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SHORT COMMUNICATION

# Pharmacokinetics of oxaliplatin in a hemodialytic patient treated with modified FOLFOX-6 plus bevacizumab therapy

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**Abstract**
*Purpose* To establish an appropriate administration schedule for oxaliplatin in FOLFOX plus bevacizumab therapy for a hemodialytic patient.
*Methods* A 50-year-old man on chronic hemodialysis was treated for colon cancer and synchronous hepatic metastasis with modified FOLFOX-6 plus bevacizumab therapy every 3 weeks. The plasma concentration of free platinum was measured at eight points, before and within the first 50 h after oxaliplatin administration. A dose escalation study of oxaliplatin was performed at doses of 60, 70, and 85 mg/m$^2$. A 4-h dialysis session was begun at the end of the oxaliplatin treatment.
*Results* The pharmacokinetics of free platinum showed a bimodal pattern at each dose: The serum concentration decreased rapidly soon after dialysis, then increased, and remained at a high level for 24 h. The areas under the curves (AUC) for free platinum were 17.6, 23.6, and 32.6 μg h/mL after doses of 60, 70, and 85 mg/m$^2$ oxaliplatin, respectively. These exceeded the AUC when 90 mg/m$^2$ was given to a patient with normal renal function (7.9 μg h/mL). Treatment was safely continued for 6 months without severe toxicity.
*Conclusion* FOLFOX plus bevacizumab therapy can be given safely to hemodialytic patients with no reduction in the dose of oxaliplatin if hemodialysis is performed soon after the administration of oxaliplatin and the dosing interval is extended to 3 weeks.

**Keywords** Colorectal cancer · Renal failure · Hemodialysis · FOLFOX plus bevacizumab · Oxaliplatin

## Introduction

The number of long-lived hemodialytic patients has been increasing with improvements in dialysis treatments. However, hemodialytic patients are potentially at increased risk of cancer for several reasons, including the presence of chronic infection, a weakened immune system, nutritional deficiencies, and altered DNA repair [1].

Colorectal cancer is the third leading cause of cancer deaths, and its incidence is also increasing yearly in Japan [2]. FOLFOX plus bevacizumab is a chemotherapeutic regimen consisting of oxaliplatin and infusional 5-Fluorouracil (5-FU)/levofolinate plus bevacizumab and is accepted widely as an initial treatment for unresectable colorectal cancer, with an objective response in up to 50% of patients treated [3]. However, there have been few reports of the use of oxaliplatin in hemodialytic patients [4–6], and little is known about the safety/efficacy of FOLFOX plus bevacizumab therapy or its optimum dosage in this patient population. Here, we report the case of a hemodialytic patient with metastatic colon cancer, successfully treated with modified FOLFOX-6 plus bevacizumab therapy.

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## Materials and methods

A 50-year-old Japanese man with gouty nephropathy had been maintained on hemodialysis since 2006. A computed tomography (CT) scan showed more than 20 metastases (up to 3 cm in diameter) scattered throughout both lobes of his liver. A colonoscopy showed a protuberant type of tumor located on the sigmoid colon. After the surgical resection of the primary tumor to prevent intestinal obstruction and bleeding, the patient received systemic chemotherapy. Chemotherapy was initiated with the modified FOLFOX-6 (mFOLFOX-6) regimen plus bevacizumab, given every 3 weeks. After bevacizumab was administered by infusion over 90 min, oxaliplatin and levofolinate were administered simultaneously for 2 h. 5-FU was then administered as a bolus injection, followed by its continuous infusion for 46 h with a pump after a 4-h dialysis session (Fig. 1). The starting dose of oxaliplatin was 60 mg/m$^2$ (70% of the standard dose of 85 mg/m$^2$) because oxaliplatin is known to be primarily excreted in the urine and was expected to be eliminated by hemodialysis alone in this patient [7]. The dose of oxaliplatin was increased to 70 and 85 mg/m$^2$, while possible adverse events were monitored. The starting dose of 5-FU was set at the standard dose, because 5-FU is largely (80%) eliminated by the hepatic metabolism and secreted into the bile [8]. Many previous reports have shown that there is no need to adjust its dose in dialysis patients [9]. During each course of mFOLFOX-6 plus bevacizumab therapy, a 4-h dialysis session was begun immediately after the administration of oxaliplatin, using a polysulfonate hollow-fiber dialyzer (APS-21SA) and acetic acid-free dialysate (Carbostar P). The blood flow rate was set at 250 mL/min and the dialysate flow rate at 600 mL/min. The patient's free platinum levels were measured. Blood samples were collected at the following eight points: before the start of oxaliplatin administration, 2 (just before dialysis), 2.25, 2.5, 3, 6, 26, and 50 h after oxaliplatin administration (the last collection was just before the second dialysis session). The blood samples were immediately centrifuged at 1,700×$g$ for 10 min, and the serum thus obtained was further centrifuged at 1,700×$g$ for 20 min in an ultrafiltration tube. The ultrafiltrate sample was then stored in a freezer until the platinum concentration was assayed by flameless atomic absorption spectrometry (NAC Co., Ltd, Tokyo, Japan). The area under the curve (AUC) for platinum in the ultrafiltrate was calculated from time 0 to 50 h after the start of oxaliplatin administration, using the trapezoidal method.

## Results

Table 1 shows the $C_{max}$ and AUC data for free platinum in the serum of a hemodialytic patient receiving mFOLFOX-6 plus bevacizumab therapy. Figure 2 shows the time course of the free platinum concentration. The level of free platinum, which is related to the antitumor activity and toxicity of oxaliplatin, decreased soon after dialysis. It subsequently increased for 26 h after the administration of oxaliplatin and thereafter remained at the same level for 24 h. These findings differ considerably from those previously reported for patients with normal renal function who received 90 mg/m$^2$

**Table 1** Pharmacokinetic parameters of platinum in plasma ultrafiltrate

| | 60 mg/m$^2$ $n = 1$ | 70 mg/m$^2$ $n = 1$ | 85 mg/m$^2$ $n = 3$ | 90 mg/m$^2$ ($n = 3$*) |
|---|---|---|---|---|
| $C_{max}$ (ng/mL) | 500 | 600 | 863 | 963.3 |
| $AUC_{0-50}$ (μg h/mL) | 17.6 | 23.6 | 32.6 | 7.9 |

*AUC* area under the plasma concentration–time curve

* Shirao et al. [10]

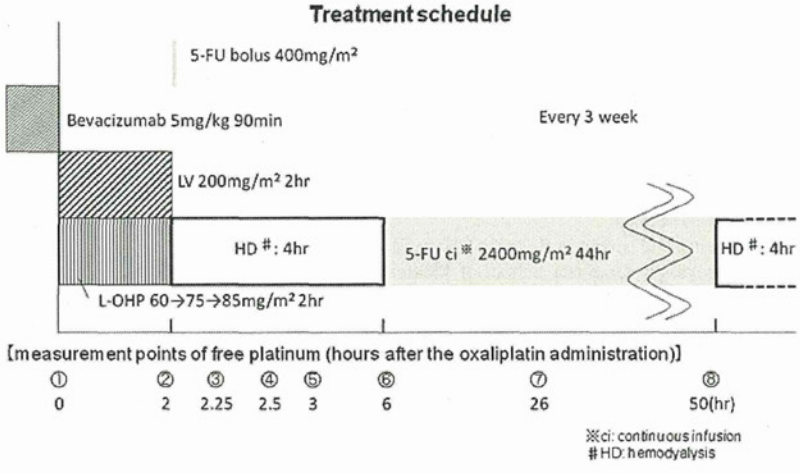


**Fig. 1** Treatment schedule

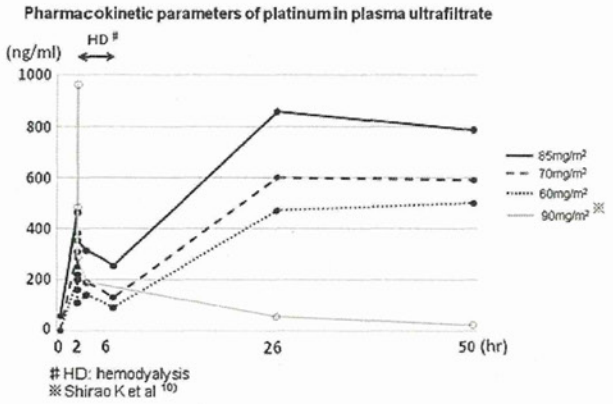


**Fig. 2** Concentration of platinum in plasma ultrafiltrate

oxaliplatin (free platinum $C_{max}$ was 963.3 ng/mL and AUC was 7.9 μg h/mL) [10]. The tolerability data and pharmacokinetic profiles obtained during each cycle were used to optimize the dose of each drug and the dosing intervals for the subsequent cycles. The free platinum AUCs were 17.6, 23.6, and 32.6 μg h/mL at doses of 60, 70, and 85 mg/m$^2$, respectively, which are about 2–4 times greater than that obtained with 90 mg/m$^2$ oxaliplatin in patients with normal renal function [11]. Therefore, a longer dose interval of 3 weeks was set for the subsequent cycles, instead of the standard interval of 2 weeks for mFOLFOX-6 plus bevacizumab therapy. The free platinum $C_{max}$ values measured in this patient were 500, 600, and 863 ng/mL at oxaliplatin doses of 60, 70, and 85 mg/m$^2$, respectively, which are about 50–90% of that obtained with a dose of 90 mg/m$^2$ oxaliplatin in patients with normal renal function [10]. Therefore, a standard dose of 85 mg/m$^2$ was given during the subsequent five cycles. In all, eight courses of mFOLFOX-6 plus bevacizumab therapy (a total of 815 mg/m$^2$ oxaliplatin) were completed, although grade 1 peripheral neuropathy by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; version 3) criteria was observed. A CT scan showed no changes in the number or sizes of the metastatic liver tumors.

## Discussion

To the best of our knowledge, this is the first report of a hemodialytic patient with metastatic colon cancer successfully treated with mFOLFOX-6 plus bevacizumab therapy. In the patient reported here, the free platinum level showed a bimodal pattern, with peaks appearing at 2 and 26 h after the start of oxaliplatin administration. The second peak was as high as the first peak. In patients treated with oxaliplatin, the serum-free platinum concentration reflects the biological activity of the drug, i.e., it determines both its antitumor activity and its toxicity [11, 12]. Previous studies have shown that most circulating platinum molecules derived from oxaliplatin are immediately bound to plasma proteins (primarily albumin) and irreversibly inactivated [13, 14]. The free platinum in the blood is serially excreted by the kidneys, and its excretion is delayed in patients with impaired renal function [15]. A second peak in the free platinum concentration between hemodialyses has also been observed in hemodialytic patients treated with cisplatin [16]. This might be caused by the dissociation of the platinum bound to plasma proteins and blood cells or by platinum in the tissues returning to the blood [17]. In patients with normal renal function, it is likely that free platinum is rapidly eliminated by renal excretion, so no second peak is observed [10].

In our patient, who was given 60 mg/m$^2$ oxaliplatin, the AUC of free platinum was about twofold greater than that observed after an oxaliplatin dose of 90 mg/m$^2$ in patients with normal renal function. Although the relationship between the AUC of free platinum and the antitumor activity of oxaliplatin is poorly understood, it has been reported that the antitumor activities of cisplatin and carboplatin correlate with the AUC of free platinum [12]. Takimoto et al. [9] reported that reductions in the dose of single-agent oxaliplatin are unnecessary, even in patients with impaired renal function, suggesting that the AUC of free platinum does not correlate with the toxicity of oxaliplatin, regardless of the patient's renal function. They proposed the hypothesis that after the administration of oxaliplatin, the majority of free platinum is in the inactive form in low molecular weight conjugates, which are cleared by glomerular filtration. Therefore, the increase in systemic platinum exposure associated with renal impairment does not increase the drug-related toxicity [18].

Giacchetti et al. [19] compared the antitumor activity and hematological toxicity of oxaliplatin in two regimens: four daily doses versus continuous infusion for 48 h. They reported that hematological toxicity was three times more frequent with the former regimen than with the latter regimen, whereas a similar tumor response was achieved with both regimens. These findings suggest that the antitumor activity of oxaliplatin does not correlate with the AUC of free platinum, whereas its hematological toxicity correlates with its $C_{max}$.

In our patient, treatment with the standard dose of oxaliplatin in the mFOLFOX-6 plus bevacizumab regimen resulted in a larger AUC with a lower $C_{max}$ for free platinum than those observed with the standard dose of oxaliplatin in patients with normal renal function. This pharmacokinetic profile might explain the significant tumor response achieved with relatively mild toxicity.

Recently, Kawazoe et al. reported that long-term FOLFOX-6 therapy given every 2 weeks with the standard dose of oxaliplatin in patients with mild renal dysfunction led to

accumulated renal toxicity, and the patients were forced to undergo dialysis [20]. However, in the patient reported here, the concentration of free platinum before the administration of oxaliplatin increased gradually (<30, 40, 50, and 80 ng/mL in the second, third, fifth, and seventh courses, respectively). The 3-week dosing interval set for this patient may have been optimal, but it is essential to monitor the serum concentration of free platinum before the administration of oxaliplatin in each course.

In contrast, it has been reported that the clearance rate of bevacizumab by hemodialysis was 0 mL/min and that the pharmacokinetic parameters in hemodialytic patients were similar to those in patients with normal renal function [21].

In conclusion, mFOLFOX6 plus bevacizumab therapy can be used safely for hemodialytic patients, with no dose reduction in oxaliplatin, if hemodialysis is performed soon after the administration of oxaliplatin and the dosing interval is extended to 3 weeks. The cumulative toxicities and long-term outcomes remain to be established. Larger studies of hemodialytic patients with longer follow-up periods are required.

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# Successful Endoscopic Submucosal Dissection for Esophageal Squamous Cell Carcinoma together with a Lipoma

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## SUMMARY

Superficial carcinomas over submucosal tumors of the esophagus have seldom been detected. Esophageal lipomas are very rare and only a few cases have been reported. We describe the case of a 73-year-old man with superficial squamous cell carcinoma overlying a lipoma. We successfully performed *en bloc* resection by endoscopic submucosal dissection (ESD) using the IT-knife. Histological examination showed curative resections. In such cases, ESD may be a promising tool to perform less invasive treatment.

**KEY WORDS:** Esophageal squamous cell carcinoma; Lipoma; Endoscopic submucosal dissection

## INTRODUCTION

A superficial squamous cell carcinoma coexisting with a lipoma is quite rare in the esophagus (1-3). Such tumors show an elevated form and this makes it difficult to diagnose the depth of invasion. Among the several procedures for endoscopic resection, endoscopic submucosal dissection (ESD) method is now considered to be useful in achieving en bloc resection (4-6). Here we reported a case of superficial squamous cell carcinoma located just over an esophageal lipoma that was successfully resected together with the lipoma by the ESD method.

## CASE REPORT

A 73-year-old man with a tumor in the middle thoracic esophagus was referred to our hospital. He had smoked one pack of cigarettes a day for 20 years and drank a glass of alcohol per day for more than 50 years. He had no significant medical history and no symptoms. The results of the peripheral blood and blood chemistry examinations were within normal limits. Esophagoscopy revealed a whitish lesion in the middle thoracic esophagus. This lesion showed a yellowish color underneath and the top of the lesion showed uneven surface and was partially coated in white (**Figure 1A**). Lugol chromoendosco-

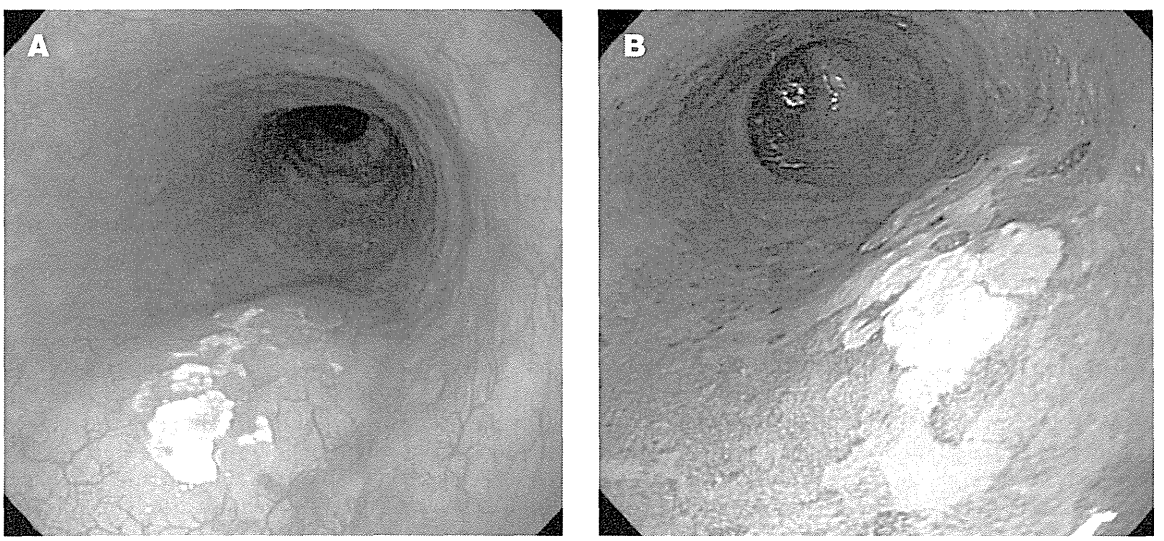


**FIGURE 1 (A)** White light endoscopy, revealing a whitish coated mucosa with erosion and uneven surface. This lesion is slightly raised by a yellowish component underneath. **(B)** Lugol chromoendoscopy, revealing a non–staining pattern coinciding with depressed area.

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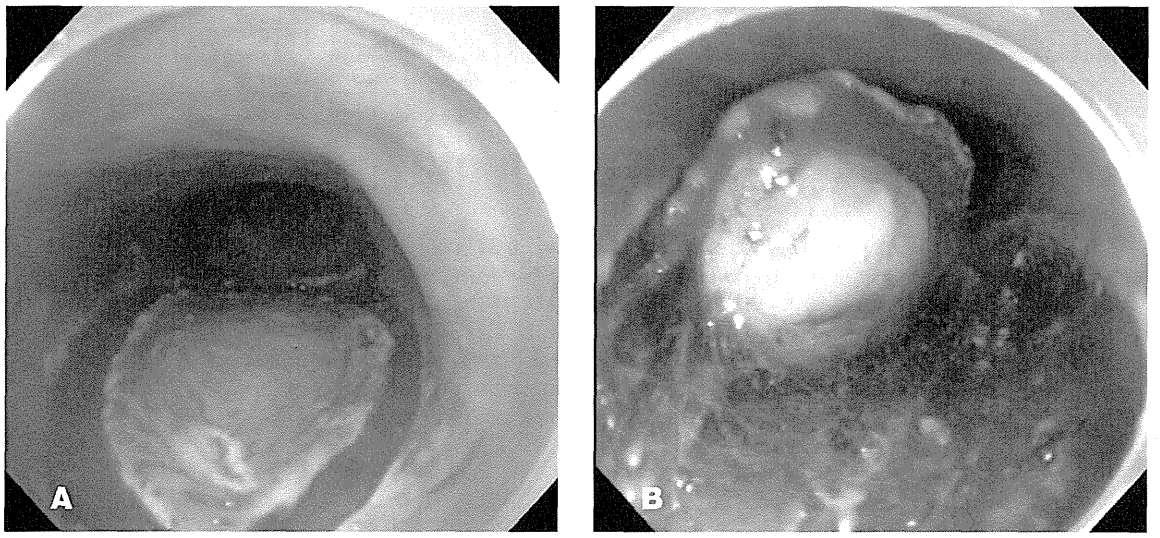


**FIGURE 2 (A)** Circumferential incision during ESD. **(B)** During submucosal dissection, a lipomatous component was clearly revealed.

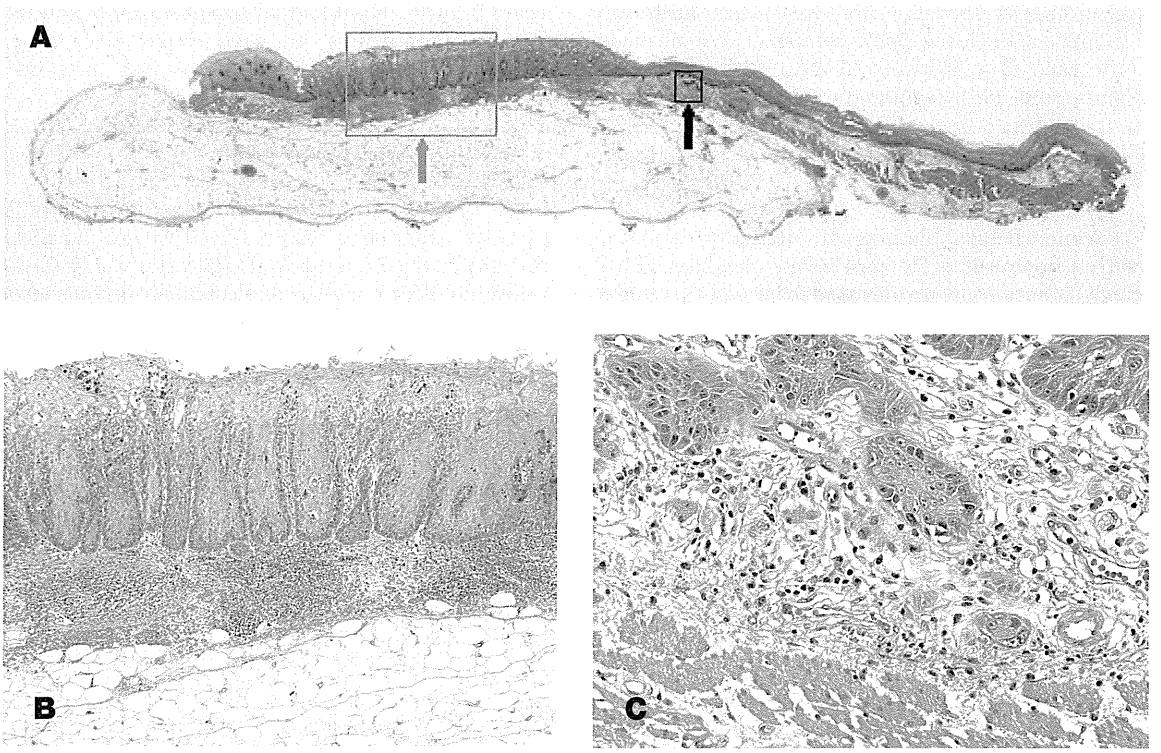


**FIGURE 3** Histopathology from the ESD of the target lesion, revealing a squamous cell carcinoma in the mucosal layer and a lipoma in the submucosal layer just beneath the cancerous lesion. **(A)** Low power view. **(B)** Squamous cell carcinoma *in situ*. **(C)** The invasive area.

py disclosed a non-staining pattern coinciding with the depressed area (**Figure 1B**). Biopsy specimens taken from the lesion revealed squamous cell carcinoma. Endoscopic ultrasonography demonstrated a hyperechoic mass localized within the submucosal layer, which had a homogenous inner echoic pattern with a well demarcated smooth outline and a clear margin. The lesion of superficial carcinoma could not be detected by endoscopic ultrasonography. The CT examination of the chest and abdomen showed no evidence of metastasis.

From these findings, we made a diagnosis of superficial squamous cell carcinoma overlying a lipoma, and endoscopic treatment was scheduled. ESD was performed using the IT-knife. After marginal cutting with the IT knife, the lipoma was clearly bared and the submucosal layer was dissected (**Figure 2A** and **B**). The lipoma and squamous cell carcinoma were successfully resected together without complications.

The resected specimen was 30×20mm in size and histological examination showed squamous

cell carcinoma overlying a submucosal tumor (**Figure 3A** and **B**). The submucosal tumor consisted of mature adipocytes, was well-defined and encapsulated with a fibrovascular septa. The invasion depth of the squamous cell carcinoma was limited to within the mucosal layer (**Figure 3C**). There was no lymphovascular invasion of carcinoma cell. The patient's postoperative course was uneventful. At endoscopy one month later there was no evidence of recurrence.

## DISCUSSION

In the alimentary tract, lipomas are relatively uncommon (7-8) and account for 4% of benign neoplasms (9). Among them, esophageal lipomas are very rare and their incidence is only 0.4% of all lipomas in the gastrointestinal tract (7). Therefore the coexistence of superficial squamous cell carcinoma with lipoma has only been reported in 3 cases previously.

Wehrmann *et al.* reported that endoscopic resection of esophageal submucosal tumors (SMTs) is safe and effective, if the tumors are small in size (<4cm) (10). Endoscopic removal using snare electrocautery is favored for smaller, pedunculated lesions, while large submucosal tumors cannot be extracted by the polypectomy method. Recently, the ESD method has been developed for en bloc resection of gastric neoplasm, which has resulted in high complete resection rates and contributed to correct histological diagnosis (11). Therefore, we introduced ESD for our case and successfully performed en bloc resection together with superficial squamous cell carcinoma and lipoma.

In conclusion, we have described a rare case of esophageal lipoma concomitant with an early esophageal carcinoma. An increased detection of superficial squamous cell carcinoma can lead to a better chance of finding out if the lesion coexists with SMT. In such cases, the ESD method should be considered as a minimally invasive treatment.

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# Long-term outcome of transoral organ-preserving pharyngeal endoscopic resection for superficial pharyngeal cancer

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**Background:** Early detection of pharyngeal cancer has been difficult. We reported that narrow-band imaging (NBI) endoscopy can detect superficial pharyngeal cancer, and these lesions can be treated endoscopically.

**Objective:** To assess the safety and long-term efficacy of transoral organ-preserving pharyngeal endoscopic resection (TOPER) for superficial pharyngeal cancer.

**Design and Setting:** Retrospective 2-center cohort study.

**Patients:** The study included 104 consecutive patients with superficial pharyngeal cancer.

**Intervention:** TOPER with the patients under general anesthesia.

**Main Outcome Measurements:** Safety of the procedure, long-term survival, clinical outcome.

**Results:** A total of 148 consecutive lesions were resected in 104 patients. There was no severe adverse event. Temporary tracheostomy was required in 17 patients (16%) to prevent airway obstruction. The median fasting period and hospital stay after TOPER were 2 days (range 1-20 days) and 8 days (range 3-58 days), respectively. Ninety-six patients (92%) had no local recurrence or distant metastases. Local recurrence at the primary site developed in 6 patients, but all were resolved by repeat TOPER. With a median follow-up period of 43 months (range 3-96 months), the overall survival rate at 5 years was 71% (95% CI, 59-82). Cause-specific survival rate at 5 years was 97% (95% CI, 93-100). The cumulative development rate of multiple cancers in pharyngeal mucosal sites at 5 years was 22% (95% CI, 12-33). The pharynx was preserved in all patients, and they experienced no loss of function.

**Limitation:** Retrospective design.

**Conclusions:** Peroral endoscopic resection of superficial pharyngeal cancer is a feasible and effective treatment with curative intent. (Gastrointest Endosc 2011;74:477-84.)

Pharyngeal cancer other than nasopharyngeal cancer (130,000 new cases and 83,000 deaths worldwide in 2002) is predominantly a cancer of men.[1] Smoking and alcoholic beverages are the class I carcinogens for these cancers.[2] Furthermore, acetaldehyde-associated alcoholic beverages were reclassified as a class I carcinogen in 2009 by the International Agency for Research on Cancer.[2]

*Abbreviations: EMR-C, EMR with a cap; ESD, endoscopic submucosal dissection; NBI, narrow-band imaging; TOPER, transoral organ-preserving pharyngeal endoscopic resection.*

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Although the definite risk factors are well known, it has been quite difficult to detect pharyngeal cancer at an early stage. Thus, most of the cases are diagnosed at an advanced stage and have a poor prognosis. In addition, the standard treatments of surgical resection and/or chemoradiotherapy worsen the patients' quality of life, resulting in speech defects, swallowing disorders, salivary disorders, and cosmetic deformities of the neck.

We previously reported that a new image-enhanced endoscopic technology,[3] narrow-band imaging (NBI), was very useful for detecting these cancers at an early stage and that these superficial cancers could be treated with peroral endoscopic resection with minimal invasiveness.[4-6] Shimizu et al[7] and Iizuka et al[8] also reported the usefulness of endoscopic resection for oropharyngeal and hypopharyngeal cancer. However, these reports included small numbers of patients, and their long-term outcome has not been reported. In addition, it seems to be premature to conduct a prospective study of peroral endoscopic resection for superficial pharyngeal cancer because its feasibility and safety have not been fully evaluated. In this study, we assess a large number of patients with a longer follow-up time to address the feasibility and usefulness of peroral organ-preserving endoscopic resection for superficial pharyngeal cancers.

**Take-home Message**

- Peroral endoscopic laryngopharyngeal mucosal resection is a feasible and effective method for superficial pharyngeal cancer. This minimally invasive procedure can preserve the organ itself and is expected to improve the patient's quality of life and survival.

## PATIENTS AND METHODS

During the period from June 2002 to April 2008, 148 consecutive superficial oropharyngeal and hypopharyngeal cancers in 104 patients were treated by transoral organ-preserving pharyngeal endoscopic resection (TOPER) while under general anesthesia at National Cancer Center Hospital East and Kyoto University Hospital. Written informed consent for the treatment was obtained from all patients, and this study was approved by the local ethics committee.

Histological diagnosis of the lesions was made according to the World Health Organization classification of the tumor (head and neck tumors).[9] Evaluation of the invasion of the tumor was also made according to the general rules for clinical studies of head and neck cancer by the Japanese Society for Head and Neck Cancer and the Japanese classification of esophageal cancer by Japan Esophageal Society.[10] According to these guidelines, carcinoma in situ and subepithelial cancers are defined as a superficial cancer regardless of lymph node or distant organ metastasis. To date, there is no generally accepted definition of superficial cancer in this field. Thus, a cancer limited to the subepithelial layer of the pharynx is defined as superficial cancer in this study.

If the lesion was evaluated as carcinoma in situ or carcinoma with invasion to the subepithelial layer (not to the muscular layer), TOPER was indicated as a minimally invasive treatment (Fig. 1). Patients who received radiotherapy to the head and neck region previously were not indicated. All patients refused radical surgical resection or chemotherapy or chemoradiotherapy. All lesions were detected by NBI with a magnifying endoscope and histologically confirmed by biopsy specimen as severe dysplasia/carcinoma in situ or squamous cell carcinoma.

TOPER was based on the methods of EMR using a cap (EMR-C)[11] or endoscopic submucosal dissection (ESD),[12] and the procedures were performed as previously reported[11,12] by using a high-definition endoscope (Q240Z, Q260J, or H260Z; Olympus Medical Systems, Tokyo, Japan). For EMR-C, a soft food attachment (D-206-06; Olympus Medical Systems) to the tip of the endoscope was used. For ESD, an insulated-tip electrosurgical knife (IT knife; Olympus Medical Systems) was used. In both methods, the lesion was removed after inserting a needle beside the lesion and injecting an adequate volume of saline solution or glycerol containing diluted epinephrine (0.02 mg/mL) beneath the epithelium to lift it above the surrounding mucosa. We used a rigid laryngoscope (Nagashima, Tokyo, Japan) to obtain a sufficient working space by lifting the larynx. Iodine staining was used both to delineate the exact margin of the cancer lesion before resection and to detect residual lesion after resection. If a small residual lesion was endoscopically identified after EMR or ESD, argon plasma coagulation was done to prevent local recurrence. To check whether the larynx was swollen after resection, an endoscopic examination was performed on the day after resection with the patient under conscious sedation by periodic intravenous administration of pethidine hydrochloride (in total 0.5 mg/body weight). If the movement of the pharynx and larynx was unimpaired, the patient was encouraged to start eating semisolid food. If the larynx was swollen, the patient continued fasting until the swelling disappeared.

All resected specimens were cut into longitudinal slices measuring 2 mm in width. The slices were embedded in paraffin and stained with hematoxylin-eosin. All specimens were microscopically evaluated by 3 pathologists (S.F., A.Y., A. Ochiai) according to the World Health Organization classification.[9]

Follow-up endoscopy was performed after 1 to 3 months to check the healing of the mucosal defect and local residue after TOPER, and thereafter every 6 months to detect metachronous superficial cancer in

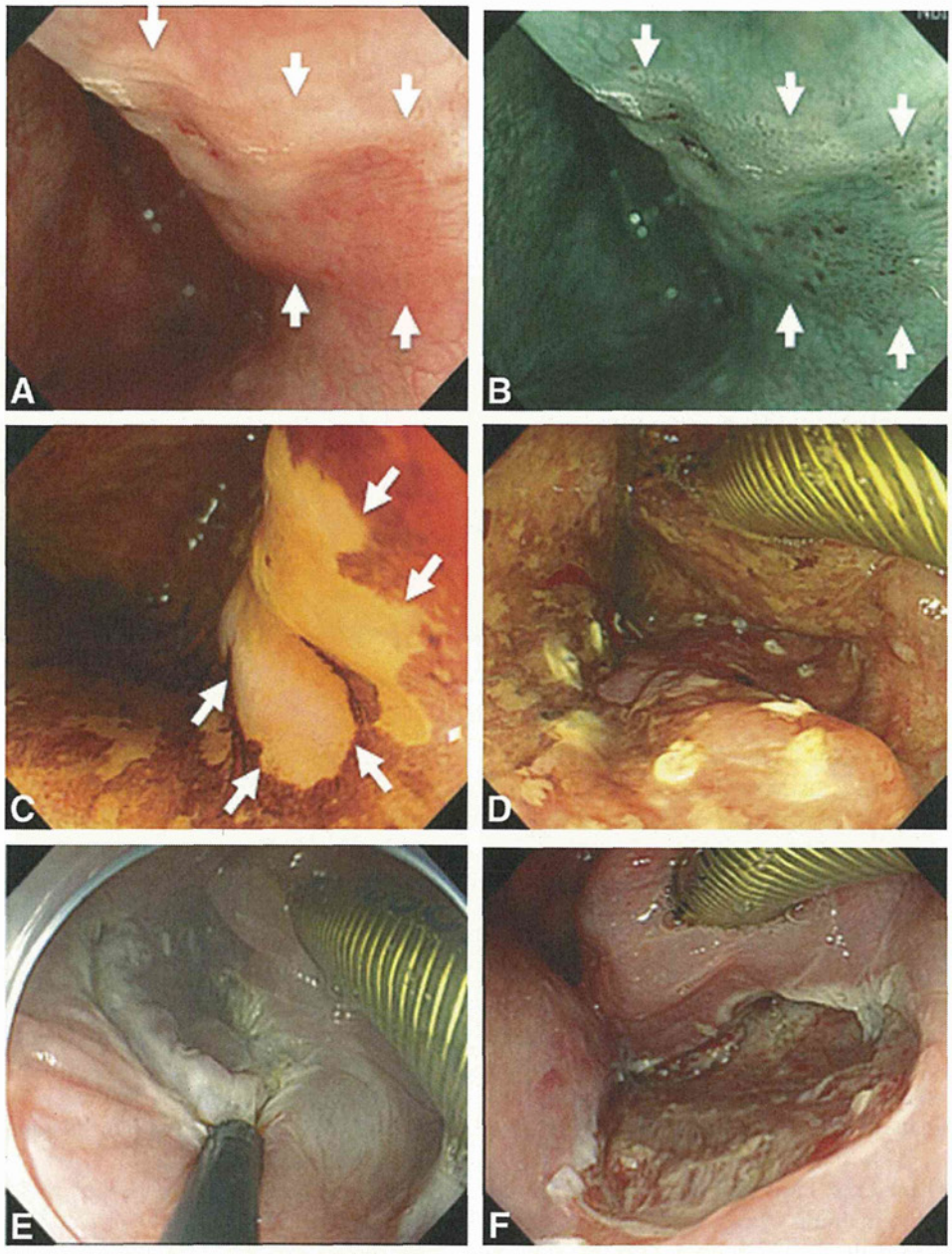


**Figure 1.** TOPER for superficial pharyngeal cancer. **A,** Endoscopic photograph showing the right piriform sinus with superficial pharyngeal cancer. The slight reddish-color mucosa is the neoplastic lesion (*arrows*). **B,** Narrow-band imaging corresponding with **A** showing well-demarcated brownish 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

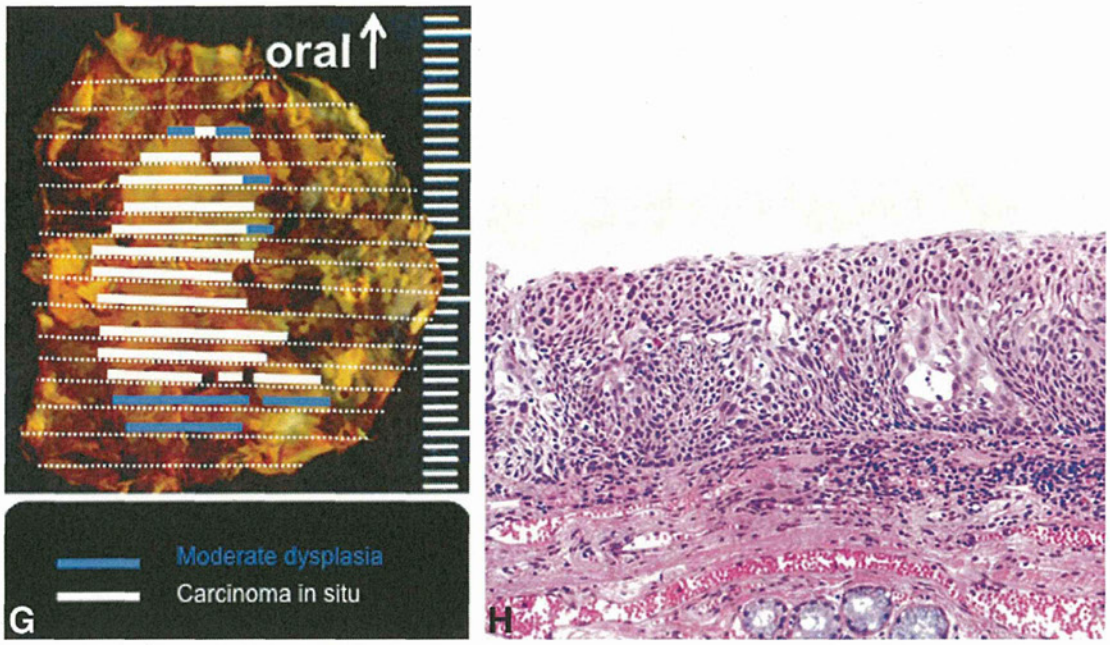


**Figure 1.** *(continued)*

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.

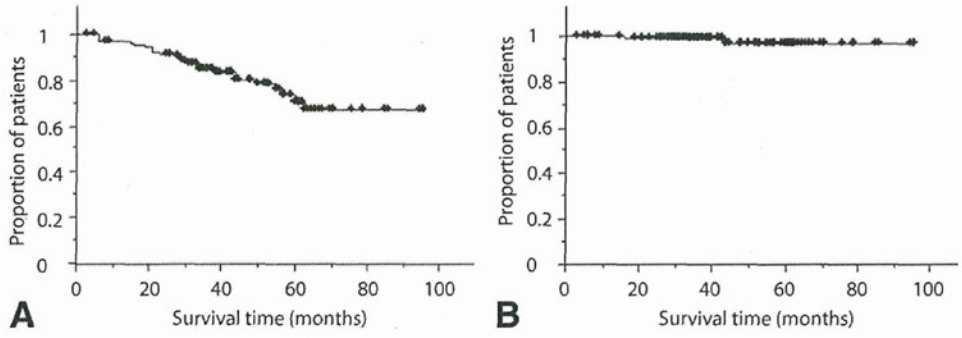


**Figure 2.** Overall survival (**A**) and cause-specific survival (**B**) after TOPER for superficial pharyngeal cancer.

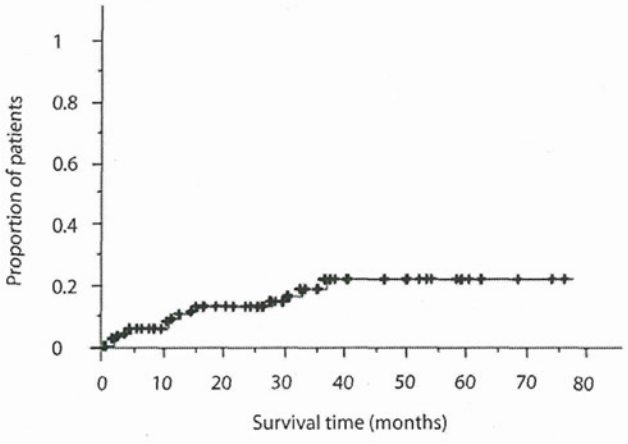


**Figure 3.** Metachronous development of superficial pharyngeal cancer after TOPER.

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

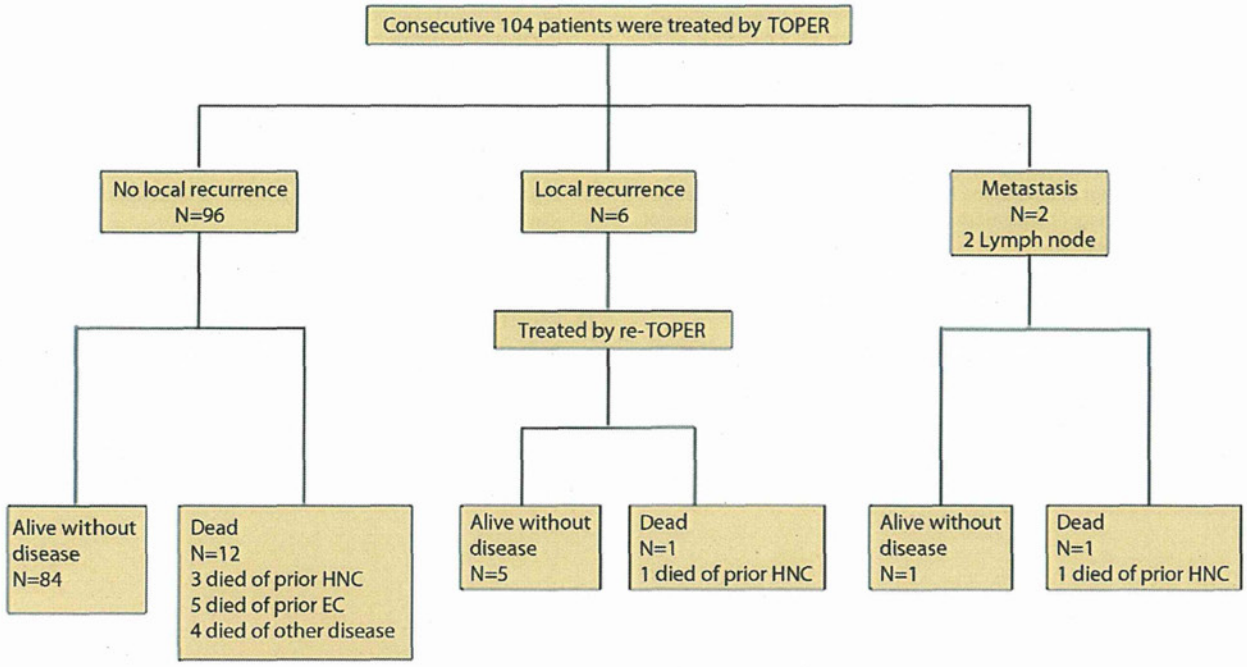


**Figure 4.** Clinical outcomes after TOPER for superficial pharyngeal cancer.

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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# 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.

Gastric 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

*Abbreviations used in this paper:* CI, confidence interval; C-WLI, conventional white-light imaging; M-NBI, magnifying narrow-band imaging; NPV, negative predictive value; PPV, positive predictive value.


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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

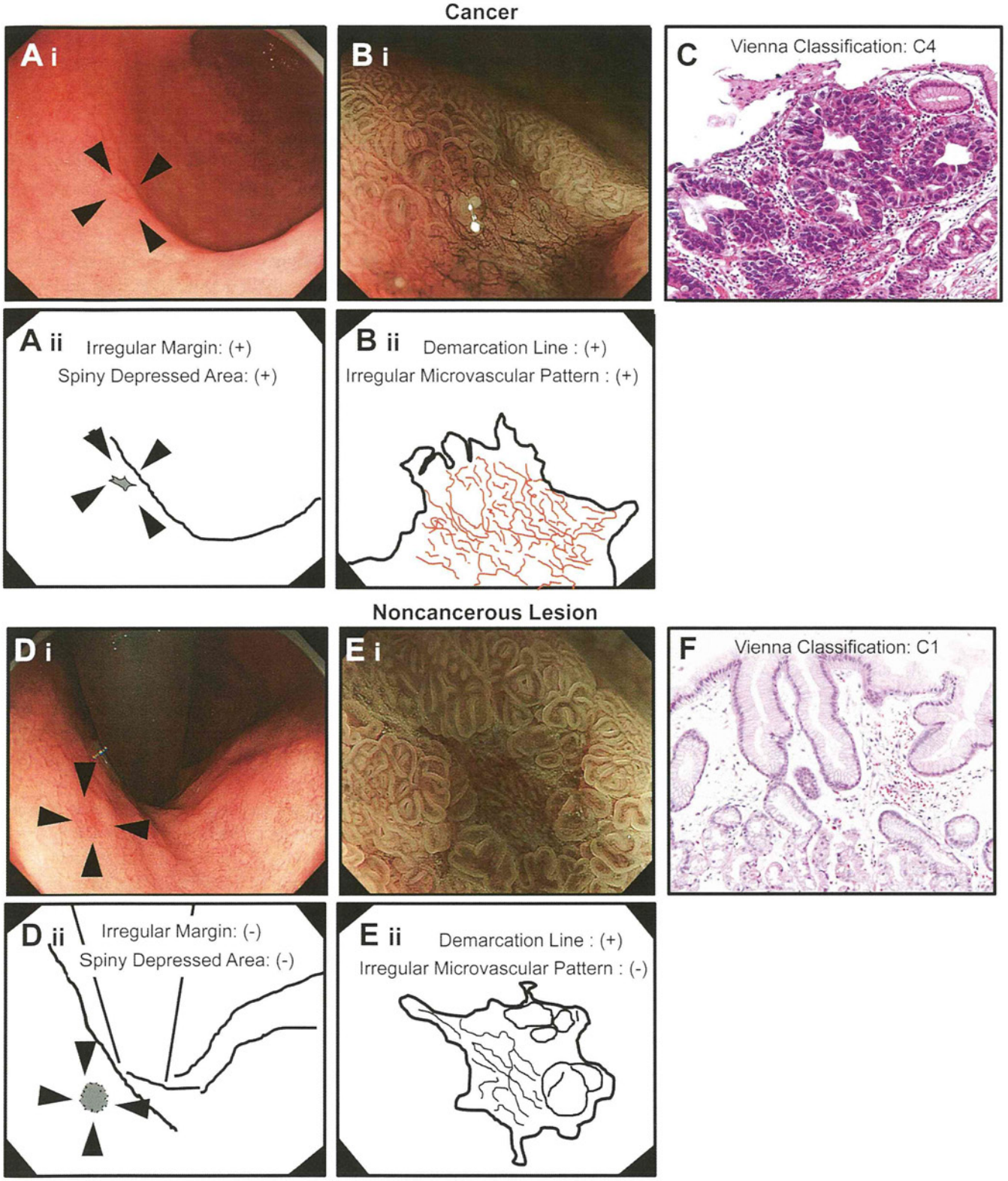


**Figure 1.** Representative endoscopic findings for gastric small, depressed lesions. *A–C* show a case of cancer, and *D–F* show a case of noncancerous lesions. *A* shows an endoscopic image obtained using C-WLI. A small, depressed lesion (*arrowheads*) is evident in the anterior wall of the lower 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.[24] 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 $\chi^2$ 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