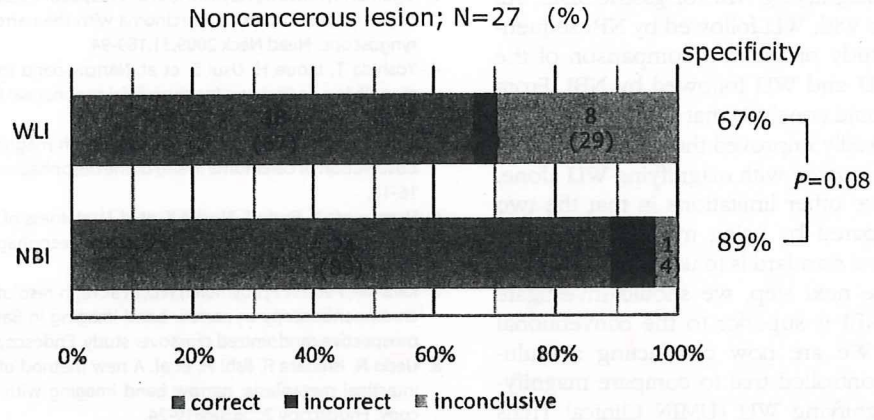

Figure 6. Diagnostic specificity of magnifying WLI and magnifying NBI. The numbers of lesions are shown. Values in parentheses are percentages of all the lesions.

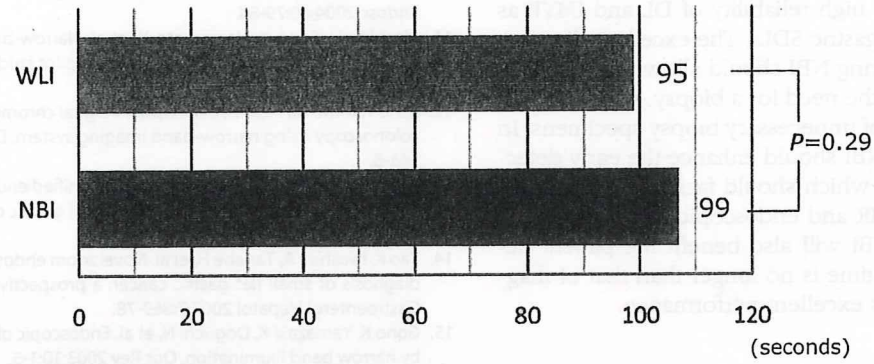

Figure 7. Time required for a diagnosis by magnifying WLI and magnifying NBI (secondary endpoint).

noncancerous lesions. Although the number of noncancerous lesions did not reach the statistically required number, we did not extend the enrollment period in this study because, judging from the rate of case collection, we considered that it would be difficult to achieve the required number of noncancerous lesions. The main reason was that we empirically excluded apparent benign lesions such as erosions and shallow ulcers from this study because this study targeted only SDLs that were suspected of being cancerous.

In this study, although the rate of misdiagnosis was lower with magnifying NBI than with magnifying WLI (14% [8/57] vs 25% [14/57]; $P = .15$), a considerable number of cases were misdiagnosed despite the clear visualization of magnifying NBI. Yao et al[14] reported that 25.3% of gastritis lesions were DL positive even by magnifying WLI. In this study, 41% and 42% of the noncancerous lesions were DL positive by magnifying WLI and magnifying NBI, respectively. Furthermore, in the stomach, the microvascular pattern shows many variations attributed to inflammatory changes. Therefore, it is sometimes difficult to judge the pattern of microvessels inside SDLs as cancerous IMVP or as an irregularity because of inflammatory changes. In this study, 17% of the cancerous lesions were negative for IMVP and 7% of the noncancerous lesions were positive for IMVP. This seems to be the main reason for misdiagnosis and thus may result in a limitation of DL- and IMVP-based diagnoses for gastric SDLs.

In this study, we performed magnifying WLI first and then magnifying NBI to compare their diagnostic accuracy. We chose this procedural order because we considered it unlikely that magnifying NBI would be conducted first followed by magnifying WLI in actual clinical practice. The possibility cannot be excluded that the results of the first examination influence those of the second examination when the comparative examinations are made in a fixed order. Therefore, the operators should be changed at each examination or each case should be randomized to either magnifying WLI or magnifying NBI. However, neither of these designs was adopted here because the former design seemed ethically equivocal for a real examination, and using the latter would make it technically difficult to identify and observe the target lesion by magnifying NBI alone. At least, this study was not a randomized comparison of

magnifying WLI and magnifying NBI for gastric SDLs. All lesions were examined with WLI followed by NBI sequentially, and then this study provided a comparison of the diagnostic yield of WLI and WLI followed by NBI. From this perspective, we could conclude that adding NBI to the WLI examination markedly improved the diagnostic accuracy of gastric SDLs compared with magnifying WLI alone.

This study may have other limitations in that the two modalities were compared by using magnifying endoscopy. The current global standard is to use nonmagnifying WLI. Therefore, as the next step, we should investigate whether magnifying NBI is superior to the conventional nonmagnifying WLI. We are now conducting a multicenter, randomized, controlled trial to compare magnifying NBI with nonmagnifying WLI (UMIN Clinical Trials Registry ID C000001072).

In summary, we demonstrated that adding NBI to the WLI examination is essential for making an accurate diagnosis of gastric SDLs compared with magnifying WLI alone and demonstrated the high reliability of DL and IMVP as diagnostic criteria for gastric SDLs. The excellent diagnostic capacity of magnifying NBI should allow the diagnosis of most SDLs without the need for a biopsy, which should decrease the number of unnecessary biopsy specimens. In addition, magnifying NBI should enhance the early detection of gastric cancer, which should facilitate endoscopic treatments such as EMR and endoscopic submucosal dissection. Magnifying NBI will also benefit the patient because its examination time is no longer than that of magnifying WLI despite its excellent performance.

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CASE REPORT

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Multiple early-stage malignant melanoma of the esophagus with long follow-up period after endoscopic treatment: report of a case

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Abstract Primary malignant melanoma of the esophagus (PMME) is a rare disease. Most patients are diagnosed at an advanced stage and few at an early stage. We report a patient with multiple early-stage PMME (tumor invasion was limited to the mucosa, and no lymph node metastasis was detected). Despite initial endoscopic treatment followed by systemic chemotherapy, frequent multiple metachronous lesions occurred. These lesions were all flat type, and disease control of the primary site was achieved only by repeated endoscopic treatment. Liver metastasis developed 7 years after the first diagnosis of this disease; however, the patient has been doing well with stable disease for 1 year after single transarterial chemoembolization.

Key words Primary malignant melanoma of the esophagus · Early stage · Endoscopic mucosal resection

Introduction

Primary malignant melanoma of the esophagus (PMME) accounts for 0.1%–0.2% of all malignant disease of the esophagus. Ninety-five percent of all melanomas are found in the derma, and only 0.5% are localized in the esophagus [1]. The prognosis of PMME is unfavorable because most patients are in the advanced stage at diagnosis and rapidly develop lymph node and distant metastases. Six cases of early-stage PMME have been reported in five papers [2–6]. Only one of these cases was treated curatively by endoscopic mucosal resection (EMR) [3]. We now report on a rare case of multiple early-stage PMME, which has been controlled for 8 years by the combination of systemic chemotherapy and repeated endoscopic treatment.

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Case report

A 75-year-old, previously healthy man underwent an esophagogastroduodenoscopy (EGD) for screening. Three black-pigmented flat lesions were detected in the middle and lower thoracic esophagus (Fig. 1), and biopsy specimens revealed features of malignant melanoma. The patient refused esophagectomy, and EMR was tried in August 2001. The resected specimen revealed that the tumor had invaded the lamina propria (Fig. 2) with no lymphatic or venous invasion and that the horizontal margin was positive. The patient again refused esophagectomy and was followed up closely in the outpatient clinic.

Five months after the first EMR, a recurrence was suspected near the EMR scar. The patient was referred to our hospital. As an alternative treatment to the esophagectomy, six courses of systemic chemotherapy comprising dacarbazine (100 mg/body on day 1, 200 mg/body on days 2–5), nimustine hydrochloride (100 mg/body on day 1), and vincristine (1 mg/body on day 1) were scheduled every 4 weeks. However, he was forced to discontinue the treatment after four courses of chemotherapy because of severe thrombocytopenia. He then underwent an EGD every 2 or 3 months, and small black-pigmented spots resembling lentigo were detected frequently (Fig. 3). A biopsy specimen revealed the typical histological pattern of melanoma, suggesting metachronous multiple lesions. Because no lymph nodes were involved and no distant metastasis developed, endoscopic treatment including EMR (six times for nine lesions) and tumor ablation using argon plasma coagulation (three times for seven lesions) or bipolar coagulation probe (four times for six lesions) were performed until June 2009. Pathological diagnosis of all EMR specimens was in situ or microinvasive PMME with no lymphatic or venous invasion. Tumor cells were positive for melan A and HMB45 immunohistochemically. A typical case of microinvasive PMME is shown in Fig. 4A,B. Three specimens of nine resected lesions by EMR showed clearly that the black-pigmented area was only part of the whole tumor, and the horizontal margin was positive. A typical

horizontal margin-positive case of PMME is shown in Fig. 5.

Seven years after the first diagnosis of PMME, multiple liver tumors (in S4, S6, and S8) were detected by screening abdominal computed tomography (CT) in December 2007 (Fig. 6A). To make a definite diagnosis, a liver needle biopsy was performed in April 2008. The needle biopsy specimens revealed the same histological pattern of PMME (Fig. 6B) and were positive for melan A and HMB45. Then, liver metastasis was confirmed. The primary lesion was well controlled, and no other distant metastasis was observed. Because the patient was too old to reintroduce systemic chemotherapy and the dynamic CT image suggested a hypervascular liver tumor, transarterial chemoembolization (TACE) was performed. After a single TACE session, the metastatic liver lesion was stable, and he was in good condition as of June 2009. The clinical course of this case is summarized in Fig. 7.

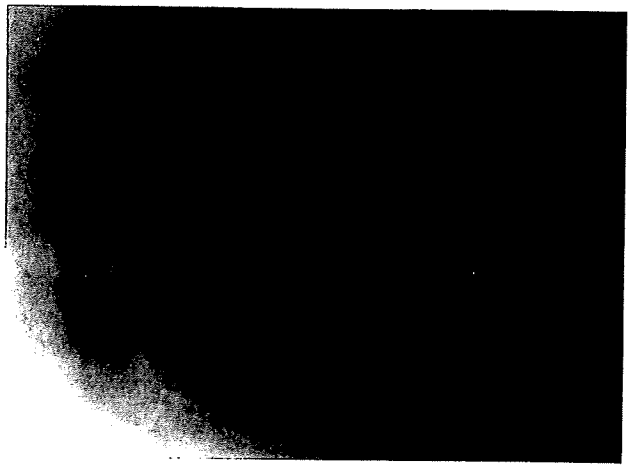


Fig. 1. Esophagogastroduodenoscopy showed a black pigmented flat lesion in the lower esophagus

Discussion

The following diagnostic histological criteria for PMMP have been suggested by Allen and Spitz [7]: (1) a typi histological pattern of melanoma and the presence of melanin granules within the tumor cells, (2) origin in an area of junctional change within the squamous epithelium, and (3) junctional activity with melanotic cells in the adjacent epithelium. Melanoma cells were positive immunohistochemically for melan A, HMB45, and S-100 protein. These stains are useful for diagnosing amelanotic melano-

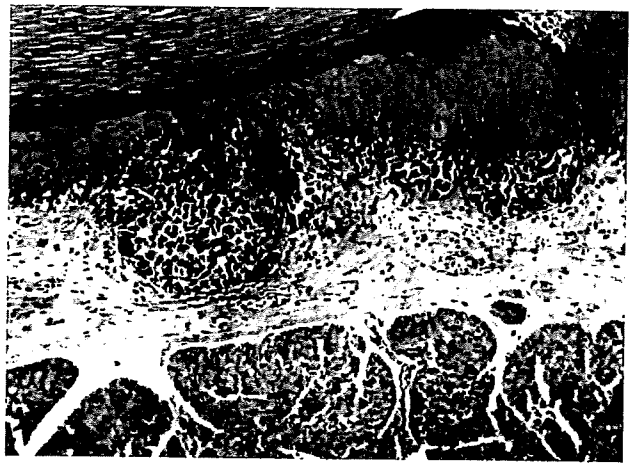


Fig. 2. A specimen of endoscopic mucosal resection revealed that the melanoma cells had invaded the lamina propria

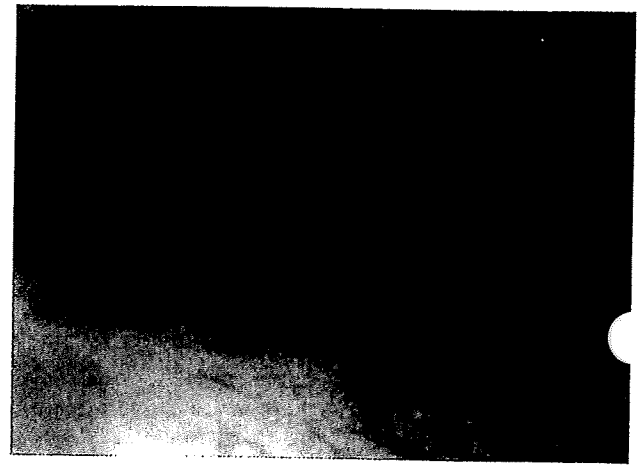
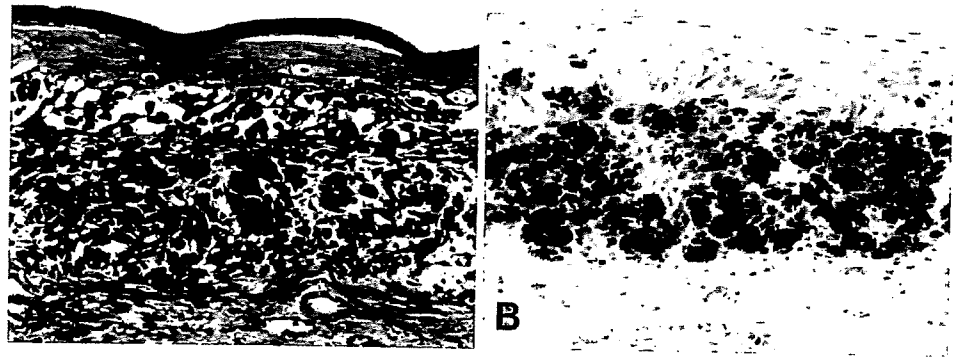


Fig. 3. Small black-pigmented spots resembling lentigo were detected frequently after the initial endoscopic treatment

Fig. 4. A specimen of endoscopic mucosal resection revealed the typical histology pattern of micro-invasive primary malignant melanoma of the esophagus (PMME) (**A**) and was positive for melan A (**B**), immunohistochemically. A chromogenic reaction was developed using alkaline phosphatase



mas in which the tumor cells show no evident melanin granules [8].

The prognosis of PMME is extremely poor because of its rapid metastatic spread via the lymphatic and blood vessels. Early death from widespread metastases is the usual clinical course. The average overall survival is only 10–13 months, and only one-third of all patients survive for longer than 1 year after diagnosis [1]. Surgical resection is considered the best method for treating PMME [9–12]. Smaller satellite nodules may present around the main tumor, and wider margins of resection are required for treating PMME than with other esophageal tumors. However, even if only the patients who have undergone radical esophageal resection are analyzed, the 5-year survival rate is less than 5% [13,14]. Therapeutic options such as radiotherapy, chemotherapy, and immunotherapy provide limited benefits, even when used in conjunction with surgery.

Endoscopically, PMME lesions appear as intraluminal, polypoid, and (usually, but not necessarily) pigmented, irregular masses, which might also be ulcerated. However, only one of six reported cases of early-stage PMME was the polypoid type [5], and the other five cases were all the flat type [2–4,6]. In contrast, no report is available about the flat-type submucosal invasive PMME. In our patients, many satellite lesions occurred in separate areas, and all lesions were the flat type. In almost 90% of patients, the lesions occur in the middle or distal one-third of the esophagus, usually as a solitary tumor, but multiple lesions have been reported in 12% of patients [13,15]. To our knowledge, ours is the first report of multiple early-stage PMME.

Especially in cases of the flat-type PMME, it is difficult to accurately define the tumor area macroscopically. Because the melanoma cells originated from the basal/deeper layers of the epithelium, it is likely that the size of the black-pigmented area depends on the number and density of the melanoma cells and does not reflect the true size of the tumor. Narrow-band imaging and/or magnifying endoscopy [16] was not useful for accurately determining the tumor area in our patient (Fig. 8A–C).

Endoscopic treatment for PMME should be considered for diagnostic purposes [17] and for treatment purposes

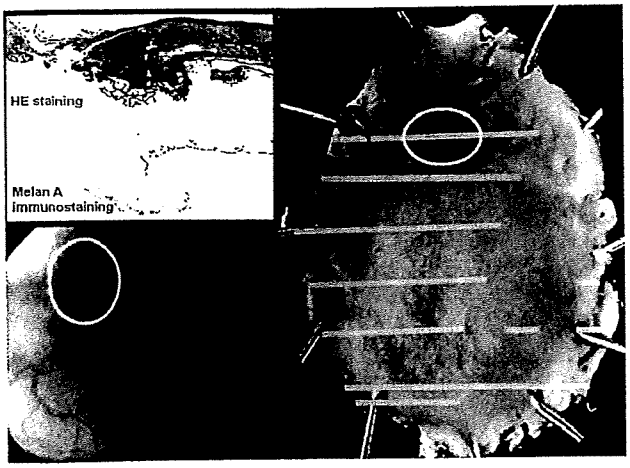


Fig. 5. A specimen of endoscopic mucosal resection showed clearly that the black-pigmented area is only part of the whole tumor, and the horizontal margin was positive. *Yellow lines* indicate the histological distribution of microinvasive PMME. *HE*, hematoxylin and eosin staining

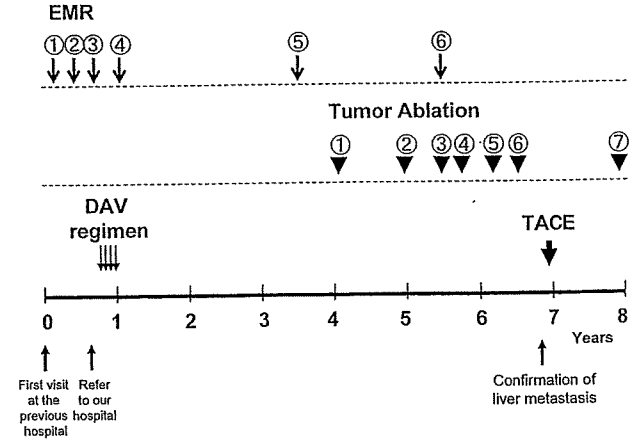


Fig. 7. Clinical course of this case. Local control of multiple early-stage PMME was achieved mainly by endoscopic treatment [six episodes of endoscopic mucosal resection (*EMR*) for 9 lesions and seven episodes of tumor ablation therapy with argon plasma coagulation or bipolar coagulation probe for 13 lesions]. *TACE*, transarterial chemoembolization; *DAV*, dacarbazine, nimustine hydrochloride, and vincristine

Fig. 6. **A** Seven years after the first diagnosis, multiple liver tumors were detected by screening abdominal computed tomography (*arrowheads* in S6). **B** A needle biopsy specimen from the liver tumor revealed the typical histological pattern of malignant melanoma

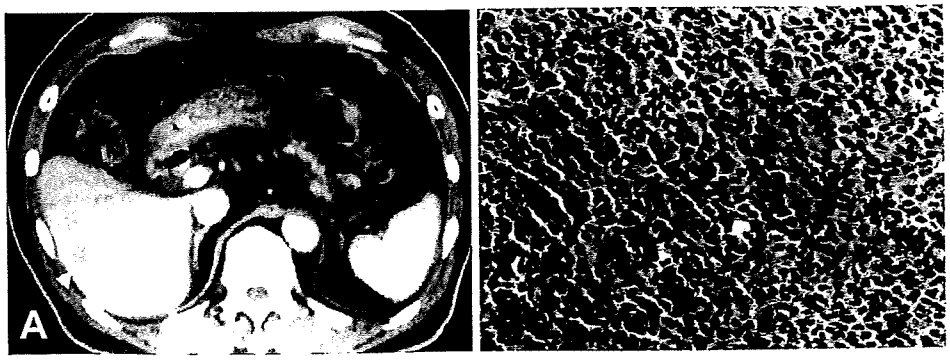


Fig. 8. Narrow-band imaging (**A**), magnifying endoscopy (**B**), and magnifying endoscopy with narrow-band imaging (**C**) were not useful for determining the tumor area accurately

only in limited cases [3,18–20]. Early-stage PMME can be removed technically by endoscopic treatment; however, indications for local therapy for this disease are still controversial because of the inaccurate diagnosis of the tumor area and uncertain tumor behavior. Further accumulation of cases of this rare disease is required.

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Clinical Trial Note

A Phase II Trial of Combined Treatment of Endoscopic Mucosal Resection and Chemoradiotherapy for Clinical Stage I Esophageal Carcinoma: Japan Clinical Oncology Group Study JCOG0508

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Standard treatment for clinical stage I esophageal cancer with submucosal invasion (T1b) has been surgical resection. We conducted a Phase II trial to evaluate the efficacy and the safety of combined treatment of endoscopic mucosal resection (EMR) and chemoradiotherapy for clinical stage I (T1b) esophageal cancer. Patients diagnosed as having clinical stage I (T1b) esophageal cancer which is considered to be resectable by EMR are eligible. When pathological examination of the EMR specimen confirms T1b tumor with negative or positive resection margin, the patient undergoes chemoradiotherapy. The study continues until 82 patients with T1b tumor with negative resection margin are enrolled from 20 institutions. The primary endpoint is 3-year overall survival (OS) in pT1b cases with negative resection margin. The secondary endpoints are 3-year OS and progression-free survival in all eligible cases, OS in pT1a-MM cases with margin-negative, complications of EMR and adverse events of chemoradiotherapy. The data from this trial will be expected to provide a non-surgical treatment option to the patients with clinical stage I (T1b) esophageal cancer.

Key words: superficial esophageal cancer – endoscopic mucosal resection – chemoradiotherapy

INTRODUCTION

According to the Japanese Classification of Esophageal Cancer by the Japan Esophageal Society, T1 esophageal tumors defined by the TNM system (6th edition) is further divided into T1a (mucosal) and T1b (submucosal) tumors by the Japanese Classification of Esophageal Cancer (1). Endoscopic mucosal resection (EMR) is usually indicated for T1a tumor, whereas the standard treatment for T1b tumors has been a surgical resection with adequate lymph node dissection in Japan because of the high incidence of lymph node metastasis (~40%) (2). However, surgical resection often deteriorates patient's general condition. Some patients with clinical T1b esophageal cancer are over-treated by surgery with a result of pathological T1a tumor, because the accuracy of diagnosis of T1b esophageal cancer is not high.

Recent advance in techniques of EMR including endoscopic submucosal dissection (ESD) enables us to remove the clinical T1b tumor and gives us accurate diagnosis of depth of invasion. However, the patients with T1b are at risk of lymph node metastasis (3) and therefore EMR alone cannot be considered as curative.

Chemoradiotherapy is one of the effective modalities for both early and advanced esophageal tumors. Since chemoradiotherapy is less toxic than surgical resection, the usefulness has been tested in several clinical trials (4,5). In Japan,

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a Phase II trial (JCOG9708) was conducted to evaluate the efficacy and the safety of concurrent chemoradiotherapy using 5-fluoraouracil (5-FU) plus cisplatin (CDDP) for T1 tumors (6). However, 22% of patients showed minor relapses that needed to be removed by endoscopic treatment. We have therefore conducted a pilot study of EMR followed by chemoradiotherapy and have reported promising results (7). Thus, the Japan Clinical Oncology Group initiated this multi-institutional Phase II trial (JCOG0508) to evaluate the efficacy and the safety of combined treatment of EMR and chemoradiotherapy for clinical stage I (cT1bN0) esophageal cancer.

The Protocol Review Committee of JCOG approved the protocol in October 2006 and the study was activated in December 2006.

JCOG0508 PROTOCOL

Purpose

The aim of this study is to evaluate the efficacy and the safety of combined treatment of EMR and chemoradiotherapy for clinical stage I (T1b) esophageal cancer.

Study Setting

The study is a multi-institutional (20 centers), single-arm Phase II trial.

Resources

This study is supported by the Grants-in-Aid for Cancer Research (17S-3, 17S-5, 20S-3, 20S-6) and Health and Labour Sciences Research Grant for Clinical Cancer Research (17-12) from the Ministry of Health, Labour and Welfare, Japan.

Endpoints

The primary endpoint is 3-year overall survival (OS) in pT1b cases with negative resection margin (comment 4). The secondary endpoints are 3-year OS and progression-free survival (PFS) in all eligible cases, OS in pT1a-MM (muscularis mucosa) cases with negative resection margin, complications of EMR and adverse events of chemoradiotherapy.

In this trial, resection margin is diagnosed from endoscopic findings immediately after mucosal resection for horizontal margin and from pathological findings for vertical margin. OS is defined as the time from registration to death from any cause, and it is censored at the last contact day for living patient. PFS is defined as the time from registration to either the first event of progression or death from any cause, and it is censored at the latest day when patient is alive without progression.

Inclusion Criteria

Patients are included in this trial if they meet all of the following criteria: (i) histologically proven squamous cell carcinoma of the esophagus by endoscopic biopsy, (ii) tumors located within the thoracic esophagus, (iii) depth of tumor invasion is diagnosed as T1b by endoscopy and endoscopic ultrasonography, (iv) the number of multiple intra-esophageal tumors is less than three, and the depths of invasion of them are diagnosed as cT1a-EP (carcinoma *in situ*) or cT1a-LPM (tumor invades lamina propria mucosa), (v) clinically node-negative (cN0) and no metastasis to other organs (cM0), (vi) size of main tumor is $\leq$5 cm, and circularity of esophageal lumen is less than three-fourths, (vii) no ulcerative lesion in the tumors, (viii) no intra-esophageal metastasis, (ix) no prior treatment of chemotherapy or radiation therapy against any other malignancies, except for previous curative EMR for pT1 esophageal cancer, (x) aged between 20 and 75 years old, (xi) performance status of 0 or 1, (xii) sufficient organ functions and (xiii) written informed consent.

Exclusion Criteria

Patients are excluded if they meet any of the following criteria: (i) iodine allergy, (ii) enable to discontinue anticoagulant or antiplatelet medications, (iii) synchronous or metachronous (within 5 years) malignancy other than carcinoma *in situ*, (iv) pregnant or breast-feeding women, (v) severe mental disease, (vi) systemic administration of corticosteroids, (vii) HBs antigen positive, (viii) active bacterial or fungous infection, (ix) concurrent unstable angina or myocardial infarction within 3 months before registration, (x) unstable hypertension, (xi) diabetes mellitus, uncontrolled or controlled with insulin, or (xii) interstitial pneumonia, lung fibrosis or severe emphysema.

Registration

After confirming the inclusion/exclusion criteria by telephoning or faxing the JCOG Data Center, the patients are registered into this JCOG0508 trial.

Quality Control of EMR

Twenty institutions among the Gastrointestinal Oncology Study Group of the JCOG participate in this trial. All participating physicians have agreed to the technical details for EMR. For quality control of EMR technique and endoscopic diagnosis, we perform central review of the photographs in all patients at the semi-annual investigators meeting. Regarding an ESD procedure, we permit it only for expert physicians who have significant experiences in ESD and EMR, and they are registered by the primary investigator (M.M.). The minimum request for ESD permission is the experience of EMR $\geq$ 50 and ESD $\geq$ 10 for esophageal

carcinoma, ESD $\geq$ 50 for gastric cancer and perforation rate $\leq$2% in total.

Treatment Methods

Endoscopic Mucosal Resection

EMR is performed against esophageal tumors within 30 days from registration. The technical methods of EMR approved in this trial are a two-channel method, a cap method or an esophageal endoscopic mucosal resection-tube method (8). Only the registered physicians are allowed to perform ESD in this trial. After EMR, it should be confirmed endoscopically that no iodine-unstained area is left. Physicians need to take pictures before and after EMR and submit them to the primary investigator for quality control of EMR technique and endoscopic diagnosis.

Chemoradiotherapy

In cases of pT1a tumor with negative resection margin and no vascular invasion, no additional treatment after EMR is given. In other cases, chemoradiotherapy was started at 29–70 days after EMR. The chemotherapy regimen is continuous 5-FU (700 mg/m^2/day, days 1–4 and 29–32) and CDDP (70 mg/m^2/day, days 1 and 29). The dose of radiotherapy is 41.4 Gy/23 Fr/5 weeks (5 days/week) for cases with negative resection margin and 50.4 Gy/28 Fr/5 weeks (5 days/week) with boost on the primary site for the case with positive resection margin, respectively.

Follow-up

Patients are followed with blood tests, upper gastrointestinal endoscopy and computed tomography at least every 4 months for 3 years.

Study Design and Statistical Methods

This trial determines the efficacy and the safety of combined treatment of EMR and chemoradiotherapy for cT1b esophageal cancer in terms of 3-year OS. Additionally, 3-year OS in all eligible patients are evaluated as the most important secondary endpoint. The sample size is 82 for pT1b cases with negative resection margin with the power of 90%. In case this hypothesis rejected, the secondary hypothesis for all eligible patients can be tested using hierarchical method keeping trial-wise α error nominal level, one-sided 5%, with the power of 80%. To test the hypothesis, 3-year OS estimated by Kaplan–Meier method and its confidence interval by Greenwood's formula is used. The total number of registered patients is estimated as 137, because the proportion of pT1b cases with margin-negative among all eligible patients is predicted as ~60%.

This study was registered with UMIN-CTR [www.umin.ac.jp/ctr/], identification number UMIN000000553.

Interim Analysis and Monitoring

Interim analysis is not planned. If the number of cases with treatment-related death, severe (Grade 4) bleeding or severe (Grade 4) perforation reaches seven, the registration will be suspended unless the JCOG Data and Safety Monitoring Committee approves to continue this trial. The JCOG Data Center is responsible for data management, central monitoring and statistical analysis. This center also provides semi-annual monitoring reports, each of which is submitted to and reviewed by the JCOG Data and Safety Monitoring Committee on demand of the JCOG Data Center. None of physicians administering the interventions are involved in the data analysis. For quality assurance, site-visit audits, not for a specific study basis but for the study group basis, are done by the JCOG Audit Committee.

Acknowledgements

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Conflict of interest statement

None declared.

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Appendix

The initially participating hospitals are as follows: Iwate Prefectural Central Hospital, Ibaragi Prefectural Central Hospital, Tochigi Cancer Center Hospital, National Cancer Center Hospital East, National Cancer Center Hospital, Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital, Showa University Hospital, Cancer Institute Ariake Hospital, Kitasato University East Hospital, Kanagawa Cancer Center Hospital, Ishikawa Prefectural Central Hospital, Saku Central Hospital, Shizuoka Cancer Center Hospital, Aichi Cancer Center Central Hospital, Kyoto University Hospital, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka City Medical Center, and Osaka Medical College Hospital.

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ENDOSCOPY MINISERIES

Improving visualization techniques by narrow band imaging and magnification endoscopy

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Key words
endoscopy, early detection, magnification, narrow band imaging, pre-malignant lesions.

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Abstract

Endoscopy plays an important role in the early detection of gastrointestinal tract neoplasms. Using conventional white light or dye-based image enhanced endoscopy, it has been difficult to assess pre-malignant and early neoplastic lesions precisely. However, narrow band imaging (NBI) dramatically improves the detection of these lesions, particularly in combination with magnifying endoscopy. This allows the endoscopist to accomplish accurate diagnosis. Such enhanced detection of pre-malignant and early neoplastic lesions in the gastrointestinal tract should allow better targeting of biopsy, improved and more appropriate treatment, and thereby contribute to optimal quality of life and patient survival.

Introduction

The ability to visualize mucosal surface abnormality of the gastrointestinal tract is essential to enhance early detection and make accurate diagnosis of the underlying disease. Recent advances in endoscopic imaging technologies have enabled endoscopists to observe microscopic structures, such as microvessels, tissue structure, cellular nuclei, and even macromolecules. These improvements of visualization are expected to provide much information, to not only physicians but also surgeons and radiologists.

Among these newer technologies, narrow band imaging (NBI) is one of the most promising. NBI is an innovative optical technology that can increase contrast of the precise morphological changes in the mucosal surface. When combined with magnifying endoscopy, use of NBI clearly visualizes microvascular structures.[1,2] These strengths have opened a brand new door for endoscopic diagnosis of gastrointestinal tract diseases. In this review, we focus on the role of NBI combined with magnifying endoscopy and discuss the clinical significance of this technique in gastroenterology.

Background of advances in optical endoscopic technologies

Videoendoscope system

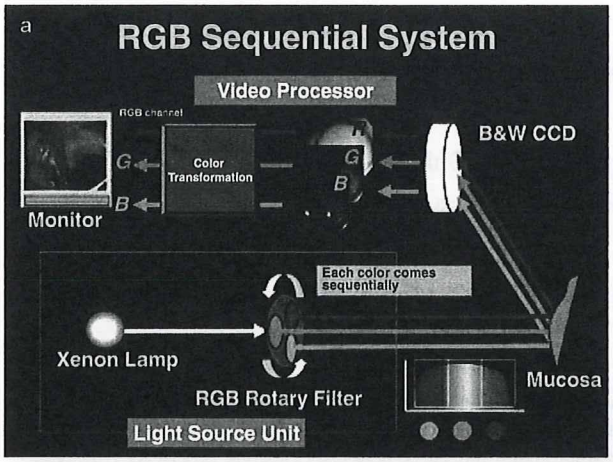
The videoendoscope mounts the charge coupled device (CCD) on the tip of the endoscope as the imaging sensing device. Two different types of videoendoscope systems are currently in use. The difference is based on how a color image is created. One is based on a black and white CCD, in which color separation is achieved through use of a red-green-blue (RGB) rotary filter wheeled equipped within the light source unit. The RGB filter consists of three broadband optical filters and covers all wavelengths of the visible spectrum, ranging from approximately 400 to 800 nm (Fig. 1a). The other system is based on a color CCD chip that has several tiny color filters in each pixel (Fig. 2a). Both systems use a xenon lamp as a light source. Usually, the RGB sequential system is considered to provide more clear images compared with the color chip system.

Narrow band imaging

The NBI system has been in use since 1999 and was developed as a part of the joint research between the Japanese National Cancer Center Hospital East and Olympus Medical Systems Corporation (Tokyo, Japan). Gono *et al.* revealed that the use of 415 nm narrowband light could improve the capillary images, which are difficult to observe under conventional white light.[1,2] Subsequently, Sano *et al.* reported the capabilities of NBI in the gastrointestinal tract in 2001.[3] The NBI system is now expected as a new promising endoscopic diagnostic tool in the gastrointestinal tract all around the world.

The NBI system uses two narrow band illuminations of 415 nm and 540 nm by NBI filter (Figs 1b,2b). Under NBI observation, the broadband white light derived from the xenon lamp splits into two bands (wavelength of 415 nm and 540 nm) and illuminates the surface of the mucosa.

When the NBI is incorporated into an RGB sequential system, the NBI filter is placed on the light path in front of the RGB rotary filters. When observing with the NBI filter, the light illumination passes only B and G filters to obtain 415 nm and 540 nm images.



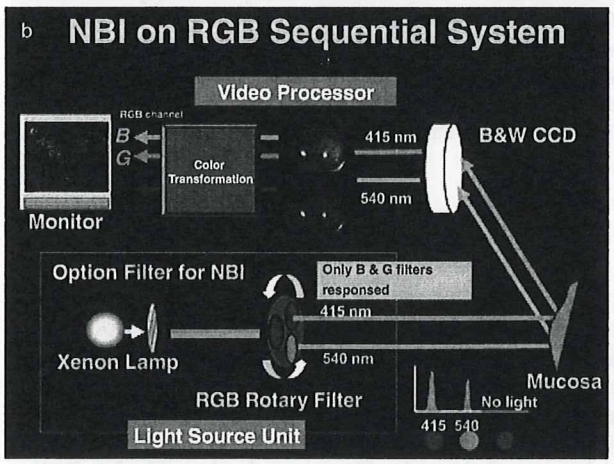
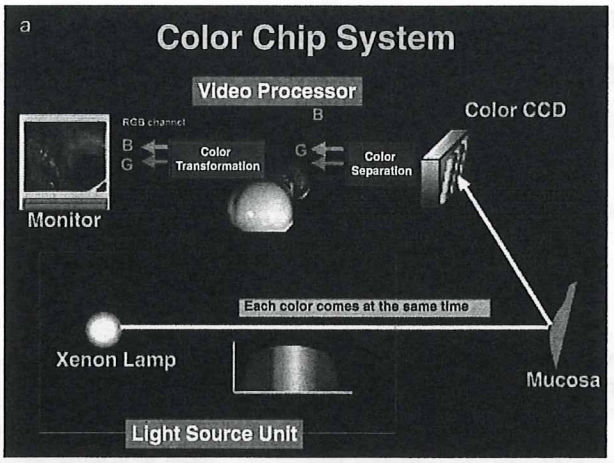


Figure 1 Schema of the red-green-blue (RGB) sequential illumination system. (a) In the RGB sequential illumination system, color separation is achieved through use of a red-green-blue rotary filter wheel equipped within the light source unit. The RGB filter consists of three broadband optical filters and covers all wavelengths of the visible spectrum, ranging from approximately 400 to 800 nm. (b) In the narrow band imaging (NBI) of RGB sequential system, the NBI filter is placed on the light path in front of the RGB rotary filters. When observing with the NBI filter, the light illumination passes only B and G filters to obtain 415 nm and 540 nm images. Subsequently, two narrow band images of 415 and 540 nm should be reproduced to visualize the images. However, to create a color image on the cathode ray tube (CRT) or liquid crystal monitor, three images are needed to be outputted to the R, B and G channels on the color monitor. For this purpose, 415 nm is allocated to the B and G channels so that the blood vessels on the mucosal surface are reproduced in a brownish color, and 540 nm is allocated to the R channel, so that the vessels in the deeper layer are indicated in a blue-color.



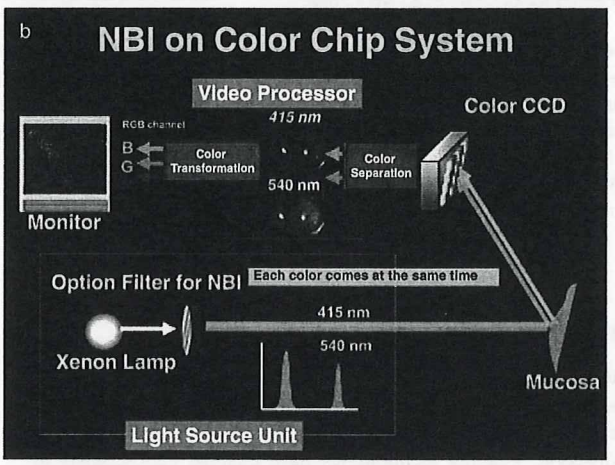


Figure 2 Schema of the color charge coupled device (CCD) chip system. (a) The color CCD chip system is based on a color CCD chip that has several tiny color filters in each pixel. (b) In the narrow band imaging (NBI) of color chip system, the NBI filter is also placed on the light.

Similarly, in the NBI color chip system (Fig. 2b), the NBI filter is placed on the light path, while this filter is removed under the conventional white light observation.

Subsequently, two narrow band images of 415 and 540 nm should be reproduced by placing the NBI filter. However, to create a color image on the cathode ray tube (CRT) or liquid crystal monitor, three images need to be outputted to R, B and G channels on the color monitor. Then, 415 nm is allocated to B and G channels so that blood vessels on the mucosal surface are reproduced in a brownish color, and 540 nm is allocated to the R channel so that the vessels in the deeper layer can be indicated in a greenish-blue color.

High definition endoscopy and monitor system

Image quality depends on its *resolution* and *contrast*. *Resolution* is the capacity to visualize minute patterns and is determined by the pixel number of each CCD. To enhance resolution, the number of pixels in the CCD has to be increased. However, a CCD with a higher number of pixels thus increases the size of the videoendoscope by expanding its outer diameter. On the other hand, if a thinner endoscope is made, the CCD must be smaller, thereby decreasing the number of pixels with a resulting reduction of image resolution. On the other hand, for insertion and operation of the endoscope, a thinner diameter tip is ideal and important. To

resolve this dilemma, a smaller sized CCD with a higher pixel count has been developed by solving several technical challenges.

Contrast is the ratio of density or brightness between a pattern and its background. Resolution is enhanced by high definition endoscopy and contrast is improved by NBI technology. High quality images are made by both high resolution and high contrast.

If the resolution of the monitor system is low, image quality will be poor even though we use a high definition endoscope. Then, we have to use both high definition endoscopy and high definition monitoring to obtain the highest quality of images. However, despite the importance of this aspect, none of the many published studies on high definition NBI appear to have described the specifications of the monitor used.

Magnifying endoscopy

Magnifying endoscopy has the capability of both standard video endoscopy and an adjustable image magnification. Using magnifying endoscopy, Kudo *et al.*,[4] Inoue *et al.*[5,6] and Yao *et al.*[7,8] have already reported the importance of the magnification in the colon, esophagus and stomach, respectively.

The RGB sequential system and the color CCD system differ in their magnification capabilities. Although the RGB sequential system allows optical magnification of the image up to 80 times, the color CCD system has digital zoom at 1.2 and 1.5 times magnification. However, high definition endoscope, even that using the color CCD system, possesses a physical zoom property that allows the tip of the endoscope to be advanced up to 2 mm away from the mucosal surface without decreasing resolution. This combination results in the capacity for at least a 50-times magnification.

Narrow band imaging combined with magnification is expected to give the maximum performance to make accurate diagnosis. Conversely, NBI observation without magnification has the potential disadvantage of producing conditions that are sometimes too dark to identify morphological and color changes. This reason for the dark image is simply because the NBI system uses only two narrow illumination lights, whereas conventional white light imaging uses a broadband visible light. For these reasons, it is important that users understand the technical backgrounds of these newer endoscopic procedures.

Improvement of visualization and clinical significance

Narrow band imaging combined with magnifying endoscopy enhances the contrast detailed morphological changes in the mucosal surface and clearly visualizes the microvascular structures. In particular, microvascular assessment is a novel target of epithelial neoplastic lesions in different organs, including oropharynx and hypopharynx,[9–11] esophagus,[5,6] stomach,[7,8] lung,[12] and colon.[13]

Inoue *et al.* first reported the importance of morphological changes of the intrapapillary capillary loop (IPCL) in making a diagnosis of esophageal squamous cell carcinoma.[5,6] Yao *et al.* also reported the importance of the irregular microvascular pattern within the gastric cancer.[7,8] However, assessment of the microvascular architecture has been difficult by conventional white light observation. In contrast, NBI made it possible to easily assess these structures. Demonstrable cases are shown in Figures 3–6.

In the head and neck region (Fig. 3) and esophagus (Fig. 4), NBI clearly visualizes the well-demarcated brownish area, while the lesion is difficult to identify by conventional white light image. In the stomach (Fig. 5), magnified NBI clearly revealed a demarcation line between non-neoplastic mucosa and the neoplastic lesion with its irregular microvascular pattern; this pattern was difficult to identify by white light image. In the colon (Fig. 6), papillary pattern was invisible in a hyperplastic polyp, while it is clearly identified in an adenomatous polyp. For such reasons, NBI is now expected to be a useful tool for endoscopic screening and surveillance for early cancers in several organs.

A recent meta-analysis revealed that NBI evaluation of epithelial lesions in the gastrointestinal tract and lung has a high level of diagnostic precision for neoplasia.[14] High diagnostic accuracy has the potential to allow accurate target biopsy, and also reduces unnecessary biopsies. In addition, NBI diagnosis has comparable diagnostic accuracy to chromoendoscopy, which has been recognized as a useful method for discriminating neoplasia from non-neoplasia. This evidence provides great merit for both patients and endoscopists, because with NBI there is no longer a need for either staining solution or spraying catheters. Dispensing with these procedures can potentially reduce the duration of the endoscopic examination and procedural cost.

Narrow band imaging has a sharp learning curve to the inexperienced endoscopist.[14,15] This is very important because educating non-experienced endoscopists to recognize early cancers is difficult. Yoshida *et al.* compared the ability of novices versus experienced endoscopists to identify and evaluate IPCL by NBI and white light observation.[16] Both assessors found that image contrast, identification and evaluation of IPCL by NBI were superior to that from white light observation. Furthermore, NBI with magnification improved the diagnostic accuracy for depth of invasion based on IPCL findings, especially for inexperienced endoscopists.

Head and neck region

Head and neck cancer

Early detection of cancers in the oropharynx and hypopharynx has been difficult even for ear-nose-throat (ENT) doctors, because image resolution of rhinolaryngoscopy is not very good for identifying epithelial neoplastic lesions. This can be partly attributed to the technological limitation of size to mount the high quality CCD to the tip of a rhinolaryngoscope.

Muto *et al.* first reported the usefulness of NBI combined with magnifying endoscopy (Q240Z, Olympus Medical Systems, Tokyo, Japan) for identification of superficial squamous cell carcinoma (SCC) in the head and neck region.[9] The NBI was based on an RGB sequential light source (EVIS 240, Olympus Medical Systems). Compared with white light observation, NBI significantly improved the visualization of cancerous lesions by enhancement of the contrast between the lesion and background non-neoplastic epithelium, as well as by clear magnification of microvascular architecture.[11] Under NBI observation, cancerous lesions are recognized as well-demarcated brownish areas, and after magnification, the micovascular irregularities can easily be identified.[9,10] These two characteristics are typical changes of epithelial neoplasms, and are histologically confirmed as

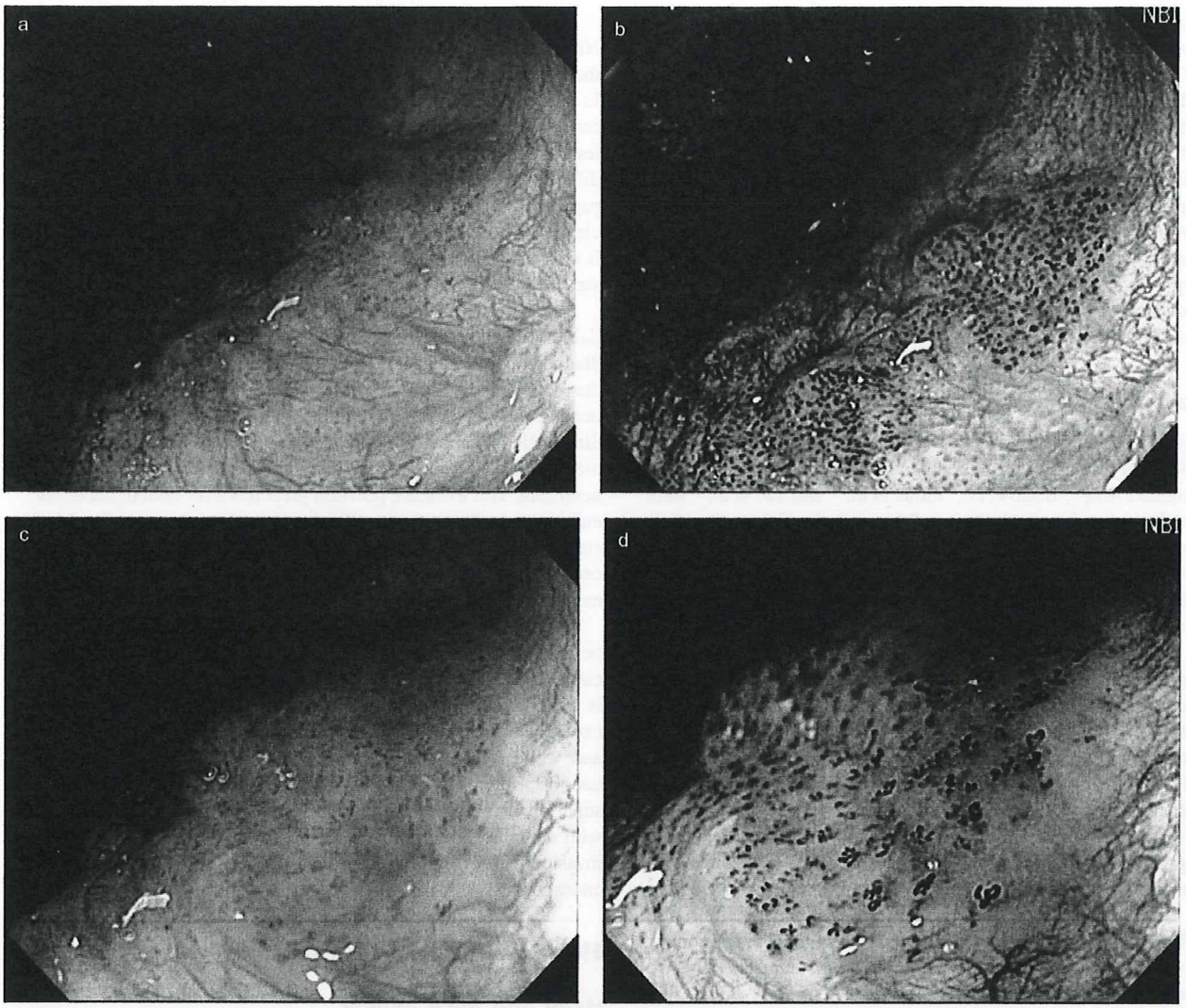


Figure 3 Superficial squamous cell carcinoma in the oropharynx. (a) Non-magnified white light image shows slightly reddish lesion with uneven surface in the posterior wall of the oropharynx. (b) Non-magnified narrow band imaging (NBI) shows a brownish area in which scattered tiny brown spots are easily seen. (c,d) Magnified NBI (d) clearly reveal irregular microvascular pattern, whereas this pattern was difficult to identify in the white light image (c).

angiogenetic changes. Based on these findings, we have proposed a new diagnostic approach to visualize angiogenesis in superficial neoplastic lesions.[10]

In the ENT field, Watanabe'*et al.* reported that NBI rhinolaryngoscope (ENF-V2, Olympus Medical Systems) with the color chip light source (CLV-160B, Olympus Medical Systems) improved the diagnostic accuracy, and negative predictive value for superficial lesions in the oropharynx and hypopharynx.[17,18]

However, there is still a critical difference in image qualities between the RGB sequential system and color chip systems, and also between high-resolution and conventional endoscopy. Using a real time approach, Ugumori *et al.* compared the images taken by color chip based rhinolaryngoscope and those taken by RGB sequential system-based high-resolution endoscopy.[19] While conventional white light rhinolaryngoscope could identify a well demarcated line between neoplastic and non-neoplastic lesions in only 10% (5/51), and microvascular irregularities in 27% (14/51), NBI rhinolaryngoscope could identify these findings in 63% (32/51) and 94% (49/51), respectively. This result indicates that even through the conventional and color CCD endoscope, NBI can improve the visualization of epithelial neoplasms.

The clinical significance of these results is exemplified by the fact that no cases of superficial cancer in the oropharynx and hypopharynx had been reported before the emergence of NBI. Early detection of cancer in this region can introduce the possibility of minimally invasive treatments, such as endoscopic mucosal

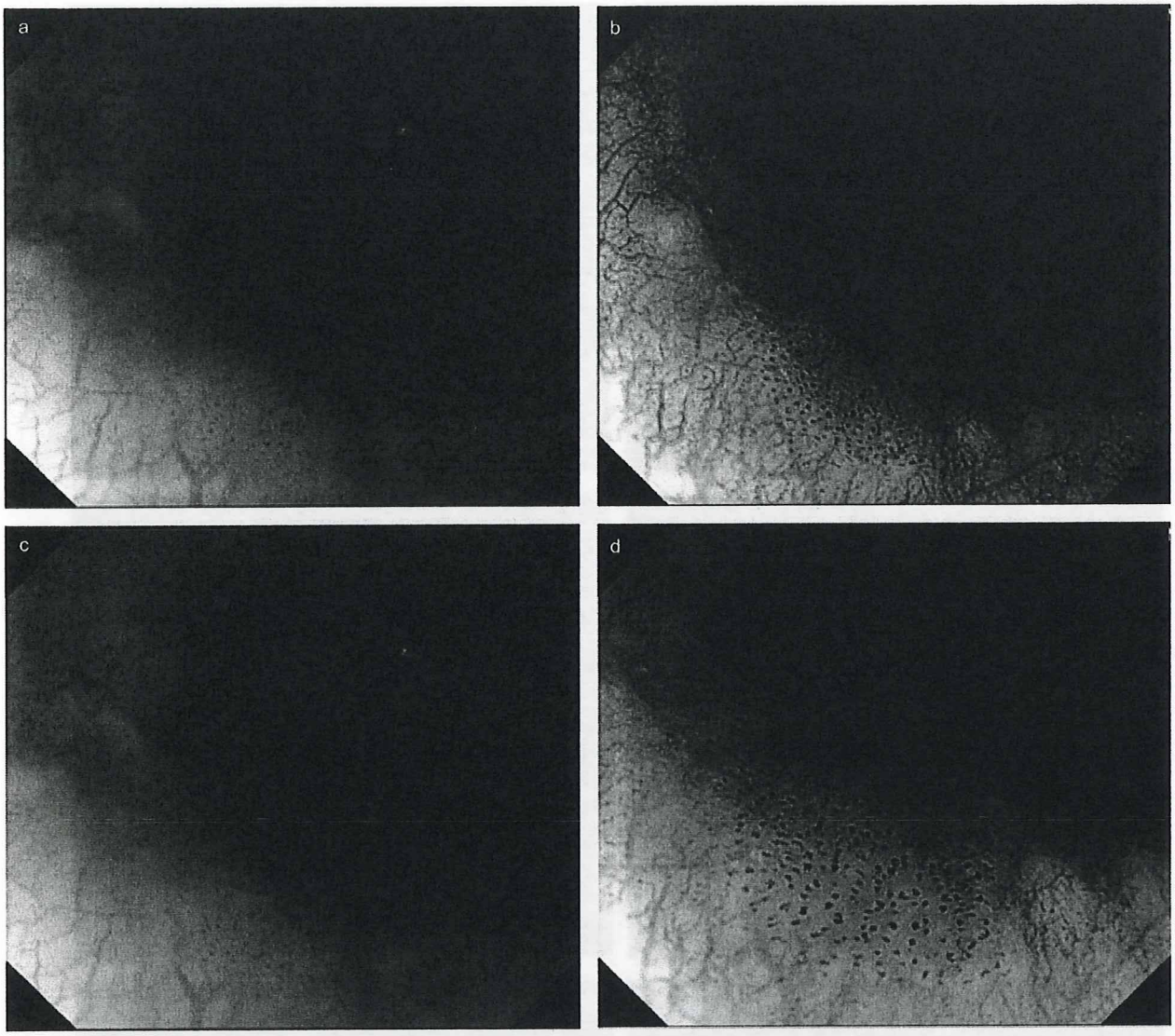


Figure 4 Superficial squamous cell carcinoma in the esophagus. Non-magnified narrow band imaging (NBI) (b) clearly demonstrates a well demarcated brownish area, while the lesion was difficult to recognize by white light imaging (a). Magnified NBI (d) clearly reveals irregular microvascular pattern, whereas this pattern was difficult to identify by white light image (c).

resection (EMR) and endoscopic submucosal dissection (ESD) methods, similar to the corresponding approaches in the gastrointestinal tract. The potential advantages to patients resulting from earlier diagnosis and preservation of organ and tissue functions are obvious.

Esophagus

Esophageal squamous cell carcinoma

Patients with esophageal SCC have a high risk of development of synchronous and/or metachronous SCC in the esophagus and head and neck region. This has long been explained by the 'cancer field' concept.[20] Thus, effective screening and surveillance are required to improve the survival and quality of life of patients with multiple SCC. Lugol chromoendoscopy is the standard method for detection of early cancer in the esophagus. However, lugol is an irritant and causes unpleasant reactions, such as pain and discomfort.[21,22] In contrast, NBI is less invasive, so it is expected to replace the role of lugol chromoendoscopy.

Preliminary results from a Japanese multicenter prospective randomized control study in a back-to-back fashion indicate that significantly high detection rates and high diagnostic accuracy of superficial SCC in the head and neck region and the esophagus are obtained using NBI compared with conventional white light observation.[23] This result may indicate that NBI should become the standard modality for examining squamous epithelium for cancer screening.

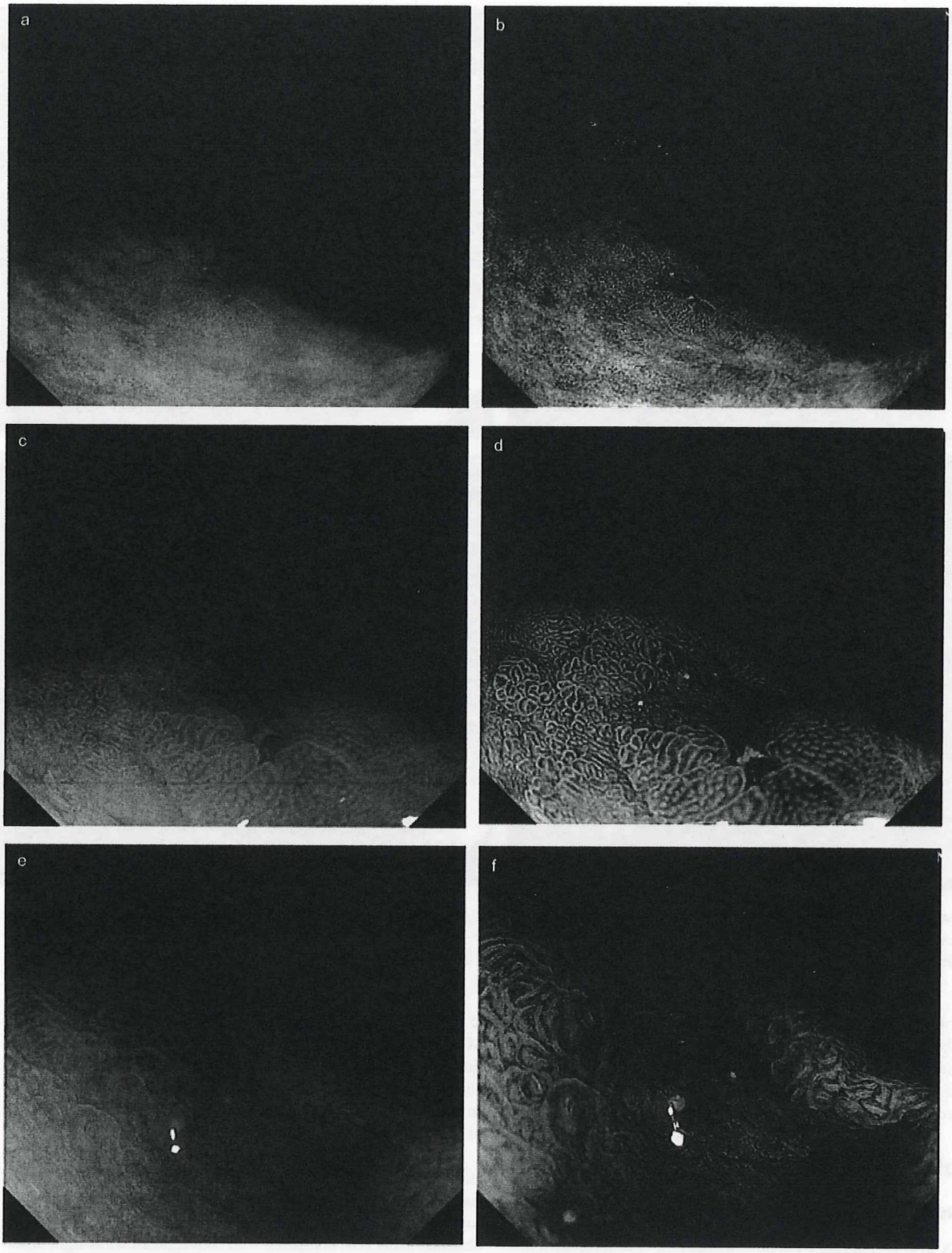


Figure 5 Mucosal cancer in the stomach. Both non-magnified conventional white light image (a) and narrow band imaging (NBI) (b) show a small depressed area in the greater curvature of the stomach. Magnified NBI (d,f) clearly reveals a demarcated line between non-neoplastic mucosa and the neoplastic lesion, and irregular microvascular pattern; this pattern was difficult to identify by white light image (c,e).

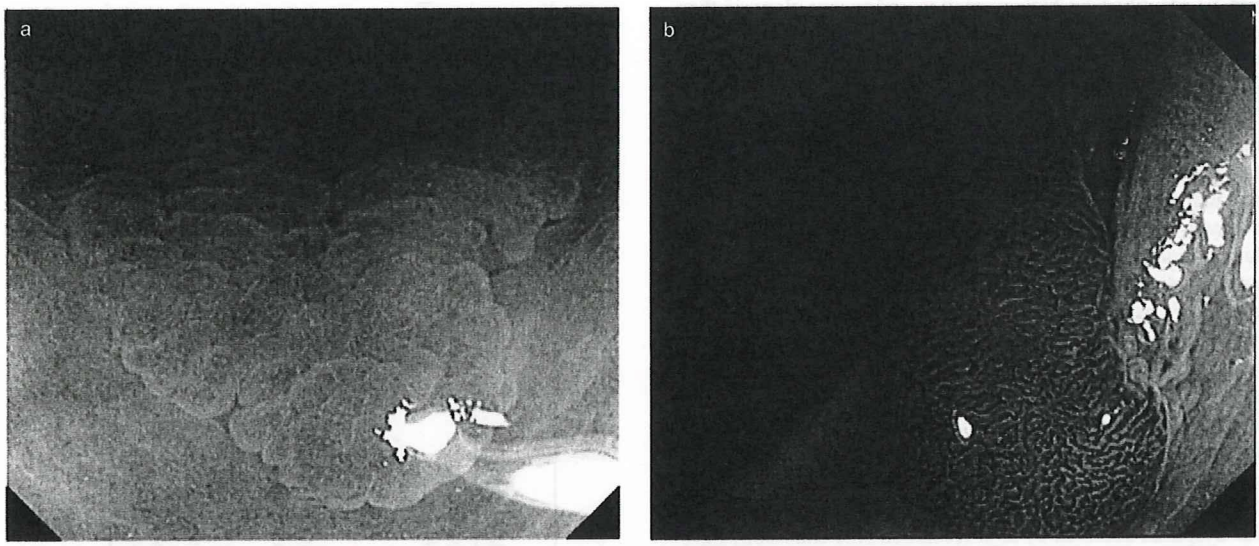


Figure 6 (a) In the hyperplastic polyp, a papillary pattern is not present. (b) In the adenomatous polyp, a papillary pattern is clearly evident.

Using an ultra-thin endoscope (5 mm in diameter at the distal end, XP260N, Olympus Medical Systems), Lee *et al.* reported the usefulness of NBI for detection and accurate diagnosis of esophageal SCC.[24] The sensitivity of NBI was significantly better than that of conventional white light observation. Specificity and positive predictive value of NBI were also better than lugol chromoendoscopy. Diagnostic accuracy and negative predictive value are comparable between NBI and lugol chromoendoscopy. These results may indicate that, even by adopting the ultra-thin endoscope, NBI is the best tool to screen superficial esophageal neoplasms.

Gastroesophageal reflux disease

Gastroesophageal reflux disease (GERD) causes heartburn and decreases quality of life. However, a significant number of patients with GERD symptoms show no signs of esophagitis endoscopically. This condition is described as endoscopy-negative reflux disease (NERD), and thus standard endoscopy has been an insensitive test for the diagnosis of GERD.

While NERD can also be considered as a 'functional' disease, there are no criteria on pH study or histology to accurately make the diagnosis of NERD. Using magnifying endoscopy based on the color chip system (EG3470ZK, Pentax, Hamburg, Germany, or 160Z, Olympus Medical Systems, Hamburg, Germany), Kiesslich *et al.* reported that patients with NERD showed endoscopic signs of minimal change esophagitis significantly more frequently than those in a non-reflux group.[25] Therefore, NBI is expected to overcome the limitation of invisible muscosal alterations, because it has the potential to visualize superficial and small esophageal lesions attributable to GERD that cannot be seen by conventional white light endoscopy.

Sharma *et al.* reported a feasibility study of NBI using a magnifying endoscope (Olympus GIF-Q240Z, Olympus Medical Systems, Tokyo, Japan) in patients with GERD.[26] Patients with GERD had increased number, dilation, and tortuosity of IPCL compared with controls. Patients with NERD also showed increased number and dilation of IPCL compared with controls. Multivariate analysis showed that increased number and dilation of IPCL were the best predictors of diagnosing both GERD and NERD. Then, 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 re-evaluated by novel technologies in prospective controlled trials.

Using a high-resolution endoscopy (Olympus GIF-H260, Olympus Medical Systems) with the RGB sequential illumination NBI system, Lee *et al.* reported that NBI improved the intra-observer and inter-observer reproducibility in grading esophagitis compared with conventional white light imaging.[27] As the observer variability in endoscopic diagnosis of GERD is an important issue for standardization, NBI is expected to improve judgment in the grading of esophagitis.

Barrett's esophagus

Barrett's esophagus (BE) is the most important risk factor for esophageal adenocarcinoma, and the incidence is rapidly increasing in developed countries.[28,29] The most important risk factors for development of BE is chronic acid reflux, which stimulates the replacement of distal esophageal squamous epithelium with specialized intestinal metaplasia (SIM). BE is defined as the presence of SIM histologically.

As esophageal adenocarcinoma has a poor prognosis when detected at an advanced stage, endoscopic surveillance has been recommended to detect high-grade dysplasia and mucosal neoplasia for patients with BE. However, it is difficult to identify the dysplastic and early neoplastic changes in SIM by conventional white light endoscopy. Four-quadrant random biopsies at 1–2 cm intervals within SIM[30,31] are widely accepted, but leads to sampling error because it is a 'blind approach'. Although Kara *et al.* reported that most high-grade dysplasias or early cancers in BE

could be identified by high resolution endoscopy alone if they showed macroscopically visible abnormalities, few cases were detected by random biopsy alone.[32] This indicates that random biopsies increase the number of negative biopsies.

To carry out the accuracy of biopsies, improved visualization of Barrett's columnar epithelium, and capability to distinguish metaplasia from dysplasia or neoplasia are needed. Chromoendoscopy using indigocarmine or acetic acid allows biopsies to be more specifically targeted. However, this requires additional equipment, solution, time and training. In contrast, NBI with magnifying endoscopy enables us to visualize the details of mucosal surface and capillary networks without additional equipment or dye solutions. Hamamoto *et al.* first reported that NBI could provide better visualization of the esophagogastric junction, net-like capillary vessels and columnar-lined esophagus (BE) than conventional white light endoscopy.[33] Kara *et al.* reported that indigocarmine chromoendoscopy and NBI were comparable to make diagnosis of high-grade dysplasia or early cancer in BE.[34]

Several studies[32,35–38] on the characteristics of SIM and high-grade dysplasia observed by high-resolution NBI endoscopy have been reported (Table 1). Most of these studies have assessed both pit pattern (mucosal pattern) and superficial microvascular pattern. SIM is generally characterized by villous mucosal pattern with regular microvasculature, whereas high-grade dysplasia shows irregular/distorted mucosal pattern with irregular microvasculature. Combination of the typical features of pit pattern (mucosal pattern) and superficial microvascular pattern confers diagnostic accuracy and reproducibility.[36,38]

Detection of mucosal dysplasia is most important in patients with BE to prevent the progression to invasive carcinoma. Using a high resolution endoscopy (H180, Olympus Medical Systems) with color chip NBI system (Evis Exera II, Olympus Medical Systems), Wolfsen *et al.*[39] reported that high resolution NBI can detect dysplastic lesions more efficiently with fewer biopsy samples compared with standard resolution white light endoscopy (Q160, Olympus Medical Systems). This means that NBI is no longer a standard examination to detect high grade dysplasia and superficial cancer in patients with BE. In addition, differences in video endoscopy systems seem to be not so important when we discuss diagnostic capabilities in BE.

Table 1 Characteristics of SIM and high-grade dysplasia in Barrett's esophagus according to NBI endoscopy

Author	Year	NBI system	Endoscope	Magnification	SIM		High-grade dysplasia	
					Mucosal pattern	Vascular pattern	Mucosal pattern	Vascular pattern
MA Kara	2005	RGB sequential illuination	240Z	+	Villous/gyrus-forming pattern	Regular vascular pattern	Irregular/disrupted pattern	Irregular vascular pattern/Abnormal blood vessel
P Sharma	2006	RGB sequential illuination	240Z	+	Ridge/villous pattern	–	Irregular/distorted pattern	–
GA Anagnostopoulos	2006	RGB sequential illuination	240Z	+	Regular microstructual pattern (tubular/linear/villous)	Absent microvascular pattern	Irregular microstructual pattern	Irregular microvascular pattern
K Goda	2007	RGB sequential illuination	240Z	+	Cerebriform fine mucosal pattern	Ivy- or DNA-like capillary pattern	–	–
R Singh	2008	RGB sequential illuination	240Z	+	Ridge/villous pattern Absent pit	Regular microvasculature	Distorted pit	Irregular microvasculature

NBI, narrow band imaging; RGB, red-green-blue; SIM, specialized intestinal metaplasia.

Stomach

Gastric intestinal metaplasia

In patients with atrophic gastritis, intestinal metaplasia (IM) is a risk factor for intestinal type adenocarcinoma.[40] However, conventional endoscopy is insensitive for diagnosing IM because of the high rate of inter-observer variability and poor correlation with histological confirmation. At present, the diagnosis of IM has to be made by histological evaluation. However, if we could correctly identify IM endoscopically, we could evaluate the risk of gastric adenocarcinoma without biopsy.

Uedo *et al.*[41] reported that the appearance of a light blue crest in the gastric mucosa by magnifying NBI was highly accurate to predict the presence of histological IM. Bansal *et al.*[42] also reported that NBI helps predict the presence of *in vivo* histopathological conditions, such as non-*Helicobacter pylori* gastritis, *H. pylori* gastritis and IM. These results indicate that the entire

surface area of the stomach can be evaluated without the need for biopsy. This would also confer the advantages of decreasing cost and unnecessary biopsy, and reducing examination time.

Gastric cancer

In the stomach, NBI should be used during magnifying observation. This is because the light intensity under the NBI filter is scant, and thus the non-magnifying image appears dark compared with the white light image. In addition, the non-magnifying NBI image becomes noisy using the electrical enhancement required to keep the endoscopic image bright. As the result of these considerations, non-magnifying NBI observation is not suitable as a screening examination in the stomach. When conducted by those disregarding these limitations, endoscopic diagnosis could be misleading and lesions could be missed.

Accordingly, we should not discuss the detection rate of cancer by NBI in the stomach. As for detailed endoscopic examination in the stomach, it has been impossible to make a correct diagnosis of flat gastric cancer by endoscopy alone, because such lesions sometimes show similar pathology to gastritis. Using only high definition endoscopy (Q240Z, Olympus Medical Systems) without a NBI system, Yao *et al.*[43] reported that magnifying observation of microvascular architecture was useful to discriminate flat reddened carcinoma from gastritis. They proposed unique endoscopic findings for intestinal type gastric cancers as follows; (i) presence of a demarcation line between the reddish lesion and the surrounding mucosa; (ii) disappearance of the regular subepithelial capillary network (SECN); and (iii) the presence of an irregular microvascular pattern within the flat lesions.[7,8] These characteristics based on mucosal and microvascular architecture are also reliable makers for differentiating between depressed gastric cancer and benign lesions.

In cases of elevated gastric neoplasia, it is sometimes impossible to visualize the microvascular architecture, because a white opaque substance (WOS) obscures the subepithelial microvascular architecture. The WOS could not be visualized by non-magnifying observations, even by high resolution endoscopy.[44] While high resolution magnifying endoscopy with both white light imaging and NBI could detect the WOS, visualization is clearer in the latter. Elevated gastric cancer showed WOS in either a regular distribution or as regular microvascular architecture. This feature is useful for discriminating adenomas from cancer of the stomach.

Nakayoshi *et al.*[45] classified the microvascular pattern of superficial gastric cancers based on their magnifying NBI images into three groups: (i) fine network pattern; (ii) corkscrew pattern; and (iii) unclassified pattern. They also compared the endoscopic pattern with the histological findings. Fine network pattern and corkscrew pattern are useful to identify differentiated adenocarcinoma and undifferentiated adenocarcinoma, respectively. Magnifying NBI is also useful to identify the lateral extension of superficial gastric cancer.[46] This strength is very important in detailed assessment of the safety margin and to improve the targeting of endoscopic treatment for neoplastic lesions.

Gastric adenoma

Most gastric adenomas are of elevated type. While depressed type adenomas are rare, they are clinically important because of the higher malignant potential than elevated adenomas. However, detection of depressed type adenomas has been difficult because endoscopic findings have not been clearly defined. Tamai *et al.*[47] reported that, by magnifying NBI, depressed type adenomas display a regular ultra-fine pattern in which a network of microvessels is composed of small and regular circles. This differs from the irregular fine network pattern of well differentiated adenocarcinomas.

Duodenum

Duodenal neoplasm

Ampullary tumors are relatively rare neoplasms and data on their endoscopic appearances are correspondingly limited. However, the assessment of ampullary lesions has particular relevance for the surveillance of patients with familial adenomatous polyposis, because such individuals are at risk of duodenal cancer. As differential diagnosis between adenomas and adenocarcinoma in the ampullary region is difficult, biopsies are routinely taken for differential diagnosis. In addition, the evaluation of lateral margins of the neoplasm is also difficult. Accordingly, the method of case selection for treatment, and the type of management remain controversial.

Uchiyama *et al.*[48] reported that inflammatory changes showed oval-shaped villi, while all adenomas and adenocarcinomas displayed pinecone leaf-shaped villi, and/or an irregular/non-structured pattern. Itoi *et al.*[49] reported that NBI is more useful than indigocarmine chromoendoscopy and white light image to identify the tumor margin at this site.

Colon

Colorectal neoplasms

Because the majority of colorectal cancers (CRC) arise from adenomas,[50] early detection and removal of colorectal adenoma is important to reduce both the incidence of colorectal cancer (CRC) and cancer-related death.[51,52] Colonoscopy is the standard method to detect adenomas.[53] However, previous studies have shown polyp miss rates of 10–30% during back-to-back colonoscopy.[54–56] The reasons for these high miss rates might include poor insertion and withdrawal techniques of the operator, poor bowel preparation, and/or limitation of imaging method, and so on.[57]

Indigocarmine chromoendoscopy significantly increases the detection rate of small flat and/or depressed lesions.[58–60] However, as was already mentioned in the 'Barrett's Esophagus' session, chromoendoscopy requires additional equipment and dye solutions, and is time consuming. Again, NBI can be done only by pushing the button on the endoscopy to change the filter. Thus, NBI is expected to be an instantaneous method to accurately detect adenoma.

As for detection capability of colorectal neoplasm, seven studies[61–67] have been published comparing NBI and white light observations (Table 2). Three studies[62,66,68] used the color CCD chip NBI system and three used the RGB sequential illumination NBI system,[62,64,66] and one did not describe the technical details. Three studies used high resolution magnifying endoscope and three did not (one did not describe any detail). Taken together,

Table 2 Comparison of colorectal adenoma detection ability between white light image and NBI

Author	Year	Evaluation methods	Institute	No. endoscopists	*n* (pts)	Endoscopy system	Magnification	Modality	Results	*P*-value	Reference no.
DK Rex	2007	Prospective RCT	Single	1	434	Color CCD chip	–		Percentage of patients with >1 adenoma (all size)	46	
								WLI	67%	NS	
								NBI	65%		
JE East	2007	Back to back fashion (WLI followed by NBI)	Single	3	62	RGB sequentia illuination	+		Percentage of patients with >1 adenoma		51
								WLI	27%	0.004	
								NBI	42%		
A Adler	2008	Prospective RCT	Single	7	401	not mentioned	not mentioned		Percentage of patients with adenoma		47
								WLI	16.7%	NS	
								NBI	22.7%		
T Inoue	2008	Prospective RCT	Single	6	243	RGB sequentia illuination	+/–		Percentage of patients with >1 adenoma		52
								WLI	34%	0.2	
								NBI	42%		
									Percentage of patients with >1 adenoma (<5mm)		
								WLI	17%	0.011	
								NBI	30%		
									Total no. adenoma		
								WLI	65	0.046	
								NBI	102		
A Rastogi	2008	Back to back fashion after polypectomy (WLI followed by NBI)	Single	1	40	Color CCD chip system	–		Number of detected adenoma	NE	48
								WLI	43		
								NBI	29 additional adenomas		
T Uraoka	2008	Back to back fashion (WLI followed by NBI)	Single	5	47	RGB sequentia illuination	+		Number of detected neoplams		
								WLI	116	0.02	
								NBI	134		
									Miss ratio of flat neoplastic lesions		
								WLI	32%	NE	
								NBI	15%		
									Miss ratio of polypoid neoplastic lesions		
								WLI	15%	NE	
								NBI	9%		
T Kaltenbach	2008	Prospective RCT	Single	6	276	Color CCD chip	–		Miss ratio of adenoma (95%CI)		
								WLI	12.1% (7.2–18.6)	NS	
								NBI	12.6% (7.5–19.4)		
									Percentage of patients with neoplasm		
								WLI	44%	0.29	
								NBI	50%		

CCD, charge coupled device; CI, confidence interval; NBI, narrow band imaging; NE, not evaluated; NS, not significant; RCT, randomized controlled trial; WLI, white light image.