Risk factors		Score (select one each for A-E)	
ALDH2 genotype and alcohol drinking			
*ALDH2*1/*1*			
Never/rare	(<1 unit/w)	-12.94	A
Light	(1-8.9 units/w)	0.00	
Moderate	(9-17.9 units/w)	1.72	
Heavy	(18+ units/w)	2.34	
Ex-drinker		2.18	
*ALDH2*1/*2*			
Never/rare	(<1 unit/w)	-0.29	
Light	(1-8.9 units/w)	1.76	
Moderate	(9-17.9 units/w)	4.02	
Heavy	(18+ units/w)	4.49	
Ex-drinker		3.92	
*ALDH2*2/*2*			
Never/rare	(<1 unit/w)	0.37	
Light	(1-8.9 units/w)	0.00	
Drinks strong alcoholic beverages frequently			
	Yes	1.52	B
	No	0.00	
Smoked 30 pack-years or more			
	Yes	0.86	C
	No	0.00	
Eats green-yellow vegetable almost every day			
	Yes	0.00	D
	No	0.49	
Eats fruit almost every day			
	Yes	0.00	E
	No	0.54	

Total score = A + B + C + D + E

Predicted risk	Total score
Bottom 25%	≤1.02
25-49%	1.03-2.33
50-74%	2.34-3.60
75-89%	3.61-4.56
Top 10%	4.57+

Figure 1. HRA model for esophageal cancer that includes ALDH2 genotype. 1 unit = 22 g ethanol.

and prospective studies among Japanese alcoholics (19, 20) have consistently shown a markedly increased risk of EPSCC in drinkers possessing *ALDH2*1/*2*. Our previous case-control studies confirmed that alcohol drinking especially in individuals with inactive ALDH2, tobacco smoking, a preference for drinking concentrated alcoholic beverages straight, and less intake of green and yellow vegetables increased the risk of EPSCC in Japanese men (12, 16, 21). Based on the data we obtained in that study, simple health risk appraisal (HRA) models were developed to be able to quantitatively assess individual risk of developing EPSCC in the form of a risk score (22). A cross-validation study, which used a simulation-based approach to assess the performance of a statistical model, predicted that ~60% of the EPSCC in the entire population could be detected by examining only people with the top 10% risk scores of the HRA models (sensitivity ≈ 60% and specificity ≈ 90%; ref. 22). Furthermore, the detection rate of esophageal SCC in people with the top 10% risk score (positive predictive value) was expected to be >2%. If it is possible to achieve these performances levels in an actual mass screening, a very efficient approach to early detection of EPSCC in Japanese men will have been achieved.

The present study was a 7-year follow-up study of cancer-free men who were the controls in our previous case-control study and was conducted to confirm that the good performance of HRA models predicted by the cross-validation study was also achieved in an actual follow-up study, where the subjects were examined repeatedly by using a combination of upper aerodigestive tract endoscopy and esophageal iodine staining.

Materials and Methods

Study Population. We previously conducted a case-control study of 234 male cases with esophageal SCC and 634 male cancer-free controls and reported the results (12). The cancer-free controls were men who came to two Tokyo clinics for annual health checkups between September 2000 and December 2001, and most of them were ordinary residents or workers living in Tokyo or surrounding areas. The cancer-free controls who had been recruited in one of the two clinics and diagnosed as cancer-free by upper gastrointestinal endoscopy when they registered to participate in the previous study were sent annual letters of invitation to be screened by endoscopy. As of April 2007, 404 (81.3%) of the 497 eligible men ages 50 to 78 years had undergone a combination of follow-up endoscopic screening and esophageal iodine staining at least once, and they were enrolled in the present study. The Ethics Committee of the Kurihama Alcoholism Center reviewed and approved the proposal for this study, and each of the participants gave his informed consent.

Endoscopic Screening. Endoscopy was done with an Olympus Q240 or Q240Z panendoscope (Olympus Optical) by one of the authors (Y.K.), who is an expert in the field of upper gastrointestinal endoscopy. The endoscope was inserted into the pharynx, and it was carefully examined while removing secretions by

suction. After advancing the endoscope beyond the upper esophageal sphincter, the esophageal mucosa was flushed with 40 mL water through the biopsy port. Conventional endoscopic inspection was done from the esophagus down to the duodenum, and the esophagus was stained with then 10 mL of 1.5% iodine solution and inspected again. Mucosal biopsy specimens were collected from lesions that remain distinctly unstained by iodine, if their greatest diameter was ≥5 mm. At the end of the screening procedure, the esophageal mucosa was rinsed with 20 mL of 2.5% sodium thiosulfate solution, and the gastric contents were removed by suction.

Measurement of Risk Factors. At the time of baseline registration for the previous study, each participant was asked to fill out a simple questionnaire that asked the questions concerning alcohol flushing responses, drinking habits, smoking habits, and diet (12). Alcohol flushing is a surrogate marker of inactive ALDH2 and the sensitivity and specificity of the flushing questionnaire for identifying inactive ALDH2 in a Japanese male population were 90% and 88%, respectively (21). The PCR-RFLP method has been done on lymphocyte DNA samples to determine their ALDH2 genotype (refSNP ID: rs671) of all participants in the previous case-control study (12).

We calculated the HRA score to assess the risk of esophageal SCC in each subject at the time of registration based on alcohol drinking, either ALDH2 genotype (HRA-G model) or alcohol flushing (HRA-F model), smoking, and intake of vegetables and fruit according to the previously reported method (22). The subjects were classified into five risk categories according to their HRA scores: bottom 25%, 25% to 49%, 50% to 74%, 75% to 89%, and top 10%. The procedures used to make these calculations are summarized in Fig. 1 (HRA-G) and Fig. 2 (HRA-F). The HRA score was calculated as the sum of the scores (A-E), which were logarithms of the multivariate odds ratio of each factor estimated in the previous case-control study (12, 21). We further simplified the HRA-F model by converting the scores to small integers ("integer score" in Fig. 2), so that the categorization of the risk group was approximately the same as the categorization based on the original scores (22).

Statistical Analyses. The cancer detection rates during the follow-up period were calculated by the person-year method, with "person-year" defined as time from the baseline examination to either cancer detection or the most recent follow-up examination, whichever came first. The 95% confidence interval (95% CI) of the detection rate was estimated based on a Poisson distribution. The relationships between the HRA score at baseline and results of subsequent endoscopic screening are expressed as relative risk of cancer detection rate adjusted for decade of age by the Mantel-Haenszel method. All statistical analyses were done with the SAS statistical package (version 9.1; SAS Institute).

Results

The mean follow-up period was 4.4 years [median (25th and 75th percentiles), 5.0 (3.3, 5.6) years; range, 0.1- 6.7 years]. There were no significant differences between the distribution of the HRA scores of the subjects who underwent the follow-up screening and those who did not ($P > 0.4$, Fisher's exact test; data not shown). Follow-up endoscopy resulted in a diagnosis of primary esophageal SCC in 6 subjects, SCC in 5 (T_{is}), and SCC

Risk factors		Original score	*(Integer score)*	
Alcohol flushing and drinking				
Any flushing				
Never/rare	(<1 unit/w)	0.00	*(0)*	
Never flushing				
Light	(1-8.9 units/w)	0.24	*(1)*	
Moderate	(9-17.9 units/w)	2.31	*(5)*	
Heavy	(18+ units/w)	2.75	*(6)*	
Ex-drinker		3.31	*(7)*	
Current/former flushing				
Light	(1-8.9 units/w)	1.90	*(4)*	
Moderate	(9-17.9 units/w)	3.75	*(9)*	
Heavy	(18+ units/w)	4.29	*(10)*	A
Ex-drinker		3.61	*(8)*	
Drinks strong alcoholic beverages frequently				
	Yes	1.28	*(3)*	B
	No	0.00	*(0)*	
Smoked 30 pack-years or more				
	Yes	0.96	*(2)*	C
	No	0.00	*(0)*	
Eats green-yellow vegetable almost every day				
	Yes	0.00	*(0)*	D
	No	0.50	*(1)*	
Eats fruit almost every day				
	Yes	0.00	*(0)*	E
	No	0.45	*(1)*	

Total score = A + B + C + D + E

Predicted risk	Total score	
	Original	*Integer*
Bottom 25%	≤1.18	*0-2*
25-49%	1.19-2.78	*3-5*
50-74%	2.79-3.80	*6-8*
75-89%	3.81-4.70	*9-10*
Top 10%	4.71+	*11+*

Figure 2. HRA model for esophageal cancer that includes alcohol flushing.

Table 1. Detection rate and relative risk of cancer during the follow-up period according to risk category based on the HRA models

	No. cohort members	Person-years of follow-up	SCC of esophagus			SCC of esophagus/pharynx		
			n	Per 100 person-years (95% CI)	RR* (95% CI)	*n*	Per 100 person-years (95% CI)	RR* (95% CI)
HRA models								
HRA-G (n = 404)								
Risk category								
Lower 25%	104	483.8	0			0		
25-49%	96	430.3	0			0		
50-74%	118	519.5	0	0.06 (0.00-0.34)	1.0 (reference)	0	0.06 (0.00-0.34)	1.0 (reference)
75-89%	44	189.0	1			1		
Top 10%	42	160.0	5	3.13 (1.01-7.29)	67.8 (6.44-714)	7	4.38 (1.76-9.01)	95.1 (10.4-1,048)
HRA-F, original score (n = 393)								
Risk category								
Lower 25%	101	463.5	0			0		
25-49%	98	446.7	0			0		
50-74%	88	394.8	2	0.13 (0.02-0.46)	1.0 (reference)	2	0.13 (0.02-0.46)	1.0 (reference)
75-89%	61	253.9	0			0		
Top 10%	45	172.3	4	2.32 (0.63-5.94)	17.5 (3.12-98.3)	6	3.48 (1.28-7.58)	26.3 (5.15-134)

NOTE: HRA-G: ALDH2 activity was assessed by genotyping; HRA-F: ALDH2 activity was assessed based on the results of a questionnaire regarding alcohol-related flushing (see also Figs. 1 and 2).
*Relative risk of person-year detection rate adjusted for age by the Mantel-Haenszel method. All $P < 0.0001$ for comparisons between the top 10% and the bottom 90% categories.

plus basaloid carcinoma in 1 (T_1) and primary SCC of the hypopharynx (T_2) and oropharynx (T_2) in 1 subject each. At baseline, all 8 subjects who were diagnosed with EPSCC at follow-up were moderate/heavy drinkers (>200 g ethanol/wk) and heterozygotes for inactive ALDH2, and 7 of them reported current/former alcohol flushing. Seven of the subjects with EPSCC had smoked ≥30 pack-years, 5 did not eat green-yellow vegetables almost every day, and 7 did not eat fruit almost every day.

Table 1 shows the detection rate of cancer during the follow-up period according to risk category based on the HRA-G and HRA-F models. Five of the 6 esophageal SCC patients and 7 of the 8 EPSCC patients had been classified in the top 10% risk category based on the HRA-G model, and 4 of the esophageal SCC patients and 6 of the EPSCC patients had been classified in the top 10% risk category based on the HRA-F model. The detection rate of esophageal SCC per 100 person-years (95% CI) was 3.13 (1.01-7.29) and 2.32 (0.63-5.94) in the top 10% risk group based on HRA-G and HRA-F models, respectively, and that for EPSCC was 4.38 (1.76-9.01) and 3.48 (1.28-7.58), respectively. The age-adjusted relative risk in the top 10% risk group was much larger than in the bottom 90% risk group and the difference was highly significant ($P < 0.0001$) in both models. The results based on the HRA-F model obtained with integer scores were very similar to the results obtained with the original scores (data not shown).

Discussion

We invented HRA models that allow prediction of ~60% of patients with EPSCC while referring only the top 10% of risk category of Japanese high-risk men for endoscopic screening (22). The present study investigated whether the HRA models would perform well in terms of actual endoscopic screening for cancer during a 7-year follow-up of Japanese men. The results showed that 7 (88%) of the 8 EPSCCs developed in individuals ranked in the top 10% risk category according to the HRA-G model and 6 (75%) developed in individuals ranked in the top 10% risk category according to the HRA-F model, showing better performance in comparison with the proportions (= sensitivity) predicted by the cross-validation method (65.4% and 57.9%, respectively; ref. 22). It was noteworthy that the esophageal cancers detected were in the very early stage (T_{is} cancer in 5 and T_1 cancer in 1). An esophageal cancer detection rate by endoscopy in men ages ≥40 years was reported to be 0.39% in the Research Center for Cancer Prevention and Screening of the National Cancer Center (23), where esophageal iodine staining was applied when the mucosal surface did not appear normal. We estimated the esophageal cancer detection rates in the top 10% category according to the HRA-G model and HRA-F model to be 2.40% and 2.12%, respectively, based on the overall detection rate (0.39%) in the Research Center for Cancer Prevention and Screening (22), and those rates were in good agreement with the results of the present study (3.13 and 2.32, respectively, per 100 person-years). The high skill level of the endoscopists and the use of esophageal iodine staining probably contributed to the high rates of esophageal cancer detection in the Research Center for Cancer Prevention and Screening and the present study, because more than half of the cases of intraepithelial or mucosal SCC in the esophagus would have been missed without esophageal iodine staining (1, 7). The precise incidence of esophageal T_{is} SCC in the Japanese general population and its natural course are unknown, and they will be topics of future research.

Our follow-up study had several potential limitations. The intervals between the follow-up screening and the baseline screening that confirmed freedom from cancer

were short, and the very small number of cancer cases may have limited the assessment of the relationship between the HRA scores and actual rate of cancer development. Although the follow-up was incomplete (81.3%), there were no significant differential follow-up biases. The performance of HRA models could depend on the difference in distributions of risk factors between the background population of the present study and the target population to which the HRA models are applied (22). Further investigation of the relationship in a large, long-term prospective study in different populations with a high follow-up rate is clearly warranted.

Our HRA-F model enables many people to identify their own risk of EPSCC very easily, and public awareness campaigns using the HRA-F model will help persuade high-risk persons to undergo endoscopic screening and enable detection of EPSCC early or enable them to change their lifestyle to prevent ESCC. Although the number of cancers detected was small, the very good performance of the HRA models in this preliminary follow-up study provided evidence supporting the validity of the HRA risk scores for selecting individuals at high-risk of EPSCC and encouraged the use of these new models for screening in larger populations of Japanese men. Further study is needed to confirm the effectiveness of this approach in large Japanese populations.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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ORIGINAL ARTICLE

PROSPECTIVE STUDY OF EARLY DETECTION OF PHARYNGEAL SUPERFICIAL CARCINOMA WITH THE NARROWBAND IMAGING LARYNGOSCOPE

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Abstract: *Background.* The newly developed narrowband imaging (NBI) gastrointestinal endoscope makes possible the detection of superficial carcinoma in the oropharynx and hypopharynx, which is difficult with the conventional laryngoscope. Here, we investigated whether the combined use of laryngoscope with NBI allows the detection of superficial carcinoma in this region.

Methods. A total of 51 superficial, histologically confirmed lesions in 29 patients were studied. The quality of visualization of superficial carcinoma in the oropharynx and hypopharynx using the NBI-equipped laryngoscope was evaluated in comparison with the results by conventional laryngoscopy.

Results. The NBI laryngoscope provided better detection of the irregular microvascular pattern of carcinoma than the conventional laryngoscope ($p < .05$) and better visualization of the demarcation line ($p < .05$), and thus significantly better visualization of the lesions.

Conclusion. The NBI laryngoscope may play an important role in the diagnosis and treatment of superficial carcinoma in the oropharynx and hypopharynx. ©2008 Wiley Periodicals, Inc. *Head Neck* **31:** 189–194, 2009

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Keywords: head and neck cancer; laryngoscopy; pharynx; narrowband imaging; squamous cell carcinoma in situ

The detection of early-stage pharyngeal cancer remains a difficult clinical challenge, particularly cases occurring in the oropharynx and hypopharynx. This difficulty contrasts with the situation in the esophagus, where Lugol chromoendoscopy greatly facilitates early detection.[1] Lugol staining cannot be used in the head and neck region, however, owing to the severe mucosal irritation it causes, which produces pain and discomfort and can result in aspiration into the airway.

The recent introduction of noninvasive narrowband imaging (NBI) gastrointestinal (GI) endoscopy for the head and neck region has allowed the detection of squamous cell carcinoma (SCC) in situ in the oropharynx and hypopharynx.[2] In present practice, the otolaryngologist observes the oropharynx and hypopharynx with a transnasal laryngoscope, but a GI endoscope cannot be used for

Table 1. Instrument specifications.

Device	Laryngoscope	Gastrointestinal endoscope
Device name	VISERA ENF-V2 (Olympus Medical Systems, Tokyo, Japan)	EVIS LUSERA GIF TYPE H260Z (Olympus Medical Systems, Tokyo, Japan)
NBI imaging procedure	Synchronous	Sequential
Zoom function	–	+
Max magnification	35	80
Distal end outer diameter (mm)	3.2	10.8
Flexible tube outer diameter (mm)	3.4	10.5
Working length (mm)	300	1030
Angulation range	Up, 130 degrees; down, 130 degrees	Up, 210 degrees; down, 90 degrees Right, 100 degrees; left, 100 degrees

transnasal observation owing to its large size. In addition, the laryngoscope uses a conventional white light sourced from a xenon lamp.

We speculated that the combined use of a laryngoscope with the NBI system may assist otolaryngologists in the early detection of cancer. To our knowledge, however, the visibility of superficial carcinomas in the oropharynx and hypopharynx on conventional and NBI laryngoscopy has not been compared.

Here, we investigated whether the NBI-equipped laryngoscope provides better detection of superficial carcinoma in the oropharynx and hypopharynx than the conventional laryngoscope.

PATIENTS AND METHODS

Equipment. The NBI system used here is based on a modification of the spectral features of the NBI GI endoscope in which an optical color separation filter was used to narrow the bandwidth of spectral transmittance. The filter, placed in the optical system of the light source, eliminates all wavelengths except 2 narrow bands with central wavelengths of 415 and 540 nm, respectively. The image is reproduced in the processor using the information provided by these 2 bands. Using a set containing 415- and 540-nm filters, the microvasculature pattern is seen in brown, and the contrast between normal mucosa and malignant lesions is more clearly enhanced. These narrow-bandwidth filters make it possible to visualize malignant lesions, in particular those lesions with a developed microvasculature.

The system is equipped with an ENF-V2 laryngoscope (Olympus Medical Systems, Tokyo, Japan), light source (CLV-160B, Olympus Medical Systems, Tokyo, Japan), and video system center (CV-160B, Olympus Medical Systems, Tokyo, Japan). Specifications of the laryngoscope and GI endoscope are compared in Table 1.

Patients Characteristics and Evaluation Methods. Patients with superficial carcinoma in the oropharynx and hypopharynx originally detected with a GI endoscope were examined using a laryngoscope in conjunction with the NBI system. The definition of superficial carcinoma is provided in Table 2.

A total of 51 superficial lesions in 29 patients were observed between May 2006 and July 2007. All lesions were histologically confirmed SCC. Laryngoscopic evaluation was performed in the seated position. The patient drank a half-cup of water immediately prior to examination to remove saliva on the mucosa of the oro- and hypopharynx. The insertion tube was introduced through a nasal passage, with the examiner observing the live images on the color video monitor. Superficial lesions initially underwent laryngoscope observation using a conventional light source, followed by NBI examination of the same area.

Table 2. Definition of superficial carcinoma.

Characteristic	Description
Macroscopic appearance	Elevated (less than 5 mm) Flat Depressed (not ulcerous)
Histology	Squamous cell carcinoma High-grade intraepithelial dysplasia

Table 3. Patient and lesion characteristics.

Characteristic	Value
No. of patients	29
Age (range), y	62 (48–74)
Sex, men/women	27/2
Smoking habit	
Yes	28
No	1
Drinking habit	
Yes	28
No	1
Esophageal cancer	
Yes	24
No	5
mLVL	
Yes	27
No	2
No. of lesions	51
Primary site	
Hypopharynx	
Pyriform sinus	29
Posterior pharyngeal wall	5
Postcricoid area	3
Oropharynx	
Posterior pharyngeal wall	4
Soft palate	4
Base of tongue	2
Tonsil	1
Larynx	
Arytenoid	2
Aryepiglottic fold	1

Abbreviation: mLVL, multiple Lugol-voiding lesion.

Superficial SCCs show several typical endoscopic findings, specifically an irregular microvascular pattern and well-demarcated line between the normal epithelium and cancerous lesion.[3,4] Here, we found that the ability to visualize the lesion using the laryngoscope depended on these 2 features for both the conventional light source and NBI system, and all lesions studied were identified by an irregular microvascular pattern and demarcation line by GI endoscope.

All images were digitally recorded and evaluated for effectiveness in visualizing lesions by 2 experienced otolaryngologists (T.U. and T.H.), who assigned a scored grade to each image according to the quality of visualization of 1, poor; 2, good; and 3, excellent.[5] Scores were then statistically analyzed using the Mann–Whitney *U* test. Procedure times were measured according to the time indicated on the monitor screen of the videoendoscope. All statistical analyses were performed with the SPSS statistical software package (version 10.0; SPSS, Chicago, IL).

All patients gave written informed consent, and the study protocol was reviewed and approved by the ethics committee of our hospital.

RESULTS

Patient and lesion characteristics are shown in Table 3. Median age was 62 years (range, 48–74), with a men to women ratio of 27:2. A total of 51 superficial lesions were evaluated in 29 patients. The pyriform sinus was the most frequent primary site (37 of 51 lesions; 73%). Endoscopic images were obtained using both the conventional and NBI systems in all cases without difficulty. The color features of images obtained by the NBI system differed from those of the conventional video endoscope system, with the NBI system images appearing brownish. The results of evaluation based on quality of visualization with both the conventional and NBI systems are shown in Table 4. The irregular microvascular pattern was better visualized by NBI than the conventional laryngoscope ($p < .05$) (Figures 1 and 2). Further, the demarcation line of the mucosa was not shown clearly with the conventional laryngoscope, but was well visualized with the NBI laryngoscope ($p < .05$) (Figures 2 and 3). The NBI laryngoscope thus provided significantly better visualization of the lesions than the conventional laryngoscope.

Representative NBI pictures of SCC in situ at the pyriform sinus are shown in Figure 4. A close-up view shows scattered brownish dots, and the demarcation line of the mucosa is clearly depicted. Median observation time by conventional white light and NBI was 75 and 121 seconds, respectively, showing no statistically significant difference.

Endoscopic mucosal resection was performed for 49 lesions. No patient had severe complications related to the endoscopic mucosal resection procedure. Of the remaining 2 patients, 1 underwent peroral excision and the second total pharyngolaryngectomy and reconstruction with a jejunal free flap because the lesion was too large for removal by endoscopic mucosal resection. Finally, 41 lesions were diagnosed as carcinoma

Table 4. Visualization quality of conventional laryngoscopy and NBI laryngoscopy.

	Conventional	NBI
Irregular microvasculature pattern		
Poor	31	2
Good	6	0
Excellent	14	49
Demarcation line		
Poor	39	11
Good	7	8
Excellent	5	32

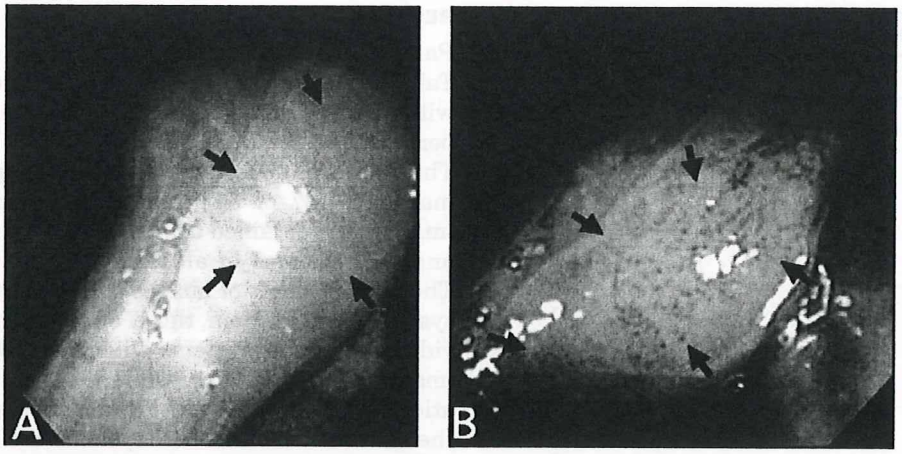

FIGURE 1. Comparison of endoscopic images of a pyriform sinus mucosal lesion. **(A)** On conventional laryngoscopy, the irregular microvascular pattern is unclear. **(B)** The irregular mucosal microvascular pattern is well visualized by narrowband imaging (NBI) laryngoscopy.

in situ and the remaining 10 as microinvasive cancer.

DISCUSSION

Here, we show that the NBI laryngoscope provides better detection of SCC in situ in the oropharynx and hypopharynx than the conventional laryngoscope. These results indicate an important role for the NBI laryngoscope in the diagnosis and treatment of superficial cancer in this region.

The development of synchronous and metachronous SCC at head and neck mucosal sites in patients with cancer of the head and neck is well recognized as the field cancerization phenomenon,[6] and multiple development of cancer in this region is closely associated with decreased patient survival.[7] Although these patients should therefore undergo intensive screening and surveillance, no effective screening or follow-up modalities have to date been developed. Muto et al[1] reported that multiple occurrence of Lugol-voiding lesions was closely associated with the field cancerization phenomenon. In this study, 27 patients (93%) had multiple Lugol-voiding lesions in the background esophageal mucosa. In addition, multifocal superficial lesions at oropharyngeal and hypopharyngeal mucosal sites were iden-

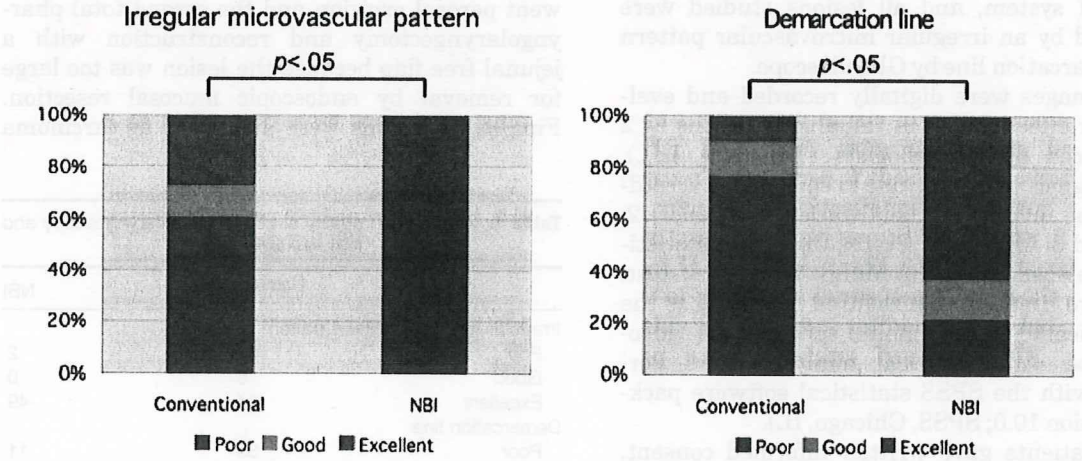

FIGURE 2. Comparison of visualization scores by conventional and NBI laryngoscopy. Both the irregular microvascular pattern and demarcation line are better visualized by NBI than conventional laryngoscopy.

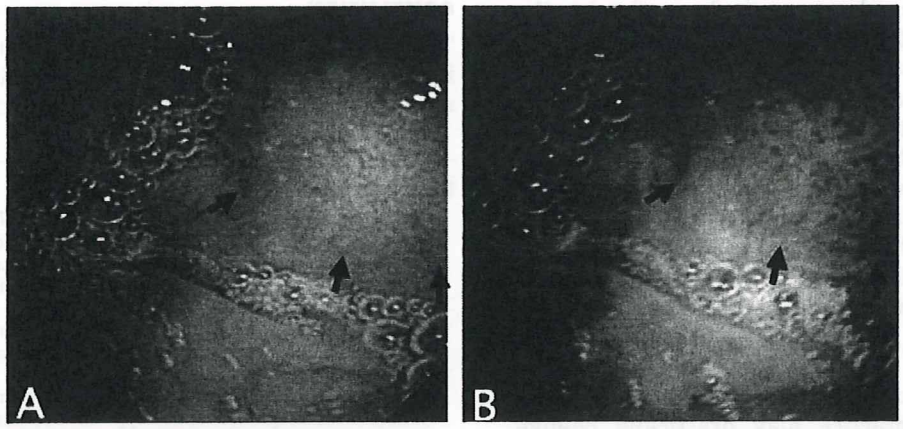

FIGURE 3. Comparison of endoscopic images of the pyriform sinus mucosal lesion. (**A**) On conventional laryngoscopy, the irregular microvascular pattern and demarcation line of the mucosa are unclear. (**B**) Compared with conventional laryngoscopy, the irregular mucosal microvascular pattern and demarcation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

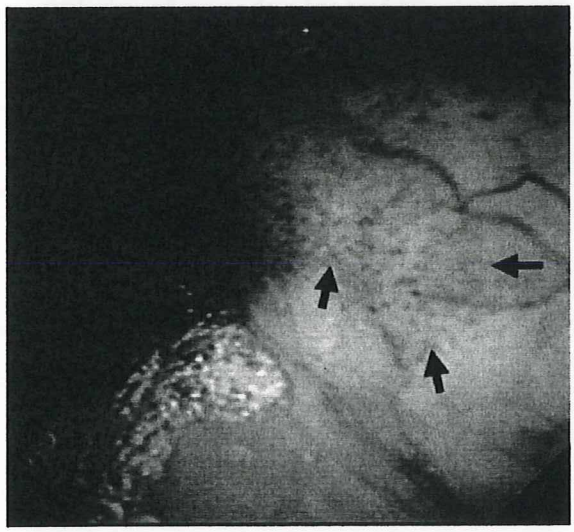

FIGURE 4. Squamous cell carcinoma in situ of the hypopharynx. A close-up view with narrowband imaging shows both a clearly irregular microvascular pattern and demarcation line of the mucosa.

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 microvasculature 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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Key words: narrow-band imaging, GI tract, early detection, diagnosis

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 contrast 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

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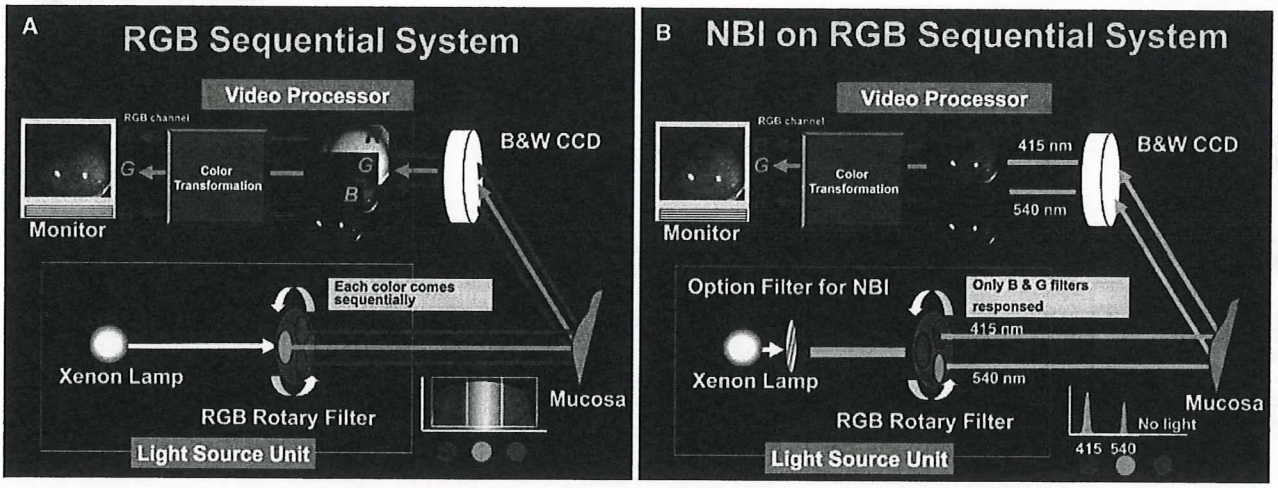

Fig. 1. **A** The red-green-blue (*RGB*) sequential illumination system. **B** A narrow-band imaging (*NBI*) system based on the RGB sequential illumination system. The NBI system uses two narrow-band illumination beams of 415 and 540 nm produced by an NBI filter

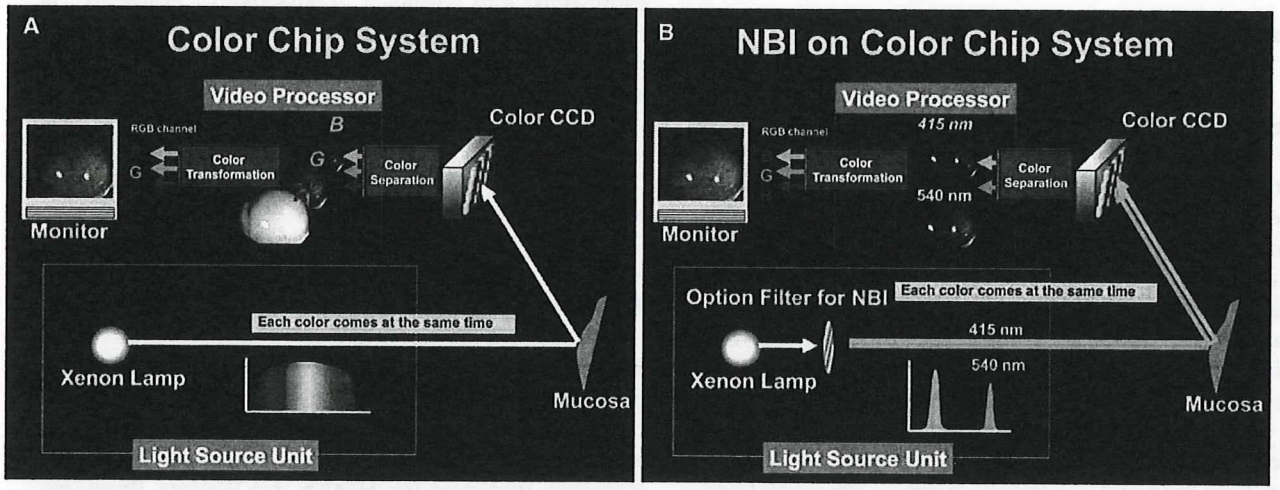

Fig. 2. **A** The color chip system uses a color charge-coupled device (*CCD*) chip. **B** The NBI system based on color chip system. The NBI system uses two narrow-band illumination beams of 415 and 540 nm produce by an NBI filter

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 × and 1.5 × 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 magnification 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 esophagogastric 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 intraepithelial 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
				Ridge/villous pattern for diagnosis of high-grade dysplasia	Sensitivity (100%), specificity (98.7%), positive predictive value (95.3%)	
2006	Kara	RGB sequential illumination system	+	Characterization and classification of mucosal morphology	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	NBI > WLI	30
				Grade of dysplasia	NBI > WLI	
				Number of biopsy sample	NBI < WLI	
2008	Curvers	RGB sequential illumination system	+	Interobserver agreement for the mucosal morphology (indigo carmine chromoendoscopy vs. acetic acid chromoendoscopy vs. NBI)	No difference	29
			+	Identification of early neoplasia (indigo carmine chromoendoscopy vs. acetic acid chromoendoscopy vs. NBI)	No difference	
2008	Singh	RGB sequential illumination system	+	Type A (round pits with regular microvasculature)	Positive predictive value (100%), negative predictive value (97%)	28
				Type B (villous/ridge pits with regular microvasculature)	Positive predictive value (88%), negative predictive value (91%)	
				Type C (absent pits with regular microvasculature)	Positive predictive value (88%), negative predictive value (91%)	
				Type D (distorted pits with regular microvasculature)	Positive predictive value (81%), negative predictive value (99%)	

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	Fine network pattern	34
				Undifferentiated adenocarcinoma	Corkscrew pattern	
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	Regular mucosal and capillary pattern	
				H. pylori gastritis	Irregular mucosal pattern and decreased capillary density	32
				Intestinal metaplasia	Ridge/villous mucosal pattern	

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	85.3	44.4	79.1	5
						Chromoendoscopy	100	75	93.4	
						NBI	100	75	93.4	
2007	Su	Blinded review of recorded DVD	110	RGB sequential illumination system	–	Conventional WLI	82.9	80	72.7	44
						Chromoendoscopy	95.7	87.5	92.1	
						NBI	95.7	87.5	92.1	
2007	Chiu	Blinded review of selected images with best quality	180	RGB sequential illumination system	–	Conventional WLI	62.1–65.2	74.4–85.4	67.2–68.3	45
						Chromoendoscopy	78.7–85.1	79.5–84.6	78.9–85.0	
						NBI	82.3–86.5	59–82.7	80.6–82.4	
					+	Chromoendoscopy	91.3–97.2	74.4–90.5	92.2–91.1	
						NBI	87.0–95.0	71.8–88.1	87.2–90.0	

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.