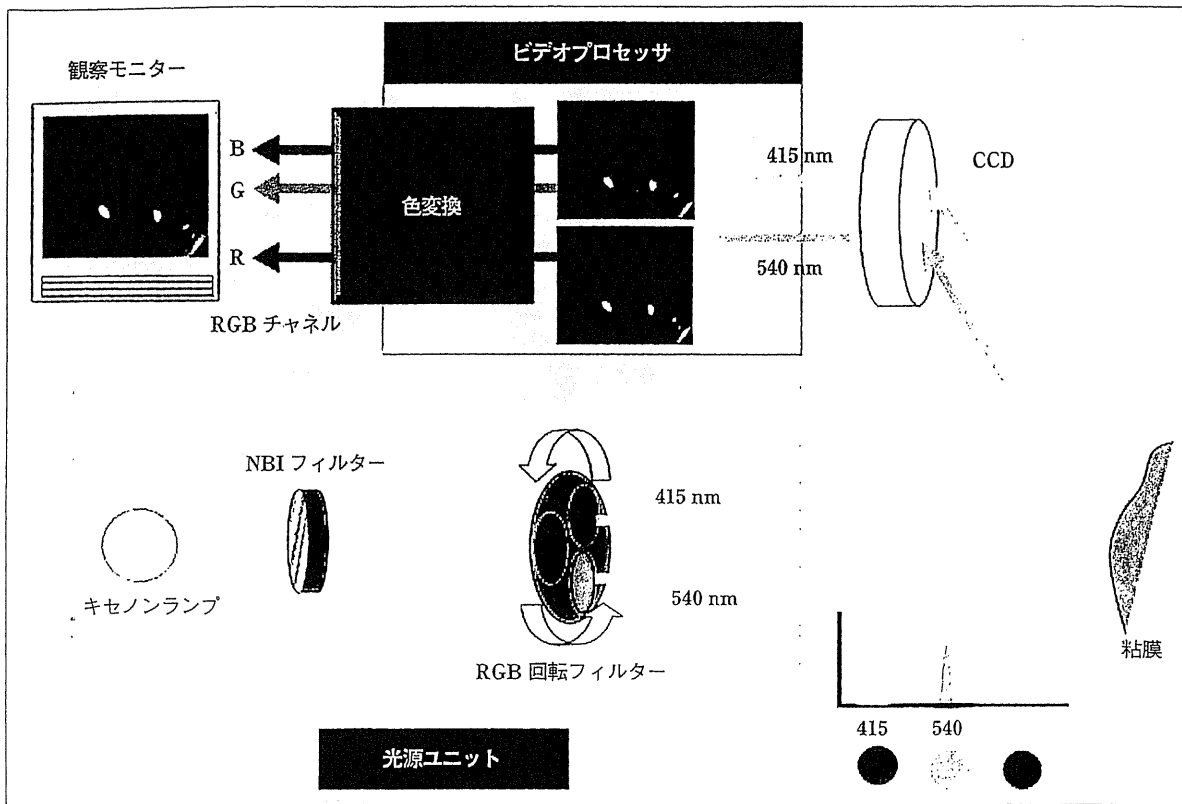


図4 NBIシステムの構成

フィルタを配置し、NBI 観察時にはフィルタが光路へと挿入されて狭帯域光となる。415 nm の波長域で得られた映像をモニタの B, G チャンネルに割り当てることで表層血管を茶色調に、540 nm の映像を R チャンネルに割り当てることで深層血管をシアン系の色調に再現している⁷⁾(図 4)。

NBI の最大の特徴は、臓器表面の微細血管構造の描出が優れている点である。NBI と後述する拡大内視鏡を併用すると、非腫瘍粘膜においても樹枝状血管網から垂直に立ち上がる上皮乳頭内ループ状血管 (IPCL : intraepithelial papillary capillary loop) を容易に視認できる⁸⁾。井上らは食道癌では IPCL が形態学的に変化することを明らかにしたが、これまでの白色光ではその視認性が困難であった。しかし、NBI の登場によってその視認性は飛躍的に向上し、その重要性が再認識されている。

NBI による食道表在癌の拾い上げ診断では、

領域性のある褐色病変 (well demarcated brownish area) (図 5) の検出が重要である。

ii) AFI : autofluorescence Imaging

物質に光 (励起光) が照射されると物質を構成する分子は励起状態となる。その後、基底状態に戻る際にエネルギーの一部を振動や熱に変換し、残りを “光” として放出する。この時に放出される光を蛍光と呼ぶ。蛍光物質を投与した場合の蛍光と区別して、励起光を照射した時に消化管壁そのものから発生する蛍光を自家蛍光と呼ぶ。消化管壁からの自家蛍光を捉え、画像化するのが AFI である (図 6)。

消化管壁には、さまざまな内因性蛍光物質が存在するが、主に粘膜下層に存在するコラーゲンが蛍光に関与すると報告されている⁹⁾。正常食道粘膜は明るい緑色調に描出され、腫瘍や炎症の存在する部位は、核の N/C 比の増大や腺管密度の増大が励起光や自家蛍光の反射・錯乱を促進するた

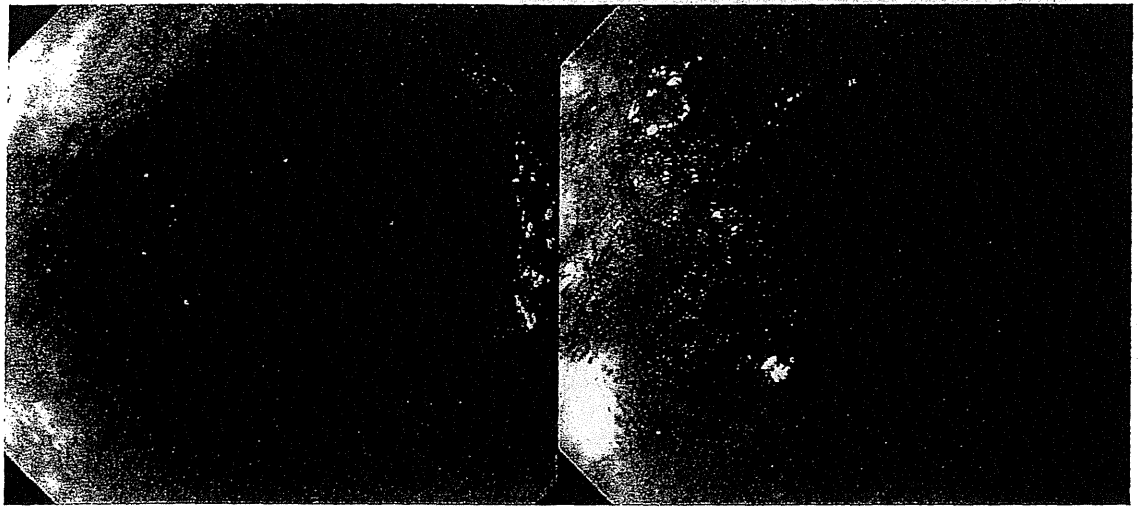


図5 食道表在癌 0-IIc NBI
境界明瞭な brownish area を認める。

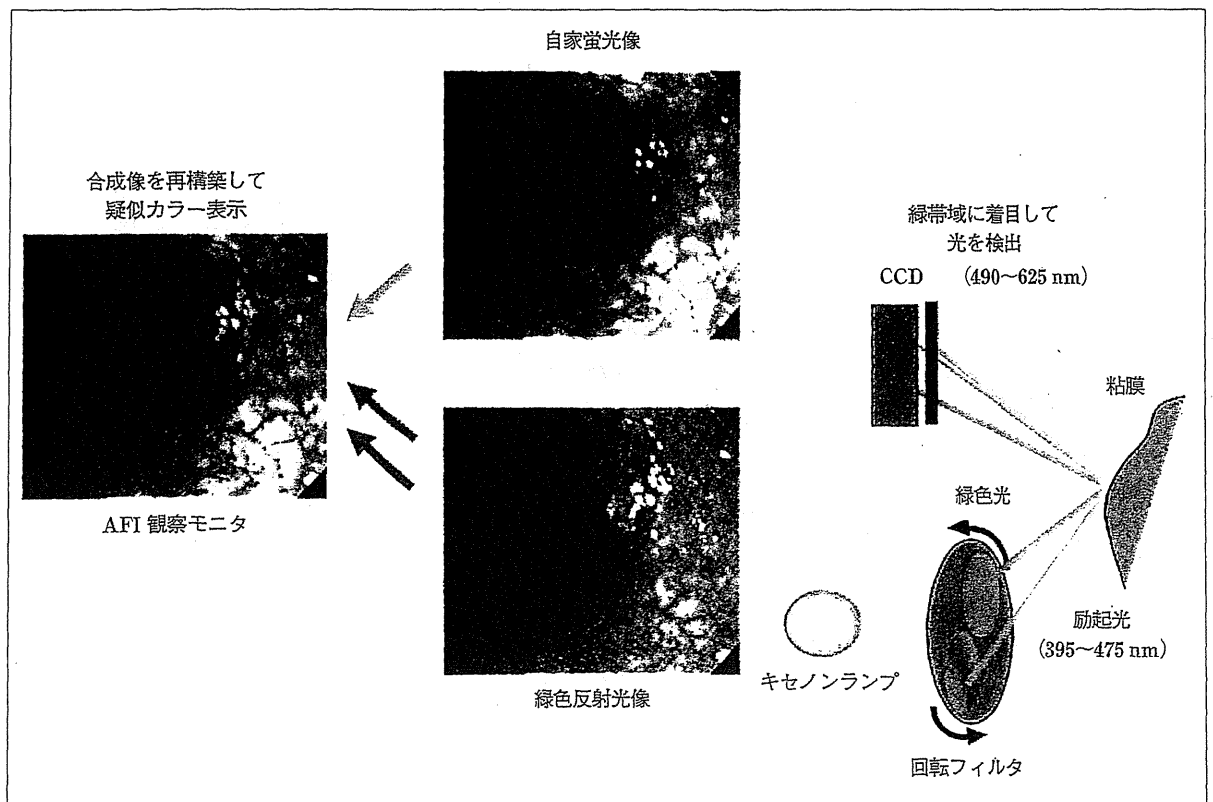


図6 AFIシステムの構成
(大阪府立成人病センター消化器内科 上堂文也先生より供与)

め、自家蛍光強度が低下してマゼンダ色調を呈すると考えられている(図7)。AFIはその色調の変化により表在性の腫瘍病変の拾い上げに優れて

いるが、偽陽性も多いのが課題である¹⁰⁾。