Figure 1. TOPER for superficial pharyngeal cancer. **A,** Endoscopic photograph showing the right piriform sinus with superficial pharyngeal cancer. The slight reddish-color mucosa is the neoplastic lesion (*arrows*). **B,** Narrow-band imaging corresponding with **A** showing well-demarcated brownish area (*arrows*). In the brownish area, tiny brown dots can be seen, which are irregular morphological changes in superficial microvessels in the neoplastic lesion. **C,** Iodine chromoendoscopy showing well-demarcated iodine voiding lesion (*arrows*). **D,** Marking around the lesion with a needle-knife with coagulation mode. **E,** Mucosal incision outside the marking after submucosal injection. **F,** The mucosal defect immediately after resection. **G,** Resected specimen with the neoplastic lesion in en bloc fashion. **H,** Histologically, this lesion was diagnosed as carcinoma in situ.

these regions. Local recurrence was defined as when the cancer was detected at the site of the TOPER scar. Patients underwent a CT scan of the neck, chest, and abdomen annually to detect lymph node and distant metastases.

StatView version 5.0 (SAS Institute Inc, Cary, NC) was used for statistical analysis. The results are expressed as median (range). The Fisher exact test was used to analyze categorical data to compare proportions. Cause-specific and overall survival rates were estimated by using the Kaplan–Meier method.

RESULTS

Patient characteristics are shown in Table 1. They were predominantly male (97%), and the median age was 63
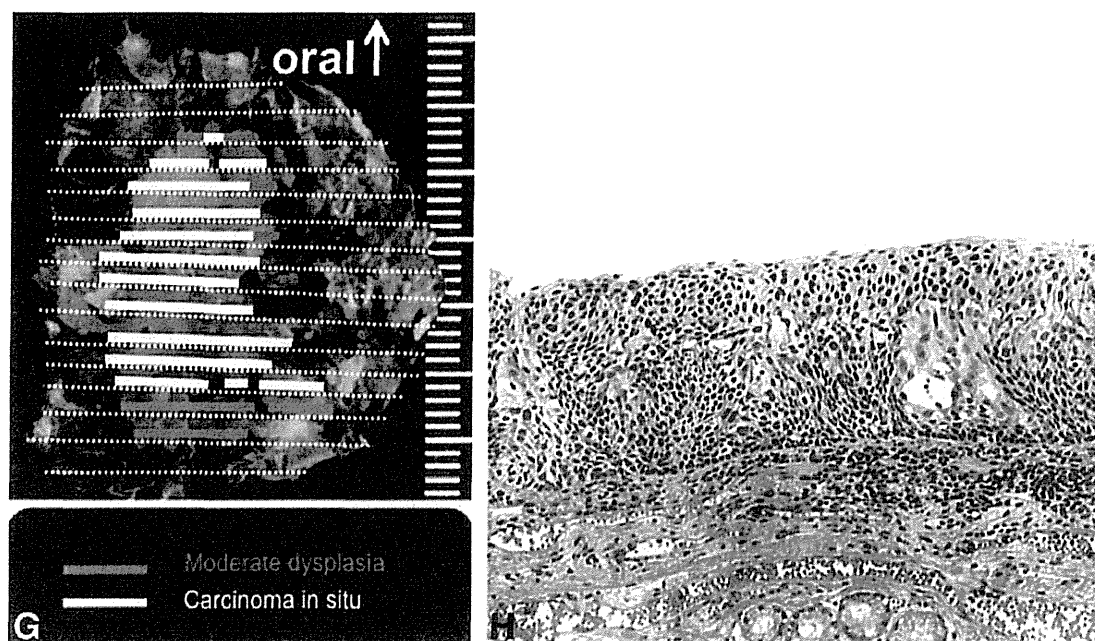
Figure 1. (continued)

years old (range 42-88 years). Of the 104 patients, 89 (86%) and 25 (24%), respectively, had esophageal cancer and/or head and neck cancer synchronously or previously. All of the cancers in the esophagus and the head and neck region were primarily treated with methods such as endoscopic resection, (chemo)radiotherapy, and surgery with curative intent. Most of the patients were identified as having cancer by follow-up examination for esophageal cancer or head and neck cancer. Of the 104 patients, 6 initially had unknown primary lymph node metastasis. Among them, the superficial lesion in the pharynx was finally found after radical dissection of the lymph node, and it was then treated by TOPER as a minimally invasive treatment.

Among the 104 patients, EMR-C method was indicated for 85 cases and the remaining 19 cases were indicated for ESD method. The selection was depended on the skill of the investigator. Before March 2006, all procedures of TOPER were performed by EMR-C method. After that, we turned to the treatment used by the ESD method for TOPER.

Lesion characteristics are shown in Table 2. Multifocal superficial cancer was found in 26 patients (25%). Nine lesions (6%) were finally diagnosed as severe dysplasia. Ninety-seven lesions (66%) were histologically confirmed to be carcinoma in situ, and the remaining 42 lesions (28%) showed slight invasion beneath the epithelium. The piriform sinus was the most frequent primary region (71%, 105/148).

The overall complication rate was 4.8% (5/104). Although subcutaneous emphysema developed in 2 patients immediately after the procedure, they improved with conservative medical management within 1 week. Aspiration pneumonia developed after 1 patient started eating. This patient improved after intravenous administration of antibiotics. Delayed bleeding developed the day after resection in 2 patients. These patients were treated with endoscopic hemostasis. Temporary tracheostomy was indicated for 17 patients because their larynx was swollen and they were considered at risk of airway obstruction after extubation. All of the tracheostomies were closed within 2 weeks. No procedure-related deaths occurred.

The median fasting period after TOPER was 2 days (range 1-20 days). The median hospital stay after TOPER was 8 days (range 3-58 days).

The median follow-up period was 43 months (range 3-96 months). The overall survival rates at 3 and 5 years were 84% (95% CI, 77-92) and 71% (95% CI, 59-82), respectively (Fig. 1). Cause-specific survival rates at 3 and 5 years were 99% (95% CI, 97-100) and 97% (95% CI, 93-100), respectively (Fig. 2). Cumulative development of multiple cancers in the pharyngeal mucosal site at 3 and 5 years were 20% (95% CI, 10-29) and 22% (95% CI, 12-33), respectively (Fig. 3).

Patterns of recurrence and the clinical course are summarized in Figure 4. Of 104 patients, 96 (92%) had no recurrence in either the primary site or lymph node or distant metastasis. Although local recurrence developed in 6 patients at the primary site, 5 of them were cured by repeat TOPER. Although the remaining patient died of the disease, this patient had a history of surgical resection of large oropharyngeal cancer 3 months earlier. We then considered the cause of death of this patient as previous

TABLE 1. Patient characteristics (N = 104)

Sex, no.	
Male	101
Female	3
Age, y (range)	63 (42-88)
History of EC, no.	89
Treatment for EC, no.	
EMR including endoscopic treatment	39
CRT/RT	37
Surgery	13
History of HNC, no.	25
Treatment for HNC, no.	
RT	4
Surgery	21
Initial reason for detection, no.	
Discomfort of pharynx	6
Pretreatment detailed examination for EC	12
Follow-up after surgery for EC	10
Follow-up after CRT/RT for EC	27
Follow-up after EMR for EC	16
Follow-up after surgery for HNC	21
Follow-up after RT for HNC	4
Unknown primary lymph node metastasis	6
Screening for upper GI endoscopy	2
Method	
EMR-C	85
ESD	19

EC, Esophageal cancer; *CRT,* chemo/radiotherapy; *RT,* radiotherapy; *HNC,* head and neck cancer; *EMR-C,* EMR with a cap; *ESD,* endoscopic submucosal dissection.

TABLE 2. Lesion characteristics (N = 148)

No. (%) of lesions per patient	
1	78 (75)
2	16 (15.4)
>3	10 (9.6)
Location of the lesions, no. (%)	
Oropharynx	20 (13.5)
Soft palate	1 (0.7)
Uvula	2 (1.4)
Posterior wall	10 (6.3)
Lateral wall	5 (3.4)
Vallecula	2 (1.4)
Hypopharynx	128 (86.5)
Left pyriform sinus	50 (33.8)
Right pyriform sinus	56 (37.8)
Postcricoid area	9 (6.1)
Posterior wall	13 (8.8)
Histological depth of the lesions, no. (%)	
Severe dysplasia	9 (6.1)
Carcinoma in situ	97 (65.5)
Carcinoma with subepithelial invasion	42 (28.3)

oropharyngeal cancer. There was no difference in the local recurrence rate between EMR-C and ESD methods. Although lymph node metastasis in the neck developed in 2 patients, their superficial cancers were initially found during surveillance of the primary site of a lymph node metastasis of an unknown primary tumor. Thus, the possibility that the lymph node metastasis already existed before TOPER could not be excluded. Ninety patients (86.5%) had survived without disease at the time of this analysis. Although it was difficult to determine the direct cause of death in those who died, 10 patients were considered to have died of previous head and neck cancer or esophageal cancer rather than superficial pharyngeal cancer because the previous cancers were far advanced. Four patients died of other diseases.

DISCUSSION

This study demonstrates that peroral organ-preserving endoscopic resection for superficial pharyngeal cancer is a feasible treatment option with no severe adverse events and an extremely good prognosis. To our knowledge, this is the largest series of the patients to show the long-term effectiveness of endoscopic resection for superficial pharyngeal cancer. A recent report by Suzuki et al[13] with 37 superficial pharyngeal cancers in 31 patients also showed the safety and effectiveness of endoscopic resection for these lesions. Until now, many patients with pharyngeal cancer were diagnosed at an advanced stage and thus required invasive surgery including the resection of the pharynx and larynx, resulting in speech defects and swallowing disorders, a major challenge from the aspect of the patients' quality of life. Our results demonstrating a new strategy of early detection and a minimally-invasive treatment for pharyngeal cancer are expected to be of great significance to these patients.
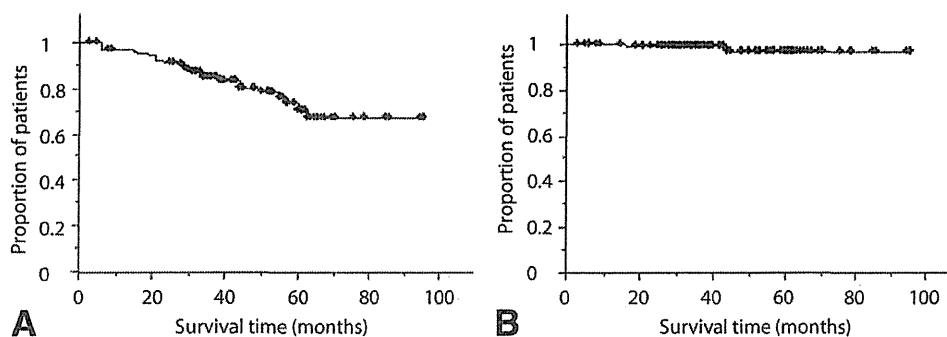
Figure 2. Overall survival (A) and cause-specific survival (B) after TOPER for superficial pharyngeal cancer.
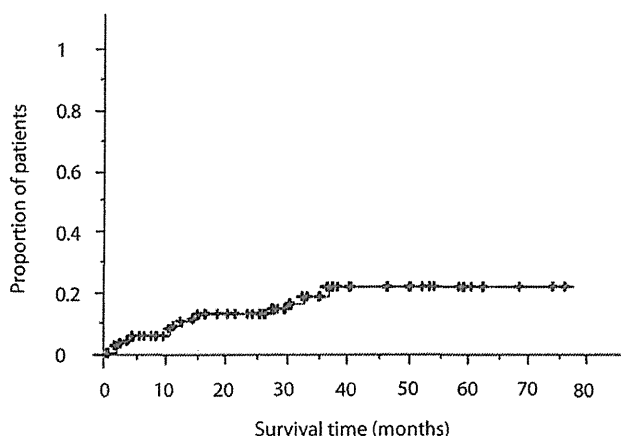

Figure 3. Metachronous development of superficial pharyngeal cancer after TOPER.

In the field of GI tract diseases, advances in the technology of endoscopic diagnosis have accelerated the detection of early cancer, leading to improvements in the technology of minimally-invasive endoscopic treatment such as EMR and ESD.[14-16] Thus, EMR and ESD are now widely accepted as standard treatments for early cancer in the GI tract. In contrast, in the region of the oropharynx and hypopharynx, a reflection occurs at the time of endoscope insertion, causing pain and discomfort for patients. Therefore, this area has not been fully examined by routine endoscopic examination, even in the field of GI endoscopy. Furthermore, the resolution of the otolaryngeal endoscope was insufficient to identify a subtle change in the structure of the mucosal surface and microvasculature, which are important characteristics of superficial pharyngeal cancer. Thus, it has been almost impossible to detect early cancer in this region.

However, we previously reported that NBI combined with a magnifying endoscope enables early detection of pharyngeal cancer.[4-6] Although this was a breakthrough in the diagnosis of cancer in the pharyngeal region, the treatment of superficial cancer has become a major issue because the standard treatment for pharyngeal cancer is surgery or chemoradiotherapy, which appears to be overtreatment for these superficial cancers. Similar to the case for early cancer in the GI tract, endoscopic resection is the optimal treatment for superficial pharyngeal cancer because it is minimally invasive and curative. However, endoscopic resection for these lesions is not established as the first choice of treatment because it is not clear whether this treatment is feasible or improves the prognosis. Our results suggest that endoscopic resection could be the first choice of treatment for superficial pharyngeal cancer.

In carcinoma in situ, there is theoretically no risk of lymph node metastasis, but in pharyngeal cancers with subepithelial invasion, there is a risk of lymph node metastasis. However, we could not estimate the risk because we saw no cases of superficial cancer before NBI was developed. In our current analysis, lymph node metastases developed in 2 patients after TOPER. However, these patients had lymph node metastasis from an unknown primary tumor before endoscopic resection. Thus, the possibility could not be excluded that the lymph node metastasis existed before TOPER was recommended for them. Except for these patients with unknown primary lymph node metastasis, no lymph node metastasis developed in any patient in our series after TOPER. This result indicates that the risk of lymph node metastasis is quite low and thus prophylactic irradiation for cancers with subepithelial invasion appears unnecessary at this time, considering its disadvantages, including salivary disorders and mucosal inflammation.

In this study, multiple metachronous cancers at a pharyngeal mucosal site (22% at 5 years) developed in many patients. Suzuki et al[13] reported that metachronous superficial pharyngeal cancer developed in 16% (5/31) of the patients. This possibly results from the "field cancerization" phenomenon.[17] All patients included in this study were screened for the presence of multiple cancers by iodine staining of the entire pharynx when they underwent TOPER under general anesthesia. The fact that metachronous cancer frequently develops despite this screening suggests that the mucosa itself in this area has a high potential for cancer development. Therefore, close surveillance may be required after less invasive therapy that
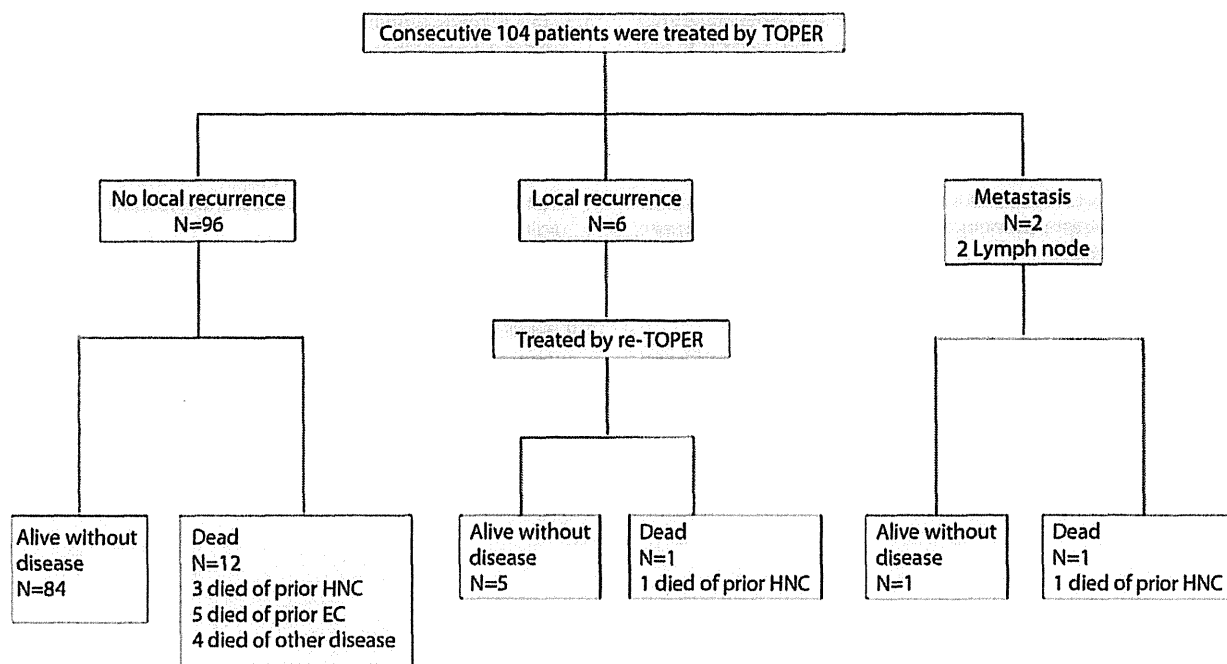
Figure 4. Clinical outcomes after TOPER for superficial pharyngeal cancer.

preserves the mucosa. Alternatively, if an effective prophylaxis were discovered, development of metachronous multiple cancers could be inhibited.

According to the TNM (tumor-node-metastasis) classification[18] of pharyngeal cancer, the depth of tumor is unrelated to the staging, and the T number increases as the tumor size increases in cases of widespread superficial cancer. However, there is no risk of metastasis in intraepithelial cancer compared with invasive cancer of the same size, and, theoretically, the rate of lymph node metastasis is anticipated to be low, even in the case of microinvasive cancer. Thus, as many more superficial cancers are detected, a discrepancy becomes apparent between the current TNM classification system and actual clinical practice. In the future, the relationship between the depth of superficial cancer in the head and neck and the risk of lymph node metastasis, as well as its prognosis after endoscopic therapy, needs to be determined.

Generally, the survival of patients with multiple cancers is reported to be poor.[19] However, the overall and cause-specific survival of the patients in this study could be regarded as acceptable because 93% (97/104) of the patients had a history of esophageal cancer or head and neck cancer and then would have poor prognosis. This result in part means that if the primary treatment succeeds with its curative intent, a second primary cancer should be detected at an earlier stage to obtain better survival. To date, there is no guideline for the optimal surveillance interval and the indication of TOPER. In addition, we have to determine the effective surveillance schedule and the limitations and indications for the TOPER method.

In conclusion, TOPER for superficial pharyngeal cancer is a feasible and effective treatment with curative intent. The strategies of evaluation of definitive risk (alcohol and smoking), identifying the superficial cancer by image-enhanced endoscopy, and minimally-invasive treatment by TOPER can provide a chance of organ preservation and survival for pharyngeal cancer patients.

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Magnifying Narrowband Imaging Is More Accurate Than Conventional White-Light Imaging in Diagnosis of Gastric Mucosal Cancer

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BACKGROUND & AIMS: It is difficult to accurately diagnose patients with depressed gastric mucosal cancer based on conventional white-light imaging (C-WLI) endoscopy. We compared the real-time diagnostic yield of C-WLI for small, depressed gastric mucosal cancers with that of magnifying narrow-band imaging (M-NBI). **METHODS:** We performed a multicenter, prospective, randomized, controlled trial of patients with undiagnosed depressed lesions ≤10 mm in diameter identified by esophagogastroduodenoscopy. Patients were randomly assigned to groups that were analyzed by C-WLI (n = 176) or M-NBI (n = 177) immediately after detection; the C-WLI group received M-NBI after C-WLI. We compared the diagnostic accuracy, sensitivity, and specificity between C-WLI and M-NBI and assessed the diagnostic yield of M-NBI conducted in conjunction with C-WLI. **Results:** Overall, 40 gastric cancers (20 in each group) were identified. The median diagnostic values for M-NBI and C-WLI were as follows: accuracy, 90.4% and 64.8%; sensitivity, 60.0% and 40.0%; and specificity, 94.3% and 67.9%, respectively. The accuracy and specificity of M-NBI were greater than those of C-WLI ($P < .001$); the difference in sensitivity was not significant ($P = .34$). The combination of M-NBI with C-WLI significantly enhanced performance compared with C-WLI alone; accuracy increased from (median) 64.8% to 96.6% ($P < .001$), sensitivity increased from 40.0% to 95.0% ($P < .001$), and specificity increased from 67.9% to 96.8% ($P < .001$). **CONCLUSIONS:** M-NBI, in conjunction with C-WLI, identifies small, depressed gastric mucosal cancers with 96.6% accuracy, 95.0% sensitivity, and 96.8% specificity. These values are better than for C-WLI or M-NBI alone.

Keywords: Gastric Cancer; Early Detection; Benign; Malignant; Neoplasm; Biopsy.

G astric cancer is the fourth most common malignancy and the second leading cause of death from cancer worldwide.[1] Early detection and curative treatment are the best strategies for improving patient survival. Esophagogastroduodenoscopy is the most sensitive method of early detection of gastric cancers. However, an accurate early diagnosis of gastric mucosal cancer is difficult with conventional white-light imaging (C-WLI) endoscopy; nevertheless, it remains the standard endoscopic examination modality worldwide.

Detection of mucosal cancers ≤20 mm in diameter is ideal, because they are curable using minimally invasive treatments such as endoscopic mucosal resection and endoscopic submucosal dissection.[2,3] Among the gastric mucosal cancers, the depressed type is the predominant morphology.[4–6] However, small depressed cancers (≤10 mm in diameter) are more difficult to distinguish from benign abnormalities (such as inflammation) compared with elevated cancers. Although chromoendoscopy using indigo carmine has contributed to an improvement in the diagnosis of gastric mucosal cancers,[7] there is no evidence of the superiority of chromoendoscopy over C-WLI. Therefore, C-WLI endoscopy remains the standard imaging modality for diagnosing gastric mucosal cancers.

Histologic evaluation of biopsy specimens from suspicious lesions is conventionally used to confirm a diagnosis. A highly accurate diagnosis without the need for a biopsy is the ultimate goal of endoscopists, because this would decrease the number of unnecessary biopsies, especially when confirming a negative biopsy of any suspicious cancerous lesion. This could reduce the risk of postbiopsy bleeding, costs associated with the procedure, and the workload on pathologists.

Magnifying narrow-band imaging (M-NBI), a recently developed advanced endoscopic imaging technology, was reported to be useful for the accurate diagnosis of gastric abnormalities such as cancers,[8–13] adenomas,[14] and intestinal metaplasia.[15] However, no randomized trials have been conducted to compare M-NBI with C-WLI. The present study was designed to assess and compare the real-time diagnostic yield of C-WLI for depressed gastric mucosal

cancers with that of M-NBI when performed by skilled endoscopists.

Patients and Methods

Study Design and Participants

This randomized, controlled, open-label, multicenter trial was conducted at 9 centers in Japan. This study was conducted according to the Standards for the Reporting of Diagnostic Accuracy Studies (STARD) initiative[16] and the Declaration of Helsinki.

The frequency of synchronous or metachronous multiple gastric cancers was reported as 3 to 5 per 100 patient-years,[17-19] which is higher than the incidence of gastric cancer in the general population. In other words, patients with gastric cancer might constitute a cancer-enriched population, which may be a more suitable model for screening of potential gastric cancers than the general population. Therefore, we recruited patients aged 20 years or older with untreated gastric cancers and patients with a history of gastric cancer. Patients who had been treated with endoscopic mucosal resection or endoscopic submucosal dissection were included in the latter group, because their stomachs were preserved with minimum injury. We excluded patients who had been treated with surgical resection, because the stomach was either removed or was reduced in size. Other exclusion criteria were serious complications that could interfere with the examination protocol and the use of medication that might interfere with the collection of a biopsy specimen. Written informed consent was obtained, and the institutional review board of each participating hospital approved the study. The clinical trial number of this study was UMIN-CTR000001072.

To detect a target lesion, screening was performed using C-WLI endoscopy. Previously undetected lesions were considered ideal potential targets for evaluating the diagnostic yield without bias. Therefore, the target lesions for this study were "newly detected and undiagnosed" small, depressed gastric lesions ≤10 mm in diameter. We did not target lesions that had been analyzed histologically. Small, depressed lesions with apparent erosion or ulceration were also not evaluated, because it is difficult to visualize surface changes in these lesions. If the patient had multiple such lesions, only the first lesion detected was selected for examination. The diameter of each lesion was estimated by comparing it with the size of the biopsy forceps.

Randomization and Masking

When a target small, depressed lesion was detected by C-WLI screening, patients were immediately assigned randomly to undergo detailed examination using C-WLI or M-NBI at a 1:1 ratio. After the randomization, all endoscopists knew which imaging method would be used for the detailed examination when making a diagnosis of the target lesion. Randomization was performed promptly on-site using tables of random numbers stratified by hospital, and the results thereof were kept in sealed, numbered envelopes. The random allocation sequence was prepared at the data management center. Both the assignment result and the corresponding envelope number were recorded by the data management center. At each participating hospital, sealed envelopes were stored by a third party who was not involved in the study, and the envelopes were opened by an assistant physician in serial order only when randomization was performed. The assigned patient identification number, envelope number, and assignment result were recorded on-site and faxed to the data management center on the day of the examination.

Procedure and End Points

The study design and the protocol examination are outlined in Supplementary Figure 1 and Supplementary Materials and Methods. The diagnosis for the target lesion was made by one endoscopist according to predetermined diagnostic criteria for C-WLI and M-NBI without any consultation with other physicians, and an assistant physician immediately recorded the results using a case report form. For each modality, the interval between the start of the observation and the time at which an endoscopic diagnosis was made was measured using a stopwatch. For the C-WLI group, M-NBI examination was performed after completion of a diagnosis based on C-WLI. This procedure was used to evaluate the effect of using M-NBI in conjunction with C-WLI. After all records were compiled, at least one biopsy specimen was obtained from the target lesion.

The primary aim of the study was to compare the diagnostic accuracy between C-WLI and M-NBI. The secondary aim was to compare diagnostic sensitivity, specificity, and examination time between C-WLI and M-NBI and to evaluate the effects of an additional M-NBI study after the initial C-WLI in terms of diagnostic accuracy, sensitivity, specificity, and examination time. Histopathology diagnosis of obtained biopsy specimens was used as a gold standard for the diagnosis.

Endoscopy System

The NBI system is an innovative optical image-enhanced technology that involves a narrow-bandwidth NBI filter in the video endoscopy system. The central wavelengths of the NBI filters are 415 nm and 540 nm, and each has a bandwidth of 30 nm. Because 415-nm and 540-nm light are well absorbed by hemoglobin, the microvascular architecture of the mucosal surface can be visualized readily. Details of this system have been reported elsewhere.[20-22]

We used high-resolution magnifying endoscopy with a capability of 80-fold optical magnification (GIF-Q240Z, GIF-H260Z, and GIF-FQ260Z; Olympus Medical Systems, Tokyo, Japan) and a high-resolution liquid-crystal monitor (OEV191H; Olympus Medical Systems). We alternated between the 2 imaging modalities (C-WLI and M-NBI) by pushing a button on the endoscope (Evis Lucera Spectrum System; Olympus Medical Systems). We used a fixed structure enhancement setting and color tone for the video processor.

Participating Endoscopists

All examinations were performed by 31 endoscopic specialists accredited by the Japan Gastroenterological Endoscopy Society in 9 institutes. Before the onset of the study, all participating endoscopists were trained using images of small, depressed lesions to minimize diagnostic variation between them.

Diagnostic Criteria for C-WLI and M-NBI

Figure 1 shows a representative endoscopic image of a small, depressed gastric cancer and a small, depressed benign lesion. The diagnostic method based on endoscopic findings is outlined in Supplementary Materials and Methods.

The endoscopic diagnostic criteria for small, depressed gastric cancers using C-WLI were defined based on previous reports of C-WLI findings: an irregular margin and a spiny depressed area.[23] The observation of 2 findings (irregular margin and spiny
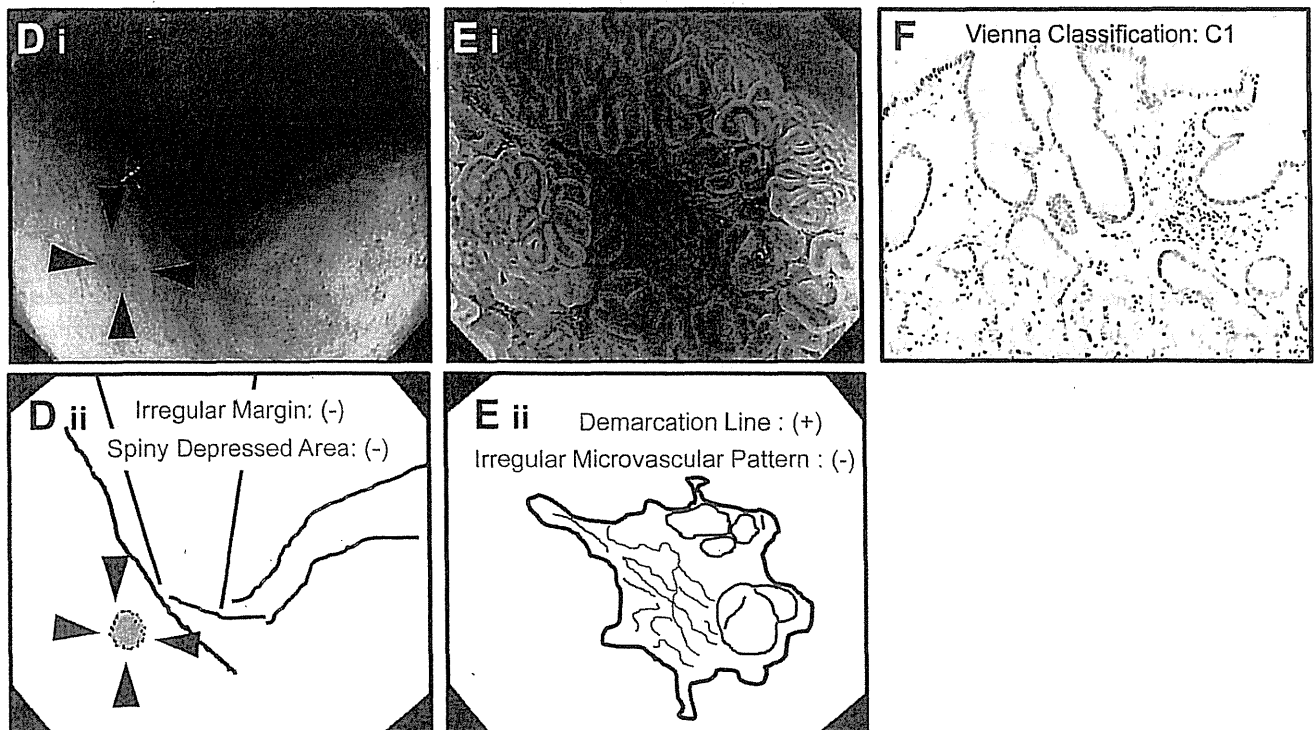
Cancer
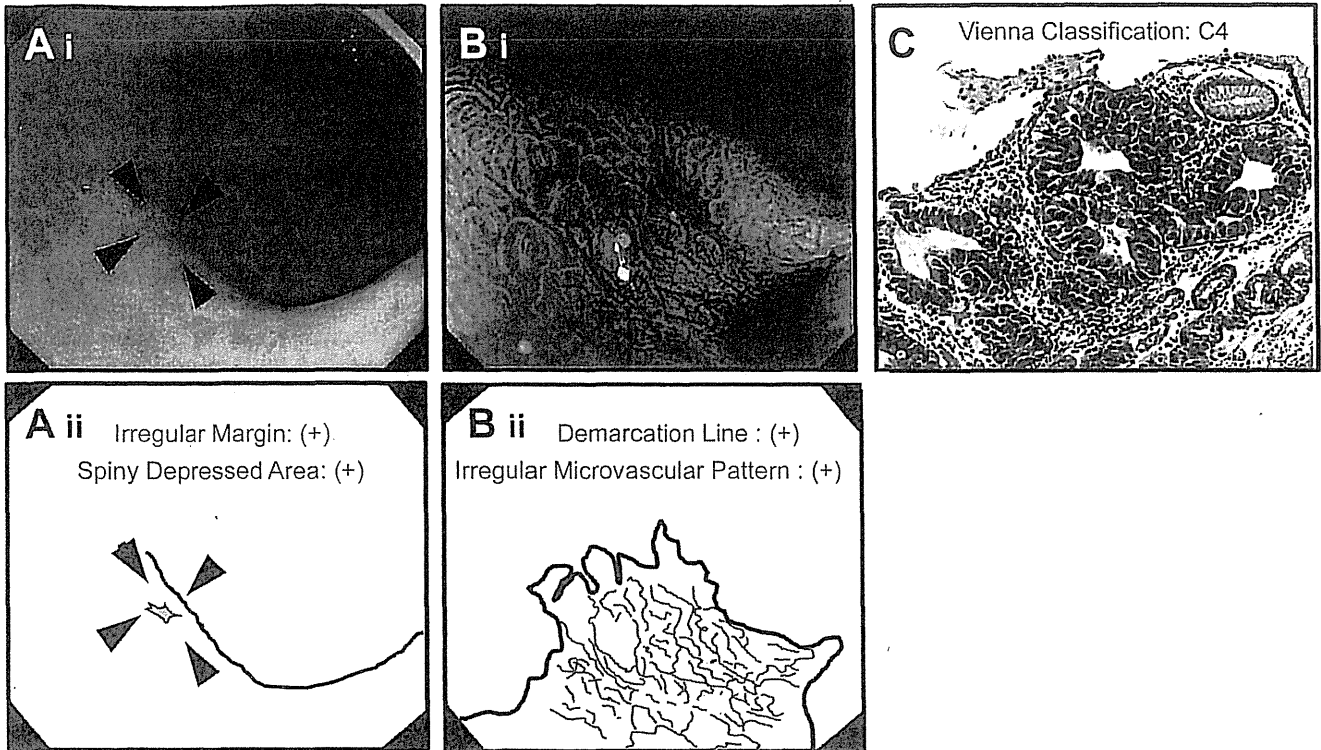
Noncancerous Lesion

Figure 1. Representative endoscopic findings for gastric small, depressed lesions. *A–C* show a case of cancer, and *D–F* show a case of noncancerous lesions. *A* shows an endoscopic image obtained using C-WLI. A small, depressed lesion (*arrowheads*) is evident in the anterior wall of the lower part of the gastric body. This lesion was evaluated as having an irregular margin and a spiny depressed area. *B* shows an endoscopic image obtained using M-NBI, which enabled clear visualization of the demarcation line and an irregular microvascular pattern. *A′* and *B′* are schematic representations of the images shown in *A* and *B*, respectively. *C* shows a lesion that was histologically diagnosed as a differentiated adenocarcinoma, Vienna Classification C4. *D* shows an image obtained using C-WLI. A small reddish area (*arrowheads*) is evident in the anterior wall of the upper part of the gastric body. Because the depressed area was not "spiny" and because a definite margin was not apparent, this case was evaluated as not having a spiny depressed area or an irregular margin. *E* shows an image obtained using M-NBI, which enabled clear visualization of a demarcation line and the absence of an irregular microvascular pattern. *D′* and *E′* are schematic representations of the images shown in *D* and *E*, respectively. *F* shows a lesion that was histologically diagnosed as gastritis, Vienna Classification C1.

depressed area) in the target lesion was classified according to 3 categories: present, absent, or indeterminate.

The endoscopic diagnostic criteria for small, depressed gastric cancers using M-NBI were defined based on previous reports by Yao et al: a demarcation line between the depressed cancerous lesion and the surrounding noncancerous area and an irregular microvascular pattern inside the lesion.[2-4] Observations of 2 findings (demarcation line and irregular microvascular pattern) in the target lesion were also classified according to 3 categories: present, absent, or indeterminate.

Endoscopic diagnoses were determined according to the combined visibility of the 2 findings as follows (Supplementary Figure 2). (1) If both findings were present, the diagnosis was "cancer." (2) If either finding was indeterminate, the diagnosis was "inconclusive." (3) If either or both findings were absent, the diagnosis was "noncancerous."

For analyzing diagnostic accuracy, sensitivity, and specificity, lesions diagnosed as "inconclusive" were considered as endoscopic "noncancerous" lesions.

Pathology Diagnosis

The biopsy specimens were evaluated using H&E staining. The diagnostic pathology criteria were based on the revised Vienna classification.[25] C4 (mucosal high-grade neoplasia) or C5 (submucosal invasion by neoplasia) were diagnosed as cancer, and C1 (negative for neoplasia), C2 (indefinite for neoplasia), or C3 (mucosal low-grade neoplasia) were diagnosed as noncancerous lesions. In this study, we used a central system of consultation with a main expert pathologist. If an indeterminate lesion were to be encountered, it was scheduled to be reviewed by this consulting pathologist in making a final diagnosis.

Statistical Analysis

We assumed that the accuracy, sensitivity, and specificity of C-WLI and M-NBI compared with histologic diagnosis would be 60% and 85%, respectively. To set a probability for error of 0.05 and attain a power of 80% for testing the superiority of M-NBI, 108 patients including at least 43 cancerous lesions were needed. Next, we calculated how many patients would need to be screened. Because the frequency of small depressed lesions was reported to be 8.1% in the general population,[9] the required size of the screening sample was 1100 patients.

Statistical analysis was performed using SPSS software, version 17 (SPSS Inc, Chicago, IL). For diagnostic performance, accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) are presented as percentages with 95% confidence intervals (CIs). Continuous variables are expressed as medians and interquartile ranges. Analyses of the difference in diagnostic performance between C-WLI and M-NBI were conducted using the population whose diagnoses had been confirmed by pathology using Pearson's χ^2 test. Analyses of the effect of additional M-NBI after the initial C-WLI on diagnostic performance were conducted using the population whose diagnoses had been confirmed by pathology and McNemar testing. Analysis of the examination duration was conducted using the population who completed protocol examination and the Mann–Whitney nonparametric test for comparisons between C-WLI and M-NBI, as well as the Wilcoxon signed rank test for comparisons between C-WLI and C-WLI plus M-NBI. All probability values calculated in this analysis were 2 sided, and $P < .05$ was considered significant.

Results

Between June 2008 and May 2010, 1365 patients were enrolled in the study. Eight patients refused to participate and 4 were registered twice; therefore, the remaining 1353 patients were registered correctly and underwent endoscopic screening. Screening was discontinued for 2 patients because of a large amount of residual digesta in the stomach and a severe vomiting reflex. Endoscopic screening was completed for the remaining 1351 patients.

Of the screened patients, 362 (26.8%) had newly detected and undiagnosed small, depressed lesions and were randomly assigned to one of 2 groups: (1) 180 patients were examined using C-WLI followed by M-NBI, and (2) 182 patients were examined using M-NBI alone. Four patients in the C-WLI group (one patient's lesion was >10 mm in diameter, one was discontinued from the examination because of Mallory–Weiss syndrome, and 2 had a missed biopsy) and 5 patients in the M-NBI group (one was examined with an unpermitted endoscope and 4 missed biopsy) were excluded. Data for 176 patients in the C-WLI group and 177 patients in the M-NBI group were used for the final analysis (Figure 2). The demographic and lesion characteristics of the 2 groups were balanced. In both groups, 13% of patients had newly diagnosed gastric cancer (20 per group; Table 1).

Table 2 shows endoscopic diagnoses for all lesions. Inconclusive diagnoses were obtained for 3 lesions (1.7%) using M-NBI, for 6 lesions (3.4%) using C-WLI, and for 2 lesions (1.3%) using C-WLI followed by M-NBI. These lesions were considered endoscopic "noncancerous" lesions for analysis.

The real-time diagnostic accuracy of M-NBI was significantly greater than that of C-WLI (90.4% [95% CI, 85.1%–94.3%] and 64.8% [95% CI, 57.2%–71.8%], respectively; $P <$ .001; Table 3). Real-time M-NBI diagnosis had greater specificity than C-WLI diagnosis (94.3% [95% CI, 89.4%–97.3%] and 67.9% [95% CI, 60.0%–75.2%], respectively; $P <$ .001; Table 3). The diagnostic sensitivities of M-NBI and C-WLI did not differ significantly (60.0% [95% CI, 36.1%–80.9%] and 40.0% [95% CI, 19.1%–63.9%], respectively; $P =$ .34; Table 3). M-NBI in conjunction with C-WLI significantly enhanced the diagnostic performance of the latter; accuracy increased from 64.8% (95% CI, 57.2%–71.8%) to 96.6% (95% CI, 93.5%–99.1%; $P <$ .001), sensitivity increased from 40.0% (95% CI, 19.1%–63.9%) to 95.0% (75.1%–99.9%; $P <$ .001), and specificity increased from 67.9% (95% CI, 60.0%–75.2%) to 96.8% (92.7%–99.0%; $P <$ .001; Table 3).

The median durations of the C-WLI and M-NBI procedures were 21 seconds (interquartile range, 12–40 seconds) and 55 seconds (interquartile range, 23–97 seconds), respectively, and this difference was highly significant ($P < .001$). The median total duration of C-WLI followed by M-NBI (72 seconds [interquartile range, 40–144 seconds]) was significantly longer than that of
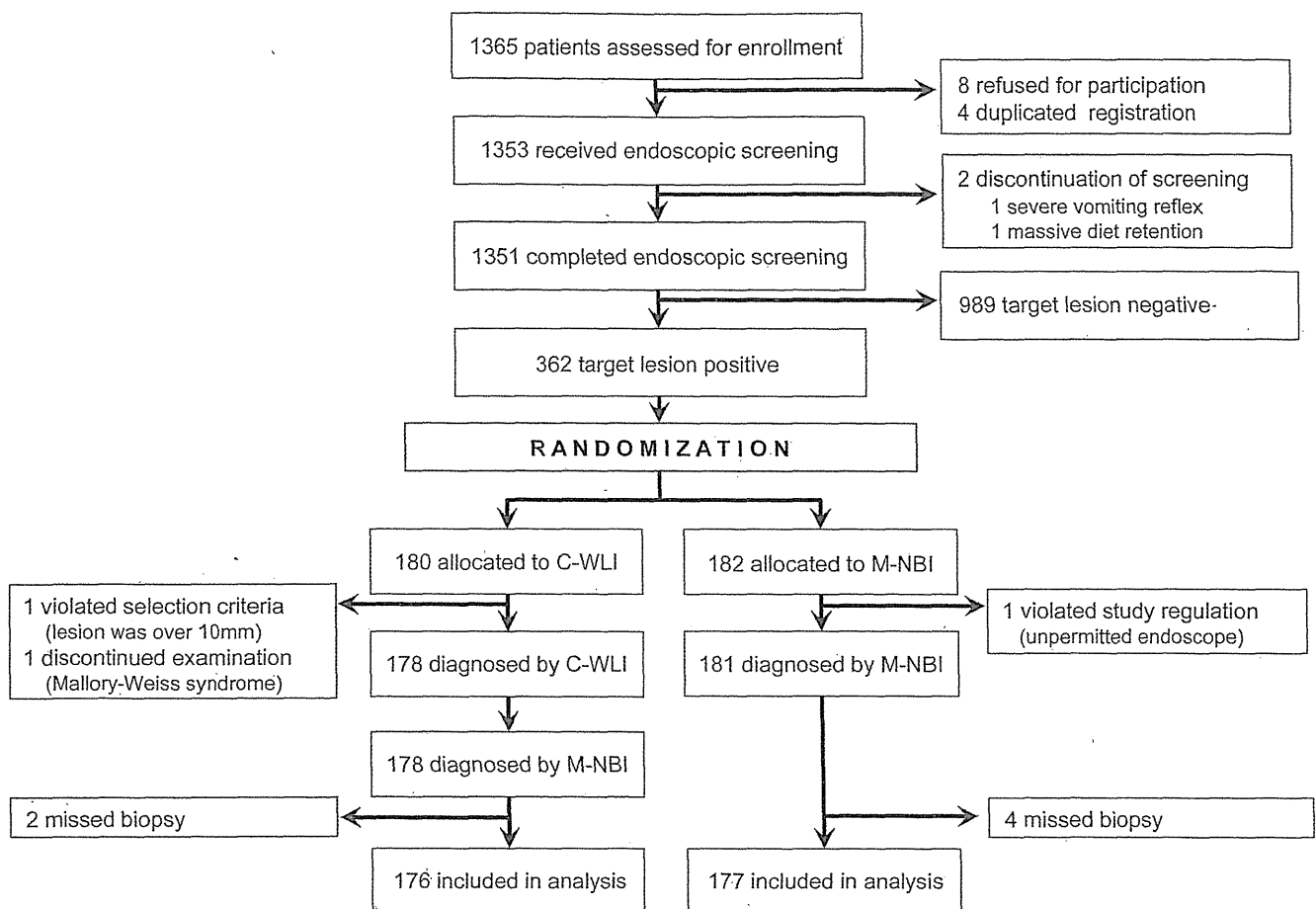
Figure 2. Patient enrollment, randomization, and examination.

C-WLI alone ($P < .001$). All patients tolerated the procedures well (Table 3).

Figure 3 shows the PPV and NPV data for each examination. M-NBI significantly improved the PPV compared with C-WLI alone to 57.1% (95% CI, 36.0%–78.3%) from 13.8% (95% CI, 2.9%–22.7%; $P = .001$). Furthermore, C-WLI followed by M-NBI dramatically improved the PPV from 13.8% (95% CI, 2.9%–22.7%) to 79.2% (95% CI, 62.9%–95.4%; $P < .001$). Similarly, the NPV of C-WLI of 89.8% (95% CI, 84.4%–95.3%) was improved by M-NBI to 94.9% (95% CI, 91.4%–98.3%; $P = .16$) and by C-WLI followed by M-NBI to 99.3% (95% CI, 98.1%–100%; $P < .001$).

Detailed C-WLI examination was discontinued during the procedure in one patient (1/362; 0.3%) because of bleeding associated with Mallory–Weiss syndrome. Although the bleeding stopped spontaneously without any endoscopic hemostatic treatment, a biopsy specimen was not obtained because the suspicious target lesion was missed. Two patients (2/362; 0.6%) were hospitalized on the day after examination because of bleeding from the biopsy site; although one patient needed a blood transfusion, both patients were discharged within a few days. None of the 3 patients experienced prolonged adverse effects. There were no serious adverse events directly related to the endoscopic observations.

Table 4 summarizes the clinical courses and pathologic diagnoses of 40 gastric cancers in 40 patients. Thirty-two patients were treated endoscopically (by endoscopic mucosal resection or endoscopic submucosal dissection). Five patients underwent surgical resection for synchronous advanced gastric cancers. The remaining 3 patients did not receive any treatment; 2 had other concomitant non-curable malignancies, and one refused treatment. Histologically, 39 lesions were of the intestinal type and one lesion was of the diffuse type. Regarding the depth of the 37 lesions that were removed, 35 were mucosal cancers, 2 of which were accompanied by submucosal invasion (0.3 mm and 0.8 mm). The depths of the 3 untreated lesions were estimated endoscopically as 2 mucosal cancers and one submucosal cancer.

Discussion

In this multicenter randomized trial, we compared the diagnostic yield of C-WLI with that of M-NBI for small gastric cancers. The primary aim of this study was to compare directly the real-time diagnostic accuracy of 2 randomly assigned endoscopic modalities. One was the worldwide standard method of C-WLI; the other was M-NBI, which is the most advanced imaging method at present. This end point is the most impor-

Table 1. Baseline Characteristics of the Study Participants According to Treatment Group

	C-WLI (n = 176)	M-NBI (n = 177)	P value
Age (y)			
Median (range)	69 (45–93)	69 (37–87)	.56
Sex			
Male	138	140	.79
Female	38	37	
Endoscope			
GIF-Q240Z	71	65	.83
GIF-H260Z	104	109	
GIF-FQ260Z	1	3	
Size of lesion (mm)			
≤5	74	71	.75
>5	102	106	
Mean	5.6	5.6	.97
Location of lesion			
Upper third			
Anterior wall	4	2	.51
Lesser curvature	9	10	
Posterior	22	12	
Greater curvature	4	3	
Middle third			
Anterior wall	7	7	
Lesser curvature	13	25	
Posterior	12	11	
Greater curvature	8	6	
Lower third			
Anterior wall	18	23	
Lesser curvature	25	33	
Posterior	26	18	
Greater curvature	28	27	
Histopathology diagnosis			
Cancer	20	20	1.00
Noncancerous	156	157	

tant aspect of this study, because if C-WLI proves superior to M-NBI, such advanced methods are not needed in practice. However, if M-NBI is indeed better than C-WLI, it should be used more in daily practice. The secondary aim of this study was to evaluate the additional effect of performing M-NBI after C-WLI. This end point is also important, because in daily practice M-NBI is usually performed after C-WLI. Therefore, the results might reflect the practical diagnostic potential. To evaluate these aims, we used a strictly controlled randomized study. Furthermore, the endoscopic diagnosis in each method (C-WLI and M-NBI) was made on-site and independently to avoid any bias.

M-NBI, especially when used in conjunction with C-WLI, significantly enhanced real-time sensitivity, specificity, and accuracy of diagnosis; therefore, we concluded that M-NBI is an essential modality for diagnosing small gastric mucosal cancer. Although there are reports on the diagnostic yield of M-NBI for differential diagnosis of gastric lesions, some were performed at only one institute,[9,10,12,13] one was evaluated by several expert endoscopists using stored images and did not involve real-time assessment,[12] and one included gastric lesions with a definite diagnosis.[13] To overcome these limitations, our study targeted newly detected and undiagnosed gastric superficial lesions, which were evaluated on-site. For these reasons, the present results are the most reliable and could be a milestone in the field of endoscopic diagnosis of early gastric cancers.

Regarding accuracy and specificity, M-NBI alone yielded excellent results (90.4% and 94.3%, respectively), which were significantly better than those obtained with C-WLI. However, the sensitivities of M-NBI alone (60.0%) and C-WLI alone (40.0%) were lower than the estimated values: 85% for M-NBI and 60% for C-WLI. The low sensitivity of C-WLI might be acceptable considering the difficulty of diagnosing small gastric cancers in daily clinical practice. Although the reason for the low sensitivity of the M-NBI group is unknown, it might be associated with the examination protocol in this study; M-NBI observation was performed without evaluating a gross finding of lesions using C-WLI. In daily practice, magnifying examinations are usually performed after C-WLI. Actually, when performed after the C-WLI observation, M-NBI yielded excellent diagnostic performance in terms of accuracy, sensitivity, and specificity (all values were >95%). In addition, M-NBI and C-WLI followed by M-NBI significantly improved the PPV and NPV compared with C-WLI alone. This has enormous significance in clinical practice, because the examination with high PPV and high NPV might enable the clinician to make appropriate judgments as to which lesion needs pathology to confirm the diagnosis. When the lesion is suspected to be a neoplasm by C-WLI followed by M-NBI, taking a biopsy specimen is highly recommended to confirm the pathology. On the other hand, when the lesion is not suspected to be a neoplasm by M-NBI alone or by C-WLI followed by M-NBI, we could avoid a negative biopsy. These results have the potential to enable so-called "optic biopsy." Taken together, C-WLI followed by M-NBI might be the best

Table 2. Endoscopic Diagnoses for All Small Depressed Lesions

		Cancerous lesion (%)			Noncancerous lesion (%)		
Group	Method	Correct diagnosis	Incorrect diagnosis	Inconclusive diagnosis	Correct diagnosis	Incorrect diagnosis	Inconclusive diagnosis
M-NBI	M-NBI	12/20 (60.0)	7/20 (35.0)	1/20 (5.0)	146/157 (93.0)	9/157 (5.7)	2/157 (1.3)
C-WLI	C-WLI	8/20 (40.0)	12/20 (60.0)	0/20 (0)	100/156 (64.1)	50/156 (32.1)	6/156 (3.8)
	C-WLI+M-NBI	19/20 (95.0)	1/20 (5.0)	0/20 (0)	149/156 (95.5)	5/156 (3.2)	2/156 (1.3)

Table 3. Diagnostic Performance of C-WLI and M-NBI for Gastric Small Depressed Lesions

Group	Method	Accuracy (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Examination time (s), median (interquartile range)
M-NBI	M-NBI	90.4[a] (85.1–94.3)	60.0 (36.1–80.9)	94.3[a] (89.4–97.3)	55[a] (23–97)
C-WLI	C-WLI	64.8 (57.2–71.8)	40.0 (19.1–63.9)	67.9 (60.0–75.2)	21 (12–40)
	C-WLI + M-NBI	96.6[b] (93.5–99.1)	95.0[b] (75.1–99.9)	96.8[b] (92.7–99.0)	72[b] (40–144)

[a]$P < .001$ for M-NBI vs C-WLI; [b]$P < .001$ for C-WLI vs C-WLI + M-NBI.

approach for making accurate diagnoses of small gastric cancers.

The durations of the M-NBI and C-WLI followed by M-NBI examinations were 34 seconds and 51 seconds, respectively, significantly longer than that required for C-WLI alone. However, these durations are clinically acceptable, because we managed to make accurate diagnoses without having to insert a spraying catheter or use indigo carmine. The importance of simple methods and accurate diagnoses for clinical practice is indisputable. Thus, Li et al showed that confocal laser endomicroscopy can be used to identify gastric superficial cancers with high validity and reliability.[26] However, confocal laser endomicroscopy requires the intravenous administration of a contrast agent. In contrast, M-NBI can be used by simply pushing a button on the endoscope. In addition, evaluation of demarcation lines and irregular microvascular patterns is sufficient for diagnosis with M-NBI, whereas confocal laser endomicroscopy requires knowledge of histopathology procedures for diagnosis.

Major bleeding caused by an endoscopic biopsy is rarely reported.[27] However, in our study, 2 patients experienced bleeding from the biopsy site. The best way of avoiding such bleeding is to avoid unnecessary biopsies. M-NBI, especially when used in conjunction with C-WLI, could help to reduce the number of unnecessary biopsies.

Our study has some limitations. First, the number of cancerous lesions was small, and it was less than the required sample size. This might be associated with insufficient power to evaluate sensitivity adequately. Then, further large numbers of patients for screening are needed to evaluate the sensitivity for diagnosing small gastric mucosal cancers of each modality. Second, this study was open labeled because the endoscopists knew which imaging modality was in use. Thus, a blinded study was impossible. Third, there is no arm that includes a dye-based imaging method such as indigo carmine or acetic acid. Indigo carmine and acetic acid are useful, but these dyes are only used in a few countries and institutes, and the standard worldwide endoscopic method to diagnose early gastric cancer is still C-WLI without any dye use. In addition, if we added a chromoendoscopy arm in this study, the required sample size would need to be enlarged and the study design and statistical analyses would be excessively complex. For these reasons, we did not include the dye-based imaging method.

Early detection of small gastric cancers makes it possible to effect a cure using minimally invasive treatments such as endoscopic mucosal resection and endoscopic
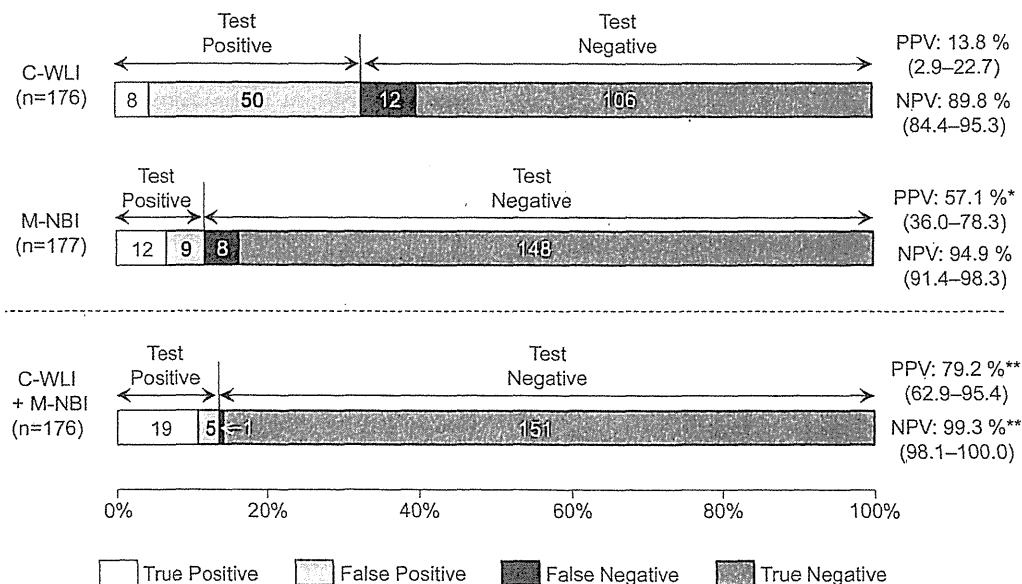

Figure 3. PPV and NPV in each examination. The PPV for M-NBI was significantly higher than for C-WLI ($P = .001$). The NPV in M-NBI was higher than that of C-WLI; however, the difference was not significant ($P = .16$). **Both PPV and NPV were significantly enhanced by additional examination using M-NBI compared with C-WLI alone ($P < .001$).

Table 4. Clinical Course and Pathologic Diagnosis of Patients With Gastric Cancers

No. of patients	40
Treatment	
Endoscopic mucosal resection/endoscopic submucosal dissection	2/30
Surgery	5
No treatment	3
Histologic type	
Adenocarcinoma	40
Intestinal type	39
Diffuse type	1
Other diagnosis	0
Pathologic depth	
Mucosa	35
Submucosa	2
Muscularis propria	0
Unknown	3

submucosal dissection. In this study, all of the newly diagnosed small gastric cancers were good candidates for these procedures. Among the 37 cancers removed, 35 (95%) were mucosal. Early diagnosis using M-NBI and minimally invasive treatment is ideal for patients with gastric cancers, because it will improve their survival and quality of life. Although eradication of *Helicobacter pylori* is effective in reducing the incidence of gastric cancer,[17,28] endoscopic examination using M-NBI in conjunction with C-WLI should be indicated for high-incidence areas such as East Asia, South America, Eastern European countries, and Russia.[29]

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi: 10.1053/j.gastro.2011.08.007.

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Epidermoid Metaplasia of the Esophagus: Endoscopic Feature and Differential Diagnosis

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ABSTRACT

Background/Aims: Despite the recent improvement of endoscopic diagnostic accuracy, there remain many undiscovered lesions in the GI tract. One such lesion is epidermoid metaplasia of the esophagus. The aim of this study is to clarify the endoscopic and pathological characteristics of epidermoid metaplasia of the esophagus.
Methodology: We reviewed all histological records of gastrointestinal endoscopic biopsy specimens obtained in our institution from September 2003 to August 2006 and identified five lesions from four patients with characteristic pathological findings of epidermoid metaplasia.
Results: All four patients were heavy drinkers and had a synchronous or metachronous squamous cell carcinoma. Three of them had multiple lugol-voiding lesions in the background esophageal mucosa. Endoscopic examination revealed common findings in these lesions: clear demarcation, slightly elevated shape, translucent white color, scaly or shaggy surface, and unstained appearance after Lugol's iodine staining. These endoscopic findings resembled those of superficial esophageal cancer. The pathological features of these lesions were uniform in hyperkeratotic and distinct granular layers of the epithelium and were very similar to those of normal epidermis of the skin.
Conclusions: Since the endoscopic features of epidermoid metaplasia resemble those of superficial esophageal cancer, we must pay enough attention to this new entity at the endoscopic examination.

INTRODUCTION

Despite the recent improvement of endoscopic diagnostic accuracy, it is likely that there are many undiscovered lesions in GI tract. One such lesion is epidermoid metaplasia, which we describe in this report. To our knowledge, there are only two previous reports of epidermoid metaplasia. In 1997, Nakanishi et al. reported similar characteristic pathological features, which they termed "epidermization" (1), detected as an irregularly shaped area that was unstained by Lugol's iodine in a surgically resected specimen of esophageal cancer; however, they did not publish an endoscopic picture of the lesion. In 2006, Fukui et al. briefly reported a minor lesion with the features of an epidermoid metaplasia located proximal to the gastroesophageal junction (2). This was the only previous report to describe both the endoscopic and pathological appearance of an epidermoid metaplasia. However, the specific characteristics of their endoscopic findings have not been clarified. To clarify the specific gross features of these lesions, it is important to find the common characteristics by reviewing a certain number of cases with epidermoid metaplasia.

METHODOLOGY

We reviewed all histological records of gastrointestinal endoscopic biopsy specimens obtained in our institution from September 2003 to August 2006 and identified five lesions from four patients with characteristic pathological findings diagnosed as epidermoid metaplasia. Thereafter, we reviewed all recorded endoscopic pictures and biopsy specimens obtained from these patients with epidermoid metaplasia.

RESULTS

The clinical background of each patient and the endoscopic findings of each lesion are summarized in **Table 1**. The four patients were two men and two women, whose ages ranged from 48 to 71 years. All reported high alcohol consumption but no special eating habits. All four patients had a concomitant or previous history of squamous cell carcinoma: three patients had a history of esophageal squamous cell carcinoma, and one had oropharyngeal squamous cell carcinoma. None of the patients had any other disease history or concomitant disease.

In two patients (patients 1 and 2), endoscopic examination was performed for the detailed evaluation of the esophageal cancer. Patient 3 was evaluated by routine follow-up after endoscopic mucosal resection (EMR) for superficial esophageal cancer, and patient 4 was evaluated by screening of the upper gastrointestinal tract before multimodal treatment for oropharyngeal cancer detected at another

FIGURE 1
Patient 1. Endoscopic images of the large epidermoid metaplasia on the oral side of the cancerous lesion. **A:** A well–demarcated, translucent white scaly lesion that involved one half of the luminal circumference. **B:** Well–demarcated unstained area seen with Lugol's iodine staining.
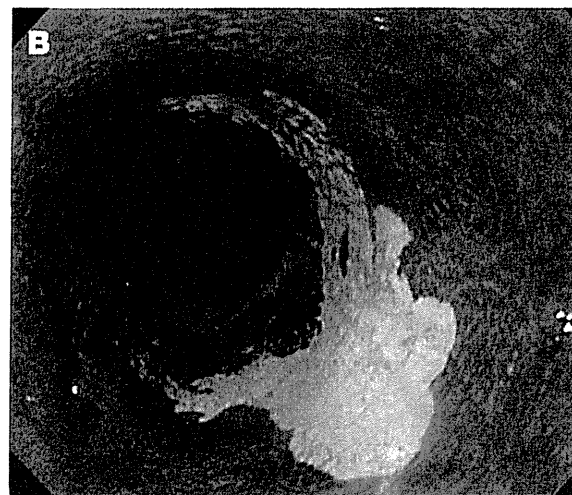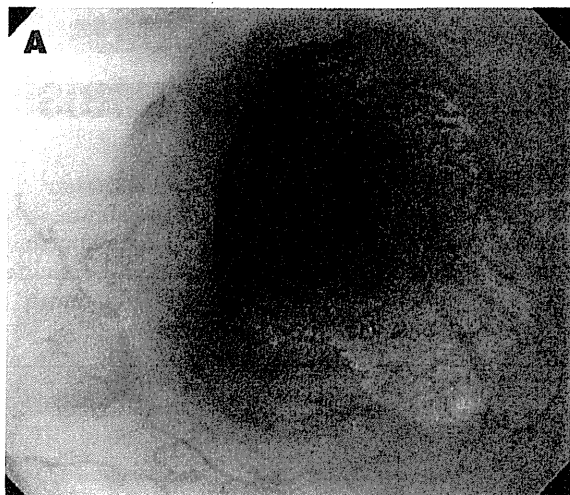
FIGURE 2
Patient 2. Endoscopic images of the small epidermoid metaplasia. **A:** A well–demarcated, white shaggy lesion that measured 15mm on its major axis. **B:** A clearly demarcated, unstained area after Lugol's iodine staining. Multiple Lugol–voiding lesions are seen all over the esophagus without any relation to the epidermoid metaplasia.
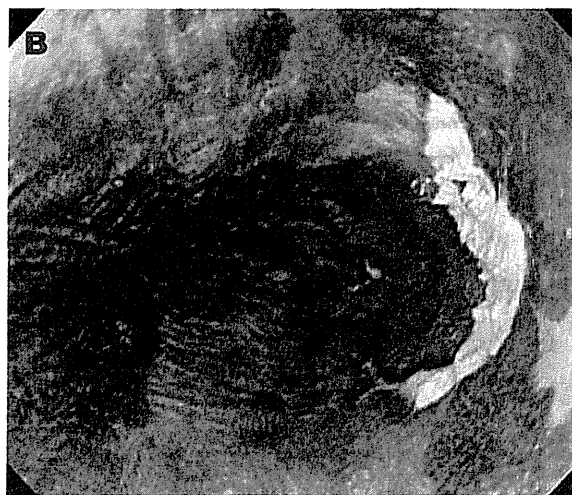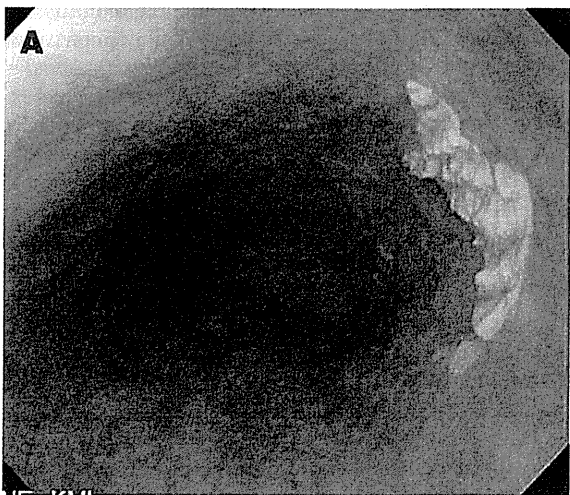
FIGURE 3
Histological features of epidermoid metaplasia (HE). There are hyperkeratotic and distinct granular layers in the epithelium and granulation tissue, with abnormal infiltration of inflammatory cells in the subepithelial layer.
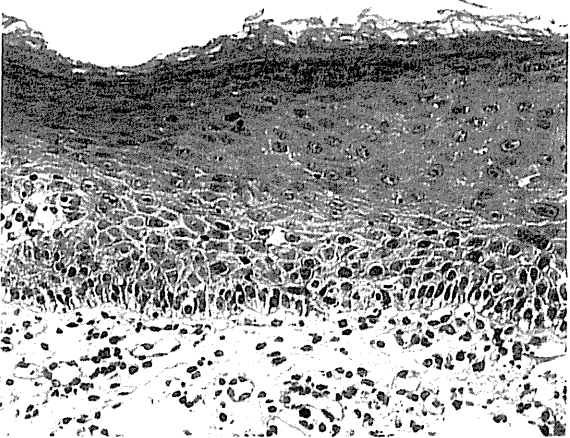
hospital. The lesions were located in the middle or lower esophagus, and the size of the major axis ranged from 6 to 40mm. Patient 1 had two lesions and the others each had one lesion.

Endoscopic examination revealed common findings of the lesions: clear demarcation, slightly elevated shape, translucent white colour, scaly or shaggy surface without erosion or ulceration, and unstained appearance after Lugol's iodine staining

(**Figures 1** and **2**). These endoscopic features differed from those associated with other esophageal abnormalities (**Table 2**), and these features seem to be specific to epidermoid metaplasia. In three patients, endoscopic examination had been performed previously. Therefore, we reviewed all of the recorded endoscopic pictures and biopsy specimens taken from the lesions and used this information to determine that both endoscopic and histological findings had not changed during the course of follow-up. In addition, there were multiple Lugol-voiding lesions (m-LVLs (3-5)) all through the entire esophagus in three of four patients. No patient had gastro-esophageal reflux disease (GERD). The pathological features of these lesions were uniform in both the hyperkeratotic and distinct granular layers of the epithelium (**Figure 3**). These histological findings differed considerably from other known histological findings in various esophageal abnormalities, but appeared very similar to normal epidermis of the skin and were also consistent with the microscopic findings in two previous reports of epidermoid metaplasia (1, 2). Accordingly, we regarded these findings as epidermoid metaplasia. In addition, one biopsy specimen obtained from the lesion contained granu-

TABLE 1 Patient Characteristics and Endoscopic Findings

		Background				Endoscopic findings								
No	Age	Gender	Alcohol abuse	History of SCC	Other concomitant disease	Location	size (mm)	Demarcation	Surface	Color	Lugol stain	Previous endoscopic examination	m-LVLs	GERD
1	58	M	yes	esophagus	no	Mt	30	clear	scaly	white	unstained	no	yes	no
2	58	F	yes	esophagus	no	Lt	40	clear	scaly	white	unstained	yes	yes	no
3	71	M	yes	esophagus	no	Lt	15	clear	shaggy	white	unstained	yes	no	no
4	48	F	yes	H&N	no	Mt	6	clear	shaggy	white	unstained	yes	yes	no
						Lt	10	clear	shaggy	white	unstained	yes		

No: Number of case; SCC: Squamous Cell Carcinoma; m-LVLs: multiple Lugol-Voiding Lesions; GERD: Gastro-Esophago Reflux Disease; H&N: Head and Neck; M: Male; F: Female; Mt: Middle Thoracic esophagus; Lt: Lower Thoracic esophagus

lation tissue in the subepithelial layer (**Figure 3**).

DISCUSSION

In all patients, the epidermoid metaplasia seemed to be adherent to the esophageal mucosa and to resemble plaques. It had a translucent white color, scaly or shaggy surface without erosion or ulceration, and retained an unstained appearance after Lugol's iodine staining. They are the common endoscopic findings of the epidermoid metaplasia of the esophagus.

Differential diagnosis needs to be made based on lesions with similar appearance, such as papilloma, hyperkeratosis, glycogenic acanthosis, plaque associated with reflux esophagitis, localized esophagitis, esophageal candidiasis and superficial esophageal cancer. Epidermoid metaplasia differs from these lesions with respect to the points shown in **Table 2**. Because epidermoid metaplasia has clear borders, it can be distinguished from inflammatory lesions (*e.g.* plaque associated with reflux esophagitis, localized esophagitis and esophageal candidiasis), which generally have poorly defined borders. Lugol's iodine solution more clearly distinguishes some lesions from epidermoid metaplasia because epidermoid metaplasia is unstained by Lugol's iodine solution, whereas papilloma and hyperkeratosis stain weakly and glycogenic acanthosis stains strongly. The most important lesion to distinguish from epidermoid metaplasia is superficial esophageal cancer because the latter is also unstained by Lugol's iodine.

Elevated superficial esophageal cancer (type 0-IIa) sometimes has a white colored surface and is therefore difficult to distinguish from epidermoid metaplasia. Superficial cancer has a dim white or slightly reddish color and multiple irregular nodules because it is a solid tumor, whereas epidermoid metaplasia has a translucent white color and a shaggy or almost flat surface. These important endoscopic features may be used to distinguish between them. In addition, after staining with Lugol's iodine, superficial cancer generally tends to be tinged with a pink color as time progresses (called the "pink color sign" in Japan), whereas epidermoid metaplasia does not show this color.

In rare cases, a hyperkeratotic layer covers the surface of depressed superficial squamous cell carcinoma (type 0-IIc), and this type of lesion resembles epidermoid metaplasia, making it the most difficult to diagnose endoscopically (**Figure 4**). If the hyperkeratotic layer covers the surface of cancer completely, the endoscopic appearance is so similar to that of epidermoid metaplasia that it may become almost impossible to distinguish them. On the other hand, when the coverage is incomplete, some details may suggest the coexistence of cancer at the gap in the hyperkeratotic layer: slightly reddish color, minute irregular surface and pink color after staining with Lugol's iodine (pink color sign).

Close endoscopic examination may provide a more exact diagnosis of epidermoid metaplasia by

TABLE 2 Endoscopic Findings of Various Lesions with Plaque—like Appearance in the Esophagus

|	Demarcation	Surface structure	Color	Lugol's iodine staining pattern
Epidermoid metaplasia	clear	shaggy	translucent-white	unstained
Papilloma	clear	papillary protrusion	discolored	weakly stained
Hyperkeratosis	clear	almost flat	white	weakly stained
Glycogenic acanthosis	clear	flat and smooth	white	strongly stained
Plaque associated with reflux esophagitis	unclear	flat and smooth	dim-white	strongly stained around the lesion
Localized esophagitis	unclear	flat and smooth	dim-white or reddish	weakly stained
Esophageal candidiasis	unclear	diffuse rice-grain sized granule	cream-white	slightly stained or stained
Superficial cancer	clear	Irregular granule or nodule	dim-white or reddish	unstained and tinged with pink color
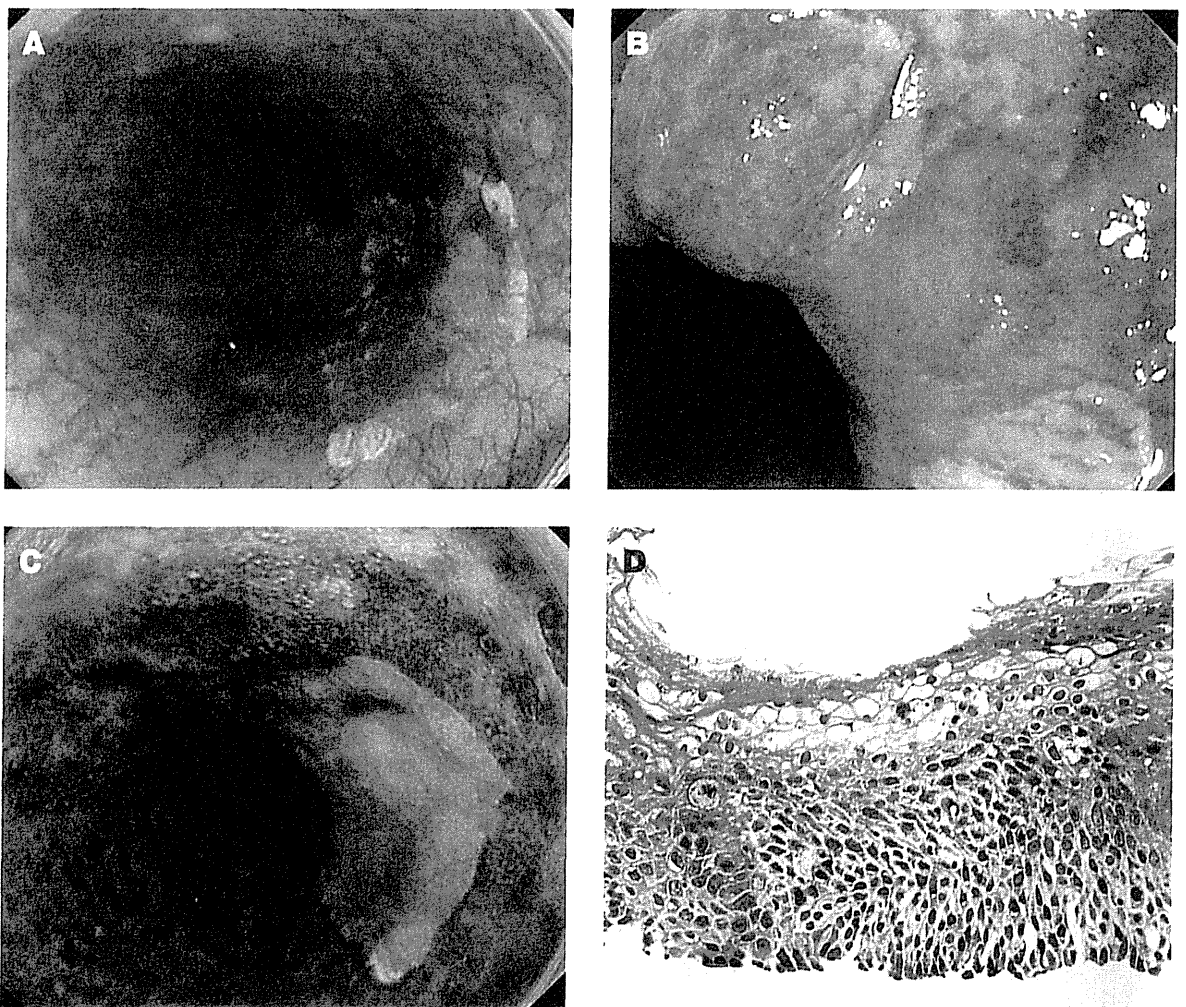
FIGURE 4 Endoscopic images of the depressed superficial carcinoma with hyperkeratosis on its surface.
A: Hyperkeratosis sometimes covers the surface of a depressed superficial carcinoma, and the endoscopic appearance of such lesions is very similar to that of epidermoid metaplasia.
B: Close endoscopic view shows several slightly reddish areas with an irregular surface. These findings are specific for the superficial carcinoma.
C: After Lugol's iodine dyeing, the superficial carcinoma tends to be tinged with a subtle pink color as time progresses. This is a specific finding for carcinoma but not for other benign lesions.
D: Histological finding of biopsy specimen obtained from superficial carcinoma with hyperkeratosis on its surface. The hyperkeratotic layer covers the surface of a superficial carcinoma.

evaluating the key findings described above. To confirm the diagnosis, it is important to collect a large biopsy specimen containing deep tissue sufficient for histological evaluation.

The etiology of epidermoid metaplasia is unknown. Fukui *et al.* speculated that epidermoid metaplasia develops as an unusual response to acid reflux, although Barrett's epithelium usually develops in response to chronic irritation (2). Dianna *et al.* reported epidermoid metaplasia in the uterine cervix and proposed that exposure of the cervix to chronic irritation was the etiology of cervical epidermoid metaplasia (3). In our series, there was no evidence of gastric acid reflux because no patient had obvious endoscopic findings or symptoms of GERD, so it did not seem likely that gastric acid was the main cause of irritation. However, biopsy specimens showed inflammatory changes microscopically, suggesting that chronic inflammation was present at the sites of epidermoid metaplasia. All four patients in this report were habitual alcohol drinkers, and chronic exposure to alcohol may be one cause of inflammation in the esophagus. The short-term natural course of epidermoid metaplasia could be assessed in three patients retrospectively (for 4-15 months), and this analysis showed no changes in the morphology or size of the lesions during the period investigated. Further long-term follow-up is needed to assess the natural course of epidermoid metaplasia and the potential for malignant transformation.

Interestingly, m-LVLs were noted in three of the four patients, suggesting the presence of multiple sites of metaplastic epithelium and parakeratosis, which are strongly associated with the development of esophageal squamous cell carcinoma (4-6). The more interesting underlying factors were a history of squamous cell carcinoma in all patients (three of the esophagus and the remaining of the oropharynx). Because of the small number of patients in the present series, we cannot compare the strength of this association between epidermoid metaplasia, m-LVLs and esophageal squamous cell carcinoma in detail. However, this may suggest that epidermoid metaplasia is a biomarker of squamous cell carcinoma, as is the case for melanosis (7).

We predict an increase in the number of case reports of epidermoid metaplasia once its endoscopic characteristics are recognized widely, and this should lead to more accurate diagnoses. Detailed investigations of a larger number of patients will help define the clinicopathological profile of esophageal epidermoid metaplasia.

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