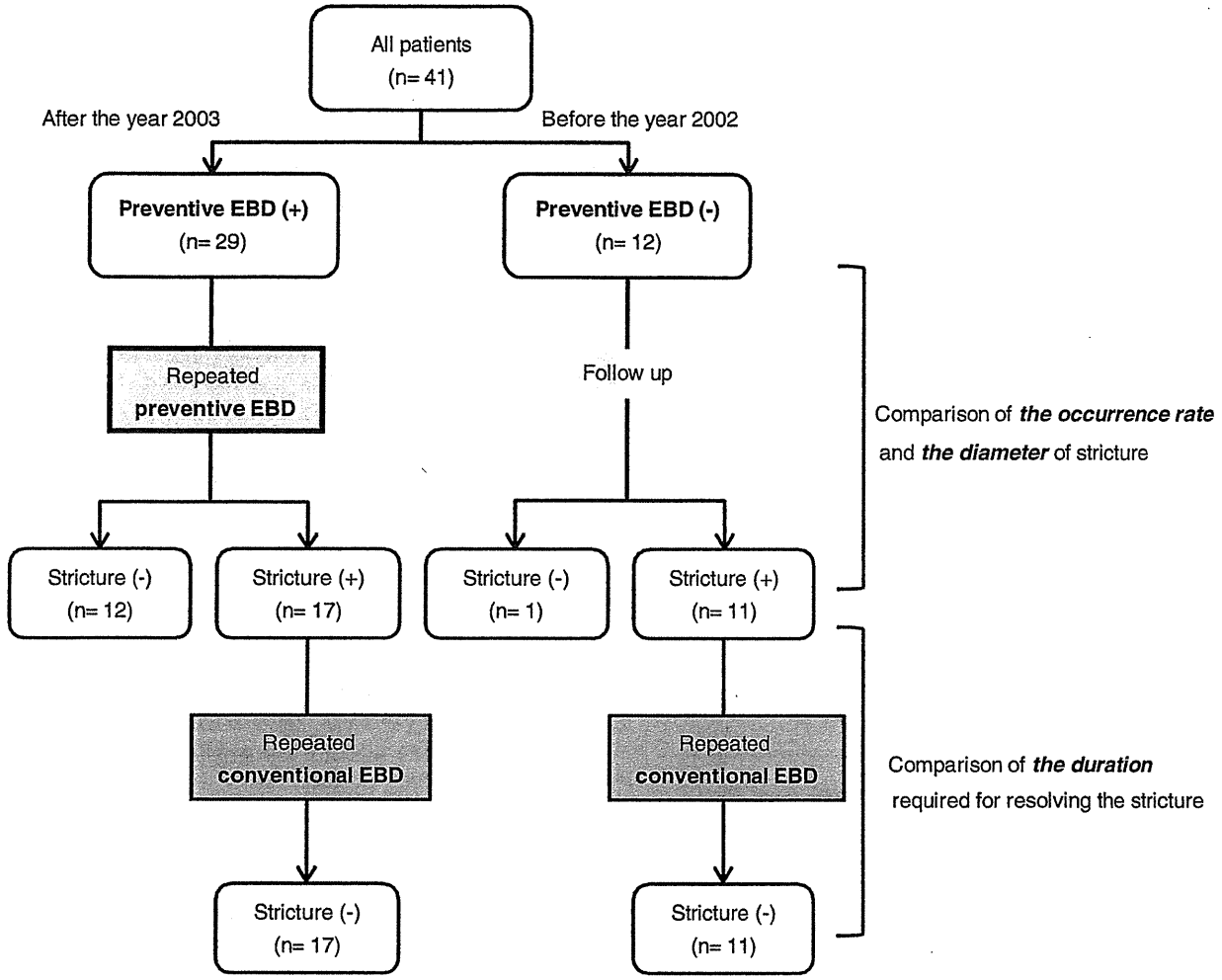

FIGURE 2. Diagram of patients flow.

Evaluation of Preventive EBD

The efficacy of preventive EBD was evaluated retrospectively by comparing the following 3 points between the patients with preventive EBD and those without it (Fig. 2); the occurrence rate of stricture, the diameter of stricture, and the duration required for resolving the stricture by repeated conventional EBD.

Statistical Analysis

Fisher exact test, or its extension when there were more than 2 categories, was used for categorical variables and the Mann–Whitney *U* test was used for continuous variables. Cox proportional hazard model was used for the multivariate analysis. A *P* value of more than equal to 0.05 was considered significant. All statistical analyses were carried out using the Dr SPSS II Statistics software package (SPSS Japan Inc., Tokyo, Japan).

RESULTS

Patient Background

Among the 64 patients with mucosal defects greater than three-fourths of the circumference of the esophagus after EMR/ESD, 3 patients did not attend follow-up consultations, 17 received additional treatment for primary lesions (chemoradiation for deep invasion of the carcinoma or EMR/ESD for local recurrence and incomplete resection), and 3 underwent surgical resection for metachronous gastric cancer immediately after EMR/ESD. We excluded these 23 patients because additional treatments had the potential to make the stricture worse. Finally, we used data from 41 lesions in 41 patients to evaluate the efficacy of the preventive EBD.

Thirty-six lesions were removed by EMR and 5 lesions were removed by ESD procedure. A histopathological diagnosis of squamous cell carcinoma was found in all lesions and 40 lesions were mucosal cancers but 1 submucosal cancer.

Of the 41 patients, 29 underwent preventive EBD and 12 did not. There were no statistical differences in the characteristics of the patients and the mucosal defects except for the endoscopic resection method between patients who underwent preventive EBD and those who did not. Because the ESD was recently established technique, there are no patients treated by ESD in the historical control group. Although the difference was not statistically significant, the rate of circumferential resections tended to be greater in

TABLE 1. Comparison of the Characteristics of Mucosal Defects After Endoscopic Resection in Patients With and Without Preventive EBD

	Preventive EBD		
	(+) n = 29	(−) n = 12	*P*
Sex			
Male	28	11	0.50
Female	1	1	
Age			
Median (range)	64 years (50-74)	60 years (48-80)	0.21
Circumference of the lumen			
Circumferential	10	6	0.49
Semi-circumferential	19	6	
Depth of resected lesion			
Mucosa	28	12	0.34
Submucosa	1	0	
Location			
Upper	3	1	0.30
Middle	13	5	
Lower	13	6	
Length of mucosal defect			
30 mm or less	6	4	0.30
More than 30 mm	23	8	
Median (range)	40 mm (10-110)	45 mm (20-70)	0.38
Endoscopic resection procedure			
EMR	24	12	< 0.001
ESD	5	0	

Number of patients are shown unless specified.
EBD indicates endoscopic balloon dilation; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

conventional EBD group [10/29 (34%) vs. 6/12 (50%), $P = 0.49$] (Table 1).

Profile of Preventive EBD Sessions

Among the 29 patients who underwent preventive EBD, the median number of preventive EBD sessions was 6 (range, 3 to 9) and the period of preventive EBD was 45 days (range, 16 to 65) (Table 3).

Efficacy of Preventive EBD

The number of patients who developed stricture after EMR/ESD was significantly lower in patients who were given preventive EBD than those who were not given preventive EBD [12/29 (59%) vs. 11/12 (92%), $P = 0.04$] (Table 2).

TABLE 2. Comparison of the Occurrence Rate and the Diameter of Esophageal Stricture Between Patients With and Without Preventive EBD

	Preventive EBD		
	(+)	(−)	*P*
No. patients who developed stricture	17/29 (59%)	11/12 (92%)	0.04
The narrowest diameter of the stricture			
≤2 mm	1/17 (6%)	4/11 (36%)	0.01
2 mm < and ≤5 mm	2/17 (12%)	4/11 (36%)	
5 mm <	14/17 (82%)	3/11 (28%)	

Number of patients are shown unless specified.
EBD indicates endoscopic balloon dilation.

The narrowest diameter of stricture in each patient was significantly larger in patients who were given preventive EBD than those who were not given preventive EBD [(≤2 mm; >2 mm and ≤5 mm; >5 mm) = (1; 2; 14) vs. (4; 4; 3), $P = 0.01$] (Table 2).

The number of days to development of stricture was 23 days (21 to 49) in patients without preventive EBD. Similarly, in patients who were given preventive EBD, tendency of stricture development was observed within 2 weeks after EMR/ESD. However, preventive EBD could prevent the patients' symptom such as dysphagea because dilation was carried out at short intervals (once a week) in all patients. Therefore, no patients suffered from dysphagea during the preventive EBD period in this study. Since the patients with preventive EBD complained the symptom of dysphagia after the completion of weekly preventive EBD, the number of days to development of stricture was 51 days (30 to 72). It was significantly longer in patients who underwent preventive EBD than those who did not ($P < 0.001$).

Seventeen patients with preventive EBD and 11 patients without preventive EBD developed esophageal stricture. Then, they were given conventional EBD repeatedly until the stricture was completely relieved. Among them, the duration required conventional EBD was significantly shorter in patients given preventive EBD than in those not given it (29 d vs. 78 d; $P = 0.04$). The number of conventional EBD sessions was smaller in patients with preventive EBD than in those without it, although the difference was not statistically significant (2 times vs. 4.5 times; $P = 0.5$) (Table 3).

The number of total EBD sessions was greater in patients with preventive EBD than in those without it, however, the difference was not statistically significant (8 times vs. 4.5 times; $P = 0.42$) (Table 3).

Safety of EBD Procedure

Among a total of 166 preventive EBD sessions for 29 patients, no complication occurred during the procedure (complication rate of preventive EBD: 0%). Among a total of 189 conventional EBD sessions for 28 patients, a perforation was occurred in 1 conventional EBD session in 1 patient (0.5% per total conventional EBD sessions, 3.6% per patient). The patient was immediately hospitalized and administered intravenous antibiotics. The patient had no symptoms or signs of mediastinitis. The fasting period was 3 days and hospital stay was only 1 week after causal EBD. No other major complication occurred.

Clinical Course of all Patients After EMR/ESD

Follow up period was calculated between the day of EMR/ESD and the day of patients' final visit. After the complete resolution of stricture, endoscopic examination was carried out every 6 months in all patients. Median follow up period of all patients was 84 months. There were no patients who suffered from dysphagea owing to the recurrence of stricture.

RISK OF STRICTURE

Risk Factors for Stricture Among Patients With Preventive EBD

The method of EMR and the longitudinal length of mucosal defect (>30 mm in length) were significantly

TABLE 3. Comparison of the Duration and the Number of EBD Sessions Required for Resolving the Stricture by Conventional EBD Between Patients With and Without Preventive EBD

	Preventive EBD		
	(+)	(−)	*P*
Period of preventive EBD*	45 d (16-65)	(−)	(−)
Number of days to development of the stricture*	51 d (30-72)	23 d (21-49)	< 0.001
Duration required for resolving the stricture*	29 d (15-169)	78 d (8-1093)	0.04
No. preventive EBD sessions*	6.0 sessions (3-9)	(−)	(−)
No. conventional EBD sessions*	2.0 sessions (2-20)	4.5 sessions (2-35)	0.5
No. total EBD sessions*	8.0 sessions (3-29)	4.5 sessions (0-35)	0.42
No. patients whose stricture was relieved	17/17 (100%)	11/11 (100%)	1

Number of patients are shown unless specified.
*Median (range).
EBD indicates endoscopic balloon dilation.

associated with the increased risk for development of stricture by multivariate analysis (Odds ratio: 20.8, 95% CI: 1.3-328.9 and 12.7, 95% CI: 1.3-126.9, respectively). Circumferential mucosal defects showed a higher rate of stricture than semicircumferential mucosal defects; however, the difference was not statistically significant (Odds ratio: 3.0, 95% CI: 0.2-40.5) (Table 4).

DISCUSSION

Technically, extended esophageal mucosal resection could be carried out. However, the development of the esophageal stricture is one of the most important problem to be solved. To date, there are no well-established methods to prevent the stricture after EMR/ESD. If we can prevent the development of the stricture after EMR/ESD by preventive EBD, the ability of the patients oral intake would be dramatically improved.

In this study, we showed that the preventive EBD reduced the incidence of esophageal stricture in patients who underwent an extensive EMR/ESD. In our preventive EBD protocol, EBD was carried out once a week for about 6 weeks [median; 44 days (16 to 65 d)] until the mucosal defect completely developed scar. Because of this strategy, the number of EBD sessions tended to be greater. Although it did not reach statistical significance ($P = 0.42$), the total number of EBD sessions was nearly twice as high compared with the conventional EBD group (8.0 vs. 4.5). However, the narrowest diameter of stricture was significantly mild in the preventive EBD group compared with the group without it (Table 2), whereas 60% of the patients in the preventive EBD group develop stricture. Clinically, the severity of the stricture is very important, because it critically affects the oral intake condition. Furthermore, the preventive EBD shortened the period to relieve the stricture even when the stricture was developed. These data indicated that the preventive EBD was a beneficial method, and thus should be considered to carry out for the patients who underwent extensive EMR/ESD as a supportive treatment.

TABLE 4. Predictive Factors for Development of Stricture After Endoscopic Resection in Patients who Received Preventive EBD

	Odds Ratio (95% CI)	*P*
Method of endoscopic resection		
ESD	1.0 (reference)	0.03
EMR	20.8 (1.3-328.9)	
Longitudinal length of mucosal defect involving over three-fourth of the esophageal circumference		
≤30 mm	1.0 (reference)	0.03
>30 mm	12.7 (1.3-126.9)	
Circumference of mucosal defect		
Semi-circumferential	1.0 (reference)	0.4
Circumferential	3.0 (0.2-40.5)	

EBD indicates endoscopic balloon dilation.

Perforation and massive bleeding were the most severe complications during the EBD procedure. However, there was no complication associated with preventive EBD procedure in this study. Thus, we could conclude that the preventive EBD was a feasible procedure. Not to develop perforation, we carefully carried out preventive EBD under fluoroscopic monitoring, to confirm with both the size of the stricture and the inflated balloon. When the patients complained of pain or when the balloon expanded exponentially, we stopped dilating the balloon immediately not to develop deep tear or perforation.

There were some imbalances of the characteristics of mucosal defect between 2 groups; the rate of circumferential resections [10/29 (34%) vs. 6/12 (50%), $P = 0.49$] and the rate of ESD resections [5/29 (17%) vs. 0/12 (0%), $P < 0.001$]. Although the difference of the rate of circumferential resections was not statistically significant, the possibility that the results of this study might be influenced by the difference cannot be denied. However, the "circumferential resection" and "noncircumferential resection" were not associated with the risk of development of stricture by the multivariate analysis even in the preventive EBD group. Therefore, it seemed that the imbalance about the rate of circumferential resection between 2 groups was not a major problem. As for the different rate of ESD resections, there are no patients treated by ESD in the historical control group because the ESD was recently established technique. These imbalances between 2 groups are unavoidable limitations of the retrospective review with small sample size.

The rate for stricture was lower in patients who underwent ESD than those who received EMR [1/5 (20.0%) vs. 16/24 (66.7%), $P = 0.03$]. Although the reason for this difference is unknown, 1 possibility is that the potent cautery effect of EMR compared with that of ESD might cause more severe submucosal injury resulting in an

increased risk for development of stricture.[15] Clarification of the precise mechanisms for developing stricture after EMR/ESD is warranted in future studies. In addition, the difference of rate for stricture between 2 groups might be influenced by the lower rate for stricture in ESD patients. However, there are no ESD patients who did not undergo preventive EBD, it is therefore impossible to evaluate real influence from ESD patients for the results of this study.

Temporary stent placement may also be a promising strategy for preventing postEMR/ESD stricture. Self-expandable removable stents or biodegradable stents have been reported to be useful for the treatment of benign stricture such as anastomotic stricture and cicatricial stricture by esophagitis.[16] However, there has been no report on the use of self-expandable removable stents for preventing the postEMR/ESD stricture. Although the biodegradable stents have been reportedly applied for prevention of the postEMR/ESD stricture, a small number of patients, short-term follow-up periods, and a high frequency of stent migration obscured its usefulness.[17,18] Thus, further evaluation of these methods is required to compare their usefulness with the EBD.

The multivariate analysis in patients with preventive EBD showed that the longer longitudinal mucosal defects (> 30 mm) was the significant risk factor for development of the stricture; in contrast, the circumferential mucosal defect was not a significant risk factor. To avoid the treatment induced esophageal stricture, these data are informative when we select the treatment modalities for the extended esophageal cancer; such as EMR/ESD, chemoradiotherapy, radiotherapy, or surgical resection. If patients prefer the remaining the sufficient ability of oral intake, extensive EMR/ESD should not be indicated, because the long term EBD would be needed and the symptom of dysphagia afflicts the patients.

In conclusion, preventive EBD could be a useful and acceptable strategy to reduce the incidence of postEMR/ESD stricture. Because there is no other effective method to prevent stricture after extensive EMR/ESD at present, preventive EBD should be considered for all patients who undergo extensive EMR/ESD. Although almost 60% of patient developed stricture despite the preventive EBD, the severity of the stricture was clearly reduced even when the stricture was developed. Since the number of patients in this study is rather small, and moreover, this was the retrospective study, a prospective study with a large number of cases is required to confirm the effectiveness of preventive EBD procedure for the prevention of postEMR/ESD stricture in patients with early stage esophageal cancer.

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Early Detection of 5-FU-induced Acute Leukoencephalopathy on Diffusion-Weighted MRI

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A 59-year-old man treated with 5-fluorouracil and cisplatin for advanced oesophageal cancer presented abnormal behaviour and subsequently developed impairment of cognitive function, dysphagia and dysarthria on the fifth day of the treatment. Although brain computed tomography revealed no abnormal findings, brain magnetic resonance imaging using diffusion-weighted imaging clearly revealed the presence of a high signal intensity in the deep white matter of the bilateral cerebral hemispheres, including the corpus callosum symmetrically. A diagnosis of acute leukoencephalopathy was reached based on these findings. His clinical symptoms normalized four days after the discontinuation of the chemotherapy. Improvement in magnetic resonance imaging findings was delayed compared with that of clinical symptoms; however, the high signal intensity detected in the deep white matter had disappeared completely five months after the onset of symptoms. Early detection of drug-induced leukoencephalopathy is important as the clinical symptoms can be reversed by early discontinuation of the causative drug. Diffusion-weighted magnetic resonance imaging is a useful modality for the early detection and definitive diagnosis of this characteristic encephalopathy.

Key words: acute luekoencephalopathy – 5-fluorouracil – oesophageal cancer – MRI – diffusion-weighted imaging

INTRODUCTION

5-Fluorouracil (5-FU) is widely used in the treatment of a spectrum of solid cancers, such as carcinoma of the head and neck, oesophagus, stomach, intestine and ovaries. Some adverse reactions of the drug, which include toxic effects to the central nervous system, have been reported (1,2). Among them, encephalopathy is rare and may present as disorientation, confusion, agitation, neurosensory hearing impairment, seizure, stupor, and even deep coma. Diffusion-weighted magnetic resonance imaging (DW-MRI) is a useful modality for the early detection and definitive diagnosis of this characteristic encephalopathy. Herein, we reported a case of 5-FU-induced acute leukoencephalopathy.

CASE REPORT

A 59-year-old man who presented with cough and dysphagia was admitted to our hospital. Oesophago-gastroduodenoscopy showed an ulcerative and localized type of tumour in the middle oesophagus with intramural metastasis to the anal side. A biopsy specimen revealed the presence of well-differentiated squamous cell carcinoma. Enhanced computed tomography (CT) demonstrated that the oesophageal wall thickness was invasive to the surrounded organs, with multiple lymph nodes metastasis at the supramediastinum and the bilateral supraclavicular fossa and with paraaortic localization. A diagnosis of stage IVB (TNM classification. cT4N1M1b) advanced oesophageal cancer was established

and the patient received systemic chemotherapy (cisplatin, cis-diaminedichloroplatinum (CDDP); 80 mg/m^2, day 1) and 5-fluorouracil (5-FU; 800 mg/m^2, days 1–5). On the fifth day of the treatment, he presented an abnormal behaviour and subsequently developed impairment of cognitive function, dysphagia and dysarthria. Vital signs and serum examination were normal, with the exception of an elevated level of ammonia (117 μg/dl; normal range, 20–60 μg/dl). No abnormal findings, including brain metastasis, were detected in the CT images (Fig. 1) and T1-weighted magnetic resonance imaging (MRI) (Fig. 2A). T2-weighted MRI faintly revealed the presence of a high signal intensity in the deep white matter of the bilateral cerebral hemispheres, including the corpus callosum (Fig. 2B). In contrast, DW-MRI clearly revealed the presence of a symmetrical high signal intensity at the same anatomical location (Fig. 2C). As drug-induced acute leukoencephalopathy was suspected based on these findings, both 5-FU and CDDP were discontinued at a total dose of 6000 and 1300 mg, respectively. Clinical symptoms disappeared after the discontinuance of the drugs. He was discharged on the twenty-first day, without recurrence of central nervous system toxicity. One month after the onset of the disease, he was asymptomatic and neurological examination was normal. In addition, the high signal intensity detected in the deep white matter of the bilateral cerebral hemispheres had almost disappeared, and there were only some remnants of it at the splenium of the corpus callosum (Fig. 3A). MRI performed at five months after the onset of the symptoms revealed the complete disappearance of the high signal intensity in both the bilateral cerebral white matter and the corpus callosum (Fig. 3B).

DISCUSSION

Leukoencephalopathy initially manifests itself as dizziness, numbness, disorientation, memory deficit, confusion, agitation, cognitive impairment and unsteady gait. In severer cases, stupor, seizure, akinetic mutism, and even comas may occur (3). Drug-induced leukoencephalopathy is mainly caused by various chemotherapeutic agents, which include methotrexate, vincristine, ifosfamide, fludarabine, cytarabine, 5-fluorouracil, cisplatin and the interferons (4). Among them, 5-FU has been reported most frequently as a leukoencephalopathy causative agent. 5-FU is a fluorine-substituted analogue of pyrimidine uracil. The main action of this agent is to block DNA synthesis by reducing the formation of thymidine monophosphate via the inhibition of the thymidylate synthetase and incorporation into RNA. 5-FU readily penetrates the blood-brain barrier; however, 5-FU-induced neurotoxicity is uncommon and has an incidence of less than 5% among patients treated with this agent. In general, 5-FU-induced leukoencephalopathy is more common in females and in patients with malnutrition or liver dysfunction (5). Hyperammonemia, lactic acidosis and hypocapnia were found to be parallel to the development of encephalopathy. Interestingly, these abnormalities were not detected in patients who did not develop encephalopathy (6). The specific mechanism that underlies hyperammonemia is unknown; however, several factors, including renal dysfunction, constipation, weight loss and infection, aggravate this condition (7).

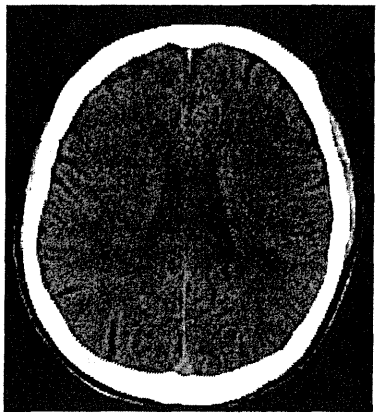

Figure 1. Brain computed tomography performed on the day of the onset of the symptoms showed an absence of abmormalities.

Dyhydropyrimidine dehydrogenase (DPD) is responsible for more than 85% of the catabolism of pyrimidine. Several studies suggest that DPD deficiency, in which the serum and urine levels of uracil and thymidine are increased, may be a risk factor for 5-FU-induced leukoencephalopathy (8).

The common radiological imaging findings of leukoencephalopathy include symmetrical periventricular hypoattenuation on CT scan and diffuse high intensity signal in the white matter and corpus callosum on T2 weighted MRI DW-MRI. DW-MRI is more sensitive than CT scan for the detection of abnormalities in the white matter (9). In the present case, it clearly revealed the presence of a high signal intensity in the deep white matter of the bilateral cerebral hemispheres, including the corpus callosum symmetrically, which was consistent with 5-FU-induced leukoencephalopathy. Cisplatin-induced neurotoxicity is rare and less likely to be present in this case, as the involvement was confined solely to the deep cerebral white matter, and did not extend to the cortex and subcortical white matter (10).

The exact pathological process associated with drug-induced leukoencephalopathy remains unknown. Elevated levels of myelin basic protein in the cerebrospinal fluid (CSF) suggest the presence of myelin destruction (11) (in our case, CSF examination was not performed). *In vitro* and *in vivo* studies suggest that segmental splitting, vacuolization and myelin swelling may occur in humans in the early stage of the disease. It has been known that DW-MRI detects molecular motion of water protons. The accumulation of many small vacuoles within the myelin may interfere with diffusion, thus leading to the appearance of high signal intensity on DW-MRI.

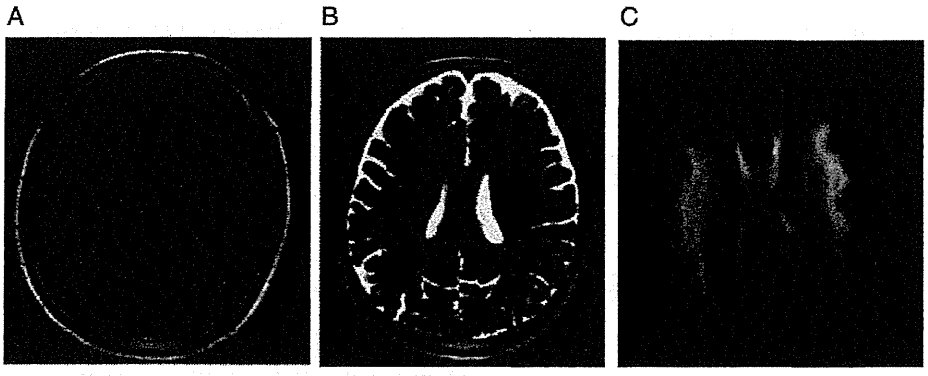

Figure 2. Brain magnetic resonance imaging (MRI) on the day of the onset of the symptoms. (A) No abnormal findings were detected on T1-weighted MRI (B). T2-weighted MRI faintly revealed the presence of a high signal intensity in the deep white matter of the bilateral cerebral hemispheres, including the corpus callosum. (C) In contrast, MRI-diffusion weighted imaging (DWI) clearly revealed the presence of a symmetrical high signal intensity at the same anatomical location. The value of b factor was 1000 s/mm^2.

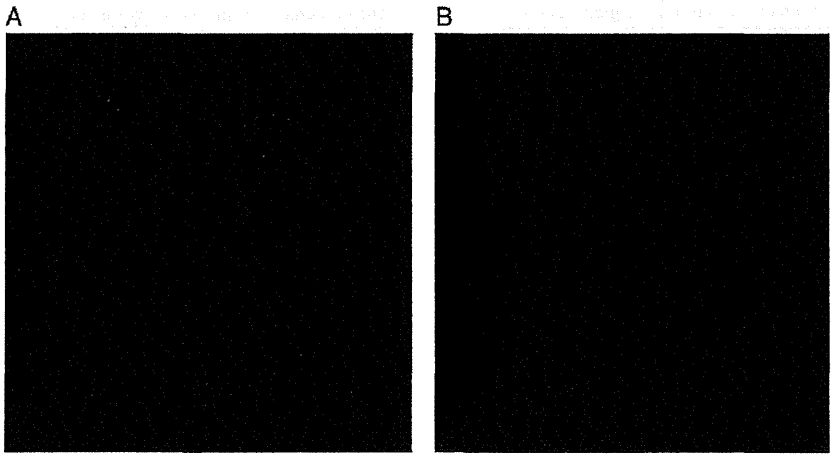

Figure 3. Time course variation of brain MRI-DWI. (A) The high signal intensity detected in the deep white matter of the bilateral cerebral hemispheres and corpus callosum was still slightly visible on MRI-DWI performed one month after the onset of symptoms. (B) These lesions had disappeared completely on the MRI-DWI performed five months after the onset of symptoms.

Drug-induced leukoencephalopathy is dose- and schedule-dependent and is reversible after drug withdrawal or dose reduction; however, in some cases it may lead to life-threatening complications. In other words, the improvement of clinical symptoms after the withdrawal of the causative drug strongly supports the encephalopathy diagnosis. The disease seems to be associated with two clinical courses, according to the time of onset. The first is an acute phase, which develops within one week after administration of the medication. The second is a subacute phase, which develops within five months after administration of the medication (12,13). The treatment modalities proposed in the literature vary considerably and range from purely supportive measures to the use of corticosteroids, thiamine (2,12,13).

Age-related periventricular hyperintensity must be differentiated from drug-induced leukoencephalopathy. Though these T2-weighted MRI findings are similar to those observed in drug-induced leukoencephalopathy, DWI findings differ between the two conditions. DW-MRI of drug-induced leukoencephalopathy revealed the presence of a hyperintensity in the periventricular white matter, whereas that of age-related periventricular hyperintensity showed an absence of any abnormal findings corresponding to the hyperintensity observed on T2-weighted images. From this point of view, DW-MRI seems to be a very useful modality to differentiate this encephalopathy from another condition.

In conclusion, the development of conscious disturbance or abnormal neurological findings in patients treated with chemotherapeutic agents (especially 5-FU) should lead to the consideration of a drug-induced leukoencephalopathy diagnosis. Moreover, in such cases it is important to perform MRI (especially DW-MRI) immediately to establish a

definitive diagnosis, as the neurological symptoms are reversible after discontinuance of the causative drug.

Conflict of interest statement

None declared.

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DISEASES OF THE ESOPHAGUS

Original article

Submucosal tumor appearance is a useful endoscopic predictor of early primary-site recurrence after definitive chemoradiotherapy for esophageal squamous cell carcinoma

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SUMMARY. **Chemoradiotherapy (CRT) for esophageal cancer is disadvantageous because of a high locoregional failure rate. Detecting early small recurrent cancers at the primary site is necessary for potential salvage treatment. However, most endoscopists are inexperienced and therefore, a role for surveillance endoscopy after complete remission (CR) has not been established. We retrospectively evaluated serial surveillance endoscopic images from patients eventually proved to have primary-site recurrence in order to identify useful endoscopic features for early diagnosis. From January 2000 to December 2004, 303 patients with esophageal squamous cell carcinoma underwent definitive CRT, and 133 of them achieved CR. The surveillance endoscopic images stored at intervals of 1–3 months for the 16 patients with recurrence only at the primary tumor site and the 61 patients with no recurrence were collected for reexamination. Among 133 patients who achieved CR, 16 (12%) developed only local recurrence at the primary site. Thirteen of the 16 primary-site recurrent tumors (81%) appeared as submucosal tumors (SMT), with the remaining appearing as erosions or mild strictures. Of biopsy-proven recurrences, 81% were preceded by newly developed lesions such as SMT, erosions, or mild strictures detected by earlier surveillance endoscopies. For all 77 patients achieving CR with no metastasis, 86% of the evolving SMT with negative biopsies were eventually confirmed as cancer at later endoscopies. Thirteen of the 21 evolving lesions were subsequently confirmed as recurrent cancer. Early primary-site recurrence of esophageal cancer after a complete response to CRT is detectable with frequent endoscopic surveillance. SMT appearance is a useful endoscopic sign of early recurrence, as well as a predictor of subsequent diagnosis of recurrence.**

KEY WORDS: **chemoradiotherapy, esophageal cancer, recurrence, surveillance.**

INTRODUCTION

Definitive chemoradiotherapy (CRT) is widely accepted as a standard treatment option in the management of locally advanced esophageal cancer because of its high response rate and significant survival benefit.[1,2] A major drawback to this nonsurgical approach is locoregional treatment failure. At least 40% of patients undergoing CRT experienced local failure, some of whom did not develop distant metastases.[1,3–5]

These primary-site recurrence patients are traditionally managed with salvage esophagectomy for a chance of long-term survival, particularly in those with an earlier pathological stage (T1N0 and T2N0).[6,7] However, high perisurgical mortality and morbidity rates are major concerns.[7,8] Recently developed nonsurgical techniques, such as salvage endoscopic mucosal resection and photodynamic therapy,

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have the advantages of greater safety and fewer treatment-related sequelae, while conferring promising survival benefits for local failures after definitive CRT.[9,10] Technically, endoscopic mucosal resection and photodynamic therapy are feasible only when the volume of the locally recurrent tumor is small enough to be amenable to these endoscopy-based procedures. Therefore, the application of these newer treatments depends crucially on the ability to identify early recurrent tumors by endoscopy.

A strategy of frequent surveillance endoscopy initiated early after remission of the cancer should theoretically improve the chances of detecting primary-site recurrent tumors in their early stages. This requires the prompt recognition of minute tumors arising from the former neoplastic bed, instead of from the uninvolved normal esophageal mucosa. However, the complete regression of cancer cells results in residual fibrosis, radiation-induced tissue injury, and the distortion of normal microstructures,[11,12] which may render relapsing neoplastic growth morphologically different from typical primary tumors. Apparently, most endoscopists are inexperienced in hunting for these difficult lesions. To our knowledge, no study of the skills in endoscopic detection of such lesions has been published. Not surprisingly, a follow-up endoscopy after the completion of CRT is considered 'optional' in the National Comprehensive Cancer Network clinical practice guidelines for esophageal cancer.[13] We believe that a reliable endoscopic diagnostic technique is necessary to support a strategy of intense endoscopic follow-ups.

As a cancer referral and research hospital, our institute is unique in its implementation of a vigorous endoscopic follow-up program after primary treatment for all patients with esophageal cancer. Therefore, it is possible to analyze the filed imaging data of endoscopic monitoring on the post-CRT mucosa. In the present study, we aimed to identify useful endoscopic findings through reviewing the image data pool to predict recurrent esophageal cancers limited to the primary site after complete remission (CR) is achieved by CRT.

MATERIALS AND METHODS

Patient population

Between January 2000 and December 2004, 303 patients with esophageal squamous cell carcinoma underwent definitive CRT at the National Cancer Center Hospital East, Kashiwa, Japan. The CRT consisted of 50.4–60 Gy irradiation, together with two cycles of continuous infusion with 5-fluorouracil (5FU) and cisplatin. Up to four courses of CRT were added for those patients who showed a good initial response to treatment.[9]

Table 1 Clinical data of 133 patients achieving complete remission with definitive chemoradiotherapy

Characteristic		Number of patients	%
Sex			
Male		110	82.7
Female		23	17.3
Age (years)			
Mean	62		
Range	39–76		
T stage			
T1		30	22.6
T2		21	15.8
T3		70	52.6
T4		12	9.0
N stage			
N0		46	34.6
N1		87	65.4
M stage			
M0		123	92.5
M1		10	7.5
Clinical stage			
I		16	12.0
II		45	33.8
III		62	46.6
IV		10	7.5
Macroscopic classification			
Type 0		30	22.6
Type 1		19	14.3
Type 2		60	45.1
Type 3		24	18.0

Response to treatment was assessed at the completion of CRT. CR was defined when all the following criteria were met: (i) the disappearance of the tumor lesion or ulcer at the primary site, with negative biopsies; (ii) no esophageal stricture or any condition that prevented a thorough endoscopic examination of the whole esophagus; (iii) no remaining measurable disease or distant metastasis on computer tomography and chest roentgenography; and (5) these criteria were met for at least 4 weeks.

Of the 303 patients, 133 (43.9%) were defined as being in CR at the completion of CRT. Of these 133 patients, 110 were men, with a median age of 62 years. Pretreatment staging of their esophageal cancers was determined with the tumor-node-metastasis classification of the International Union Against Cancer.[14] Seventy (52.6%) patients had T3 tumors; most patients had N1 (65.4%) or M0 (92.5%) disease. Forty-five (33.8%) and 62 (46.6%) patients were classified as clinical stages II and III, respectively (Table 1).

Study design

After achieving CR, initial follow-up endoscopy to confirm CR was scheduled within at most 1–2 months for each patient, accompanied with other necessary studies for the assessment of metastases. After the confirmation of CR, follow-up endoscopy was scheduled every 2–3 months for the first year and every 4–6

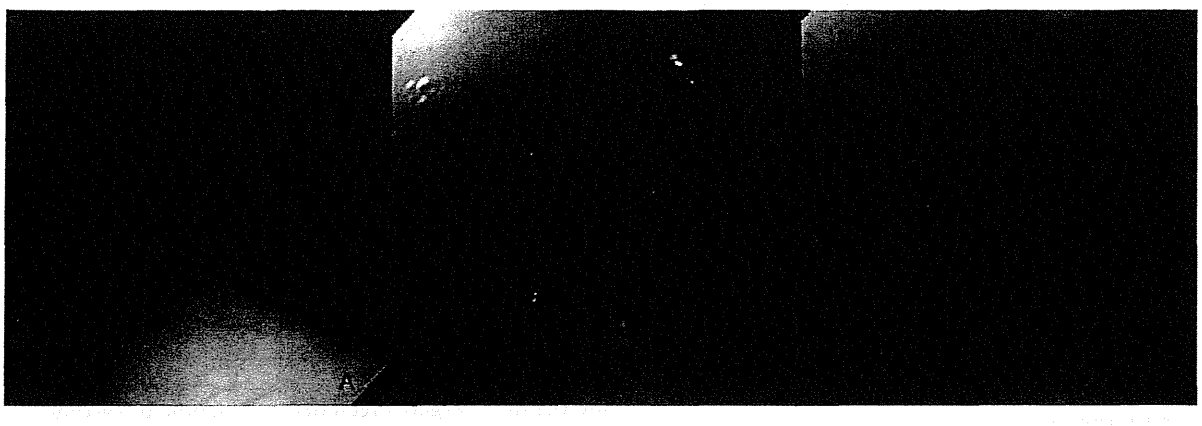

Fig. 1 Initially growing recurrent esophageal cancer at the primary tumor site after complete remission was achieved with chemoradiotherapy may be detected by endoscopy, with features of a submucosal tumor (A), a submucosal tumor with superficial ulcer (B), or a flat erosion (C).

months for 2 years thereafter. Lugol staining and multiple biopsies at the primary site were routinely required.[15] The diagnosis of local recurrence was determined by a positive biopsy.

Of the 133 CR patients, 61 had no recurrence, 56 developed lymph node or distant metastases, and the remaining 16 developed local recurrence at the primary tumor site with no evidence of metastasis. We excluded the 56 patients with lymph node or distant metastases from this study because for them, evaluation of the primary site was not important and only those patients eligible for salvage treatment on local tumors were of interest. Therefore, the endoscopic images of the remaining 77 patients were retrospectively enrolled. This population comprised patients with esophageal squamous cell carcinoma who achieved CR after the initial CRT and developed no metastasis during follow-up, regardless of local recurrence. All of the filed endoscopic images stored after achieving CR, both conventional endoscopy and Lugol-stained chromoendoscopy, were retrospectively collected for reexamination. The stored endoscopic images were evaluated by consensus among three endoscopists experienced in upper gastrointestinal cancer diagnosis (K. T., M. M., K. M.).

RESULTS

Upon the diagnosis of primary-site recurrence for the 16 patients, 13 (81%) had endoscopic findings resembling submucosal tumors (SMT), typically a focal bulge mostly covered by normal-appearing mucosa (Fig. 1A).[16] Eleven of the 13 tumors contained central eroded areas recognized as ulcers or erosions (Fig. 1B and 1C). The remaining three tumors were detected as flat erosions without features of SMT (Table 2).

Images of surveillance endoscopies performed at intervals between CR and the diagnosis of recurrence in the 16 patients were sequentially examined. Newly developed gross lesions at the primary site with negative biopsies were interpreted as recurrent lesions. Evolving lesions were discovered in 13 (81%) patients, including six (38% of the 16 patients) SMT, five (31%) erosions, and two (12%) mild luminal strictures (Table 3).

For all 77 patients achieving CR and free of metastasis, lesions newly developed between CR and the most recent endoscopic surveillance were considered evolving lesions. Therefore, an evolving lesion may be eventually proven to be a recurrence or remain biopsy-negative at the most recent endoscopy. Six of the seven (86%) evolving SMT were subsequently confirmed as recurrent cancer by follow-up

Table 2 Endoscopic findings at primary-site with biopsy-proven recurrence

Endoscopic finding	Number of patients	%
SMT	13	81
SMT with erosion or ulceration	11	
SMT without erosion or ulceration	2	
Erosion	3	19
Total	16	100

SMT, submucosal tumor.

Table 3 Endoscopic findings of newly developed lesion for primary-site recurrent tumors

Preceding newly developed lesions with negative biopsies	Findings at diagnosis of recurrence	Number of patients
SMT	SMT	6
Erosion	SMT	4
Erosion	Erosion	1
Mild stricture	SMT	2
No newly developed lesion	SMT	1
No newly developed lesion	Erosion	2
Total		16

SMT, submucosal tumor.

Table 4 Primary-site biopsy results of the latest surveillance endoscopy for patients who achieved complete remission and remained free of metastasis

Evolving lesion found at preceding endoscopies	Numer of patients (%)	Biopsy result of the latest endoscopy	Number of patients (%)
SMT	7 (9)	Recurrence	6 (86)
		Negative	1 (14)
Erosion	8 (10)	Recurrence	5 (63)
		Negative	3 (37)
Mild stricture	6 (8)	Recurrence	2 (33)
		Negative	4 (67)
No evolving lesion	56 (73)	Recurrence	3 (5)
		Negative	53 (95)
Total	77 (100)		

SMT, submucosal tumor.

endoscopic biopsies. Similarly, five of eight (63%) evolving erosions and two of six (33%) evolving mild strictures were finally confirmed as recurrence. Fifty-six patients were never found to have evolving lesions throughout the follow-up, including three (5%) who were confirmed as recurrence upon the first appearance of an endoscopic lesion. In total, eight of the 21 (38%) patients who developed evolving lesions remained biopsy-negative at their most recent endoscopic follow-up (Table 4).

DISCUSSION

We discovered that the most frequent (81%) endoscopic indicator of primary-site recurrence at its earliest possible stage for a histological diagnosis is SMT. Eighty-one percent of biopsy-proved recurrences were preceded by newly developed lesions such as SMT, erosions, or mild strictures detectable with surveillance endoscopies. Most (86%) evolving SMT with negative biopsies were eventually confirmed as cancer at later endoscopies, but the proportions were lower for other evolving lesions such as erosions (63%) and strictures (33%). This is the first study to describe the morphological changes of early recurring tumors by serial endoscopic observations at short intervals. Our findings will be helpful for improving the skills to detect potentially treatable primary-site recurrence after definitive CRT for esophageal squamous cell carcinoma.

For the endoscopic diagnosis of primary esophageal cancer, several features have been previously described to detect early stage squamous cell carcinoma: localized mucosal erosions in contrast to normal surrounding mucosa; circumscribed mucosal protuberances with irregular configurations; focal areas of mucosal coarsening and congestion; and, rarely, white mucosal plaques.[16] However, these features are not reliable when applied to early recurrent tumors arising from the mucosal bed of a former primary cancer that regressed after CRT. The original esophageal layering and vascular structures have been disrupted by the primary tumor. Furthermore, the expansion and arrangement of recurring neoplastic cells are disrupted by tissue reactions to previous chemotherapy and radiotherapy, as well as by subsequent repair processes. Tumor necrosis, foam cell formation, vascular granulation, inflammatory exudation, and fibrosis are frequent histological sequelae of CRT.[17,18] The minute foci of the initial neoplastic growth may arise from scattered residual cancer cells in deeper tissues, rather than from the superficial mucosal layer, as does the primary cancer.[11] These factors have largely precluded endoscopic ultrasound as a feasible tool in the assessment of residual or recurrent esophageal cancers.[19,20] For the same reason, the endoscopic diagnostic features for recurrent tumors are likely to be different from those for primary tumors.

We speculate that most of the SMT lesions discovered in our study were formed by expanding tumor cells in the submucosal layers, but barely reached the luminal surface because of their depth and constraining fibrosis. Although the overlying mucosa appeared normal, they manifest their first sign by bulging outward. Malignant cells can be captured by biopsy forceps only when they reach the surface in sufficient numbers, or more efficiently, destroy the surface to make an erosion. This might explain why all of the six newly developed SMT yielded negative results at their first biopsies but eventually proved to be recurrences (Table 3).

Several previous studies have aimed to improve the detection of local recurrence by measures other than endoscopy. In addition to pretreatment staging, F-18-fluorodeoxyglucose–positron emission tomography (FDG–PET) is highly sensitive (up to 96%) in detecting recurrent esophageal cancer, but with somewhat lower specificity (68–82%).[21–23] However, its utility in detecting locoregional recurrence is limited by its low specificity (57–75%) for postesophagectomy patients. Postsurgical inflammation and anatomical changes are largely responsible for the false positivity. Detecting small residual or early recurrent cancers is even more challenging because low tumor volume could greatly reduce the sensitivity of FDG–PET. Moreover, such lesions are not distinguishable from post-CRT inflammation or regional lymph-node metastasis.[24,25]

The results of our study disagree with the conventional belief that endoscopy is of limited utility in the management of esophageal cancer after CRT.[13,26] We believe that routine endoscopy, particularly focused on the primary tumor site, is advisable for all patients with esophageal squamous cell carcinoma after the completion of CRT. We also suggest regular endoscopic surveillance at least every three months for those who have achieved CR. The occurrence of

SMT-like lesions after CR is an alarming sign that deserves intensive investigation and follow-up if a modality of salvage treatment is available. Any evolving lesion at the primary site with negative biopsy should be followed closely.

Our retrospective study design has introduced a knowledge bias because the evaluating endoscopists were not totally blinded to the outcomes. Therefore, a randomized controlled trial comparing the clinical outcomes is necessary to establish the role of surveillance endoscopy after definitive CRT for esophageal squamous cell carcinoma.

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ORIGINAL REPORT

Early Detection of Superficial Squamous Cell Carcinoma in the Head and Neck Region and Esophagus by Narrow Band Imaging: A Multicenter Randomized Controlled Trial

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ABSTRACT

Purpose
Most of the esophageal squamous cell carcinomas (ESCCs) and cancers of the head and neck (H&N) region are diagnosed at later stages. To achieve better survival, early detection is necessary. We compared the real-time diagnostic yield of superficial cancer in these regions between conventional white light imaging (WLI) and narrow band imaging (NBI) in high-risk patients.

Patients and Methods
In a multicenter, prospective, randomized controlled trial, 320 patients with ESCC were randomly assigned to primary WLI followed by NBI (n = 162) or primary NBI followed by WLI (n = 158) in a back-to-back fashion. The primary aim was to compare the real-time detection rates of superficial cancer in the H&N region and the esophagus between WLI and NBI. The secondary aim was to evaluate the diagnostic accuracy of these techniques.

Results
NBI detected superficial cancer more frequently than did WLI in both the H&N region and the esophagus (100% *v* 8%, $P < .001$; 97% *v* 55%, $P < .001$, respectively). The sensitivity of NBI for diagnosis of superficial cancer was 100% and 97.2% in the H&N region and the esophagus, respectively. The accuracy of NBI for diagnosis of superficial cancer was 86.7% and 88.9% in these regions, respectively. The sensitivity and accuracy were significantly higher using NBI than WLI in both regions ($P < .001$ and $P = .02$ for the H&N region; $P < .001$ for both measures for the esophagus, respectively).

Conclusion
NBI could be the standard examination for the early detection of superficial cancer in the H&N region and the esophagus.

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INTRODUCTION

Esophageal cancer is the eighth most common cancer worldwide, accounting for 462,000 new cases in 2002, and is the sixth most common cause of cancer-related death (386,000 deaths).[1] Squamous cell carcinoma (SCC) is the most common histologic type worldwide.[1] Head and neck (H&N) cancer accounted for 607,000 new cases and 261,000 deaths in 2002.[1] The most common histologic type of H&N cancer is also SCC.

The early detection of cancer offers the best prognosis. Currently, however, esophageal SCC (ESCC) and H&N SCC (HNSCC) are detected at a late stage and then have poor prognoses.[1] Early detection of these cancers is difficult by conventional endoscopic white light imaging (WLI). Lugol chromoendoscopy can be used to detect superficial ESCC, but it causes unpleasant adverse effects such as severe chest pain and chest discomfort,[2-4] and it cannot be used for HNSCC screening because of the risk of aspiration.

The narrow band imaging (NBI) system is an innovative optical image-enhanced technology that uses narrow bandwidth NBI filters.[5,6] The central wavelengths of the NBI filters are 415 and 540 nm and each has a bandwidth of 30 nm. This system is easily activated by pushing a button on the endoscope. NBI combined with magnifying endoscopy can clearly visualize the microvascular structure of the organ surface,[6,7] because the 415-nm light is well absorbed by hemoglobin. Surface microvascular irregularities provide useful landmarks for identifying an early neoplasm in the H&N region, bronchus,

and the GI tract.[7-15] We previously reported that NBI was useful for identifying HNSCC at an early stage.[8] Watanabe et al[16,17] also reported the usefulness of NBI rhinolaryngovideoscopy for the diagnosis of HNSCC. Yoshida et al[18] reported that NBI improves the accuracy of magnifying WLI in the assessment of ESCC.

However, the diagnostic yield of NBI in the early detection of superficial SCC has not been investigated. We conducted a prospective randomized study to directly compare WLI and NBI in the early diagnosis of SCC in the H&N region and the esophagus among high-risk patients.

Study Rationale

Because ESCC patients frequently develop multiple intraesophageal SCC and second primary HNSCC synchronously and metachronously,[4,19-22] they provide a good cancer screening model. Whereas massively invasive SCC is easy to detect by endoscope, superficial cancer has been difficult. Furthermore, detection of high-grade intraepithelial neoplasia (HGIN) is clinically important because HGINs have the potential to become malignant invasive cancers.[23,24] Therefore, in this study, we targeted only macroscopic superficial cancer including HGIN that appeared as slightly elevated lesions lower than 5 mm, flat lesions, and lesions with a shallow depression. Lesions with an apparent elevation greater than 5 mm or those with apparent deeper ulceration were not evaluated.

The primary analysis of this study was a comparison of the detection rates of superficial cancer (HGIN, carcinoma in situ, and microinvasive SCC) using WLI and NBI. The secondary analysis was a comparison of the diagnostic accuracy (sensitivity and specificity) of the two imaging methods, size of the lesion detected, and the examination time. To evaluate diagnostic accuracy, we used the histologic diagnosis from a biopsy specimen as the gold standard diagnosis.

Study Populations

The protocol and consent form for this study were approved by the institutional review board at each participating institution, and written informed consent was obtained from all patients. The inclusion criteria were histologically confirmed present or previous ESCC and an age of 20 years or older. Although this study included patients with advanced ESCC, we evaluated only concomitant superficial cancer but not primary advanced cancer. Patients who had been previously treated for ESCC by endoscopic mucosal resection were included, because their esophagus was preserved with minimal damage. Patients with prior chemotherapy, radiotherapy, chemoradiotherapy, or surgical resection for ESCC or HNSCC were excluded, because their esophagus or pharynx was removed or too damaged to evaluate. Patients referred from another hospital with newly diagnosed ESCC were also included because they required more detailed examination (Fig 1) . The endoscopists were blinded to the endoscopic information. Patients with esophageal stricture, esophageal varices, or allergy to lugol dye solution were excluded.

Study Design

Patients were randomly assigned to receive primary WLI or primary NBI. To investigate whether a lesion detected by primary imaging could be identified subsequently by the other type of imaging, or whether a lesion missed by primary imaging could be identified subsequently by the other type of imaging, we performed both imaging methods in a back-to-back fashion so that primary WLI was followed by NBI and primary NBI was followed by WLI. To avoid affecting the first imaging results, the report of the first examination was completed before the second imaging was started.

To improve the quality of the reporting in the diagnostic accuracy study, we complied with the Standards for Reporting of Diagnostic Accuracy (STARD) initiative.[25] We set WLI as reference standard and NBI as index test.

Random assignment was performed in each case by an investigator using a computer-aided system on Medical Research Support Web site (Kyoto, Japan). This Web site was available only to the study participants. Using a minimization algorithm, the selection of the primary examination was balanced with respect to five stratification variables: institution, age (< 60 and ≥ 60 years), sex, alcohol consumption, and smoking habit.

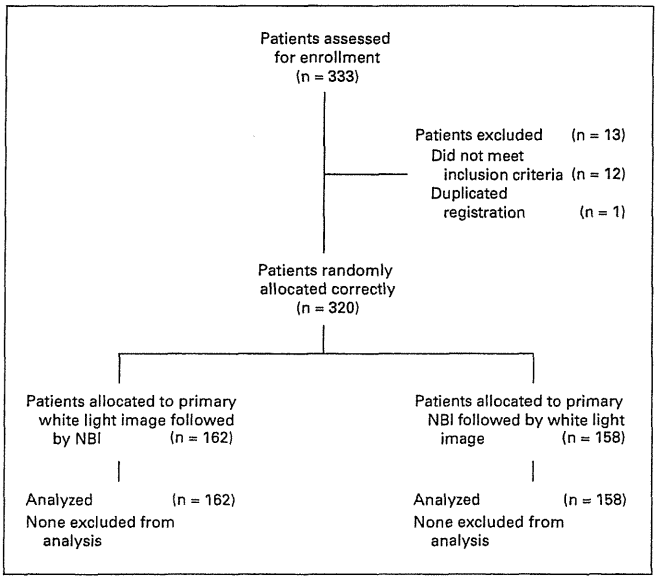

Fig 1. CONSORT diagram; overview of the study design. NBI, narrow band imaging.

Calculation of the Sample Size

For the purposes of this study, we set the probability for error (α) to .05 with a power of 0.80 (reflecting a β error of .2). Because there are no published comparative studies of NBI in ESCC patients, we estimated that the NBI system would increase the detection yield for superficial cancer by at least threefold compared with conventional WLI. This resulted in a calculated sample size of 250 patients (125 per group). Finally, we recruited an additional 50 patients in anticipation of instances of ineligibility or withdrawal during the examination because of discomfort (25 per group).

Endoscopic Examination

We used the same magnifying endoscope, with the capability for 80 times optical magnification (GIF-Q240Z, Olympus Medical Systems, Tokyo, Japan) for both WLI and NBI. The two imaging methods can be performed in a same video-endoscopy system (EVIS LUCERA system, Olympus Medical Systems, Tokyo, Japan). The details of the NBI system have been published elsewhere.[1,2,26,27] To maintain the quality of the endoscopic images, we used the same liquid-crystal color display for both imaging methods. Before the study started, all the participating endoscopists were trained using a central review of demonstrable NBI images of superficial squamous lesions (13 neoplasias and seven non-neoplastic lesions).

All endoscopic observations were made according to the protocol. During the first imaging, all parts of the oropharynx and hypopharynx were evaluated. The nasopharynx was not included the examination. After the first imaging was completed, an assistant physician immediately recorded the results on the case record form (CRF). After completion of the first imaging CRF, the second imaging of the oropharynx and hypopharynx was performed and the results were recorded on the CRF.

Next, all parts of the esophagus were evaluated using the same imaging as used for the H&N region. The endoscope was inserted to gain a view from the cervical esophagus to the esophagogastric junction, and the results were recorded on the CRF. The second imaging was performed on withdrawal of the endoscope, and the results were recorded on the CRF. During the procedure, we measured the examination time from start to finish of each imaging at each site. These procedure times included the evaluation of the lesion but not the biopsy procedure. The findings obtained by lugol chromoendoscopy are not included in this study.

Endoscopic Evaluation of Superficial Cancers

In this study, the real-time on-site diagnosis was evaluated because making an accurate diagnosis during an examination is clinically more important than a retrospective evaluation using a stored database. On WLI, if the lesion showed both a reddish color with uneven surface and disappearance of the vascular network pattern (Fig 2A), we diagnosed it as endoscopically suspected "superficial cancer." On NBI, if the lesion exhibited a well-demarcated brownish area as well as irregular microvascular patterns (Fig 2B), we diagnosed it as endoscopically suspected "superficial cancer." Details of these findings have been described previously.[7,8] If the lesion did not show these characteristics, the lesion was diagnosed as "non-cancer." Mucosal abnormalities were recorded with regard to endoscopic diagnosis, location, and size of the lesion.

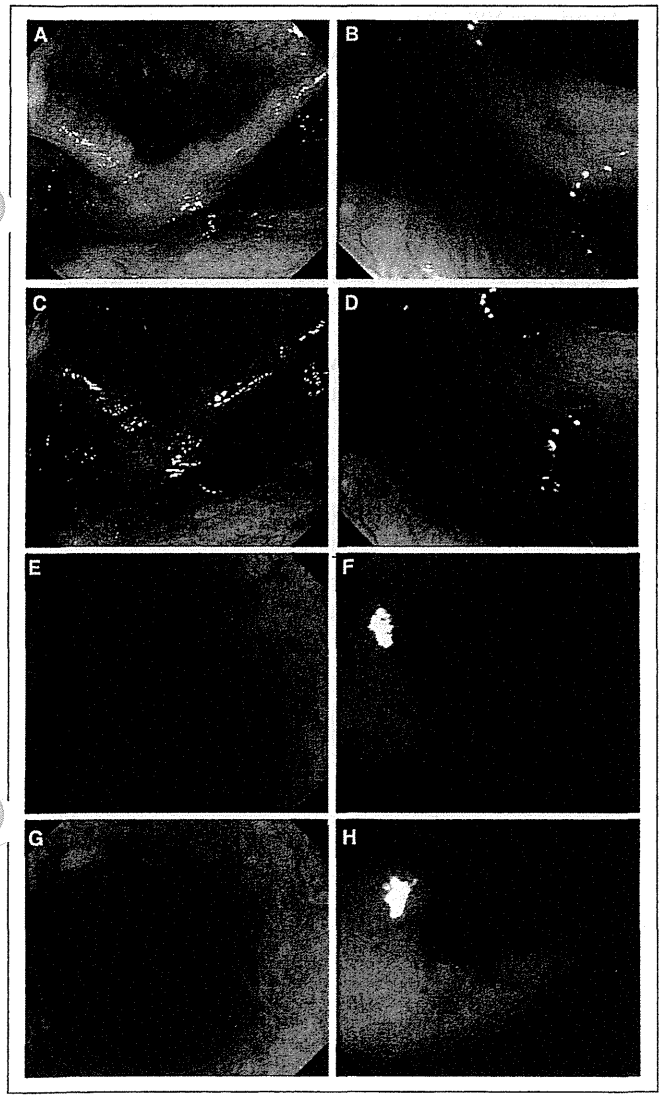

Fig 2. Superficial cancer in the head and neck region and esophagus. (A) White light imaging (WLI) shows a small reddish area (arrows) in the posterior wall of the hypopharynx. (B) Magnifying WLI shows a slightly reddish area with tiny microdots. (C) Narrow band imaging (NBI) shows a well-demarcated brownish area (arrows) in the posterior wall of the hypopharynx. (D) Magnifying NBI shows many tiny dots in the brownish area. This lesion was diagnosed histologically as squamous cell carcinoma in situ. (E) WLI shows a slightly reddish and depressed lesion (arrows) in the esophagus, although it is difficult to detect by WLI alone. (F) Magnifying WLI shows a slightly reddish area with an irregular microvascular pattern. (G) NBI shows a well-demarcated brownish area (arrows). (H) Magnifying NBI shows many tiny dots in the brownish area. This lesion was diagnosed histologically as high-grade intraepithelial cancer.

Pathologic Evaluation

Biopsy specimens were taken from each lesion after the completion of both types of imaging. Histologic evaluation was performed by central review by four experienced pathologists (H.S., A.O., T.S., and H.W.) who were blinded to the recorded endoscopic assessment. Histologic diagnoses were made according to WHO criteria[23] and were classified into two groups. One group included superficial cancers and the other group included non-cancers such as parakeratosis and inflammation. Microinvasion was estimated by the subepithelial invasion. The final pathologic diagnosis was made by the agreement of three of the four pathologists.

Statistical Analysis

The absolute and relative frequencies for qualitative variables were calculated for each group. Statistical analysis was performed using SPSS version

Table 1. Characteristics of Patients

Characteristic	Primary WLI (n = 162) No.	%	Primary NBI (n = 158) No.	%	P
Age, years					
Median	64		64		
Range	39-84		46-84		.99
Male sex	143	88	141	89	.86
Alcohol habit					
Drinking duration, years	157	97	148	94	.19
Median	41		40		.17
Range	10-63		5-60		
Favorite beverage					
Beer	61	38	59	37	1.00
Shochu	66	41	55	35	.30
Sake	43	27	48	30	.71
Whisky	22	14	24	15	.75
Wine	8	5	7	4	1.00
Others	1	0.6	0	0	1.00
Hot flashes					
Formerly had hot flashes	117	72	109	69	.62
Currently has hot flashes	75	46	70	44	.91
Smoking habit					
No. of smokers	145	90	142	90	1.00
Smoking duration, years					
Median	37		40		
Range	1-61		5-61		.41
No. of packs per day					
Median	1		1		
Range	0.05-4		0.125-4		.64
No. of packs per year					
Median	41		42		
Range	0.5-180		1.3-160		.89
Esophageal cancer					
No. of patients newly diagnosed	110	68	115	73	.39
Previously treated EMR	52	32	43	27	.39
Duration from previous EMR, years					
> 1	17	10	20	13	.60
1	45	28	33	21	.16
Depth of invasion					
Tis-T1a	74	46	67	42	.57
T1b	25	15	20	13	.27
T2	12	7	22	14	.07
T3	49	30	46	29	.90
T4	2	1	3	2	.68

Abbreviations: WLI, white light imaging; NBI, narrow band imaging; EMR, endoscopic mucosal resection.

17 software (SPSS, Chicago, IL). The continuous variables are expressed as medians and ranges. Continuous data were compared using the Mann-Whitney U test. Pearson's χ^2 test or Fisher's exact test was used to analyze categoric data to compare proportions. All P values were two-tailed, and a P value of $< .05$ was considered significant.

Results

Between March 2005 and December 2005, 333 patients were enrolled onto this study (Fig 1). Twelve patients did not meet the inclusion criteria, and one was registered twice, so the remaining 320 patients were randomly assigned correctly into two groups: (1) 162 patients who underwent primary WLI followed by NBI, and (2) 158 patients who were examined by primary NBI followed by WLI.

The characteristics of the two groups are listed in Table 1. The two groups did not differ significantly in age, sex, alcohol consumption, smoking habits, or history of esophageal cancer treatment. In both groups, approximately 70% of the patients had newly diagnosed ESCC. Sixty-three (39%) patients in the primary WLI group and 71 (45%) patients in the primary NBI group had advanced ESCC deeper than the submucosal layer.

Table 2 provides the distribution of histologically confirmed superficial cancers. The total numbers of superficial cancer in the H&N region and the esophagus were 28 and 212, respectively. Total numbers of histologically confirmed non-cancer were 36 and 38 in each region. In all patients, superficial cancers were detected in 8% (26 of 320) in the H&N region and in 38% (121 of 320) in the esophagus. Multiple cancers were found in 0.6% of the patients in the H&N region and in 12% in the esophagus. The number of patients with superficial cancer, total number of superficial cancers, and their sizes and distribution did not differ between the two groups.

The diagnostic yields for superficial cancer using primary WLI and primary NBI detection are summarized in Table 3. The total numbers of superficial cancers detected by primary imaging differed between the two groups. In the H&N region, primary NBI detected all (100%; 15 of 15) of the superficial cancers, but primary WLI detected only one lesion (8%; 1 of 13). In the esophagus, only 58 (55%) lesions were detected by primary WLI, whereas 104 (97%) lesions were detected by primary NBI. All these differences were statistically significant ($P < .001$). The detection rate was significantly higher with primary NBI than with primary WLI, even for small lesions (< 10 mm in diameter) in both the H&N region ($P < .001$) and the esophagus ($P = .03$).

In the back-to-back analysis, secondary NBI after primary WLI significantly increased the detection rate in both the H&N region (8% v 77%; $P < .001$) and esophagus (55% v 95%; $P < .001$; Appendix Table A1, online only). In contrast, secondary WLI after NBI significantly decreased the detection rate (Appendix Table A1). Moreover, 16 (57%) superficial cancers in the H&N region and 48 (23%) superficial cancers in the esophagus were detected only by NBI (Appendix Table A2, online only). In contrast, no lesion was detected only

Table 2. Distribution of Histologically Confirmed Superficial Cancer According to Lesion in the Head and Neck Region and the Esophagus

Variable	Primary WLI (n = 162)			Primary NBI (n = 158)			P
	No.	%	95% CI	No.	%	95% CI	
Head and neck region							
No. of patients	12	7	3.3 to 11.4	14	9	4.4 to 13.3	.66
No. of lesions per patient							
1	12	7	3.3 to 11.4	14	9	4.4 to 13.3	> .999
≥ 2	1	0.6	−0.6 to 1.8	1	0.6	−0.5 to 1.9	
Total No. of superficial neoplasias	13			15			
Size threshold, mm							
< 10	7			10			.50
11-20	5			5			
≥ 21	1			0			
Histologic diagnosis							
High-grade intraepithelial neoplasia or carcinoma in situ	10			15			.09
Microinvasive cancer	3			0			
Esophagus							
No. of patients	58	36	28.4 to 43.2	63	40	32.2 to 47.6	.49
No. of lesions per patient							
1	39	24	17.4 to 30.7	43	27	20.3 to 34.2	> .999
≥ 2	19	12	6.7 to 16.7	20	13	7.4 to 17.9	
Total No. of superficial cancers	105			107			
Size threshold, mm							
< 10	18			18			.91
11-20	21			19			
≥ 21	66			70			
Histologic diagnosis							
High-grade intraepithelial neoplasia or carcinoma in situ	73			84			.16
Microinvasive cancer	32			23			

Abbreviations: WLI, white light imaging; NBI, narrow band imaging.

Table 3. Diagnostic Yield of Primary WLI and Primary NBI for Detection of Superficial Cancer in the Head and Neck Region and the Esophagus

Variable	Primary WLI (n = 162) No.	%	95% CI	Primary NBI (n = 158) No.	%	95% CI	P
Head and neck region							
No. of superficial cancers	1/13	8	0.2 to 36.0	15/15	100	78.2 to 100	< .001
Size of superficial cancer, mm							
< 10	0/7	0	0 to 41.0	10/10	100	69.2 to 100	< .001
11-20	1/5	20	0.5 to 71.6	5/5	100	48.7 to 100	.12
≥ 21	0/1	0	0.0 to 0.0	to			—
Esophagus							
No. of superficial cancers	58/105	55	45.2 to 65.0	104/107	97	92.0 to 99.4	< .001
Size of superficial cancer, mm							
< 10	7/18	39	17.3 to 64.3	17/18	94	72.7 to 99.9	.03
11-20	7/21	33	14.6 to 57.0	18/19	95	74.0 to 99.9	.02
≥ 21	44/66	67	54.0 to 77.8	69/70	99	92.3 to 100	< .005

Abbreviations: WLI, white light imaging; NBI, narrow band imaging.

by WLI, except one lesion of > 20 mm in the esophagus. No lesions were undetected by both WLI and NBI in either region.

Table 4 summarizes the diagnostic performance of primary WLI and primary NBI for detecting superficial cancer. The sensitivity of primary NBI was significantly higher than that of primary WLI in both the H&N region (100% *v* 7.7%; $P < .001$) and the esophagus (97.2% *v* 55.2%; $P < .001$). Accuracy was also significantly higher for primary NBI than for primary WLI in both regions (85.7% *v* 62.9%, $P = .02$ and 88.9% *v* 56.5%, $P < .001$, respectively). Specificity was not significantly different in the two regions ($P = .28$ and $P = .33$, respectively). The positive predictive value did not differ between the two imaging techniques, but the negative predictive value was significantly higher for primary NBI than for primary WLI in both the H&N region ($P = .02$) and the esophagus ($P < .002$).

The median procedure times of primary WLI and primary NBI for the H&N region were 120 seconds (range, 34 to 275 seconds) and 162 seconds (range, 30 to 525 seconds), respectively. Those for the esophagus were 95 seconds (range, 30 to 360 seconds) and 135 seconds (range, 30 to 616 seconds), respectively. These differences were statistically significant ($P < .001$). The procedure times in the secondary imaging in the back-to-back experiments also differed significantly between WLI and NBI in both regions (Appendix Table A3, online only). There were no serious adverse events related to examination with either procedure. All patients tolerated both procedures well.

DISCUSSION

This study clearly demonstrates that NBI is a more sensitive method for detecting and diagnosing superficial SCC in the H&N region and the esophagus. According to the concept of "field cancerization,"[28] patients with ESCC or HNSCC are at high risk for the development of multiple SCCs. In the clinical context, the early detection strategy for superficial SCC is the same between patients at high risk and those at risk because of heavy drinking, smoking, or aldehyde dehydrogenase 2 deficiency.[20-35] In addition, detection technique should not only be sensitive but should also be easily applicable. From this perspective, NBI is easily applied with a modicum of experience and will have a rapid learning curve compared with WLI. Thus, NBI is the ideal method for effectively detecting superficial SCC.

Table 4. Diagnostic Performance of Primary WLI and Primary NBI Observation for Detection of Superficial Cancer in the Head and Neck Region and the Esophagus

Variable	Primary WLI No.	%	95% CI	Primary NBI No.	%	95% CI	P
Head and neck							
Sensitivity	1/13	7.7	0.2 to 36.0	15/15	100	100	< .001
Specificity	21/22	95.5	77.2 to 99.9	11/14	78.6	54.6 to 98.1	.28
Accuracy	22/35	62.9	47.6 to 76.4	26/29	86.7	72.6 to 97.8	.02
PPV	1/2	50	1.3 to 98.7	15/18	83.3	58.6 to 96.4	.37
NPV	21/33	63.6	54.1 to 79.6	11/11	100	100	.02
Esophagus							
Sensitivity	58/105	55.2	45.2 to 65.0	104/107	97.2	92.0 to 99.4	< .001
Specificity	12/19	63.2	38.4 to 83.7	8/19	42.1	20.3 to 66.5	.33
Accuracy	70/124	56.5	47.3 to 65.3	112/126	88.9	82.1 to 93.8	< .001
PPV	58/65	89.2	79.1 to 95.6	104/115	90.4	85.3 to 95.1	.80
NPV	12/59	20.3	11.0 to 32.8	8/11	72.8	39 to 94	< .002

Abbreviations: WLI, white light imaging; NBI, narrow band imaging; PPV, positive predictive value; NPV, negative predictive value.

Detecting cancer at an early stage is an optimal strategy for preventing the development of advanced cancer and improving survival. Furthermore, early detection uses a minimally invasive treatment (eg, endoscopic resection) with curative intent.[8,36-38] In fact, in our study, 75% (21 of 28) of the superficial HNSCCs were completely removed by endoscopic resection or biopsy alone, while early detection of HNSCC had been quite difficult. These results provide us with new diagnostic and treatment strategies for ESCC patients, because the risk of development of HNSCC after esophagectomy is quite high.[21]

As the criteria for diagnosing superficial SCC by NBI, we used two endoscopic findings: a well-demarcated brownish area and an irregular microvascular pattern.[7-9] Using only these two findings, the sensitivity of primary NBI for the diagnosis of superficial SCC was 100% in the H&N region and 97.2% in the esophagus. The diagnostic accuracy was nearly 90%. These results indicate that these NBI findings are quite useful for the accurate diagnosis of superficial SCC.

Lugol chromoendoscopy is useful for the detection of superficial ESCC.[2-3] However, the administration of lugol solution is time-consuming, and accurate diagnosis by lugol chromoendoscopy is difficult[4] because the staining pattern shows wide variations.[2] This increases the incidence of false-positive lesions and leads to unnecessary biopsies. In contrast, NBI is easily manipulated and shows high sensitivity. Thus, NBI could reduce the number of unnecessary biopsies and shorten examination time. Furthermore, lugol chromoendoscopy is more invasive than both WLI and NBI, and WLI is still the gold standard for cancer screening. Therefore, we did not compare the diagnostic yield of NBI and lugol chromoendoscopy, and we used WLI as the standard reference to compared the diagnostic yield of WLI and NBI.

NBI required a significantly longer examination time than WLI. This might be related to the high detection rate and more frequent time spent in magnification during NBI, because if the lesions were not seen by WLI, no magnification was performed. The actual time difference between NBI and WLI was only 20 to 42 seconds. This is clinically acceptable, because the important time issue is not that NBI takes slightly longer than WLI, but rather that endoscopists spend more time in the careful observation of high-risk patients.

In this study, ESCC patients referred from another hospital were included. Even if the biopsies were previously done, the earlier biopsy sites were healed by the time of this study and were not generally detectable by either imaging method. Therefore, we thought that it was not a confounding factor.

The same endoscopists performed both imaging procedures in this study, whereas the endoscopists ideally should be separated and blinded to each imaging procedure. However, it was clinically impossible to change and blind the endoscopists during this series of examinations. Furthermore, the result produced with NBI first followed by WLI might underestimate the benefit of NBI because NBI is more sensitive than WLI. However, the detection and diagnosis of superficial SCC by NBI was significantly better than that using WLI in both the H&N region and the esophagus, regardless of whether NBI was primary or secondary. These results indicate that NBI should be the standard examination.

Significant detection results seen in this study were all achieved without the newest generation high-definition endoscope. If we use the newest high-definition endoscope with NBI, the rates of detection might increase compared with those found in this study. Furthermore, the endoscopy system used in this study and in most Asian countries was different from those used in North America and Europe.[26,27] However, we previously reported that even the nonmagnifying laryngoscope based on same system as that used in North America and Europe could dramatically improve the visualization of both the brownish area and irregular microvascular patterns.[39] Therefore, we believe that differences in the system are no longer as important as careful observation by NBI.

In conclusion, NBI combined with magnifying endoscopy significantly improved the detection rates for SCC with quite high sensitivity, and this new image-enhanced technology can be applied easily in clinical practice. Furthermore, early detection facilitates the potential of minimally invasive treatment, such as endoscopic resection or partial surgical resection.

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